Schizophrenia Treatment Outcomes

An Evidence-Based Approach to Recovery

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Foreword

Thinking About Therapeutics for Persons with Schizophrenia

This book addresses many aspects of clinical care relevant for persons with a diagnosis of schizophrenia. Organized around the evidence gathered within schizophrenia, the various chapters will prove relevant for many psychotic disorders. It is impossible to be comprehensive since there are so many variables involved and so much variation between patients. But this is the most comprehensive effort to date, with presentations in a brief and understandable framework. This foreword provides a view on concepts related to understanding schizophrenia and the integration of therapeutics at the individual level.

The Biopsychosocial Medical model provides the framework for integrating patient-centered information. This model calls attention to levels in human function where therapy can be initiated. More fundamentally, the model is a general systems concept calling for integration across each level. For example, if blushing were a disease, a vascular physiologist could explain the physiology of reddening of the face, but the causative role of shame is understood at the psychological level, and why the blush occurs in public requires explanation at the social level. So it is with schizophrenia, where a cognitive intervention at the psychological level seeks understanding of effects on brain physiology and simultaneously observes effects on social cognition and function.

Conceptualizing schizophrenia is important, and for too long the field has held the view that schizophrenia is a disease or, to be more specific, a brain disease. A brief history will clarify. Kraepelin initiated this view with dementia praecox and put in place the expectation of a chronic and deteriorating course. He held that dissociative pathology and weakening of the wellsprings of volition were the core pathologies that, together with a poor prognosis, defined a disease entity. Bleuler proposed that the dissociative pathology was the core pathology in all cases of schizophrenia, hence meeting the concept of a specific disease entity based on shared pathophysiology. Bleuler, by the way, viewed hallucinations and delusions as secondary pathologies and not core manifestations of schizophrenia. This, with the defining of manic-depressive psychosis, places conceptual approaches to schizophrenia in the disease entity category. In the 1960s and 1970s the observations of substantial heterogeneity in development, manifestation, and course challenged the

single disease concept. This heterogeneity may be the result of a broad, overinclusive diagnostic practice. An alternative view held that nuclear or true schizophrenia based on specific criteria provided a disease entity consistent with the concept following Kraepelin and Bleuler. But note that the key diagnostic criteria advocated were symptoms of first rank described by Schneider as meaning the presence of schizophrenia in the absence of delirium. These special forms of hallucinations and delusions quietly shifted the concept from dissociative pathology and avolition to reality distortion. This view was sufficiently influential for DSM-III in 1981 to highlight these first-rank symptoms as sufficient to meet the A criteria. Negative symptoms were omitted altogether.

The International Pilot Study of Schizophrenia was initiated in 1968 to determine if schizophrenia was similar in different locations. Similar cases were found in all nine countries, but a broader concept was used in some centers, including the NIMH center where John Strauss, John Bartko, and I were working. We found the Schneiderian first-rank symptoms in bipolar and other psychotic conditions in our center and confirmed in other centers. Dividing our broad schizophrenia sample into nuclear or true schizophrenia versus pseudo schizophrenia, we falsified the developmental and course predictions based on first-rank symptoms. Our conclusion was that schizophrenia is a clinical syndrome rather than a specific disease entity and that the study of schizophrenia required deconstruction and the component parts were the targets for discovery and for clinical application. These conclusions were published in 1974 [Strauss JS, Carpenter WT Jr, Bartko JJ. The diagnosis and understanding of schizophrenia. Part III. Speculations on the processes that underlie schizophrenic symptoms and signs. Schizophr Bull. 1974 Winter; (11):61–9] but failed to influence DSM-III, and it was not until DSM-5 that first-rank symptoms lost their special status and schizophrenia as a clinical syndrome was made explicit. While schizophrenia as a disease is still in common use, the twenty-first century has brought a major shift to the clinical syndrome view, with science moving rapidly to deconstruction, and clinical application aimed at specific aspects of psychopathology and function, with diagnosis only as a starting point. There is wide recognition that symptoms cross diagnostic boundaries. It is within this clinical syndrome concept that the present book addresses schizophrenia.

The 29 chapters in this book inform the reader on many of the conceptual issues and therapeutic opportunities in the clinician's tool box. Individuals with a schizophrenia diagnosis will vary in which domains of pathology are present and what functional areas need to be addressed. Chapters range from pharmacotherapy to pathways and approaches for recovery; from directly addressing impairments to approaches based on compensatory and resilience mechanisms; from medical attention to metabolic and comorbid pathology to peer support and holistic approaches; from individual issues such as suicide and cannabis use to population issues such as challenges in low-income countries and therapeutics at different life stages. And much more.

Persons with a diagnosis of schizophrenia face many challenges in life, and these vary across individuals. Clinical care must identify and address the full range, and this book provides critical knowledge on many of the issues

common to this diagnosis. Integration of these many elements is difficult. Low-income countries lack the professional workforce and financial ability, but some remarkable programs are developed. High-income countries sometimes provide support for integrated care of the mentally ill. But many patients are treated in circumstances where the care advocated in this book is simply not available. The USA is a sad example of not providing a medical system that integrates the essential clinical care elements.

The busy clinician cannot be knowledgeable in the full range of issues that require therapeutic attention. Questions about the use of cannabis will arise. One patient avoids social encounters because of stigma, another has suicidal thoughts, and others will not understand the role of metabolic effects of lifestyle and medications, nor appreciate the role of physical exercise. The clinician needs to address a shortened life expectancy and which therapies and behavioral changes can reduce risk. How is sleep disturbance to be addressed? And what special form of CBT is required for each symptom? It is in the context of so many therapeutic issues that the present book provides critical information in 29 chapters. Each chapter addresses a specific issue allowing the reader to focus on specific needs for information. This book provides much information on what is needed and how to effect clinical application.

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Preface

Schizophrenia is a neurobehavioral disorder which affects about 0.7–1% of people in the world. The plight of patients suffering from schizophrenia has been due to stigma as well as poor access to care. Both of these factors lead to treatment resistance. We could never find a convincing and effective treatment for schizophrenia until the last 25 years, when both pharmacotherapy and psychosocial treatments started showing a remarkable change in the life of such patients. Though effective treatments have been available, it has been very difficult to extend the benefit to a large number of people.

On one side we are lacking directions in the search for specific treatments for schizophrenia, and on the other side we have serious limitations in health systems management and capacity-building for the disorder. We will be excited the day we get a treatment which will change the lives of patients with schizophrenia; however, we will remain worried to take such treatments to people. More specialized treatments are more complex, and it requires specially trained therapists. Besides, these psychosocial treatments are no less expensive than newer medication. More patients live in the less privileged parts of this world, and thus treatments have to be effective but at the same time should be within reach of patients.

With more facilities, awareness, and changes in the socioeconomic situation, there is increased hope and expectation, and thereby newer demands by the relatives, service users, and caregivers. The scientific community has responded to such requirements and several social treatments are being tried in unique settings, which keeps patients close to their families and away from the hospital while encouraging them to seek employment, develop relationships, have a positive attitude, and becoming economically productive. These treatments have goals which restore dignity and promote human rights of these patients while setting a higher benchmark and encouraging clinicians to achieve the same.

We have compiled this book in order to provide specifics of each of the psychosocial treatments currently used in schizophrenia, based upon the recovery model. We are thankful to all our contributors who have taken extraordinary care to keep the chapters focused and to the point so that clinicians as well as students find it easy to read and practice it in their patient care. The book also deals with the conceptual issue as well as controversies but not beyond a point.

All chapters highlight the opinion, experiences, and evidence for recovery in schizophrenia. We thank all our authors and coauthors for their valuable contributions in the making of this handbook. We hope that this book makes interesting reading for everyone.

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Abbreviations

AACAP	American Association of Child and Adolescent Psychiatry
ACh	Acetyl choline
ACT	Assertive community treatment
AD	Alzheimer's disease
ADHD	Attention-deficit hyperactivity disorder
ADLs	Activities of daily living
AMHM	Avon Mental Health Measure
AMHS	Area mental health services
APA	American Psychiatric Association
APSS	Attenuated Positive Symptom Syndrome
AUDIT	Alcohol Use Disorder Identification Test
BACS	Brief Assessment of Cognition in Schizophrenia
BD	Bipolar disorder
BDNF	Brain-derived neurotrophic factor
BIPS	Brief Intermittent Psychotic Syndrome
BLT	Bright light treatment
BMD	Bone mineral density
BMI	Body mass index
BPRS	Brief Psychiatric Rating Scale
BPSD	Behavioral and psychological symptoms of dementia
BS	Bariatric surgery
CAARMS	Comprehensive Assessment of At-Risk Mental States
CACR	Computer-assisted cognitive remediation
CAD	Coronary artery disease
CAMHS	Child and adolescent mental health services
CAMI	Community Attitude toward the Mentally Ill (scale)
CAN	Camberwell Assessment of Needs
CAN-R	Camberwell Assessment of Need-Research version
CAP	Cannabis and psychosis (therapy)
CATIE	The Clinical Antipsychotic Trials in Intervention Effectiveness
CBCL	Child Behavior Checklist
CBD	Cannabidiol
CBT	Cognitive behavioral therapy
CBT-p	Cognitive behavioral therapy for psychosis
CBT-R	recovery-oriented cognitive behavioral therapy
CCMHI	Canadian Collaborative Mental Health Initiative

CD-RISC	Connor-Davidson Resilience Scale
CDSS	Calgary Depression Rating Scale for Schizophrenia
CG	Comparison group
CGI	Clinical Global Impression
CHR	Clinical high risk
CIHR	Canadian Institutes of Health Research
CLIPP	Consultation and Liaison in Primary-care Psychiatry [program]
CNS	Cardinal Needs Schedule
CNTRICS	Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia
COMT	Catechol-O-methyltransferase
COPS	Criteria of Prodromal Syndromes
COS	Childhood-onset schizophrenia
CPP	Canadian Pension Plan
CR	Complete recovery/cognitive remediation
CSQ	Client Satisfaction Questionnaire
CVD	Cardiovascular disease
D-2	Dopamine-2
DALI	Dartmouth Assessment of Lifestyle Inventory
DALY	Disability-adjusted life years
DAST	Drug Abuse Screening Test
DGPPN	German Society for Psychiatry, Psychotherapy and Neurology
DHEA	Dehydroepiandrosterone
DLB	Dementia with Lewy bodies
DOSMeD	Determinants of Outcome of Severe Mental Disorders
DST	Dexamethasone suppression test
DUP	Duration of untreated psychosis
ECT	Electroconvulsive therapy
EDIE	Early Detection and Intervention Evaluation
EE	Expressed emotion(s)
EG	Experimental group
EIP	Early intervention for psychosis
EOI	Emotional overinvolvement
EOS	Early-onset schizophrenia
EP	Emotional processing
EPINET	Early Psychosis Intervention Network
EPS	Extrapyramidal symptoms
ERI-BAPPSS	Basic and positive psychotic spectrum symptoms
ERI-BS	Basic symptoms
ERI-PPS	Attenuated positive symptoms
ESRS	Extrapyramidal Symptom Rating Scale
FDA	Food and Drug Administration
FEP	First episode psychosis
FGA(s)	First-generation antipsychotic(s)
fNIRS	functional Near-Infrared Spectroscopy
FROGS	Functional Recovery Scale in Schizophrenia

FTD	Frontotemporal dementia
GABA	Gamma amino butyric acid
GAF	Global Assessment of Functioning [scale]
GAS	Global Assessment Scale [Global assessment score]
GDP	Gross domestic product
GFS	Global Functioning Scale
GR(s)	Glucocorticoid receptor(s)
GRD	Genetic Risk and Decline
HAS	Helping Alliance Scale
HDL	High-density lipoprotein
HDRS	Hamilton Depression Rating Scale
HERVs	Human endogenous retroviruses
HPA	Hypothalamic-pituitary-adrenal (axis)
HRSD	Hamilton Rating Scales for Depression and Anxiety
HVN	Hearing Voices Network
ICF	International Classification of Functioning, Disability and Health
IDEAS	Indian Disability Evaluation and Assessment Scale
IMR	Illness Management and Recovery
IPI	Integrative psychological intervention
IPS	Individual Placement and Support
ISOS	Integration/Sealing Over Scale
IsoS	International Study of Schizophrenia
KAPQ	Knowledge About Psychosis Questionnaire
LAI	Long-acting injectable
LAMI	Low and middle income
LGI	Leucine-rich glioma inactivated [gene]
LMICs	Low- and middle-income countries
LOCUS	Level of Care Utilization System
LOS	Late-onset schizophrenia
MADRS	Montgomery-Asberg Depression Rating Scale
MAST	Michigan Alcohol Screening Test
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MBSR	Mindfulness-based stress reduction
MCCB	MATRICS Consensus Cognitive Battery
MetS	Metabolic syndrome
MHC	Major histocompatibility [gene]
MHRM	Mental Health Recovery Measure
MMN	Mismatch negativity
MR(s)	Mineralocorticoid receptor(s)
MRS	Mania rating scale
NAPLS	North American Prodrome Longitudinal Study
NET	Norepinephrine transporter
NICE	National Institute for Health and Clinical Excellence
NIMH	National Institute for Mental Health
NMDA	N-methyl-D-aspartate
NSAID(s)	Nonsteroidal anti-inflammatory drug(s)

OCD	Obsessive-compulsive disorder
OCDUS	Obsessive-Compulsive Drug Use Scale
OCS	Obsessive-compulsive symptoms
OR	Odds ratio
PACE	Personal Assessment and Crisis Evaluation
PAIN-AD	Pain Assessment in Advanced Dementia
PANSS	Positive and Negative Syndrome Scale
PCCP	Person-centered care planning
PCP	Phencyclidine
PFC	Prefrontal cortex
PIR(s)	People in recovery
POPS	Presence of psychotic symptoms
PORT	Patient Outcomes Research Team
PPI	Pre-pulse inhibition
PRIME	Prevention through Risk Identification Management and Education
PSE	Present State Examination
PST	Processing speed task
PTSD	Post-traumatic stress disorder
PUFA	Polyunsaturated fatty acids
QLS	Quality of Life Scale
QOL	Quality of life
QPR	Questionnaire about Personal Recovery
RAISE	Recovery After an Initial Schizophrenia Episode
RAS	Recovery Assessment Scale
RCT(s)	Randomized controlled trial(s)
RPI	Recovery Process Inventory
RSWG	Remission in Schizophrenia Working Group
rTMS	repetitive transcranial magnetic stimulation
SAD	Social anxiety disorder
SAFTEE	Systematic Assessment For Treatment Emergent Events
SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for Assessment of Positive Symptoms
ScoRS	Schizophrenia Cognition Rating Scale
SD	Sexual dysfunction
SDM	Shared decision-making
SERT	Serotonin transporter
SGA(s)	Second-generation antipsychotic(s)
SIPS	Structured Interview for Prodromal Syndromes
SMI	Serious mental illness
SOCRATIS	Social Cognition Rating Tools in Indian Setting
SOFAS	Social and Occupational Functioning Assessment Scale
SOPS	Scale of Prodromal Symptoms
SPEM	Smooth-pursuit eye movement
SPORT	Schizophrenia Patient Outcomes Research Team
SSRI(s)	Selective serotonin reuptake inhibitor(s)
SST	Social skills training
STAR	Scale to Assess the Therapeutic Relationship

STORI	Stages of Recovery Instrument
T2D	Type 2 diabetes
TAG	Threshold Assessment Grid
TAU	Treatment as usual
tDCS	transcranial direct current stimulation
TEOSS	Treatment of Early Onset Schizophrenia Spectrum Disorders Study
TGA(s)	Third-generation antipsychotic(s)
THC	Tetrahydrocannabinol
TIA(s)	Transient ischemic attack(s)
TIPP	Transition Into Primary-care Psychiatry [program]
ToM	Theory of mind
TRACK	Transitions of Care from Child and Adolescent Mental Health Services to Adult Mental Health Services
TRAM	Transformational Research in Adolescent Mental Health
UHR	Ultrahigh risk
UKU	UKU Side Effect Rating Scale
UPSA	University of California, San Diego Performance Skills Assessment
VaD	Vascular dementia
VLOSLP	Very-late-onset schizophrenia-like psychosis
VSSS	Verona Service Satisfaction Scale
WHO	World Health Organization
WHODAS 2.0	World Health Organization Disability Assessment Schedule-Second Version
WRAP	Wellness Recovery Action Plan
YMRS	Young Mania Rating Scale

Part I

Recovery and Return to Wellness

1 Among Patients with Schizophrenia: A Learning Curve for Psychiatrists

Avinash De Sousa and Amresh Shrivastava

Introduction

Schizophrenia is a complex neuropsychiatric disorder that affects millions of patients worldwide. It is a chronic disorder that may remain lifelong and has multiple relapses that affect the quality of life of the patient suffering from it. Schizophrenia and its management have shown rapid strides over the past three decades, both from a pharmacological and a psychotherapeutic standpoint [1]. The management of patients with schizophrenia can be quite vexing for both seasoned and novice psychiatrists. The reasons why many psychiatrists may face issues in the management of schizophrenia are manifold and shall be discussed in this chapter. In fact, with experience, psychiatrists improve in their competence to handle a complex disorder like schizophrenia and may develop their own methods to handle particular symptoms and manage the patient in different phases of the disorder. This chapter posits that disorders like schizophrenia and treating patients who suffer from schizophrenia serves as a learning curve for the psychiatrist, who grows clinically and personally when handling such patients.

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Schizophrenia as a Learning Curve

There are many reasons why schizophrenia can serve as a learning curve for psychiatrists and other mental health professionals. We shall now discuss some of the reasons why this is so and how a psychiatrist may show personal and clinical growth while handling different facets of the disorder. This shall also aid the psychiatrists in fostering better outcomes and recovery for patients with schizophrenia. The reasons are elucidated below.

The Complexity of Schizophrenia as a Disorder

Schizophrenia is a disorder that affects millions of patients and shows marked heterogeneity in its clinical presentation, course, and prognosis [2]. There may be some patients in whom the disorder may be episodic, with long inter-episode recovery periods. There may be other patients in whom the disorder may have a relapsing and remitting course, with multiple episodes and waxing and waning occurring annually. There are other patients who have complex symptoms that never abate and are present throughout the illness and where they are never symptom-free and have a chronic and almost progressive form of the disorder. This heterogeneity in presentation also affects the course, recovery, and outcome of the disorder.

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The complexity of schizophrenia also carries over to variances in caregiver burden that may be experienced across patients and that, in turn, affects patient outcome [3]. Thus, with varied symptoms and non-predictability of outcome, schizophrenia needs the psychiatrist to be prepared for any form of the disorder, and it serves to help the professional grow when handling the disorder (from personal clinical experience).

The Effects of Schizophrenia on Quality of Life of the Patient

The patient receiving a diagnosis of schizophrenia may very often see it as a near-death warrant, for in common circles, schizophrenia is seen as a severe psychiatric condition with poor recovery. Schizophrenia affects most patients in the prime of their life and robs them of their best years of work and productivity [4]. The most intelligent and the borderline intellectually functioning patients show an equal incidence of schizophrenia. The patient loses career opportunities, employment chances, and marriage prospects as a result of the disorder. Hiding the diagnosis from work and close relatives also is looked at with disdain, leaving the patient in a quandary about what he must do or not do. This is coupled with streaks of odd behavior and violence or aggression that may be displayed by the patient, often affecting personal and professional relationships alike. Breaking a diagnosis of schizophrenia to patients and their relatives, especially the parents, is a learning curve for psychiatrists, as facts have to be conveyed while allaying fears of the patients and answering all the queries they have [5]. Handling these episodes and explaining the disorder to relatives is itself a learning curve for psychiatrists.

The Variable Symptomatology of Schizophrenia

Patients with schizophrenia show immense variation in symptoms, both at the time of presentation and during the emergence of new symptoms over the course of the illness. Some patients recover and work well, while some may never recover at all. Some patients have almost clear insight into their illness, while some patients gain insight intermittently, and others have poor insight throughout the illness [6]. Some patients show stable symptoms, while others show variable symptoms throughout the disorder. Some patients have delusions and hallucinations that are very amenable to treatment, while others have resistant and persistent delusions or hallucinations that do not respond to any form of treatment, including electroconvulsive therapy. Many patients also show depressive features and anxiety symptoms during the course of the disorder, while others may show somatic symptoms and dissociative features. While these clinically may not be core symptoms of schizophrenia, they manifest and complicate the clinical picture of the illness. There is a need for psychiatrists to be armed and ready to handle the variance in symptoms while altering pharmacological and non-pharmacological approaches when needed [7]. All this requires clinical vigilance and foresight that one develops over years of experience, and this serves as means of clinical growth for mental health professionals.

The Challenge of Negative Symptoms on Schizophrenia

Negative symptoms are some of the most challenging symptom domains in schizophrenia. The negative symptoms remain very often, even after resolution of the positive symptoms, and are difficult to treat [8]. There is a marked effect of negative symptoms on work, family life, and recovery from schizophrenia. Negative symptoms are often misconstrued by relatives as being due to laziness and lack of desire for work. The negative symptoms are very often non-amenable to medical treatment and psychotherapeutic treatments. The negative symptoms may also manifest with symptoms suggestive of depression and may not respond to antidepressant therapy. These

symptoms may often frustrate the patient, caregiver, and clinician alike, as there may be no improvement seen, and the patient's illness moves into a course that appears stagnant [9]. Handling patients and caregivers with patience during the negative symptom phase of schizophrenia is also a learning curve for the psychiatrist.

Medical Treatment of Schizophrenia

There have been vast advances in the psychopharmacological management of schizophrenia, with development of various second-generation antipsychotics, depot preparations, and many new drugs in the pipeline. The emergence of drugs like clozapine has opened up new avenues for the drug treatment of schizophrenia and helped many patients recover [10]. Drug treatment of schizophrenia is not devoid of side effects. The typical or older antipsychotics had extrapyramidal reactions, and tremors are side effects. The atypical antipsychotics, while having lesser degree of such reactions, are fraught with hyperglycemia, hyperlipidemia, and weight gain. Getting the right psychopharmacological combination to suit every patient is an art that comes from years of experience. Diligent management and prevention of side effects, while using the right medication at the right dosage, is a nuance in the fine art of psychopharmacology that develops after years of clinical experience [11].

There is also a need to psychoeducate patients and caregivers about the need for treatment compliance, as well as side effects that may ensue while on treatment. Nowadays, the emergence of clinical entities like treatment-resistant schizophrenia and clozapine-resistant schizophrenia has led to further clinical woes in the medical management of schizophrenia. Using medications and add-on drugs in these patients is a trial-and-error process that may take time to master [12, 13]. The ability to fit biological treatments like electroconvulsive therapy and transcranial magnetic stimulation correctly in the algorithm of medical management is prudent for them to have a synergistic effect with medicines. All this permutation and combination of medical treatments, while handling compliance and side effects, is a learning curve for psychiatrists.

Toward a Psychotherapy for Schizophrenia

Schizophrenia has always been treated using medication-based therapy, but psychotherapy also has a role in the management of this disorder. Recent developments in the psychotherapy of schizophrenia have integrated educational methods, skills training, family-based stress management, and specific cognitive-behavioral strategies, with optimal pharmacotherapy [14]. These approaches have demonstrated considerable promise in alleviating the impairments, disabilities, and handicaps associated with schizophrenia. There is no standard guideline for an office practice-based psychotherapeutic approach toward schizophrenia which can be thwarted with a strong psychological approach. No single school of psychotherapy has been found to be effective in the disorder, and an eclectic approach with a mix of approaches is what works best with the disorder. There are no clear-cut psychotherapeutic guidelines for the management of schizophrenia [15]. There is a need for stringent methods right from the choice of patient, type of symptoms present, insight into the illness, readiness for psychotherapy, and openness to challenge one's false beliefs that all play a role in effective psychotherapeutic outcomes. There is also a need for psychiatrists to be trained in techniques that may be useful in the psychotherapy for schizophrenia while having ample time and energy to devote for the same. Relatives and patients may not always be open to psychotherapy as a treatment and need to be convinced of its efficacy. It is important to note that mental health professionals who successfully manage schizophrenia often employ nonmedical approaches in synergy with medical ones that serve to alleviate symptoms better and bring about better

recovery. Psychotherapy for schizophrenia when done in itself shall serve to foster maturity and growth in a psychiatrist.

Religious and Cultural Factors and Myths in Schizophrenia

Many religious and cultural factors affect the treatment of illnesses like schizophrenia. It is perceived in India and some other cultures that schizophrenia and mental illness are due to demonic possession and can only be treated by divine and religious interventions [16]. Many patients are often taken to temples, churches, or dargahs (shrines), where various forms of exorcisms are practiced, and the patient may be chained, whipped, and branded. It is vital for the psychiatrist to treat schizophrenia while keeping in mind the wind of religion and culture in patients and their caregivers, as the mental health professional during his treatment must by no means mock and hurt the religious sentiments of patients. It is also important to be open to all faiths and be open to religious intervention like prayer and healing, as long as the patient is not harmed in any way [17]. Nonscientific practices must be discouraged while dispelling the myths prevalent about psychiatry and psychiatrists alike. Tactfully managing these issues is an area for personal growth of a psychiatrist.

The Complex Neurobiology and Genetics of Schizophrenia

Schizophrenia is a condition of which we have not yet understood the neurobiology and genetic basis. While structural and functional neuroimaging studies have yielded immense value in understanding the structures implicated in the genesis of schizophrenia, we also have a fair understanding of neural circuits that underlie the disorder. Neurobiology is evolving, and it is difficult for professionals in clinical practice to keep abreast with the advances in neurobiological understanding that keep happening from time to time. While the role of dopamine and serotonin in schizophrenia has been defined, there are many new neurotransmitters that have now been postulated to play roles in pathogenesis [18]. Genetic studies have yielded useful information in schizophrenia, though no single gene has been identified. There is a lack of genetic know-how among clinical psychiatrists, and psychiatric genetics has been understudied [19]. The neurobiology of schizophrenia has today extended to mitochondrial dysfunction [20], glutamate [21], mirror neurons [22], neuro-inflammation, [23] and DNA methylation [24]. It is not easy to be aware of the neurobiological and translational implications of these advances clinically. Thus, reading and keeping track of the latest neurobiological advances in schizophrenia is also a learning curve for psychiatrists.

Schizophrenia and its Management in Various Settings

While, as a disorder, schizophrenia remains complex, the approach to its management may vary based on the setting in which it presents. Patients in urban settings either visit a general hospital or a private psychiatric clinic. General hospital psychiatric units focus more on pharmacological management and cost-effective aim at getting the patient symptom-free at the earliest [25]. Psychoeducation in groups is used in most general hospitals. In a private clinic setting, detailed family evaluations and psychotherapy may be employed, along with family therapy if needed. This may cost the patient and may thus be a recurring expenditure to many. In private settings, there is a tendency for many patients to seek second opinions, and they may move from doctor to doctor, which also affects treatment compliance and outcome. It is important that a clinician be given time before the patient gives up on him and moves ahead, but this seldom happens [26]. In rural settings, very often there is one psychiatrist available in the district, and his management approach is followed rigorously by the patient. Education levels of the patient and caregivers may vary across settings, and this may result in the caregivers

seeking information online and then questioning the judgment of the psychiatrist, which is commonplace today. Thus, management of schizophrenia across settings is also a learning curve for the psychiatrist.

The Doctor–Patient Relationship on Schizophrenia

The doctor–patient relationship in psychiatry is one of the most coveted bonds compared to other medical specialities, as many secrets are shared with the doctor in trust and confidence, including many facets of the patient's life that even family members may not be aware of. In schizophrenia, the doctor–patient relationship is built on trust in a disorder where paranoia is a symptom. The patient may many times end up hating the psychiatrist and getting upset and angry with him and may even be abusive and aggressive. This may be coupled with days where the patient may put more trust in the doctor than even his own parents. The patient may tend to develop positive, negative, and even hostile transferences to the treating doctor, which demands therapeutic neutrality from the psychiatrist [27]. The patient may try to even incorporate the psychiatrist as a member of the team that is plotting against him or her. It is important that in the face of such events, the psychiatrist remains unfazed and maintains unconditional positive regard for his patient. This is a tough task, and the ability to do so is also a learning process for the psychiatrist. It is very important that this develops, as the patient may be under treatment for years, and this bond plays a vital role in recovery and outcome.

Conclusions

Schizophrenia is thus a complex, yet treatable, disorder. There are various aspects of the disorder as described that keep the psychiatrist frazzled, yet make him or her learn and professionally grow in its wake. Schizophrenia with all its paradigms is indeed of paramount importance for therapeutic and professional growth of a psychiatrist and exposes him to various aspects of his professional work that many disorders would not. Handling caregivers and patients with schizophrenia thus embarks the psychiatrist on a journey of both personal and professional transformation that is always positive just akin to various life epochs.

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Living Healthy with Schizophrenia: A Consumer's Approach

2

Michael Alzamora

Introduction

My name is Michael Alzamora. I am 52 years old and have been living with schizophrenia for 29 years since 1988. I was born in Bogota, Colombia, in 1964 and immigrated to Toronto, Canada, in 1975 at the tender age of 10. My adolescence and early adulthood were very turbulent times. I remember being extremely depressed and anxious. I had a difficult time with my studies and making friends. In elementary school, I remember excusing myself to go to the bathroom and find an empty room where I could hide under a table for long periods of time. My years of secondary school became more turbulent. I was terrified of public speaking and started to skip class frequently. Because I was not attending class, I wasn't learning the concepts or doing homework. The end result was failing many courses, and in turn, I failed grade 11 and again in grade 13 (back then, it was the senior year).

In 1986, I commenced studies for Electronics Technology at Seneca College in Toronto. The stresses of college life got to me. In 1988, I had my first of a number of breakdowns. They included hearing voices and thoughts of persecution. Soon, I was a member of the mental health community. Finally, I had no more stresses about school commitments and finally started making friends. This was my first step toward social integration.

A major component for social integration was the intervention of antipsychotic medications. Back in the early 1990s, these medications gave me some adverse side effects. They included restlessness, impaired vision, and most of all tardive dyskinesia. On public transportation, teenagers would mock my involuntary arm movements.

The next step toward social integration was the introduction of the new type of antipsychotics in the 1990s. My psychiatrist chose for me clozapine. Although clozapine is not a new antipsychotic, it behaves like one. I don't know if it is just me, but I think clozapine cured me from the involuntary movements of my arms. Clozapine does, however, have its share of side effects. They include weight gain, especially around the circumference of the stomach. I drool a lot, especially at night, and I have high triglyceride levels, i.e., fat in the bloodstream, and stuttering when speaking. I also have cognitive impairment in the form of gaps in my speech because I lose my train of thoughts. My short-term memory is severely incapacitated. I don't know if these are symptoms of mental illness, clozapine, or both. I also take clonazepam, an antianxiety pill, for the side effects of clozapine, as well as for anxiety. I have noticed some cognitive impairment when my dosage of clonazepam is increased.

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A major component of social integration is financial stability. This includes the means to pay rent for housing and to eat healthy—as I will discuss later on. Financially, I am very stable. I get a monthly check from the government as disability income (ODSP). I also live in subsidized housing (Houselink) bachelor apartment and pay rent geared to income.

Finally, social integration is an ongoing commitment. This is because an integral part of achieving a state of well-being involves an ongoing partnership between diet and exercise.

Diet Is a Lifelong Commitment

I knew I had to change my diet when my psychiatrist read me the results of a fasting blood test conducted on February 20, 2008. He told me that my triglyceride level was high. Triglycerides are responsible for carrying fat in the blood. Fortunately, he said that I am not close to have heart disease. He told me that if I change my diet, this blood level will normalize. I took this blood result as a wake-up call.

I realized I had to take immediate action because I have schizophrenia and take clozapine—one of the newer antipsychotic medications. As I have said before, one side effect of some newer antipsychotics is a substantial weight gain in partnership with high cholesterol. Another side effect that I will mention now is a predisposition to develop diabetes due to elevated sugar levels. In my case, my sugar levels measured normal. Nevertheless, I decided to tackle both cholesterol and sugar intake as a preemptive measure to a healthy lifestyle.

There is not much literature about nutrition and schizophrenia, so I will share my story. I did some research, talked to people, and came to some conclusions.

The very first thing I found out is that diets do not work. People who go on diets lose weight, but as soon as they go off the diet, they gain the weight back, plus some extra pounds. My number one priority was to make a commitment to change my eating habits to healthy eating for the rest of my life. I started by identifying the foods that were harming me and that I needed to eliminate. Although I recommend my diet to everyone, it specifically targets people with schizophrenia, especially those with high cholesterol and/or high blood sugar levels.

My second revelation was that weight loss should be the last priority. People on diets use weight loss and muscular definition as the first signs that a diet is working. Consumers should use other barometers to measure progress. They should look for physical signs like a glowing complexion, clearer white of the eyes, and as a bonus, less fat. Mental signs are more alertness, more energy, less anxiety, better concentration, and better sleep.

The First Eight Weeks

My first 6 weeks of changing my diet were "do or die." I noticed that I was highly addicted to sugar as well as fatty foods. I used to sit on a chair for many hours, watching television and drinking a liter of cola with sweet pastries. Other times, I would eat enormous amounts of ice cream, also watching television. For breakfast and lunch, I would have coffee, with a lot of sugar, and donuts.

During this time, I started seeing a wonderful registered dietician at Mount Sinai Hospital Academic Family Health Team in Toronto. Her name is Lisa Vesik, RD. She educated me in nutrition and gave me moral support. I highly recommend a dietician at this stage of your new diet. (Not all dieticians are covered by health plans for those on disability. You have to research which dieticians are covered.)

I began my new healthy lifestyle by having for breakfast a bowl of fiber 1 cereal with 1% milk. It has no sugar and contains 56% of your daily fiber. Sometimes, I had a coffee with milk and no sugar and a whole wheat bagel with cheese.

For lunch, I mostly ate a turkey sandwich with whole wheat bread and no sauces, followed by an orange juice.

In the evenings, I ate two drumsticks of skinned chicken, steamed vegetables, garden salad, and beans. My research recommends lentils, chickpeas, and kidney beans that are canned in a solution of only water, salt, and very few preservatives. These types of beans are very low in

sugar and cholesterol. Avoid canned beans with pork or sauces. Sometimes, I incorporated pasta for supper. I ate salmon twice a week.

I snacked in between meals with bananas, oranges, and yogurt several times a day whenever I felt hungry. I limited my coffee intake to no more than one cup a day.

To complement my dietary regime, I took the following vitamins:

Centrum multivitamins, B complex with vitamin C, vitamin E, calcium magnesium with vitamin D, and omega-3.

Immediately upon starting my diet, I began to have severe withdrawal symptoms. I would break into a sweat. Other times, I would become irritable or restless. I also craved fatty, greasy foods as well as other foods I normally would not eat.

During this period, I lost 9 pounds and was happy with my progress. I looked and felt healthier. I developed rosy cheeks and clearer eyes. Mentally, I felt strong and confident. I lost a lot of fat in my abdomen. My potbelly shrank significantly—two waist sizes to be exact.

Dealing with a Potbelly

If you have developed a potbelly over time due to your antipsychotic medication, or simply poor dieting and lifestyle, I have some tips for you.

A swollen tummy could be the result of poor digestion. You probably have a blockage in your intestines with stool that has not passed in days or maybe over a week. Poor regularity leads to a lot of gas being produced in the abdomen. This gas expands the abdomen. To become regular, I recommend natural fiber powder dissolved in a glass of water until you enter a cycle of regularity. You should also add fiber-rich foods to your diet like fiber cereal, beans, and whole wheat multigrain breads.

A lot of people with schizophrenia do not go out much and spend a lot of time in bed. When a person lies down in bed for prolonged periods of time, the abdominal muscles weaken and the stomach expands when the person is standing up. I recommend physical activity during the day. Leisurely walks can be stimulating, so it can be core exercises to strengthen the abdomen (if you don't have a physical limitation like back pain). Core exercises are the ones you do while lying flat on your back. There are two basic abdominal crunches: In one of them, you raise your torso while keeping your legs flat on the ground. In the other, you raise your legs while keeping your torso flat on the ground.

If you follow a healthy diet and an exercise routine, your stomach will shrink, thereby needing less food. When you need less food, you shed pounds.

Dietary Changes

Start eating a high-fiber diet with plenty of fresh fruits and leafy green vegetables, legumes, whole grains, nuts, and seeds. Eliminate table sugar and white flour. Add some of the essential fats if you are on a low-fat diet. Some of these include omega-3 or omega-6. See below for a section on vitamin supplements for those with schizophrenia.

Avoid constipating foods and drinks such as white flour, cheese, fried foods, sweets, salt, beef, pasteurized milk, all junk food, wine, carbonated drinks, and coffee. Avoid using laxatives and antibiotics when possible. Overuse of these products can remove the "good bacteria" that helps with digestion.

A traditional method used in inpatient units is the prescription of prune juice. This is not recommended on a long-term basis because it acts as a mild laxative, and the intestines become dependent on it to function properly.

Habits

Go to the bathroom at the same time each day, even if nothing happens; relax and don't force the stool.

- Do not spend more than 5 minutes every time you sit.
- Do not suppress the urge to go.
- Do not strain to have a bowel movement.

Exercise at least four times per week for a minimum of 20 minutes each time.

Supplements

- *Folic acid.* Take 60 mcg of folic acid daily. No dietary sources contain enough, so supplements are necessary.
- *Iron.* Take chelated iron supplements for better absorption.
- *MSM (methylsulfonylmethane).* A natural organic sulfur essential mineral. It reduces inflammation and helps the digestive system work better.
- *Vitamin B1 (thiamin).* Only if you have a deficiency.
- *Vitamin C.* Taking vitamin C with meals will help digestion and absorption.

Ten Steps for Successful Fat Loss

If you are still not completely satisfied with the advice I have given you so far, and want visual results, here are some tips for safely losing weight and keeping it off:

1. *Write it down.* Keep an accurate record of everything you eat. By keeping an account of food intake, you can spot weaknesses, i.e., binging patterns. You can go online to find out how to calculate the amount of calories you need per day, based on your height, weight, and activity level. Take the time and do the math. Read the labels of all food products you consume, and make sure you don't pass the suggested calorie limit.
2. *Front-load your calories.* We have all heard the saying, "Breakfast is the most important meal of the day." This is more than true for weight loss. Many nutritionists suggest having a bigger breakfast and lunch and a lighter dinner.
3. *Eat slowly.* Your brain needs time to receive the signal that you've eaten your fill, so when you eat slowly, it gives your brain time to catch up, and you will eat less.
4. *Eat your favorite foods.* If your diet is poor, I caution you to follow a healthy diet on the most part. There will be times when you will crave unhealthy food. This is the time to give in to your cravings so that you don't binge down the road and gain all the weight back.
5. *Avoid temptation.* If you have a sweet tooth for junk food and enjoy trips to your local convenience store for ice cream, chips, chocolate bars, cookies, colas, etc., do not frequent these places.
6. *Keep a list of nonfood activities.* Many people eat when they're bored, stressed, or tired, but they're not really hungry. Learn to recognize this, and do something on your activity list instead of eating. Some nonfood choices include healthy living activities such as exercising, reading, or writing. Eating while watching TV is something you should monitor and try to avoid.
7. *Make a realistic eating plan.* It is a misconception that a weight loss plan means losing weight every day. Give yourself the flexibility to lose weight progressively, taking into account that some days you may actually gain a pound or two.
8. *Schedule appointments for exercise.* Although physical fitness is an integral part of an overall healthy lifestyle, it is worthy of an article of its own. Due to its vastness and complexity, it is beyond the scope of this article. Make time at least three times a week to exercise. Choose an activity you enjoy. People who choose activities that they don't enjoy often abandon exercise all together.
9. *Make sleep a priority.* A lot of the newer antipsychotics have a strong sedative effect. This makes people tired the next day. Sluggishness the next day prevents people from exercising, also affecting cognitive functioning. Poor sleep may contribute to bad health habits such as staying at home lying in bed or watching TV. Inactivity may lead to binge eating.
10. *Think fit and healthy.* Try to visualize yourself being fitter and leaner. Give yourself a daily pep talk about healthy eating and living, and give yourself small, nonfood rewards along the way, like a new book or piece of clothing, when you meet a specific goal such as losing 5 pounds.

Part II

Current Status of Outcome, Recovery

3 Gender and Outcome in Schizophrenia

Mary V. Seeman

Introduction

The meaning of the word "outcome" as applied to schizophrenia has changed over time. In the nineteenth century, when persons with psychotic illness spent whole lives in an asylum, the therapeutic focus was on adaptation to the routines of the institution and obedience to rules. For patients, becoming calm and orderly was the goal. A good outcome meant fitting in well and being able eventually to help out in the asylum. Being "farmed out" to Open Family Care, away from the institution, was considered an exceptional mark of successful treatment [1]. There was no treatment for psychotic symptoms; the symptoms that were targeted in the asylum were agitation, excitement, and aggression, and these were treated with a variety of sedatives and also hydrotherapy [2]. As newer treatments emerged in the first half of the twentieth century—fever therapy [3], shock treatments [4], and lobotomy [5]—their relative merits were judged on the basis of two main factors: how rapidly and for how long they could calm agitated behavior. Lobotomies won this competition; for the first time, large numbers of patients were able to leave the asylum and return home to live. Discharge from the institution then became the new standard measure of outcome [6]. When effective antipsychotic drugs were made available in the 1950s, hospital discharge as the main criterion of outcome was gradually replaced by a new measure: cumulative days spent in hospital and frequency of readmission [7].

It was only with the advent of the Brief Rating Scale (BPRS) [8] in the early 1960s that psychotic symptom reduction became the gold standard for evaluating the outcome of schizophrenia. This is still the case today, although many other end points, beyond symptoms, are now also considered. As hospitalized patients began to return to live in their communities, the adversities they sometimes encountered—addiction to cigarettes, alcohol, and drugs; homelessness; ill health; imprisonment; suicide—became additional measures of outcome. So did positive eventualities such as educational achievements, gainful employment, artistic creations, expanding social networks, marriage, procreation, and parenting. These markers of success and failure were included under the outcome umbrella.

The concept of outcome grew more complex as many of the intermediate measures used, and even some of the end points, were found to be of mixed valence; they were both good and bad. For instance, adherence to medication reliably reduced symptoms and improved functioning. It was, therefore, a sign of a promising outcome. But patients who faithfully adhered to

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their prescribed medicines over long periods of time developed unpleasant side effects that affected mobility and health and increased the risk of early death, an extremely negative outcome. A global measure was needed that could balance positive and negative components of outcome from the patient's viewpoint, and that measure has been called "quality of life" or "recovery." The two terms are used somewhat differently, but both encompass personal satisfaction, met versus unmet needs, fulfilled versus dashed hopes, attained or failed goals, and quests for meaning rewarded or renounced.

Marked gender differences have been noted in many, but not all, of the various elements of global outcome, and this is the topic of this chapter. There is evidence for gender differences in many aspects of schizophrenia, not least of which is outcome.

Gender Difference in Individual Outcome Components

Hospitalization

Most patients with schizophrenia are hospitalized at least once in the course of their illness, and often repeatedly. Short hospital stays and few readmissions are traditionally considered positive outcomes, and women show a definite advantage over men in this regard [9]. They are in hospital for less time over the course of their life than are men. It is not at all clear, however, whether living outside of hospital is an improvement over life inside the institution [10]. For some patients, long hospital stays may provide a better quality of life than life on the street or in shelters, boarding homes, or prisons, or even in households. Women with schizophrenia are hospitalized for fewer days than men, but whether this represents a better outcome continues to be debated.

Homelessness

Rootlessness and lack of a permanent place to live are considered an unhappy way to live one's life, but it is nevertheless the fate of many individuals with schizophrenia. The prevalence of homelessness in this condition is variously reported to range between 1% and 45%, a very wide range, artificially expanded because of different definitions of homelessness [11]. Approximately 11% of all homeless people are reportedly diagnosed with schizophrenia, four males to every female [12, 13], but when the study limits the participants to those living in shelters, the gender ratio becomes roughly equal [14]. Shelters are often viewed by the homeless as places to avoid at all costs, so these statistics probably mean that homeless women are less rejecting of shelters than are homeless men. Women may also be less often rejected from shelters because of factors such as alcohol and drug abuse, or antisocial behavior, all critical elements of homelessness. A third important element, absence of family support, has been shown to be more prevalent in homeless women than in homeless men [15]. All in all, men with schizophrenia live on the street more often than women do, and this may be viewed as a comparatively poorer outcome for men. But it can also be interpreted differently. It may mean that men value their independence and perhaps hone their survival skills more effectively than women do, allowing them to more easily meet the considerable challenges of street living. Viewed from that perspective, acquiring the skills to live on the street can be seen as a positive.

Living Alone/Independently

Men with schizophrenia tend also to live alone more often than women. This is already evident early in the illness, as shown in a 5-year follow-up study of a first-episode cohort [16]. Living alone may be a sign of alienation and isolation, in other words a bad outcome. But it may also be a sign of self-confidence and independence, a good outcome. Statistics cannot distinguish one from the other.

Employment

Between 11% and 37% of individuals with schizophrenia in North America and Europe

reportedly hold paid jobs (this percentage includes sheltered employment) [17]. Specific employment figures vary with place, time period, and regional economics. In the 5-year follow-up of first-episode psychosis patients by Thorup et al. [16], more women than men were found to be either in school or to be working versus being without occupation. One would perhaps expect women with schizophrenia to be more employable than men because their cognitive functioning is on average less impaired by illness, but there is no overall consistency in reports of sex differences in employment rates [18, 19].

Employment for people with schizophrenia usually means entry-level jobs that do not pay well, that are not challenging, that are often perceived as personally demeaning, and that offer no opportunity for advancement. Those who are not employed may, in many ways, see themselves as better off—able to pursue their talents in the creative arts and spend time in leisure activities while supported by disability pensions that, often, pay nearly as well as entry-level employment [20]. Knowing whether a person is employed or not does not necessarily provide insight into how well that person is recovering from his or her illness.

Marriage and Parenting

More women than men with schizophrenia are partnered or married [21] perhaps because negative symptoms (seen more in men) stand as barriers to intimacy but also because women, whose illness begins later, often marry before their illness begins. Whether one marries or not is mainly determined by social and cultural factors, however, and not by how free of illness one is. For example, arranged marriages in many parts of the world are less affected by the mental health of the two partners than marriages in the West where a substantial degree of social skills is necessary to navigate the demands of courtship [22]. Marriage is considered an advantage in the context of schizophrenia because permanent households and family bonds provide emotional and instrumental support should symptoms reemerge; marriage has been shown to be a source of stability [23, 24]. On the other hand, women with schizophrenia are reportedly more often than other women the victims of domestic abuse [25–27], frequently seeking protection from violent spouses. The partners of women with schizophrenia often have a history of psychotic disorder themselves; more than half are alcohol and drug users, and many are unemployed [28, 29]. Marriages between two unstable partners are not durable [30], and the married state may, for some, cause more unhappiness than the single life. For instance, being married is reported to be a risk factor for suicide in both men and women in the context of schizophrenic illness [31].

Parenting as well as marriage is more common among women with schizophrenia than it is among the men [32]. Thorup et al. [16] found that 17.5% of women compared to less than 5% of men were living with children 5 years after a first episode of schizophrenia. The comparison may not be valid, however, because the men were probably significantly younger. Becoming a parent is considered a good outcome because children bring meaning to life [33], but many parents with schizophrenia, because of health-related problems, lose custody of their children [34, 35] and consequently suffer from the trauma of loss and separation. Parenting is also inherently difficult and can be especially challenging for parents struggling with psychotic symptoms [36]. Parenting can easily be experienced as a chronic source of stress, so that its status as a sign of positive outcome remains debatable.

Substance Abuse

Substance abuse is significantly more prevalent among men with schizophrenia than among women, the differential sex ratio already evident as early as the first few years following a first episode [16]. Substance abuse correlates with violence, unemployment, homelessness, nonadherence to treatment, poor relationships, and poor health. It is considered to be a bad outcome for people with schizophrenia and yet, here again, there is a paradox. Some studies have shown that a majority of those with a diagnosis of schizophrenia who drink alcohol and use

drugs of abuse show better symptomatic and functional outcomes than those who abstain [37]. A prospective 7-year study of patients with a dual diagnosis (schizophrenia and substance use disorder) found that most such patients (though not all) showed substantial improvement over time in symptoms, employment, maintenance of independent housing, and life satisfaction [38]. Contrary to expectation, in many cases, cognitive functions in dual diagnosis patients were found to be less impaired than in patients with schizophrenia alone [39, 40]. There are several hypotheses for these counterintuitive findings that need to be tested in the future. One is that those diagnosed with a substance use disorder quickly become abstinent after a psychotic episode and are more inclined to stay abstinent than individuals with schizophrenia who drink or use drugs only sporadically. Another hypothesis is that a starting high level of cognitive functioning and social skill is initially required in order to develop and maintain an addiction. It is also possible that those whose brains succumb to psychosis only when exposed to toxic substances may have been born with an inherently "healthier brain" than those who become psychotic in the absence of substances. Various comorbidities other than substance abuse also seem to bode well for cognitive function in the context of schizophrenia [41]. It may be that, under the weight of comorbidity, the threshold for schizophrenia is crossed even when cognition is relatively intact so that, when the comorbid condition is successfully treated, the person emerges in relatively good mental shape. This does NOT, of course, mean that the comorbidity itself helps cognition in any way.

It is also possible that a person who suffers from a substance use disorder in addition to schizophrenia is perceived by others as "a lush" or "a junkie" rather than as "a loony" and that the former characterizations are less stigmatizing than the latter. Poor social and cognitive outcomes may result from biased public attitudes toward illness as much as they result from the illness itself [42]. These are all speculations that have not been tested. Neither is it known whether substance abuse affects outcomes differently in men and women with schizophrenia, although the deleterious effects of toxic substances physiologically impair women more rapidly than they do men [43, 44]. More men than women with schizophrenia are addicted to drugs and alcohol, but the negative effects of substances may take a greater toll on women.

Violence

Men with schizophrenia are reported to commit severe acts of violence more frequently than women [45]. However, less severe aggressive behaviors, such as verbal insults and threats, are seen more frequently among women. In a study by Fazel et al., almost 11% of men with schizophrenia in this sample and 3% of women were ever convicted of a violent offense [46]. This difference is linked to an interaction of psychosis with substance abuse, an interaction that paves the way to violence, legal problems, imprisonment, and coercive treatment measures such as physical restraints and isolation rooms, involuntary treatment, and community treatment orders. Not all of these, however, are more prevalent in men. Physical restraint measures are used more often with male patients than with females, but forced medication and seclusion have been reported to be more often used with female patients [47]. The fact is that studies disagree widely on sex difference in coercive treatment measures [48–51]. It is possible that violence is more frequently associated with males in this population primarily because violent men do more damage than violent women.

Suicide

The lifetime mortality from suicide in schizophrenia is 4–6% [52]. As in the general population, most studies report higher suicide rates in male than in female patients [53, 54]. The preponderance of males committing suicide can already be seen in the first-episode population [16, 55] where 2–3% of men and 1–5% of women die by suicide within 5 years of their

first diagnosis. Significantly more women than men, however, attempt suicide [56].

More suicide attempts by women is to be expected because more women than men with schizophrenia suffer from depression [57], the main trigger to suicide. In addition, there is the relatively greater male access to lethal means of suicide such as guns, the greater male tendency, in the context of schizophrenia, to social withdrawal and isolation, to the absence of emotional and instrumental support, and to aggressive urges that can be turned inward toward the self. In fact, however, the male/female difference in suicide rate in schizophrenia is not as marked as in general population. In a meta-analysis of published studies of psychiatric inpatients, Large et al. [58] found no gender-related suicide difference, suggesting that women who are ill enough to be hospitalized are as likely as men to find the lethal means they need to end lives that have become subjectively intolerable. Suicide has only a negative valence. Even though it may theoretically be viewed as an act of courage and determination, it is always a tragedy for family, friends, and care providers.

Mortality

The only potentially positive side to suicide is when it avoids an alternative death that would be comparatively more painful to patient and family. For instance, it may be more painful to be a victim of homicide, and this happens to individuals with schizophrenia more often than to individuals in the general population [59], especially so if they also abuse alcohol and drugs. Because of poverty, lifestyle, medication, stigma, and disparities in the provision of health care, this population also suffers disproportionally from a number of serious diseases [60]. Cardiovascular disease is a prominent cause of mortality in schizophrenia, as common (if not more so) in women as in men [61]. There are specific cardiovascular risk factors for women in this population, namely, polycystic ovarian syndrome, early menopause, gestational hypertension and gestational diabetes, and susceptibility to drug-related prolongation of cardiac depolarization. Chronic smoking is more hazardous for women than for men as a risk for heart disease [62]. Diabetes and metabolic disease pose potentially fatal risks to both men and women with schizophrenia [63]. Lethal accidents such as poisoning or dangerous falls account for twice as many deaths as suicide in schizophrenia patients [64, 65] even in first-episode samples [66].

Overall, life expectancy is lower than national standard by over 18.7 years in men with schizophrenia and by 16 years in women [67]. Premature death from any cause occurs in this population in 3.3% of men and 2% of women [46]. What is most troubling is that the survival gap between those with schizophrenia and the rest of the population appears to be increasing rather than decreasing with time [68]. A critical question: what is the role of antipsychotic medication in premature death? It is a question that remains unresolved [69].

Symptom Response to Drugs

Antipsychotic drugs are critical to outcome studies, not only with respect to their effect on symptoms of schizophrenia but also because of the range of side effects they produce—side effects which may to some degree contribute to the mortality statistics. Men and women differ in very many aspects of antipsychotic drug response. To begin with, differences between the sexes have been reported in the quality of the relationship between patient and prescriber, an important factor in subsequent adherence to prescribed drug regimens [70]. There are also fundamental, gender-based attitudinal differences toward therapeutic drugs in general, with men more than women starting off with a negative attitude toward all medication [70]. Once the drug enters the body, there are important sex differences in absorption, distribution, metabolism, and elimination (pharmacokinetics) and in the action of the drug at target brain sites (pharmacodynamics) [71, 72]. Because women take more different kinds of drugs, they are more exposed to drug interactions [73]. These differences lead to

gender disparities in both the clinical effectiveness of antipsychotics and in the extent and severity of their side effects.

In general, women's psychotic symptoms appear to respond better than men's to antipsychotic medication, perhaps because (a) women are more likely to take their pills as prescribed; (b) the metabolism of these drugs results in higher blood levels in women than in men; (c) estrogenic factors at brain receptor sites enhance drug activity; and/or (d) women have more of the kinds of symptoms that are responsive to drugs (delusions and hallucinations) and fewer of those that are not (negative symptoms and cognitive symptoms) [74]. Interesting to keep in mind is the observation that women with schizophrenia also tend to do better than men in the absence of drugs. A 10-year follow-up from the Danish Opus trial found that 30% of schizophrenia patients on no medication had achieved a remission of symptoms at 10 years, women more so than men [75]. This means that women's relative superiority in achieving remission cannot be attributed solely to a better response to drugs. Nevertheless, a portion of women's superior symptom outcome is likely to be attributable to higher blood levels, given that women report more side effects [76].

Side Effects

Despite such reports, systematic reviews of adverse effects of antipsychotics find no clear objective differences in prevalence by gender [77, 78]. In all drug categories, however, women *report* more adverse effects than men, perhaps because women report all adverse effects even when they are minor, whereas men tend only to report more serious effects [79].

Women may also have lower tolerance for specific side effects, such as those that undermine their appearance [80, 81]. Certain side effects *are* objectively more prevalent in women (weight gain, prolongation of the QT interval, and prolactin-induced side effects such as a heightened risk of breast cancer) [82, 83]. All statements about the prevalence and severity of side effects, however, must be tempered by contributory factors such as age, reproductive status, and, to a lesser extent, the phase of the menstrual cycle phase [84, 85]. Pregnancy is a very important consideration as antipsychotics predispose to gestational diabetes and raise the specter of potential harm to the fetus, neonate, and child [86–89].

Even though women's psychotic symptoms on the whole appear to respond better to antipsychotic medications than men's do [90], weighing side effects and reproductive issues, women may subjectively see their welfare on antipsychotics to be worse than that of men.

Functional Outcomes

When focusing on functional rather than symptomatic outcomes of schizophrenia, numerous studies agree that women do better than men [91, 92]. Functional outcome refers to educational achievement, occupational functioning, and social functioning [93]. As such, it is a concept that substantially overlaps with issues of quality of life and recovery.

Quality of Life/Recovery

"Recovery" in the context of schizophrenia has been differently defined in different studies. It usually refers to a subjective sense of finally being in charge of one's illness whether or not symptoms remain and whether or not objective function has been restored. Thorup et al. [16] as well as others [94, 95] found that women achieve better recovery in the early and medium term, but longer term differences are less clear [96]. Jääskeläinen and colleagues [97] conducted a meta-analysis of gender and recovery and found no significant difference. This may be explained by the strict definition and exclusion criteria they employed: Recovery was defined in their analysis as improvement in both clinical and social domains for a minimum of 2 years.

Finding a gender difference in recovery may depend on the age of the sample at the time of

evaluation, with women initially doing better [98–100]. It may also depend on the region of the world that is sampled [101]. The Novick et al. review [101] found that, in most regions, females had a later age at first service contact for schizophrenia, a lower level of overall/negative symptom severity, lower rates of alcohol/substance abuse and paid employment, and higher percentages of having a spouse/partner. In Europe, women who lived on their own had slightly higher rates of clinical and functional remission and recovery than males at 36 months' follow-up. The regional differences suggest that male/female differences in schizophrenia outcomes are not based on biological predetermined factors but, rather, on sociocultural and experiential features of living in different parts of the world and being subject to gender-determined pressures and expectations. Medical approaches to men and women also differ, depending on culture and tradition and economics. For instance, there are countries where women may not have equal access to health care and, therefore, will not be identified as suffering from schizophrenia unless their illness becomes very severe.

Conclusion

Over the years of studying outcomes in schizophrenia, the meaning of "positive" outcome has changed. While various components of outcome are acknowledged, a person's subjective sense that illness has been at least in part overcome and that life is meaningful has currently come to be viewed as the most valid signpost of a good outcome. Because subjective measures are always problematic to compare, it is, therefore, difficult to make definitive statements about the differences between male and female outcomes in this illness. Women have certain advantages in that their illnesses start later than men's and, on the whole, their symptoms respond better to available treatments. These advantages serve them well at the outset of illness but appear to dissipate in time. Gender differences thus vary depending on the age of the patient. They also vary with the social and cultural background of the study population.

While few authoritative answers have been provided in this chapter as to which sex fares better in the context of schizophrenia, the study of differences in outcome continues to enrich the field.

Questions to Ask about Gender, Outcome, and Schizophrenia

- Days in hospital–is this a good outcome measure?
- Homelessness–are men more vulnerable than women?
- Is living alone considered a good outcome?
- What does being employed depend on?
- Is being married linked to suicide?
- Is it good to be a parent even if one loses child custody?
- Why are patients with schizophrenia and substance abuse less cognitively impaired than those with schizophrenia alone?
- In schizophrenia, are men more violent than women?
- Does suicide depend on access to lethal means?
- Why is the schizophrenia-associated mortality gap increasing?
- Is it better to have fewer symptoms or fewer side effects?
- Is "recovery" a nebulous concept?

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4 Outcome of Schizophrenia in Low- and Middle-Income Countries

Thara Rangaswamy, Greeshma Mohan, and Vijaya Raghavan

Introduction

Schizophrenia was identified as early as 1896 by Kraepelin, who called it "dementia praecox," distinct from the broad spectrum of psychoses seen within his clinic [1], and Bleuler renamed it schizophrenia in 1908 [2]. Illnesses are usually identified and defined in terms of their clinical presentation, course, and outcome. Kraepelin's identification of what we now call schizophrenia rested almost exclusively on course and outcome [3]. The study of course and outcome continues to remain one of the most fascinating aspect of schizophrenia research. Even though predominant research in this area does come from Europe and the USA, the past two decades has witnessed a rise in literature from Asia and Africa as well [4, 5].

A review of follow-up studies suggests that heterogeneity in outcome across individuals with schizophrenia remains the norm [6]. Reviews have indicated that though "schizophrenia is nevertheless a disorder with relatively poor outcome" [7], it is not uniformly poor, and, on an average, a substantially high proportion of persons who receive a diagnosis of schizophrenia experience reasonably good clinical and functional outcome [8–10]. The heterogeneity stems from several sources: nature of sampling, criteria used to diagnose schizophrenia, use of modern treatment—particularly antipsychotic medications—provision of psychiatric services, and others [5].

Outcome in low- and middle-income countries was concluded to be better, and this had become an "axiom in international psychiatry" [4]. The ground was laid from a long history of cross-national research [11–15], with the most often cited evidence coming from three studies by the World Health Organization (WHO): the International Pilot Study of Schizophrenia, the Determinants of Outcome of Severe Mental Disorder (DOSMeD), and the International Study of Schizophrenia (ISoS). However, a series of publications in the past decade has challenged the finding, and now the better prognosis hypothesis keeps looming in international research and debates. Schizophrenia, a biological illness, is influenced by society and culture. It was felt that research concerning the issues pertaining to better outcome of schizophrenia in developing countries in the context of sociocultural differences was woefully lacking [16].

Outcome: A Multidimensional Construct

The "outcome" is the status of the individual at a point in time (end of 2, 5, 10 years, and so on) or at the endpoint. Depending on the length of time

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for which the patient is followed up, the outcome can vary from one point in time to another. For chronic illnesses such as schizophrenia, it is more relevant to study the outcome at the end of 5 or 10 years. Outcome being a multidimensional construct consisting of several independent domains [17], the assessment of variables is a daunting task. It consists of several independent domains, including clinical symptoms and their improvement, and social functioning, especially the ability to relate to people and performance at work (including employment, housework, and tasks). Family burden and quality of life are other outcome measures considered important in recent times.

Researchers such as Bowie and Harvey [18] and Nuechterlein et al. [19] have also pointed out the need to add neuropsychological measures such as cognitive functioning as outcome indicators, since there is an emerging connection between neurocognitive deficits and poor outcome in schizophrenia.

However, as Burns exemplified "...outcomes we need to measure are not fixed. They will continue to change as society's preoccupations change, as our measurement technologies change and as treatments improve. What is clear, however, is that keeping abreast of developments in schizophrenia outcomes is a challenge for clinicians and researchers alike" [3].

Based on data accruing from several long-term studies [20], some variables have been associated with good and poor outcomes (Table 4.1).

Table 4.1 Factors indicating good and poor outcomes in individuals with schizophrenia

Factors indicating good outcome	Factors indicating poor outcome
Female gender	Male gender
Married status	Unmarried status
Early treatment	Earlier age of onset of illness
Acute onset of illness	Delayed treatment
Rural background and cohesive family	Irregular treatment
Absence of negative symptoms	Gradual (insidious) onset of illness
Predominance of florid positive symptoms	Lack of social support
Short duration of first episode	More negative symptoms
Fewer episodes of similar illness in the past	Positive family history of schizophrenia or major psychoses
Good premorbid personality and adjustment	Poor social and occupational functioning before the onset of the illness
Good occupational history	Large size of ventricles of the brain, presence of subtle neurological signs
	History of substance abuse or alcohol dependence

Course and Outcome

The outcome studies from the developing countries have shown a better prognosis and outcome in individuals with schizophrenia. In a study conducted in individuals with first-episode schizophrenia, about 67% had a good outcome [21]. Good drug compliance, short duration of illness, absence of economic difficulties, absence of dangerous behavior and delusions of persecution at intake, acute onset, and younger age of onset predicted good outcome. In the Madras longitudinal study, follow-up for 25 years has shown that outcome was good in 13 (27.7%), poor in 9 (19%), and intermediate in 25 (52%). More men were single and more women were either married or separated. There were no marked gender differences [22]. Contrary to these findings, some studies from other developing countries have shown unfavorable outcomes. In a study by Teferra et al., only 6% had received antipsychotic treatments continuously during the five-year follow-up period; 45% of participants were continuously symptomatic, with 30.3% having had a continuous psychotic episode [23]. Being single, on antipsychotic treatment for at least 50% of follow-up time, and having a diagnosis of paranoid subtype of schizophrenia were associated with longer period of remission.

Employment

When compared with patients with schizophrenia from the western world, patients from low- and middle-income countries (LMIC) are found to be more employed [22, 24]. For example, in the 10-year follow-up of a cohort of patients with first-episode schizophrenia in India, the annual employment rate was found to be between 63%

and 73%, while most of the western studies report a rate between 10% and 20% [25]. Moreover, nearly one-third of untreated patients with schizophrenia were found to be employed in India [26]. Similar results were observed from studies conducted in China [27].

It is of interest to note that even though the percentage of untreated patients with schizophrenia is more in the developing world, the employment rate is higher. This could be an important factor that could contribute to better remission and outcomes in LMICs. Various societal factors contribute to this high employment of patients with schizophrenia in developing countries, such as social bonding.

Lack of social welfare measures and absence of insurance coverage for mental disorders also drive the person with schizophrenia to find some kind of remunerative employment to fend for himself and his family.

Marital Status

Marriage holds an important position in the traditional societies of LMICs and contributes to the social identity of a person. The marriage and its continuation are determined by more sociocultural factors such as stigma, and failure to get married, especially for women, is also stigmatized in traditional societies. While marriage can indicate social functioning and adjustment of persons, it cannot be a comparable outcome measure across cultures.

The age of onset of schizophrenia and the average age of marriage are nearly the same—around 20 years of age. While low marriage rates are reported in patients with schizophrenia from the western world [28, 29], it is found to be high in India, an LMIC country [30]. This shows that the marriage rate in developing countries is much higher than western world. Also, this could contribute to the better outcome in patients with schizophrenia in LMICs as they live with their partners and tend to get support from the family.

Moreover, patients face discrimination and hostility from the family members and society when their marriages are broken down. This could cause significant stress and contribute to the outcome in traditional societies [31]. It is important to explore whether there are any differences in the marriage rates of men and women with schizophrenia in these societies.

Mortality and Suicide

Mortality and suicide are important measures of outcome in patients with schizophrenia. The mortality rates range from 9.0% to 30.7% from different studies and study sites [4]. The one important drawback of most of the long-term follow-up studies that explored the mortality and suicide in patients with schizophrenia is high percentage of lost for follow-up. For example, in Madras longitudinal study, at the end of 25 years of follow-up, 25% were dropped out of the study and lost for follow-up [22]. This could lead to the underestimation of mortality and suicide rates of patients with schizophrenia in LMICs.

The major causes of mortality of patients with schizophrenia from LMICs include heart diseases, infection, and suicide [23]. Suicide is highly prevalent in patients with schizophrenia when compared with the general population, and it is one of the leading causes of early deaths in these individuals. But with fractured reporting system and societal stigma, suicide rates calculated in patients with schizophrenia from the community could be a gross underestimation. Robust reporting system with meticulous follow-up could throw light on the actual suicide rates in patients with schizophrenia from LMICs.

Gender

Many studies have consistently showed that women with schizophrenia have better outcomes when compared with men [32–34]. The studies from the developing countries have shown mixed results. While many studies from India found women to have better course and outcome [35, 36], studies from Colombia have shown that men have better outcomes [37]. In the International Study of Schizophrenia (ISoS) China study, there

were few gender differences, but women tended to do better in a study by Ran et al. in rural China [37, 38]. In Nigeria, women seemed more likely to suffer from continuous psychosis and were particularly prone to relapse [39], and their social and work functioning was also worse. Women in Ethiopia tend to show greater improvement in functioning during follow-up [40]. In the developing world, we have had mixed results with gender and outcome.

Treatment

Many individuals with schizophrenia from the developing and underdeveloped countries remain untreated or inadequately treated [41]. Even though the situation is changing with the increased assess to mental health and awareness among the public on mental illness, the percentage of untreated is high when compared with the developed countries. Studies from India and China have shown that nearly one-third of the individuals with schizophrenia in the community were never treated [26, 38]. Moreover, long duration of untreated psychosis (DUP) is associated with poorer outcomes. In rural Ethiopia, a community survey identified 321 individuals with schizophrenia, of whom 88.8% had never received treatment with antipsychotic medication [40]. It can be reasonably conjectured that the baseline high rate of continuous course of illness (67.2%) among patients was, at least in part, the result of lack of treatment.

Medication nonadherence plays an important role in the treatment outcomes in schizophrenia. Various studies from the developing world have shown high rate of treatment nonadherence in individuals with schizophrenia and place them in high risk for relapse, illness exacerbation, and rehospitalization [42]. One of the factors that contribute to nonadherence is the cost of treatment and nonavailability of treatment in the vicinity. The medication nonadherence could be reduced or prevented by free or subsidized antipsychotic medications and easy access to mental health facility/provider.

Family and Social Support

Generally, it is accepted that family and social support plays a vital role in the outcomes in schizophrenia [43–46]. Even though the trend is changing in the developing countries, the majority of individuals with schizophrenia live with their family members [47, 48]. This could play an important role in their better outcomes when compared with the developed countries. Migration, urbanization, changes in family structure, and social support networks, plus the increase in economic insecurity and widening social inequalities which are evident in low- and middle-income countries, will change the social support available for people with schizophrenia and influence their outcome [17].

Challenges: Studying Outcome in LMI Setting

The "better prognosis" hypothesis in LMI setting has evoked a spate of debates in international research as it needs reexamination for five reasons: methodological limitations of the World Health Organization studies, the lack of evidence on the specific sociocultural factors which apparently contribute to the better outcomes, increasing anecdotal evidence describing the abuse of basic human rights of people with schizophrenia in developing countries, new evidence from cohorts in developing countries depicting a much gloomier picture than originally believed, and rapid social and economic changes are undermining family care systems for people with schizophrenia in developing countries [17].

Several explanations have been offered for what was thought to be this unequivocal finding, but these have been broad themes such as family support, better tolerance, and the black box of culture, whose elements have never really been teased out. Again, none of these factors have been individually addressed by research.

Cohen et al., in a seminal paper in 2008, questioned the interpretation of some of the findings in the Determinants of Outcome of Severe Mental Disorders (DOSMeD) study [4]. While high rates

of complete clinical remission were significantly more common in developing countries (37%) than in developed countries (15.5%), the proportions of continuous unremitting illness (11.1% and 17.4%) did not differ significantly across the two types of setting. Patients in developing countries experienced significantly longer periods of unimpaired functioning in the community, although only 16% of them were on continuous antipsychotic medication (compared with 61% in developed countries).

Across all centers, the best predictors of outcome ($P < 0.001$) were type of onset (insidious versus acute) and type of setting (developed versus developing country), followed by marital status ($P < 0.01$), gender ($P < 0.05$), social isolation ($P < 0.05$), and drug abuse ($P < 0.05$). Neither type of family household (extended versus nuclear) nor experienced avoidance by others (a putative marker of stigma) reached statistical significance as predictor of outcome. Having excluded a number of potential confounders, the paper concluded that "it is unlikely that the variation in course and outcome could be reduced to a single variable" and considered "the possibility that the clinical conditions meeting the inclusion criteria of the study in the two types of setting may be heterogeneous and include varying proportions of etiologically and genetically different disorders which may be indistinguishable from one another at the level of the phenotype." This possibility exists, but it cannot be properly examined or tested now, in the absence of established genetic markers, indicators of etiology, or other underlying mechanisms of disease. Gureje and Cohen have referred to the importance of studying differential outcomes [49]. They cite the study by Haro who compared north Africa/Middle East with Latin America [50]. While the clinical outcomes in the two regions were similar, they were widely divergent in functional outcome.

The data on whether the finding that the outcome is better in the developing world can be applied to migrants in other settings remains unclear. Immigrants treated for first episode of schizophrenia in the UK suggest that while Asian patients have a lower relapse and readmission rate than the locals, Afro-Caribbean patients show a higher rate. The marked social and family differences suggest that the likelihood of a more benign course in a new setting may depend on the extent to which immigrants retain their traditional values [51].

Conclusion

Longitudinal measures of outcome have been exhaustively documented, but very few studies have adequately dealt with all major sources of error and confounding, including sample selection, definition of outcome, and diagnostic criteria used. The outcomes we need to measure are not fixed, and hence demystifying the disorder to overcome the limitations remains a challenge for clinicians and researchers alike. Moreover, the outcome variables will continue to change as society's preoccupations change, as the measurement technologies change, and as treatments improve.

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Neurocognition and Treatment Outcomes in Schizophrenia

5

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Introduction

Schizophrenia is a debilitating neurodevelopmental disorder that affects many aspects of psychosocial and interpersonal life. Cognitive and motivational disturbances are conceivably the most debilitating and pervasive aspects of the schizophrenia syndrome, in the midst of the other better-recognized psychotic symptoms (i.e., delusions and multimodal hallucinations). Whereas psychotic symptoms often fluctuate with clinical state, cognitive symptoms are present early in the disease course and persist even in the absence of the more clinically apparent psychotic symptoms. Current pharmacologic therapies largely target the positive symptoms and have little effect on cognitive and motivational aspects of the disorder. Neurocognitive disturbances, particularly to executive function, contribute to substantial disability and loss of functioning in schizophrenia. Here, we will discuss that cognitive and executive functioning affect treatment outcomes and functional impact in schizophrenia, and we will also discuss current treatment strategies for cognitive and psychosocial intervention.

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Metrics of Functional Outcomes in Schizophrenia

A central problem in schizophrenia research has been the development of treatment modalities for functional impairments in our patients. Several lines of evidence have demonstrated that cognitive and behavioral aspects of the disorder are present in unaffected relatives. The concept of an endophenotype implies that certain phenotypes, be it cognitive, behavioral, or neurophysiologic, are present in patients with schizophrenia, but less so in unaffected relatives, and absent in healthy controls. Like many aspects of the disorder, daily functioning has been thought to be a heritable and measurable trait of the disorder [1–3]. Therefore, as a putative endophenotype, if it can be reliably quantified, it can be directly compared to other aspects of the disorder and can be investigated in genome-wide studies [2].

Various tools have been developed to assess social and occupational functioning, but there is a lack of a generally accepted tool for assessing functional capacity [4, 5]. Outcomes in schizophrenia are commonly measured in terms of level of independence, employment, interpersonal relationships, and quality of life. Currently, the University of California, San Diego Performance Skills Assessment (UPSA) is the most widely applied tool for clinical and research studies of schizophrenia and other mental disorders [6–8], as it has been shown to have stable psychometric

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properties and has been translated into several other languages [9]. A common caveat for most studies is that functionality is ascertained in terms of relative functioning at the time of assessment. That being said, functional capacity is seldom a static process; it can vary by clinical state and as our patient's age. Therefore, investigators have also attempted to ascertain measures of lifetime achievement and functionality, to better bridge this gap [10].

Neurocognition and Executive Dysfunction in the Schizophrenias

Global Cognitive Impairment

Clinicians have long appreciated the effects of cognitive dysfunction in the daily lives of patients with schizophrenia. Decades of research of cognitive functioning in schizophrenia have revealed consistent deficits across virtually all cognitive domains tested (i.e., IQ, working memory, executive function, episodic memory, sustained attention, processing speed, etc.); further, these observations have been relatively consistent, despite variation in neuropsychological instruments over time [11]. Global cognitive deficits have been reported early in the schizophrenia spectrum, although deficits to verbal memory, processing speed, and working memory are particularly salient as early as first-episode psychosis [12]. Global impairment has been related to poor global impairment in domains such as everyday care [13] and social and occupational functioning [14]. It is also of interest that neuropsychological impairments are not static, as the rate of cognitive decline rapidly accelerates at age 65, which is in stark contrast of normal aging [15], suggesting that schizophrenia portends a stage of accelerated brain aging.

Neurocognitive Effects on Clinical and Psychosocial Outcomes

Outcomes in schizophrenia are generally defined as either clinical or psychosocial outcomes. Clinical outcomes commonly refer to response to neuroleptic medications. Symptomatic remission is construed as a measurable reduction in positive and at times negative symptoms. Psychosocial outcomes attempt to quantify independent living, employment, interpersonal relationships, and overall success in the community.

Clinical Outcomes

Neuroleptic medications revolutionized the treatment of schizophrenia, whereby patients who were previously confined to lifelong institutionalization were able to participate in community living and had the opportunity to thrive. Broadly speaking, clinical outcomes refer to a patient's response to antipsychotic medications, i.e., symptomatic remission, and, by extension, the ability to keep community-dwelling patients living outside the confines of locked psychiatric units. Poorer performance on verbal memory and working memory predicted worse clinical outcomes in first-episode psychosis (FEP) 6 months after their first hospitalization, whereas processing speed and executive functions had little predictive value [16]. At 3-year follow-up, verbal memory appeared to predict symptomatic remission for FEP [17]. In chronic patients with schizophrenia, other neurocognitive measures such as verbal fluency [18] and gross metrics of executive function [19] predicted symptomatic remission. In contrast, in a relatively homogenous population cohort, a generalized pattern of cognitive deficits was shown to be associated with non-remission [20], which again is consistent with the notion of a global cognitive impairment. Of note, symptomatic remission has shown benefit to quality of life measures and other clinical outcomes, but generally has little significance on cognitive functioning [21].

Psychosocial Outcomes

Cognitive deficits are prominent at all stages of schizophrenia. Generally speaking, poor neuropsychological performance predicts worse psychosocial functioning [22–24]. Executive dysfunction and deficits to other cognitive domains negatively impact multiple aspects of psychosocial functioning, beginning from the most basic management of activities of daily

living (ADLs) [13, 25] to broader community functioning [26]. Other neurocognitive variables have been implicated in other measures of psychosocial functioning, such as verbal memory and working memory, which predicted employment status in chronic patients with schizophrenia [18].

A striking feature of the schizophrenia spectrum is that neurocognitive deficits are present early on in the illness course. Of these, executive function, verbal memory, and processing speed were significantly worse for patients with poor outcomes compared to those with relatively good outcome in ultrahigh-risk (UHR) populations [24]. Further, UHR populations who demonstrate worse deficits to attention and working memory are more likely to convert to manifest psychosis [27], with worse verbal memory predicting faster time-to-conversion [28]. Ultimately, clinically high-risk populations suffer worse clinical and psychosocial trajectories, such that individuals who do not convert to full-blown psychotic illness still experience attenuated positive symptoms and poorer social and role functioning than healthy age-matched controls [29].

In first-episode schizophrenia, baseline executive functioning also predicted global functioning at 1-year follow-up [30]. Further, verbal memory impairment predicted long-term remission of psychosis at 3-year follow-up, which also portended better social functioning [17]. Curiously, negative symptoms have been thought of as possible mediators of cognitive functions on psychosocial outcomes such that one study suggested that negative symptoms may contribute to the impact of verbal memory deficits in relation to social and occupational functioning during early psychosis [31]. The relationships between neurocognitive measures, negative symptomatology, and psychosocial function are complex, but similar patterns are seen in chronic schizophrenia [32, 33].

In chronic schizophrenia, there are similar patterns for cognitive metrics as UHR and FEP; however, graduated distributions of disability and cognitive deficits exist varying by stage of psychotic illness. A small but interesting longitudinal study assessed the long-term functional outcome 15 years' post cognitive testing. It suggested that verbal memory deficits strongly predicted community functioning and integration, whereas executive functions predict total duration of hospitalizations over the 15-year period [26]. This complex pattern of phenotypic variation suggests that cognitive metrics may co-segregate, but they may also have phenotypic exclusivity. Executive function as measured by performance on WCST predicted better social functioning during an eight-month rehabilitation program [34]. Further, executive functions would go on to predict general functioning, but specifically occupational and household functioning, in a group of 96 patients 1 year after discharge from an inpatient unit [14].

Generally, cognitive dysfunction predicts poorer psychosocial function. Interestingly, in a Swedish population cohort study of over 500 patients with schizophrenia, baseline executive function was an independent predictor of premature death on 20-year follow-up [35]. In the duration of the study, roughly 13% of patients passed by age 60.5, which is 20 years earlier than the national mean. Curiously, these deaths were not attributable to suicide, as the rate was less than 0.01%. This study is also important as it shows that symptomatic remission has little to no predictive value in determining the longitudinal status of survival in this patient population. It is also worth mentioning that in treatment-refractory populations, which generally have more pronounced deficits to executive function, cognitive flexibility, verbal fluency, and processing speed than other patients with schizophrenia, these effects also appear to be modulated by negative symptoms [36].

Interventions for Cognitive and Psychosocial Functioning

Cholinergic Systems

Central cholinergic tone is critical to learning and memory. Antipsychotic medications are plighted with affinity toward multiple receptor types, which lead to a multitude of side effects. Among these are anticholinergic effects which can negatively affect cognition and affect the

outcomes of intensive cognitive training [37]. Adjunctive acetylcholinesterase inhibitors, such as donezepil, have some evidence to support their use in improving executive function as well as other cognitive deficits [38]. Other forms of cholinergic modulations, particularly through alpha-7 nicotinic acetylcholine receptors, are being investigated. An alpha-7 receptor agonist, encenicline, was shown to enhance several domains of cognitive functioning, improved negative symptoms, and daily functioning in a phase 2 clinical trial [39]. Mechanistically, alpha-7 nicotinic receptors are thought to enhance cognition through modulation of NMDA receptors and dorsolateral prefrontal circuit engagement [40].

Glutamatergic Systems

The glutamatergic system has shown great promise for novel therapeutics for cognitive enhancement in schizophrenia [41]. Interestingly, minocycline via putative neuromodulatory and neuroinflammatory mechanisms has shown to be beneficial to negative symptoms and social and occupational functioning. It has led to improvements in executive functions after six-month follow-up early in the course of schizophrenia [42]. A small study suggested that L-carnosine improved executive functions, such as cognitive flexibility and set-shifting [43], although this was limited by tolerability. Other glutamatergic modulators, such as D-serine, have shown modest improvement in negative symptoms and executive functions [44] and composite MATRICS battery scores at higher doses [45]. However exciting these studies may be, they are limited by small sample sizes and lack of robust replication. That being said, the modulation of NMDA-mediated signaling has functional implications on learning and memory and therefore is a promising target for cognitive enhancement strategies in schizophrenia [46]. Medications targeting NMDA receptors, such as memantine, have shown promise in schizophrenia. Memantine initially showed no benefit to cognitive symptoms, but has shown some benefit in negative symptoms in clozapine-treated patients [47, 48]. Recent work suggests that memantine may be used to augment cognitive training strategies [49] and that it may be clinically useful in treatment-refractory subtypes of schizophrenia [50].

Cognitive Remediation

Although much emphasis has been placed on the potential of cognitive remediation for the cognitive symptoms of schizophrenia, much work needs to be done to refine pipeline and stratify patients based on neurophysiologic parameters. Wherein some studies do support a role for cognitive remediation, others studies suggests that the benefits of intensive cognitive training is only limited to the tasks at hand and do not generalize to other cognitive domains as they were intended. Overall, this places some doubt as to whether such intensive, and costly, trials produce clinically meaningful benefit [51–53]. Interestingly, patients who had significant improvement in verbal memory and executive functioning as a result of cognitive remediation had longer time-to-relapse, which provides evidence of cognitive remediation having sustained effects on clinical course [54]. Therefore, much work has been aimed at using biomarker-based strategies to identify individuals likely to benefit from the cognitive remediation [33].

Conclusions

Neurocognitive deficits have a profound impact on many facets of neurobehavioral and psychosocial outcomes in schizophrenia [55, 56]. With the concept of the schizophrenias—genetically and phenotypically distinct disease entities—resurfacing and that of a biologically informed nosology, we are at a time where cognitive and functional outcome measures can inform treatment strategies. Over the course of the years, several neuropsychological batteries and tests have been devised to assess for cognitive and psychosocial functioning. Currently, the most well-adopted batteries for cognitive studies are MATRICS consensus battery and CogState schizophrenia battery. These tools have been developed for sole purpose of ascertaining reliable cognitive metrics for pharmacologic and

cognitive interventions. Similarly, various measures of psychosocial functioning exist, the most widely applied being the UCSD Performance Skills Assessment. The benefit of standardized metrics would be to leverage direct comparisons on a population level. As both neurocognitive domains and overall global functioning have been reported as heritable traits, these can be theoretically studied through a genomic lens. Further, parsing and identifying subsets of patients who suffer from worse neurocognitive and psychosocial functioning profiles can lead to targeted therapies and interventions for those individuals most at need.

The cognitive deficits seen in the schizophrenias are present at all stages of the disorder and can be the defining clinical feature in certain cases. Investigators have vigorously studied the cognitive sequelae of the schizophrenias across the world and have found generalized deficits across all neurocognitive domains; hence, the concept of the global cognitive impairment [11] has been proposed.

Intuitively, one would presume that poorer neurocognitive performance portends worse prognosis and psychosocial functioning. However, this leaves much to desire in terms of mechanistic strategies for intervention and cognitive rehabilitation programs. Several studies have implicated various aspects of cognition with features of psychosocial and treatment outcomes; however, executive function, verbal memory, and processing speed appear to be individual measures with the most promise for targeted neurocognitive interventions, as they consistently relate to psychosocial and clinical outcomes across all stages of schizophrenia. It is important to note that cognitive dysfunction extrapolates to the most basic day-to-day functions, such as grooming and hygiene, to keeping up with their medications, to more complex tasks required for occupational and physical well-being. Further, the finding that baseline neurocognitive deficits were independent predictors of premature death in chronic psychosis only underscores the impact of neurocognitive functioning in the lives of our patients.

Currently, pharmacologic strategies for improving cognitive functioning in schizophrenia are limited, but there are many active areas of research, including augmenting glutamatergic and cholinergic signaling pathways, which are promising. The future holds promise for cognitive remediation, as new studies are showing novel ways of augmenting cognitive remediation with targeted pharmacology [49, 57], and recent advances in neurostimulation techniques are paving the way for neuroplasticity-mediated therapies. The ultimate goal of the research is to improve the way our patients think, feel, and live their lives.

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Cannabis and Recovery in Schizophrenia

6

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Introduction

In this chapter, we will explore the nuanced topic of cannabis and recovery in schizophrenia. Addressing this demands knowledge of what cannabis is and a broader understanding of how it relates to schizophrenia. Therefore, we will first explore the composition of cannabis before considering its role in causality and relate this to the question of why it is used so prevalently in those suffering from this condition. From this platform, we will then review and compare recovery-based interventions. Ultimately, the conflicted nature of cannabis will be considered with attention paid to its potential role in the treatment of schizophrenia.

Does Cannabis Cause Schizophrenia?

This commonly asked question implies a compositional unity; it suggests that cannabis is a single article. It is therefore first important to understand what we are describing with the term cannabis and appreciate its complexities before attempting to answer this question. Knowledge of the plant, its components, and its apparent contradictions will allow us to consider its influence in the context of recovery in schizophrenia.

Cannabis is at present the most-consumed illicit drug in the world—the prevalence of which in 2010 was 2.6–5.0%, amounting to 120–224 million users. It is produced and consumed in every country in the world and in amounts that far exceed other illicit drugs. The proportion of people with schizophrenia who use cannabis varies, yet surveys commonly find prevalence rates to be about 40%, much higher than the general population. It is a plant that grows wild throughout the world [1]. It has been used to make rope and material and has been used as a psychoactive drug for at least 2700 years. When used as a recreational drug, it is normally consumed either as a compressed resin or made from the flowering tops and leaves, which is then either smoked or ingested.

The myriad properties of cannabis are better understood by appreciating that it is composed of a range of substances. It is known to contain over 400 compounds, including over 60 cannabinoids, most of which are classed as aryl-substituted meroterpenes unique to the plant genus Cannabis [2]. Amongst these exists the best-known cannabinoid, the major active psychoactive constituent Δ^9 tetrahydrocannabinol (Δ^9-THC, or THC). THC produces a euphoric high, a feeling of relaxation, and intensification of sensation but is notorious for its apparent ability to induce psychotic symptoms.

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Alongside this may be found various cannabinoids, which range from producing synergistic, additive, or antagonistic effects with THC. Cannabidiol (CBD) is one such coexisting counterpart. As neither a spare part in the cannabis plant nor a psychoactive co-conspirator with THC, cannabidiol is in fact theorised to play an antipsychotic role. This component will be explored in greater depth later in the chapter.

The cultural change in cannabis cultivation has heralded a shift in the average baseline composition of street-bought cannabis. In the mid- to late twentieth century, less THC content existed in the naturally grown plants. However, with the advent of hydroponic growing systems and a culture that favoured more densely THC-laden product, a change was observed that found customers buying cannabis with an increasingly potent psychoactive profile. It is suggested that over time, the average THC content of a joint transitioned from approximately 10 mg in the 1960s and 1970s to 150 mg in the present day [3–7]. What is the relevance of a cannabis market offering high THC content? An understanding of the role of cannabinoids in relation to psychosis is key to answering this question. Let us consider some essential pharmacokinetics and pharmacodynamics.

Inhalation of cannabinoids produces rapid absorption into the bloodstream and prompts contact with the brain. Oral bioavailability is vastly lower, with approximately 25–30% of the blood concentration seen when taken via inhalation [8]. This is in part due to the first-pass metabolism via the liver. Metabolites formed in this process include 11-hydroxy-THC, which is theorised as being equally if not more potently psychoactive than Δ^9-THC. This is touted as being responsible for the delayed, yet intense, psychoactive sensations experienced following the ingestion of cannabis [9]. When ingesting cannabinoids, the onset of psychoactive effects is delayed but endures longer due to a process of slow release from the gut. As highly lipid-soluble compounds, cannabinoids sequester in adipose tissue following distribution via the bloodstream. This trait leads to a tissue elimination half-life of approximately 7 days. Furthermore, one dose may take up to 30 days to undergo complete elimination form the body's tissues [10].

Following metabolism in the liver, excretion occurs partly via urine, yet predominantly via the gut. Difficulties in accurately representing the degree of intoxication via urine and plasma analysis arise due to the confounding influence of sequestration in fat and the presence of active metabolites.

With regard to exerting their effects, cannabinoids primarily act through cannabinoid receptors, CB1 and CB2. Neuronal CB1 receptors are distributed within the central nervous system, as well as in various peripheral organs and tissues. CB1 neuronal receptors occupy sites in the cerebral cortex, basal ganglia, thalamus, brainstem, cerebellum, and limbic regions such as the hippocampus and amygdala. This distribution is broadly mirrored by uptake patterns of THC [11]. The location of CB receptors may explain the effects of cannabis use on learning, memory, emotion, motivation, and motor ability [12]. In the absence of ingested cannabis, these receptors are activated by endogenous cannabinoids, the major effects of which are largely mediated by their control of neurotransmitter release such as gamma-aminobutyric acid (GABA) and glutamate within the brain. These substances have been explored in terms of their influence with relation to a diaspora of functions including appetite, memory, stress response, and immunity.

It is clear that an endogenous framework exists for cannabinoids. Without digressing into discussions on this vast topic, let us interrogate instead the influence of exogenous cannabis on this system in terms of psychoactivity. This will form a key part of our attempt to consider whether cannabis is a cause of schizophrenia.

When interrogating a cause, it is useful to define what is meant by the term "cause." Cecile Henquet suggests that causality is generally found to be plausible in the context of studies if they (i) report an association between the exposure and the outcome consistently and with a strong effect size, (ii) show dose–response relationships between the exposure and the outcome,

(iii) show that the exposure precedes the outcome, and (iv) show that there is a plausible biological mechanism linking the exposure and the outcome [13].

On mechanism, the psychomimetic properties of cannabis have long been observed, and research into plausible avenues for these effects has been conducted. Moreover, the direct mimicry of schizophrenia-like symptoms has been demonstrated using the intravenous injection of D-9-THC in double-blind, randomised controlled trials (RCT). It is not simply a matter of casual observation. Deepak D'souza used a 3-day, double-blind RCT to assess the behavioural, cognitive, and endocrine effects of variable concentrations of intravenous THC with a view to investigating its induction of psychosis [14]. The trial was conducted over 3 days in 22 healthy individuals before post-study data was collected at 1, 3, and 6 months. The investigating team observed that THC led to the following outcomes: It produced schizophrenia-like positive and negative symptoms, altered perception, increased anxiety, and euphoria, as well as disrupted immediate and delayed word recall whilst sparing recognition recall. It impaired performance on tests of distractibility, verbal fluency, and working memory and yet did not impair orientation. Importantly, however, all of these findings in healthy individuals were transient.

In a useful review collating evidence on the major mechanisms by which cannabis may contribute to psychosis, Don Linszen explores further the possible mechanisms that might explain the apparent psychotogenic effects of cannabis [15]. It has been observed that memory impairments can be induced by cannabis use, yet Linszen suggests that no evidence points to long-term cognitive disruption following cannabis use. Alterations in patterns of cerebral blood flow have been found, with short-term increases and long-term attenuation; however, the longevity and impact of such changes remain questionable. Work has been performed assessing the influence of THC on dopaminergic neurotransmission in brain regions implicated in psychosis. It has been observed in animal models, specifically in mice, for example, that mesolimbic dopamine transmission occurs via a common opioid receptor mechanism located in the ventral mesencephalic tegmentum [16]. The relevance of this in relation to psychosis, and indeed the propagation of long-term psychotic-type disorders, remains unclear. Further studies have looked at how genetic vulnerability might predispose individuals to be easier targets for the development of cognitive deterioration and psychosis following cannabis use. A study using a New Zealand birth cohort sample demonstrated a functional polymorphism in the catechol-O-methyltransferase (COMT) gene-led individuals who were homozygous for the COMT allele to be more likely to exhibit psychotic symptoms and schizophreniform disorder following adolescent exposure to cannabis [17]. Others again focus on the transient emergence of psychotic-like states and memory changes in healthy individuals following THC administration.

We have thus explored in general terms the major theorised mechanisms of cannabis-induced psychosis. Yet it is worth considering at this point the focus of trials assessing mechanism necessarily concentrates on psychosis as a description of symptoms. They generally focus on transient psychosis. In reviewing the role of cannabis in schizophrenia, we are drawn to consider the long-term studies which review causality in wider terms. Unfortunately, randomised controlled trials are scant in this sphere.

Nonetheless, major reviews of the available trials exist. In a short yet compelling summary of the suggested role of cannabis use in schizophrenia, Henquet et al. amasses the major prospective studies published up to 2005 and considers their evidence [13].

A meta-analysis of the odds ratios of these included prospective studies found a pooled estimate for the development of psychosis associated with prior cannabis use at an odds ratio (OR) of 2.1 (95% CI: 1.7–2.5; test for heterogeneity: $Q = 5.0$, $p = 0.54$). This outcome appears to agree with the general assertion that cannabis use can lead to psychosis. Let us consider some counter-arguments to this weighty statistic.

Confounders clearly exist in populations exposed to higher cannabis use, and the potential

influence of these must be acknowledged when determining causality. Known risk factors such as sex, age, social class, ethnicity, family psychiatric history, urban living, and concomitant substance misuse all cloud the water. It is a function of observational studies that confounding factors cannot be eliminated; however, Henquet affirms that the included studies attempt to take account of these factors in adjustments and concludes it is unlikely given the lengths taken that confounding factors alone suffice to explain the outcomes.

Related to the concept of confounding influences is that of reverse causality. It asserts that sufferers of social anxiety and subtle expressions of psychosis-like experiences are more likely to attempt ameliorating these feelings through use of cannabis. This touches on the dissociative and apathy-inducing properties of cannabis. Alterations in striatal dopamine synthesis, for example, have been touted as a mechanism underlying reduced reward sensitivity and a motivation that associates with chronic cannabis use [18]. The activity of THC as a dissociative agent has been explored in terms of its effects as an analgesic via amygdala-mediated actions [19]. The relevance of these properties of cannabis in the setting of psychosis may be profoundly relevant. It has been suggested that individuals suffering psychotic-type disorders might "self-medicate" on the basis of these properties, achieving transient states of apathy and dissociation from their conditions. This could prove a major incentive for sufferers of schizophrenia to continue cannabis use despite the possible long-term consequences of its use on their condition. In terms of its relevance in the reverse causality argument, the assertion states that those more predisposed to use cannabis for these purposes on account of their proclivity to psychotic-type experiences will also be those individuals more likely to go on to develop psychotic-type illnesses. In this argument, their psychosis comes as a result of other factors, and their cannabis use is secondary.

Henquet references longitudinal studies that attempted to account for this phenomenon. A Dutch cohort study excluded at baseline all individuals who reported having ever had psychosis-like experiences and still found an association with psychosis and cannabis use [20]. A New Zealand study assessing for associations between cannabis use at age 15 and schizophrenia at 26 years in a birth cohort study found a significant association, even on adjusting for psychosis liability at 11 years [17]. We have therefore prospective evidence suggestive of an association between cannabis use and the development of psychotic symptoms whilst accounting for confounders.

We know that schizophrenics use cannabis at higher rates than the general population. Therefore, despite the possibility that cannabis may well be a factor in causing psychosis, its transient promotion of apathy and dissociation is a plausible incentive for its continued use. This bidirectionality is not contradictory, nor is it aberrant. We observe the use of drugs and substances for their escapist properties across the world, in spite of the fact that users acknowledge their deleterious long-term impact.

A review for the *British Journal of Psychiatry* by Arseneault et al. concludes that the relationship between cannabis use and schizophrenia is dose-dependent, [17] and that the relationship is linear in temporal terms. In D'Souza's randomised controlled trial utilising IV Δ^9-THC in healthy subjects, transient effects are found, including on positive symptoms, negative symptoms, and perceptual alterations as referenced earlier in this chapter [14]. It appears that these effects are dose-dependent across the 2.5 mg and 5 mg preparations. However, they remain transient, and the work concludes that further work is needed to clarify whether cannabis consumption does indeed contribute to the pathophysiology of psychosis or by extension, schizophrenia, despite the increasingly wide body of literature in this field.

When referring back to Henquet's criteria for cause, we can say that the prospective studies give evidence of an association between exposure and outcome (lacking a large effect size), a dose-dependent relationship, and a temporal relationship. Further studies offer possible mechanisms, with their plausibility open for discussion. Henquet concludes that cannabis use is

a co-dependent cause of schizophrenia, one that is dependent on the presence of other variables. If we are to take the available evidence as representative of this view, and agree with this assertion, it has clear implications for the healthy cannabis user. The possibility of vulnerable individuals developing psychotic-type illnesses such as schizophrenia via the co-dependent cause of cannabis use has profound public health implications.

For the practicing clinical psychiatrist, however, the daily focus is patients suffering psychotic-type illnesses, not healthy individuals. Therefore, whilst we might be ready to accept the influence of cannabis as a co-dependent cause in schizophrenia, a study of the effects of cannabis use on the outcomes of psychotic disorders may be more pertinent. In a comprehensive systematic review of this point, Stanley Zammit and colleagues suggest that evidence specifically indicative of worse outcomes amongst patients with psychotic-type disorders using cannabis is interestingly not watertight [21].

The team claim the achievement of presenting the first systematic review into outcomes in the field of cannabis and schizophrenia. Their literature search amassed 15,303 references before they brought down the number suitable for analysis to 13. The vast number excluded was felt to lack suitable relevance, and then studies were further discounted if they included cross-sectional analyses or cannabis as an endpoint exposure. It should be noted that the authors acknowledge all of those studies excluded on the basis of the latter two points pointed towards worse outcomes with cannabis use. Each included study was longitudinal in design, and in the absence of suitable randomised controlled trials, such studies are often seen as second best for assessing causality.

The outcomes included focused on relapse and rehospitalisation, severity of symptoms, and response to treatment.

The burden of relapse on patients and inpatient units is familiar in clinical psychiatry. A rigorous review of the factors involved in this process is, of course, desirable. In the clinical sphere, it is broadly agreed that cannabis associates with more frequent visits to units. Here, the review attempts to consider the longitudinal studies that have sought to critically assess this point. Concerning relapse, the review highlights two studies which use the Brief Psychiatric Rating Scale (BPRS) score to report increased risk of relapse with cannabis use. One included study conducted in Brisbane cites an apparent dose-dependent relationship between cannabis use recorded over days per week and an increased risk of relapse in psychosis [22]. Continued use of cannabis at follow-up was also highlighted as associating with increased relapse rates with seemingly clear differentiating stats between users (64%) and non-users (17%). With regard to readmission, the review includes three studies which point towards associations. One study found associations between cannabis use and rehospitalisation, [23] whilst another pointed towards a greater number of overall admissions [24]. Overall, four studies included in the review contained focuses on relapse, and three on rehospitalisation. The review notes here that of the four studies included for comment on relapse, two of them failed to define relapse. Nevertheless, the studies seem to portray strong effect sizes and adherence to Henquet's definition of what constitutes an identified cause, particularly with attention to the dose-dependent relationship. This study claims to have controlled for medication adherence, other substance use, and duration of untreated psychosis.

It may seem intuitive that relapse rates and rehospitalisation would correlate with symptom severity. If cannabis is reportedly an independent variable for prompting more frequent relapses and more numerous hospital visits, one might assume that the symptom severity of cannabis-using schizophrenics is greater. The review by Zammit et al. included seven studies that examined psychopathology symptom scores covering measures of psychosis, mood, aggression, and cognitive function. Of these, one reported a slight increase in BPRS score at follow-up with cannabis use after making adjustments for baseline BPRS scores [25]. Less change was noted in the cannabis misuse group compared against non-users with regard to their scoring on the Positive and Negative Syndrome Scale (PANSS) in

another study, [26] yet the review notes that statistical power was reduced due to a lack of combined analyses across the two trial groups. In one further study based at the South London Hospitals, baseline regular cannabis use was associated with increased levels of positive symptoms at follow-up [27]. None of the other seven studies focusing on symptom severity found a change in symptom scores from baseline to follow-up. Here, we find a minority of studies amongst a small pool able to demonstrate any clear change in positive symptoms severity on account of cannabis use. Only one of seven found a reduced PANNS score in relation to negative symptoms at follow-up. In the three studies that considered other measures such as depression and anxiety, no association was found between cannabis misuse and participants scores. In terms of neurocognitive ability, the one study assessing this demonstrated an apparent improvement from baseline in participants' neurocognitive ability [28]. The lack of substantial evidence indicating an association between cannabis use and more intense psychopathology is an interesting feature of this review.

Response to treatment is the final area considered in the scope of the review. Numerous outcomes relevant to treatment response were considered across the included studies: length of inpatient stay, course of illness, presence of deficit schizophrenia, global assessment score (GAS), service contact, productivity or employment, marital status, living alone, and quality of life [17]. Here again, we find a reasonably sparse set of evidence in support of anything like an arresting disruption of treatment response. In the study conducted in South London, it is suggested that a more continuous illness course was seen in individuals who used cannabis more frequently. This generalised assertion is supported by weak data. More interesting evidence from the study performed in Madrid suggested that baseline cannabis use was associated with non-adherence at follow-up; however, a dose-dependent link was found not to be statistically significant when adjusting for confounding [29]. A study in Navarra matched this assertion yet again presented fallible data ($p = 0.06$) [23].

Interestingly, two studies included in the review found associations between cannabis and improved outcomes. The study reviewed from Sydney found weak evidence that baseline cannabis use conferred a clinically important shorter admission duration $p = 0.07$, whilst one performed in Manchester suggested that a state of deficit schizophrenia was less common in baseline cannabis users [26, 29]. In relation to response to treatment therefore, we once again encounter an area vexed by confounders. It is difficult to confidently isolate cannabis use as a clear independent variable in conferring worse outcomes for patients in this specific area.

It is of significance to note the indication that cannabis use appears to associate with more frequent relapse and more recurrent hospital stays yet interesting to note the weak associations in terms of treatment response and psychopathology evidenced here. It is highly unlikely, however, that the lack of resounding evidence on latter two points serves as sufficient grounds to reverse the trend of discouraging cannabis use amongst patients.

If then we have concluded thus far that there is an imperative on clinicians to reduce cannabis use amongst schizophrenics, the question turns to how this is best done. The 2014 Cochrane Review considers this point primarily. This full-scale literature review identified a total of 250 references, with three more found through other sources; 226 studies were identified for initial screening once duplicates had been removed. Fifty studies were then screened via the abstract, resulting in 15 studies retrieved in full text that were assessed for eligibility. Finally, eight studies were considered acceptable for inclusion in the quantitative analysis. [1]

The interventions focused on cannabis use reduction and included psychoeducation versus psychological treatment (cannabis and psychosis therapy), treatment as usual versus psychological treatment, clozapine versus any antipsychotic, olanzapine versus risperidone, and amisulpride versus cannabidiol. These were interrogated using a number of measures for outcomes: rating scales, global state, behaviour, general functioning, adverse effects, and dichotomous data (this

last outcome measured whether the participant had used cannabis in the past 4 weeks, either yes or no). Here, we will review in turn each of the compared interventions, with summaries of the results.

The first section of the review considered "cannabis reduction: adjunct psychological therapy versus treatment as usual." In relation to behaviour, the main aim of the three studies selected was to see if there was a decrease in cannabis consumption and if there was any subsequent improvement in schizophrenia symptoms; however, the comparison suffered due to the trials being small, and little data were directly comparable. None of the studies demonstrate any significant difference between treatment as usual and the psychological intervention being tested for outcomes of cannabis use, mental state, or general functioning. The majority of the data for this outcome was skewed. Skewed data marred any meaningful conclusions for general functioning where none of the outcomes showed a significant difference in general functioning between psychological intervention and treatment as usual. In terms of mental state, only three studies could be included due to skewed data where useful conclusions could not be drawn, and seven may have been eligible had their authors responded to requests for further information.

The review concluded that more research would need to be conducted to see if the extra psychological interventions improve outcomes, for as the data stands at the moment, they provide no evidence of improvement.

The second comparison was entitled "cannabis reduction: psychological therapy (specifically about cannabis and psychosis) versus non-specific psychoeducation." In relation to cannabis use specifically, the aim of the included study was to minimise the usage of cannabis in people with first-episode psychosis. None of the outcomes revealed any significant difference between groups. Had the study been larger, it was felt differences might have emerged. On global state, the Knowledge About Psychosis Questionnaire (KAPQ) was used to inform participants about psychosis but did not reveal any differences in the groups' understanding at the 3- and 9-month assessment points. It was felt to have been possible that the lack of significant differences to emerge may, in part, have been due to using an active control group. Again, in terms of mental state, using the available data on the positive symptoms of psychosis measured with the Brief Psychiatric Rating Scale (BPRS), no differences emerged that demonstrated an overall benefit for cannabis and psychosis (CAP) therapy compared with psychoeducation. Other scales were used, but these reported skewed data. On social functioning, that of the participants' did not improve in either group during the trial whilst interventions were given for 3 months or at the follow-up stage 6 months later.

The scope of the comparisons was not limited to psychological interventions solely. The next comparison looked at "cannabis reduction – antipsychotic A versus antipsychotic B." Here, the review compared antipsychotic medication in those with schizophrenia and who used cannabis, comparing the ability to alter the amount of cannabis consumed and comparing antipsychotic side-effect profile in specifically that group of patients. Three studies looked at differing antipsychotic medication interventions and their effect on cannabis usage. Two studies looked at olanzapine versus risperidone, and the other study looked at clozapine versus the participant's current antipsychotic medication.

The objective of the three trials that measured the impact of antipsychotics on cannabis usage was to deduce whether use and/or cravings subsided differentially when comparing exposure to certain drugs. In none of the outcomes did any study provide evidence for significant differences between groups. Each trial was limited by a small sample size and skewed data; therefore, reliable conclusions regarding the comparative effect of antipsychotics could not reliably be drawn. In Brunette et al. 2011, [30] data suggest therapy with clozapine may reduce cannabis use more than treatment as usual amongst patients with schizophrenia and co-occurring cannabis use disorder; however, data were again skewed and the sample size small. It was concluded nonetheless that there appears to be scope for further exploration of the comparative utility of antipsychotics

in future trials with larger sample sizes. Adverse events of interventions were considered in two trials relating to this comparison.

In Brunette et al. 2011, significant differences in somnolence and hypersalivation were observed that suggest clozapine associates with better outcomes here. In all other adverse effects measured in Brunette et al. 2011, there were no significant differences between groups; however, in several instances (including constipation, weight gain, and dizziness), the differences were almost significant. In Akerele et al. 2007, [31] there was no significant difference in terms of movement disorders between groups using the Simpson–Angus Scale. The study noted that sedation was reported as the most common side effect by both groups; however, no patient was withdrawn due to side effects, suggesting a limited need for future investigations into the comparative side effects of olanzapine and risperidone in this context. No significant differences were found in the time until dropout in the olanzapine and risperidone groups in Akerele et al. 2007, and nor were there any significant differences in the reasons for dropout between participants across the two groups. In neither group were intolerable side effects cited by participants as a reason for dropping out. On the outcome of mental state, in van Nimwegen et al. 2008, there were no significant differences found between groups relating to the Obsessive Compulsive Drug Use Scale (OCDUS), which pertains to craving for cannabis [32]. The study noted that most of the changes associated with the scale took place in the first week of the trial; thus, it was felt a trial extension is unlikely to have uncovered further changes.

Across these three overarching comparisons from the most pertinent, least biased randomised controlled trials, we are shown that evidence for superiority amongst psychological or pharmacological measures for reducing cannabis use amongst schizophrenics is lacking. Treatment as usual appears to be non-inferior to any of the reviewed novel techniques. Clinicians can take reassurance from this point in so far as knowing that normal practice is not inferior to other novel strategies. However, in the absence of larger trials, we are left without clear guidance on what strategies to pursue should cannabis reduction be felt to be of paramount importance amongst schizophrenic patients.

In the fourth comparison of the study, there is a departure from a focus on cannabis reduction towards a seemingly disparate concept: that of cannabinoids as treatment. In this final portion of the chapter, we will consider the role of cannabidiol in terms of its role in cannabis and recovery in schizophrenia.

Cannabidiol is a cannabinoid that has received much attention for a number of touted potential properties, encompassing analgesic, anti-inflammatory, antineoplastic, and chemopreventive effects. It is marketed to relieve spasticity in multiple sclerosis and as a treatment in a form of juvenile epilepsy. However, it is its potential utility as an antipsychotic agent that warrants its inclusion here.

A study marked for inclusion in the Cochrane review by Leweke et al. 2012 [33] compares it against amisulpride for the treatment of schizophrenia. The study proposed that the mechanism of its impact in psychosis may relate to its enhancement of anandamide.

This substance has been found to attenuate psychotic-like behaviours in rodent models where amphetamine and phencyclidine were used [34, 35]. A derivative of arachidonic acid, a fatty acid, its name hails after the Sanskrit word for bliss. It appears to play key link in effecting the actions of cannabinoids as diverse as THC and cannibidiol, and more recent work suggests that a whole network of cannabinoid receptors and anandamide-related substances could exist. Anandamide(s) appear to reside alongside their receptors within neuronal lipid membranes and neuromodulate via intracellular G-proteins controlling cyclic adenosine monophosphate formation and Ca^{2+} and K^{+} ion transport[2].

Cannabidiol is suggested to enhance endogenous anandamide signalling by inhibiting anandamide's degradation via its influence on fatty amide hydrolase, the enzyme responsible for anandamide's breakdown [36]. The idea of CB1 receptor inhibition as a useful antipsychotic mechanistic pathway was largely refuted by large-scale trials exploring this option.

Cannabidiol nonetheless binds loosely to CB1 receptors. A focus on the anandamide pathway as its sole point of action is almost certainly reductive; however, it may be a useful starting point.

More striking than the theories surrounding mechanism in this case is the suggested impact cannabidiol could have as an antipsychotic agent. Exploring mental state in the Cochrane review, BPRS total endpoint scores appeared to favour cannabinoid compared to amisulpride at 7 days; however, the difference in scores was not significant, and this slight advantage for cannabinoid was not apparent at days 14, 21, and 28. Leweke et al. 2012 also measured mental state using the PANSS and found no differences in mental state using this scale. The apparent difference in mental state at 7 days is an interesting finding as there is some slight suggestion that cannabidiol may have some antipsychotic characteristics; however, this result is based on one short-term follow-up and from a very small trial. This overall lack of effect may have been because there was a lack of power to detect a difference in this one very small study.

The drudgery of tolerating the side-effect profile of neuroleptics is a recognised reason for poor compliance. That of cannabidiol appears to be very minimal, and it is generally very well tolerated. In Leweke's study, the side-effect profile for cannabidiol seemed to be superior to that of amisulpride. However, it must be noted that the data were once more heavily skewed.

Excitement around cannabidiol in psychosis treatment has driven patents to be filed and large-scale investment to be injected into the area by GW Pharmaceuticals. They currently market Sativex for MS and in 2015 released a summary announcing positive proof of concept data in schizophrenia:

> Over a series of exploratory endpoints, CBD was consistently superior to placebo, with the most notable differences being in the PANSS positive subscale ($p = 0.018$), the Clinical Global Impression of Severity ($p = 0.04$) and Clinical Global Impression of Improvement ($p = 0.02$). The proportion of responders (improvement in PANSS Total score greater than 20%) on CBD was higher than that of participants on placebo, with an Odds Ratio of 2.65. In the area of cognition, CBD was superior to placebo ($p = 0.07$) with marked differences being seen in subdomains of particular relevance to improving the outlook for people suffering with schizophrenia. With respect to negative symptoms, the Scale for Assessment of Negative Symptoms showed a trend in favour of CBD, which reached statistical significance for patients taking CBD together with one of the leading first line anti-psychotic medications. The majority of other endpoints in the study were in favour of CBD and approached statistical significance in many cases [37].

This was drawn from a trial meeting this description: "The multi-center, double-blind, placebo-controlled trial enrolled a total of 88 patients who were treated over a period of 6 weeks. Participants must have been treated for a minimum of 4 weeks on a first line anti-psychotic medication and still have a PANSS Total score in excess of 60."

The only reference listed with this release by GW Pharmaceuticals was that of Leweke et al. 2012.

GW Pharmaceutical will, it seems, continue to work through the relevant trial phases with a view to obtaining license for cannabidiol as a lone treatment or adjunct for schizophrenia. This may provide an exciting, novel, and largely unanticipated use for cannabinoids in schizophrenia.

Conclusions

The relationship between cannabis and recovery in schizophrenia is nuanced. Its suggested role in causality and relapse instils it as a thorn in the side of any treating clinician. Yet despite its evidenced influence in relapse and rehospitalisation, questions remain over its role in exacerbating psychopathology and interfering with treatment response. Clearly, the causal relationship is complex, and the field would benefit from further rigorous work on this point. Techniques to reduce its consumption amongst patients are limited, and the evidence for more novel strategies is limited. However, perhaps the most exciting prospect with regard to cannabis and recovery is the potential role cannabidiol could play in treatment. Many questions remain over its potential utility here, including how this might influence the

cannabis-use habits of patients. Further exploration of the endocannabinoid system is needed, which may provide interesting answers on mechanism in schizophrenia and guide future treatment approaches.

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Part III

Conceptual Issues in Recovery of Schizophrenia

Concept and Model of Recovery

7

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Introduction

As suggested by this chapter's title, the term "recovery" has come to refer both to a concept and to a model in contemporary psychiatry. In the following, we hope not only to show how these approaches to recovery depart from the more traditional, clinical sense of the term and to clarify the confusions between the two, but also to suggest how the concept of recovery offers the foundation for a significant transformation of psychiatric practice, much of which remains as a hopeful vision to be actualized in the future.

First, we describe the origins of two very different conceptions of recovery, arguing that while they remain distinct, they are also highly compatible, if not complementary. Then we turn to the various models of "being in recovery" [1] or "personal recovery" [2] that have emerged in the field within the last two decades and explore briefly the implications they generate for changing all forms of psychiatric practice, from inpatient care to community-based rehabilitation—a sphere that increasingly incorporates persons "in recovery" as staff (a phenomenon very much related to recovery, as described in detail in Chap. 21).

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Recovery as a Concept

Before broaching that form of recovery that is relatively new to psychiatry—dating back to the late 1980s—we begin with the traditional, clinical concept of recovery that goes back as far as the discipline itself. This concept of recovery is imported from medicine and refers to a complete resolution of all of the signs, symptoms, and impairments that had been associated with a person's experience of mental illness. Someone who has recover*ed* either has been cured of the illness or has otherwise found a way to overcome it; while it may have left social-emotional scars, for all intents and clinical purposes, the person no longer has the condition in question. Although within the mainstream, psychiatric perspective, the researchers who concurred on the identification of the criteria for "remission" in schizophrenia stopped short of addressing the possibility of such a complete recovery [3], this notion has a long and distinguished history in the field.

Philippe Pinel, for example, spoke and wrote about this form of recovery in the late eighteenth century, at the dawn of the moral treatment era, as when he told the members of the Society for Natural History in Paris in 1794 that:

> One cannot ignore a striking analogy in nature's ways when one compares the attacks of intermittent insanity with the violent symptoms of an acute illness. It would in either case be a mistake to measure the gravity of the danger by the extent of trouble and derangement of the vital functions. In both

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> cases a serious condition may forecast recovery, provided one practices prudent management. [4]

Despite the widespread belief that he distinguished "dementia praecox" (which later came to be called schizophrenia) from manic depression based on its inevitably deteriorating course over the shortened remainder of the patient's life span, even Kraepelin wrote that "dementia fortunately does not occur in all cases" [5]. In fact, he observed that the possibility of a form of recovery that could be "considered equivalent to cure" was "not at all unusual," as he wrote in this passage:

> The prognosis, however, is really by no means simple. Whether dementia praecox is susceptible of a complete and permanent recovery answering to the strict demands of science is still very doubtful, if not impossible to decide. But improvements are not at all unusual, which in practice may be considered equivalent to cures. [6]

Once the location for longitudinal clinical research shifted from the long-stay hospitals of Kraepelin's time to the community, during and following deinstitutionalization, a heterogeneity in outcomes became established both within and across individuals [7]. That is, a series of long-term follow-up studies of persons diagnosed with schizophrenia conducted as early as the 1970s found up to 67% of their samples to experience significant improvements over time, many recovering fully [8–12]. Among those who did not recover fully, there was a broad diversity in functioning across a number of only loosely linked domains, with some people improving in some areas (e.g., symptoms) while not others (e.g., social functioning) [13, 14]. Only about 33% of these samples showed a course and outcome similar to Kraepelin's predictions, ranging from clinical stability (i.e., little if any improvement) to progressive deterioration. It is an open question as to why these findings related to the possibility of clinical recovery continue to be overlooked by many in the field [15]. It would appear, however, that since there has been a discipline of psychiatry, there consistently have been people who have recovered fully, and many more who have recovered at least partially, from schizophrenia. We can debate the various percentages that might fall into each category, but—and despite the fact that we have yet to discover a "cure"—clinical recovery, as first documented by Pinel, remains a possibility.

Were this all there is to what has come to be called the "Recovery Movement," though there would be no need for this chapter. But beginning in the 1970s, as these more optimistic data on the outcomes of people living outside of hospitals were starting to appear in academic journals, persons who had been hospitalized began to come together to advocate collectively on their own behalf as part of a Mental Health Ex-Patient/Survivor/Consumer Movement [16]. In part as a protest against the dismal prognoses, they had been given, as well as against the poor treatment they had received, members of this movement pushed back against the profession of psychiatry, proposing to create alternatives to the mental health system that were based on self-help and mutual support [17]. By the late 1980s, some people within this movement began to view these "alternatives" as complementary to, rather than as replacements for, clinical and rehabilitative services and began to advocate for conventional care to be reoriented to promote the dignity, self-determination, and sovereignty of persons with serious mental illnesses.

These advocates took up this cause based on their own "lived experiences" of the harm perpetrated by disrespectful and coercive care and of their own struggles and successes of living meaningful and productive lives in the face of what psychiatric professionals described as mental illnesses. There continue to be deep divisions within this community with respect to whether such conditions as mental illnesses truly exist or not and whether collaboration with mental health services and providers is possible without leading inevitably to the co-optation of the perspective of persons with lived experience. Out of the interaction between mental health consumer advocates and progressive mental health researchers and practitioners, though, the "Recovery Movement" was born.

Perhaps the best—and as far as we can find, the first—example of this confluence of perspectives was captured by Pat Deegan, Ph.D.,

a person who experienced involuntary, harmful psychiatric treatment but then went on to become a clinical psychologist herself. In one of her first publications, Deegan defined and articulated a different conception of "recovery" than that used in clinical research. She wrote that:

> Recovery refers to the lived … experience of people as they accept and overcome the challenge of the disability … they experience themselves as recovering a new sense of self and of purpose within and beyond the limits of the disability. [18]

There are at least two new and important components to this statement that help to clarify the essential difference between this form of recovery and recovery as a clinical phenomenon, as defined above. First, Deegan defines this concept of recovery as grounded in the "lived experience" of persons with mental illness. This is a form of recovery, in other words, that is to be understood from the perspective of the person with the condition rather than from that of the clinician or clinical investigator. Drawing from Deegan's own background in phenomenological philosophy, this shift to first-person experience as a source of credible and useful knowledge laid the groundwork for the development of "lived experience" into "lived expertise." Now a central tenet of the Recovery Movement, the notion of "lived expertise" established the basis for the pursuit and use of the wisdom and practice-based evidence accumulating among persons living effectively with serious mental illnesses. This form of evidence is proposed as being at least equally as valid and complementary to, if not more relevant than, third person, traditionally defined empirical or scientific knowledge about mental illness. As a result, a case is being made for the centrality of "service user involvement" in all types and across all phases of psychiatric research [19], an increasing expectation in psychiatry that parallels the increasing call for "patient," or primary stakeholder, involvement in medical research more broadly [20–22].

The second new and important component of Deegan's highly influential definition is the use of the term "disability" to refer to serious mental illness. This article was published 2 years prior to passage of the landmark legislation of the American with Disabilities Act and in this way reflects what had become a key advocacy strategy of the Consumer/Survivor Movement. If we redefine serious mental illnesses as disabilities under the law, then all of the civil rights and associated responsibilities of community inclusion afforded to persons with physical or developmental disabilities come to pertain to persons with "psychiatric disabilities" as well [23]. While this concept of mental illnesses as disabilities remains somewhat contentious within the broader consumer/survivor community (because it suggests lifelong impairment), the civil rights and community inclusion aspects of the law do not. Rather, they provide a conceptual foundation for the Recovery Movement, which took its inspiration in part from the civil rights movements of persons of color, women, and the LGBT community beginning in the 1960s, as well as more directly from the Independent Living Movement of persons with other types of disabilities, who had been successfully advocating for their civil rights, including the right to community inclusion, since the early 1970s [24].

What are the implications of adopting a disability rights view of the effects of serious mental illnesses? On the one hand, this could simply be a way of characterizing the condition of those people who do not fully recover according to the clinical criteria described above. In other words, if we know that there is a heterogeneity in outcome within and across individuals, some people, those who experience long-term functional impairments, might be described accurately as being "disabled" by mental illness. Perhaps Deegan was referring to those people who do not recover and who therefore continue to have their lives limited and constrained by the symptoms and deficits associated with schizophrenia. They would appear to be disabled in the conventional sense of the term. But on the other hand, Deegan would appear to be referring to something other than being disabled when she writes about such people "recovering a new sense of self and of purpose within and beyond the limits of the disability." How can people who have not yet recovered recover a new sense of self and purpose?

It is in this way that "recovery" for these people is based on the disability rights view articulated in the Americans with Disabilities Act. Persons with disabilities—whether physical or psychiatric in nature—are to be afforded access to a self-determined, full life in the community, as are all other law-abiding citizens, and should "accommodations" be required to afford such access, they are to be provided. By the concept of accommodations, we typically refer to such things as wheelchairs, wheelchair ramps, and handrails in bathrooms that are provided so that persons with mobility impairments will be able to access public spaces as much like everyone else as possible. Similarly, Braille signs and service dogs are accommodations for persons with visual impairments, and sign language for those with hearing impairments. While we are still learning what psychiatric accommodations may end up looking like, adoption of a disability model has allowed advocates such as Deegan to insist that people need not be cured or symptom-free before rejoining community life as full, autonomous, contributing members.

Adoption of this model thus has dramatic and far-reaching implications for how mental health care needs to change to support people in "recovering a new sense of self and of purpose within and beyond the limits of the disability." In addition to reducing symptoms as much as possible, mental health care must focus at least as much, if not more, on restoring functioning and, in areas in which functioning has not yet been fully restored, in enabling people to join in those aspects of community life that they value even while they may remain disabled by a mental illness [25, 26].

This brings us to the second concept of recovery substantially different from, if still somewhat related to, full recovery. As we noted above, this form of recovery—alternatively described as being "*in* recovery" with, as opposed to recovering *from,* a serious mental illness [1], as a "consumer" model of recovery as opposed to a "scientific" one [27], or as "personal recovery" compared to "clinical recovery" [2]—is most applicable to and relevant for those persons who still experience symptoms. This situation has led to innumerable misunderstandings and concerns about [28], as well as uses and abuses of [29], this second concept of recovery and leaves us far from being in an ideal position to discern implications of this concept for practice. Yet that is precisely what we shall do before turning to different models of this form of recovery.

A first implication of this concept is that people with even the most severe forms of mental illness such as schizophrenia remain people first and foremost and are thereby deserving of dignity and respect. In fact, Deegan once wrote: "The concept of recovery is rooted in the simple yet profound realization that people who have been diagnosed with a mental illness are human beings" [30]. In order to operationalize this insight—with which no one would disagree in principle—it becomes incumbent upon practitioners to tailor the care offered to the unique needs, preferences, and goals of each person, to provide what has come to be called "person-centered care" [31]. In addition to being person-centered, such care needs to identify and build on each person's unique strengths and both internal and external resources (i.e., be strength-based), maximize self-determination (i.e., be respectful of the right to make treatment and life decisions), actively take into account the person's sociocultural background and identity (i.e., be culturally competent), and capitalize on healing relationships beyond the formal treatment system (i.e., be inclusive of identified natural supporters and "family" as defined by the individual). Finally, care needs to be oriented to empowering and enabling the person to pursue the kind of life he or she wishes to have, and would find value in, within his or her local community, offering environmental accommodations or community supports that may be required to compensate for enduring difficulties associated with the disability. As the 2003 U.S. President's New Freedom Commission Final Report [32] concluded, it is no longer enough to treat symptoms and simply accept long-term disability if more can be done to improve the person's quality of life or, in Deegan's words, to assist him or her in "recovering a new sense of self and of purpose within and beyond the limits of the disability."

From a conventional clinical or scientific view, such things as a sense of self or purpose may sound highly subjective and beyond the scope of the provision of health care per se. The Recovery Movement can be understood, however, as both a social movement and as a movement to bring about what the New Freedom Commission report characterized as a "transformation" of all mental health care [32]. The social movement aims to combat the stigma, stereotypes, and discrimination associated with having a mental illness in contemporary society so that persons with mental illnesses can, in fact, be viewed and treated as human beings worthy of dignity and respect. The call for transformation begins with, but goes beyond, recognition of these persons' fundamental civil rights to promote an approach to care that elicits, encourages, and honors the person's autonomy, capabilities, and valued roles within his or her chosen community. The major responsibility for this form of recovery lies with the person him- or herself but is also understood to be social in nature [33] and to rely heavily on caring and trusted others and on access to welcoming and supportive communities [34].

Within this context, the role of the practitioner shifts from the sole expert who makes decisions about the person's treatment and overall life (e.g., where and with whom people will live, how they will spend their time, etc.) to that of an expert consultant who has information, skills, education, treatments, supports, and other interventions to offer in promoting the person's, and family's, own efforts at recovery. Each party, including the local community, possesses strengths and resources that can be identified and built on in the recovery process, which evolves in many different ways for different people. But to be supported in their recovery, people need to be respected and treated with dignity as whole human beings who are more than just their diagnosis or illness, need to be offered hope, and need to have their cultural identity, values, affiliations, and preferences honored by their health-care providers [26]. Once we have reviewed the different models of this form of recovery, we will be able to add more specificity to what this kind of care looks like in practice.

Models of Recovery

As discussed in the previous section, a major development in broadening the field's understanding of recovery was to distinguish between the two central types, which Davidson and Roe [1] referred to as "recovery from" versus being "in recovery" and Slade [2] as "clinical recovery" versus "personal recovery." The first, "recovery from" or "clinical recovery," refers more to the scientist-practitioner perspective while being "in recovery" or "personal recovery" alludes more to the person's experience-based perspective [35]. In this section, we will describe recent advances in developing models and frameworks of the later form of personal recovery.

In an attempt to create an empirical conceptual framework for recovery, Leamy and colleagues [36] conducted a systematic review which included 97 published papers from which 87 distinct studies were identified (which were selected from over 5000 that were identified and over 366 that were reviewed). Once the articles were selected, efforts were directed at developing a conceptual framework. First, inductive, open coding techniques were employed to identity central themes. Next, analysis focused on the *relationships within* and *between studies.* Finally, a thematic analysis was conducted until category saturation was achieved and was subject to comments by an expert consultation panel. The final conceptual framework comprises three interlinked, superordinate categories: characteristics of the *recovery journey*, *recovery stages*, and *recovery process*es which we elaborate on below.

In all 87 studies, characteristics of the *recovery journey* were identified. By far, the most common characteristic mentioned was recovery as an active process. This was mentioned in half of the studies, suggesting it might be the major hallmark. There is a sharp contrast between recovery as an "active process" in which the person is engaged and the traditional approach to care in which patients were perceived as passive recipients of care provided by others and were limited in what they could do to primarily complying with or adhering to what these expert others had prescribed for them.

Twenty to thirty percent of the studies stressed how recovery was an individual and unique nonlinear process and journey. This highlights the need for care to be personalized and attuned to improvements as well as setbacks. Several other characteristics were mentioned less frequently (in 7–17% of the studies). These included recovery occurring *as stages* which poses the challenge of phase-specific care which would require identifying stages of recovery as well as what kind of care would be most helpful at each stage. While efforts in this direction may have some promise [37, 38], it is important to point out that personal recovery has also been described as being nonlinear in nature and that the transtheoretical model of behavioral change [39] on which such models are typically based is limited in its application to mental illness [40]. Rigid interpretations of this model can inadvertently lead to structures in which people are prevented from participating in potentially healing, recovery-based services based on a professional assessment that such participation is not "stage appropriate"—a practice that is not consistent with the spirit and intent of recovery-oriented care [40].

Recovery was also referred to as a struggle, life-changing, multidimensional, and gradual process. These are important reminders not to confuse the greater optimism embedded in recovery with it often being extremely challenging and influencing several life domains which take time to recover from. Other mentioned characteristics were that recovery can occur without cure or professional intervention, at times by trial and error and often facilitated by supportive environments. These have important implications as it suggests that one can live a personally meaningful life even if still experiencing ongoing symptoms and that this process can be facilitated by supportive environments and various personal efforts and not necessarily as a result of services alone or at all. This calls for the need to broaden care systems and focus more on modifying environments and providing support for goal-setting and attainment that is not contingent on symptom remission.

Finally, the systematic review revealed five categories of *recovery processes* which were frequently mentioned: *c*onnectedness, *h*ope and optimism about the future, *i*dentity, *m*eaning in life, and *e*mpowerment (yielding the acronym CHIME). All of these processes can be viewed as basic human building blocks on which most people construct their lives and which might be particularly crucial at times of despair when coping with psychiatric symptoms. Given what is known about these processes, what implications does this have for the design and delivery of psychiatric care? Translation to practice will, of course, vary depending on personal preferences as well as social, organizational, and political-economic context. But in the following section, we offer representative strategies for professionals who are committed to the principles of recovery-oriented care but uncertain as to what this might look like in routine service settings.

Recovery-Oriented Practice

Whereas "recovery" is what the *individual* does to manage his or her condition and reclaim his or her life from the direct and indirect effects of the illness, r*ecovery-oriented care*, on the other hand, is what *health-care providers* offer in support of the person's own efforts to move forward and pursue a "a meaningful life in the community" [32]. Recovery is not something you can do "to" or "for" someone else. While recovery, much like learning, is the primary task of the individual, there is still much that caring others can do to facilitate this process through the actions of both formal (i.e., health-care providers) and informal (e.g., family, friends, employers) supporters. It is within this arena that we see the great potential of the recovery-oriented approach, which has increasingly been recognized as a powerful source of encouragement in recovery among persons living with serious mental illnesses [41].

Consistent with the five CHIME recovery processes identified above, recovery can be promoted at the individual level through the following:

Connectedness

> The biggest thing that is stirring all of this recovery for me is the love that I have in my life today.

Nurturing relationships that afford people a sense of belonging and self-worth is central in recovery. Connectedness is crucial yet not always easy to form due to illness-related factors such as impaired social cognition, environmental factors such as public stigma and lack of opportunities, as well as consequent personal ones such as loss of confidence and self-esteem. Nurturing connection can, and should, involve relationships both within and beyond the formal treatment system, that is, with both professionals and natural supporters. This is consistent with the view that recovery is not seen as a solitary process but rather as a journey toward interdependence with one's community of choice.

What representative strategies might this entail? In the context of inpatient care settings, this may begin by reflecting on the flow of the person through services and even on the environmental space occupied by carers and service users and the extent to which it enhances, versus hinders, opportunities for connection and authentic interactions. How are people greeted upon transfer to a psychiatric inpatient unit? Is someone available to give them a tour and orient them to the program, perhaps a peer specialist? Are they offered personal introductions to those with whom they will be expected to share their story and to whom they will be expected to entrust their care? Are there user-friendly orientation materials or postings that make clear each person's role, perhaps even including a picture of various staff and their roles or "go-to" areas of responsibility. Even the structural layout of the inpatient milieu can have a marked impact on the nature of connectedness in psychiatric care. Are there opportunities for fluid interactions throughout the day in an open setting, or do staff spend the vast majority of their time behind closed doors in off-unit offices or behind the plexiglass border of a centralized nursing station? These spatial layouts can be powerful reminders—both literally and figuratively—of the "us–them" divide that perpetuates distance, rather than promotes connection, between professionals and persons in recovery.

In the context of assessment and planning procedures, connection is also supported through thoughtful consideration of the strengths and resources beyond the formal treatment system, that is, within the individual's family, natural support network, and community at large. For example, at the person's discretion, he or she might extend an invitation to a natural supporter to participate directly in his or her person-centered care planning (PCCP) process [42]. As with any participant in person-centered planning, it is important for family members and other invitees to be oriented to the process so they can be effective members of the team and learn what might be helpful, versus not-so-helpful, ways of contributing.

For example, while a family member should be encouraged to share his or her concerns so that the team can collectively brainstorm strategies and solutions, family members may also need to be redirected if they approach the meeting as an opportunity to align with professionals and to apply undue pressure on the person in recovery around key treatment and life decisions. When the care planning process has uncovered key connections in the person's life and those individuals are willing and able to lend their time, energy, and enthusiasm to the person's recovery vision, then these contributions should be documented as action steps in the recovery plan alongside those services offered by professional providers. Doing so represents an important opportunity to help the person build or expand upon the natural network that can help sustain their recovery over time.

Hope

> Hope just started to flow all over me. I could just all of a sudden feel brand new. The recovery model helped me feel brand new again.

Second is the capacity of professionals to instill hope and optimism for the future. This includes such things as believing in the possibility of recovery, inspiring motivation to change, helping the person to reconnect with their dreams and

aspirations, and offering exposure to peer supporters as a living embodiment of hope in recovery. Such exposure is critical in instilling hope not only among persons with mental illnesses but also in the professionals who serve them.

Take, for example, the often-encountered debate that arises in the process of setting goals and envisioning a more hopeful future in recovery within the context of person-centered care planning. Professionals may be hesitant to support an individual's expressed goal out of concern that it is somehow "unrealistic" and that offering such support might set someone up for failure and disappointment. Practitioners cannot predict the future and should not presume to do so. In fact, many people who currently work as peer staff within the mental health system report being told by practitioners early on in their recovery that they would never be able to return to work due to the severity of their illness. Such pronouncements are not only demoralizing but convey a sense of certainty that is simply not warranted by the available data.

When collaborating with service users to explore recovery goals, it is far more helpful for the practitioner to help the person in recovery to "think big" as this presents an opportunity to demonstrate faith and hope in their recovery process and to help them live beyond the legacy of low expectations that has, for too long, pervaded mental health systems. Outcomes for people with mental illnesses need to include the expectations and aspirations shared by all humans (e.g., living, working, learning, playing, and loving in one's chosen community), not just lower-order thresholds or standards commonly valued in the human service system (e.g., stability, adherence, satisfaction with services). High expectations should be the norm for all people and not reserved only for those who are judged by practitioners to have reached a certain stage of recovery.

Identity

> I can look the world in the eye today and I respect myself a lot more. I'm more daring to try new things and some of the things I've discovered are things I really like.

Closely linked to this is the third category of identity, which involves using a strengths-based approach to help the person overcome stigma and to develop and maintain a positive sense of identity apart from the illness or disability [1]. This can be particularly challenging when people are constantly confronted with persistent distressing symptoms as well as explicit and implicit stigmatizing messages and attitudes that are encountered both within, and beyond, the mental health system. When facing such circumstances, practitioners need to conceptualize one of their first steps as assisting the person to get back in touch with his or her previous interests, talents, and gifts, using a range of strategies to help the individual to discover him- or herself as a healthy person with a history, with a future, and with strengths and interests beyond their deficits or functional impairments.

This may start with the consistent use of respectful, non-stigmatizing language. At all times, *person-first* language should be used to acknowledge that the disability is not as important as the person's individuality and humanity, for example, "a person with schizophrenia" versus "a schizophrenic." Employing person-first language does not mean that a person's disability is hidden or seen as irrelevant; however, it also is not to be the sole focus of any description about that person and his or her care. To make it the sole focus is depersonalizing and derogatory. While strengths-based, person-first language has long been recognized as an expected standard in mental health service delivery, the translation of this standard to consistent use in day-to-day practice has proven a far more elusive goal.

Formal strengths-based assessment procedures may also be employed to help people reclaim their personhood in the face of ongoing difficulties associated with the experience of mental illness. In some cases, however, simply inquiring about strengths may not be enough to elicit information regarding resources and capabilities that can be built upon in the recovery planning process. Creativity in the dialogue and in how one frames questions may be needed to unlock buried sparks of interest. For example, you can express genuine curiosity by exploring the following types of questions. *If you could design the "perfect day," what would it look like? What was the best compliment you ever received?*

When you were younger, what did you dream of doing when you grew up and why? What are you most proud of in your life? What is the one thing you would not change about yourself?

Strengths uncovered in this assessment process should then be actively used in the cocreation of the individual's recovery plan. Focusing on strengths is a powerful engagement strategy that can help people to develop hope for the future and establish motivating recovery goals. For example, a woman with a love of animals who is struggling with social isolation might be motivated by regular walks to the dog park. A person with a love of books might be engaged by being asked to help organize materials in the agency library or consumer resource center. Or a patient about to transition to the community from an inpatient program may have as a part of his discharge plan not simply a prescription for meds and an appointment for follow-up at the local community mental health center but also a prearranged ride to Sunday services at his local house of worship if faith-based coping is a central part of his recovery. The essential point is that uncovering strengths is not sufficient in and of itself to generate a strengths-based, recovery-focused care plan. Rather, practitioners must think creatively about how best to actively use the individual's strengths and interests as a way to help her or him reclaim a positive sense of identity beyond the experience of illness.

While the adoption of a strengths-based approach is often thought of at the microlevel and how it plays out in a 1:1 treatment relationship, it has similarly cogent implications for changes in the structure and design of services across a range of psychiatric care settings. For example, there have been attempts to organize mental health services according to participants' primary psychiatric diagnoses or even based on their assessed level of functioning or degree of cognitive impairment. The rationale for such "tracks" in programming includes the ability to group participants according to level of need and to assign staff with specialized clinical and rehabilitative expertise. While there may be value to the person in recovery to interact with others with shared lived experiences and to receive more targeted programming and intervention, such structures should be pursued with certain cautions in mind as they can be used as a means of rigidly tracking people into one predetermined set of treatments and rigidly excluding them from others. Specialty tracks can easily take on a demoralizing tone (e.g., the specialty track for "low-functioning psychosis" is quickly recognized by both staff and patients alike), and they may leave little room for exposure to a wide range of recovery-based interventions while reinforcing the internalization of illness as one's primary identity.

Meaning

> It's an awakening to all that you could be doing, and in my case, the fact that life was worth living.

The fourth category is meaning in life, which includes finding meaning in illness experiences that would require valuing lived experience and encouraging curiosity- and meaning-making processes rather than simply accepting others' explanations for one's own difficulties. Consistent with Nietzsche's famous adage that "He who has a why to live for can bear almost any how," this calls attention to the opportunities and supports people need in order to create meaning in their lives. Traditional models of care do not necessarily view meaning as an important or valued goal and are not always designed to encourage or support such efforts. In contrast, a recovery-oriented system makes space for each person's own unique understanding of what has happened to him or her and how she or he make sense of these experiences, even when such conceptualization may challenge traditional notions of psychiatric illness.

For example, the Hearing Voices Network (HVN) [43], a peer-focused international community of persons with the lived experience of voice-hearing, has emerged as a platform to question how mental health treatment currently understands, categorizes, and responds to mental distress. Rather than seeing voices, visions, and extreme states as symptoms of an underlying illness, HVN members believe it is helpful to view them as meaningful experiences—even if we don't always yet know what that meaning is. This position has an important role to play in a recovery-oriented system of care as it aims to keep the service user in the driver's seat and

encourages him or her to define his or her own experiences and how they should be managed.

For some individuals, this may translate into a process of shared decision-making in which a practitioner is open to alternative approaches beyond antipsychotic medication to help manage an individual's distress. In other cases, it may mean honoring that the person may not perceive the experience as a manifestation of psychiatric illness to begin with, may not find it to be that distressing, and may not choose to "manage" it at all as it may hold important meaning for them in their lives and their identities. In this sense, it respects that fact that people who have lived with what we refer to as "mental illness" have learned much in this process and are the foremost experts on their own lives and recovery. As such, they are in the best position to speak to the strengths and limitations of current treatment systems, and they should be actively involved in recovery transformation efforts at all levels [44].

Empowerment

> It used to be me coming to the mental health center expecting them to fix me. Now I can better manage my own care. I'm able to set goals for myself and go to new heights.

Finally, the last recovery dimension focuses on empowering people in recovery to exercise enhanced self-care and a range of fundamental rights including the rights to citizenship, social inclusion, and active participation in care planning. Similar to other categories, there is a great need to change what we have traditionally focused on to assure people have the chance to engage in these kinds of recovery processes.

Recovery-oriented care is based on the premise that mental illnesses can be managed through the concerted efforts of the person, his or her most significant supporters, and skilled and knowledgeable practitioners. This remains true even in the lives of those people who have been demoralized by a mental illness and the discrimination associated with these conditions. For such individuals, an early step in recovery-oriented care may then be to help the person and his or her loved ones to view the person as a capable agent in his or her own life who can learn how to exercise some degree of self-care. Doing so does not minimize the role that family and professionals can play but encourages the person to occupy a valuable, central role in his or her own life. Taken together, the focus in recovery-oriented care shifts from what the practitioner needs to do to treat the illness to what the person and his or her loved ones need to know how to do in order to exercise good management of the illness on an everyday basis.

Examples of specific strategies may include encouraging (but not mandating) the creation of a Wellness Recovery Action Plan (WRAP) which is a personalized recovery system born out of, and rooted in, the principle of self-determination [45]. WRAP helps people to utilize simple, safe, and effective strategies to more effectively respond to distressing symptoms and maintain their wellness on a day-to-day basis. Similarly, practitioners can promote empowerment by ensuring people have opportunities to write their own crisis and contingency plans. Often referred to as "psychiatric advanced directives," these plans provide detailed instructions regarding an individual's preferred interventions and responses in the event of a psychiatric crisis in which a person may be temporarily unable to speak for him- or herself. As such, they represent a promising tool to help a person maintain as much dignity and autonomy as possible at a time where practitioners may need to exert greater influence over treatment decisions.

Recovery-oriented self-management tools such as WRAP and psychiatric advance directives should actively inform a formal person-centered care plan (PCCP) within the person's individual medical record. As mentioned above, PCCP is a collaborative process in which service providers and people in recovery work together (sometimes 1:1 or sometimes in a team) to cocreate a plan that helps the individual achieve their most valued life goals [42]. PCCP rests on the premise that people are the experts on their own lives and experiences and, therefore, the professional plan of care should start with, and stay true to, what people have come to learn is helpful (or not) in the management of their own recovery.

If we take for a moment the analogy of recovery being a "journey" and the care plan being the "road map" to the hoped-for destination, then what we are trying to do in person-centered planning is to help the person get into the "driver's seat" of their care as much as possible. The approach of person-centered planning recognizes that the degree of participation and self-direction for each person is going to vary based on a number of factors, including individual and cultural preference, clinical status, communication abilities, confidence level, stage of change, skills and experiences, etc. In addition, the approach does not invalidate the clinical expertise of professional staff. Rather, it is a model based on *partnership* in which there is mutual respect between the person and his or her caregivers. The person seeking care is an autonomous individual who deserves respect, and the ultimate decision-making rests with this autonomous individual. However, the expertise of the practitioner is also recognized, and high regard is given to his or her professional opinion and experience.

This means that as professionals, we need to be willing to shift seats, become a copilot, and share power with the individual throughout the care planning process. Just as this involves a role shift and a competency shift for practitioners, the same may hold true for many persons in recovery who may not yet be comfortable being in the driver's seat. This is especially true when they have become accustomed to being viewed and treated as more of a "passenger" where their typical participation in the care plan may have been limited to the expectation that they sign it. In order to overcome these traditions, it is critical that mental health systems offer advance notice of planning meetings, as well as education in/preparation for PCCP (i.e., "driver's education"), so that people in recovery can gain the confidence and competence to actively partner in the PCCP process.

It is important to note, though, that as the concept of personal recovery has made its way across the globe, this core emphasis on self-determination has come to be called increasingly into question. Even within the US, persons from Hispanic and African American cultures have found such a narrow focus on the person, extracted as it were from out of his or her family and community context, to be culturally ***un***responsive. Similar critiques have been made from the perspective of Chinese culture [46, 47] and, more recently, from Indian culture [48] as well. For individuals who prefer to have others involved in their decision-making, practitioners are to honor these preferences as it would not be very "person-centered" to insist that people make their own decisions when their cultural preference would be to defer to the wisdom of family or elders [49].

As seen with other core recovery processes, what it means to promote empowerment must be considered at both the micro (i.e., individual treatment relationship) and the macro (i.e., organizational context and structures) levels. This requires an honest self-reflection on the range of coercive practices in mental health systems that strip people of their choice and autonomy rather than promoting their personal empowerment. For example, "clinical gatekeeping" (e.g., being denied access to a supported employment program based on a clinician's assessment that an individual is not "work ready," when such assessments have been shown to have limited predictive validity in vocational outcomes) has no place in a recovery-oriented system of care. In contrast, promoting empowerment means honoring a "no wrong door" approach that provides direct access to a diverse array of services to which individuals can self-refer without the need for referral or approval from a primary clinical provider.

Similarly, certain methods of behavioral programming, such as token economies or level systems often seen in inpatient or congregate residential settings, undermine empowerment by substituting an external locus of control for efforts to promote self-management and autonomy. Whether or not these methods effectively prepare someone for discharge and transition to a lower level of care also remains a point of contention in our field. What we do know is that while there is some evidence showing that problematic behaviors can be successfully shaped through the use of token economies in the inpatient or residential contexts, there is no token

economy to follow the person into the community [50]. A person can learn to comply with an externally imposed structure while in the hospital, but in the absence of that structure, we would suggest that what is needed is effective self-management and wellness skills similar to what can be taught in such evidenced-based practices as WRAP or Illness Management and Recovery (IMR). In these models, the person is seen as an active partner in his or her own recovery rather than a passive recipient of care—something that is more consistent with a recovery orientation as well as the type of self-management we have seen for decades in the treatment of chronic medical illnesses such as diabetes. At the same time, systems of care need mechanisms in place to manage acute psychiatric issues that can lead to serious safety issues, as well as disruption of the healing environment for everyone. In this circumstance, a recovery-oriented approach might challenge practitioners to develop personalized safety plans or Positive Behavioral Support Plans to be proactive and responsive in addressing individualized needs rather than defaulting to a more coercive "one size fits all" behavioral program.

Conclusions

The concept of clinical, or full, recovery has been around since the birth of the discipline of psychiatry itself, yet it is questionable the degree to which this concept has informed the routine practice of mental health care in either inpatient or outpatient settings. Most programs, that is, have assumed a long-term or chronic care perspective and have done little to inspire hope for a full recovery, which admittedly may require a longer period of time than most programs allow. Meanwhile, the concept of personal recovery has now been around for roughly 30 years and has stimulated the rapid development and expansion of self-help/mutual support and peer support approaches, both outside and inside of mental health systems. Aside from the impact of these new alternative or complementary supports—and despite the global proliferation of government mandates and policy statements endorsing recovery as an overarching vision for mental health care—a broader and deeper transformation of routine clinical practice remains largely a task for the future.

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8 A Model and Evidence Base for Achieving Complete Recovery in Schizophrenia

Ananda K. Pandurangi

Introduction

Schizophrenia is a persistent major mental illness that has been recognized in its current form for over 120 years. Throughout this period, a characteristic feature of schizophrenia has been a declining course, albeit to variable degrees in different individuals. It is generally agreed that about 65% or more of persons suffering from schizophrenia show a decline in social and occupational function. Despite much progress in pharmacotherapy and psychosocial therapies, the unfortunate fact remains that persons suffering from schizophrenia continue to be disabled [1]. The challenge to professionals, patients, and advocates is not only to research the cause, symptoms, course, and therapeutics of schizophrenia, but more importantly, embrace and develop a comprehensive approach of interventions that recognizes the full extent of the devastation created by schizophrenia. Adding insult to injury, in most societies, mental illnesses are severely stigmatized. Thus, the person suffering from schizophrenia is in triple jeopardy: from the illness, from lack of effective treatments, and from the stigma. The combined losses suffered as a result by the patient, and the range and severity of its full impact, beg a more meaningful and effective approach than is currently the standard.

Two major ingredients of such an approach have been recently labeled as clinical recovery and personal recovery [2]. Especially the recent development of concepts and interventions under the umbrella of personal recovery offer much promise in addressing this challenge. However, even this recognition may not be sufficient in and of itself, and a more comprehensive approach is needed. Such an approach is both desirable and possible. Most importantly, complete recovery may be the right of a person with schizophrenia.

Lost in Schizophrenia

To lay the foundations of an effective approach toward complete recovery first requires a comprehensive understanding of what is lost and is to be recovered. Traditionally, in training and clinical practice, it is recognized that the young person experiencing psychosis suffers losses in at least three domains: increasing loss of contact with the real world or so-called symptoms and behaviors of the illness, alienation from family and friends, and loss of abilities to function in expected role. These may be referred to as clinical losses. Families and professionals are quite aware of these losses. Less recognized in the scientific and professional literature until recently are more vital losses such as sense of purpose,

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direction, and meaning in life and loss of self-esteem. Ultimately and tragically ones' dignity and humanity itself may be lost. These losses have been better recognized in nonfictional and documentary literature [3]. First-person accounts by literate patients vividly capture the blow to one's esteem and dignity that both schizophrenia and society's reaction to it cause them to suffer. The recognition, understanding, and interventions to recover both the clinical and personal losses constitute the complete recovery approach.

We list below the nature and range of these personal losses.

1. *Self-Reflectivity*: While a distinction is made between clinical deficits and personal losses, indeed this is arbitrary and simplistic. For example, metacognitive self-reflectivity is likely impaired in schizophrenia, heavily contributing to misperception and/or misinterpretation and consequently adding to the personal losses in hope and self-esteem [4]. Also see item 6 under Challenges in Implementing a Program for CR for more on this.
2. *Empathic Ability*: The individual's own ability to empathize might get impaired. This is often described by patients as "feel numb" and "feel no emotions." [5, 6] Awareness of this loss is most disturbing to the individual, leading to perpetuation of the "diminished" or "less than others" identity. For more on impaired empathy, see item 5 below and in the section *Approach to Complete Recovery,* item9.
3. *Sense of Control*: Does the person with schizophrenia feel any degree of control over his or her life? Schneiderian First-Rank Symptoms often seen in schizophrenia emphasize loss of ownership of one's thoughts and feelings. Psychological and somatic passivity are part of this experience. Adding to this subjective loss of control are the dry and technical nature of professional assessments, infantilizing responses, and societal fears and harsh regulations (example: persons with schizophrenia are violent and be transported in hand cuffs); all conspire to reduce the individual to a helpless and sick individual, someone with no will and autonomy.
4. *Hope and Faith:* Yet another personal loss in schizophrenia is that of hope and faith. These are the very values that help us survive and drive us to excel. It appears that the combination of losses, both clinical and personal described above, make a severe dent in the ability to feel hope and have faith in oneself, one's family, providers, community, and even a higher spirit [7]. Studies have indicated that persons with schizophrenia often experience a sense of not belonging or alienation and lack of parental or God's love toward them, ultimately leading to loss of faith [8, 9].
5. *Diminished Self:* Persons with schizophrenia often see themselves as "diminished" compared to their own previous self and less than others [10]. Perceived correctly or incorrectly, their ongoing experience validates this and further reinforces them. Even worse, an unfortunate consequence of stigma is that it often gets internalized, resulting in shame making the individual his or her own victim. An additional complication arises when the result of shame is depression [11]. Ultimately, respect as an individual is not experienced, and the person's dignity as a human being and member of society is endangered. Once a unique individual with aspirations and vitality now becomes a shadow of oneself.

In laying a firm foundation to a successful recovery approach, all stakeholders would do well to appreciate the above losses, the complexity and nuances of these losses, and the dynamic interplay between clinical and personal losses.

Clinical Recovery

The targets of clinical recovery pertain to the well-recognized symptoms, behaviors, and deficits of schizophrenia. This is understandable given the very disruptive nature of these symptoms and behaviors, the severely limited resources within the mental health-care delivery systems, and the absence of proven causes and pathology of schizophrenia. Most pharmacotherapies target hallucinations, delusions, and disorganized

behavior, and psychosocial therapies focus on ensuring basic survival supports. Only about 65–70% of patients benefit from current medications in the reduction of positive symptoms. Sustainable outcomes with long-term antipsychotic treatment is not fully established, and substantial questions remain about their role in full recovery [12]. In the last two decades, we have recognized other symptoms and behaviors, such as negative symptoms and cognitive impairments, as relevant targets for therapy, although as of now no effective treatment exists for these domains. Within clinical recovery, the emphasis had been mostly on symptomatic recovery rather than functional recovery, until about early 2000. As cognitive impairments were recognized as barriers to functional recovery, projects such as MATRICS were developed to standardize tests and assessment methods, and better define these deficits, as well as suggest therapeutic targets. Research continues both in pharmacology (to develop newer compounds with newer mechanisms of action such as glutamate modulation) and in psychosocial therapies such as cognitive mediation and cognitive behavior therapy to address these limitations. None of these well-intentioned, well-studied interventions can currently claim to reverse or overcome the core deficits of schizophrenia and the ensuing disabilities. Most importantly, such pharmacological and psychosocial therapies do not adequately address the personal losses described in the earlier section.

Complete Recovery

We describe here the concept of complete recovery (CR) to include clinical, functional, personal and material recovery, with subjective and objective dimensions as applicable, and based on a fundamental principle of acceptance of the person with schizophrenia as a complete individual with dignity and respect.

A major challenge to studying the progress toward CR is that there is significant variation in terms and definitions used to describe outcomes. These terms include symptomatic response, symptom resolution, symptomatic and functional remission, recovery, clinical recovery, personal recovery, etc. The Remission in Schizophrenia Working Group (RSWG) reviewed the literature and published operationalized criteria which are heavily focused on symptomatic remission in 2005 [13]. Even with narrower definitions of remission, rates of clinical recovery/remission vary widely, likely due to varying methods of assessment and patients moving in and out of remission. In one review, the range was as wide as 17–88% [14]. A 2013 meta-analyses of 50 studies indicated the median remission rate to be 13.5% [15]. Thus, it is evident that a substantial number of persons with schizophrenia do not experience full recovery [16]. However, this disappointing statistic should not deter us from building a complete recovery program.

The CR definition proposed here may appear daunting to achieve. Can an individual, after having suffered from schizophrenia and lost not only cognitive and emotional abilities but dignity and respect, hope to attain a state of CR? The recovery movement differentiated clinical recovery, related to the disorder's symptoms and behaviors, from personal recovery, consisting of a state of feeling well, feeling in control, and feeling hopeful. Based more on the latter concept of recovery, a process gathered momentum that has been termed the Recovery Movement. Many concepts best described as positive psychology were incorporated into this. Negative aspects such as hopelessness, lack of joy, and suicidal feelings were put into a wider perspective that included a more positive self-image and self-esteem and sense of control. Resilience emerged as something very possible for the person with schizophrenia, who now was seen as accepting and adapting to the illness and its impact rather than being passive and hopeless. More importantly, this approach created a sense of purpose and direction to work towards. This opens the possibilities of feeling happy, being satisfied, and being a full person. The emphasis shifts from dealing with symptoms and avoiding relapse to managing one's life and setting goals and direction like every other human being [17]. A recent review of empirical evidence about recovery concluded that rather than frame a

person's outcome in terms of symptoms and disability assessed by professionals, it is possible to adopt a positive framework and approach how to *live well* despite mental health problems, to de-emphasize diagnosis as a constant label, and be flexible with regard to treatment, including the fact some people may not need formal medical treatment [18]. An important aspect of the complete recovery state is the ability to experience happiness. There have been suggestions that people with schizophrenia can experience an overall sense of happiness in their lives [19] and happiness can be a goal of therapy. Likewise, subjective well-being is also very possible in persons with schizophrenia [20]. Thus, CR appears to be achievable.

The central core of recovery may be conceived of as a sustained state of mind wherein the person experiences acceptance, dignity, and respect. This aspect of recovery is similar to insight. It is understood that such a state is not absolute and can vary with circumstances, events, and people. However, models and treatment approaches that assess a person as being sick, or judge as being impaired, cannot be part of any recovery model. All therapies aiming at recovery should understand and accept this fundamental principle. Most importantly, such subjective recovery is critical to proceeding toward recovery in the other more objective domains. Another analogy might be that of the victim with trauma, such as sexual trauma or torture. Can such a person ever feel like a complete human being again? In schizophrenia, while the trauma is not a single discrete event, the sheer persistence of the losses and society's reaction constitute severe trauma. True CR under current conditions might not be achievable in most, but we will not know to what extent we can achieve it, unless a CR model is accepted and built, resources are allocated, training is accomplished, and therapies are developed, fine-tuned, and implemented. A note of caution regarding recovery and insight: CR does not require the person to develop complete insight, often considered a positive mental health attribute and a target of therapies. The role of insight in recovery is controversial because of the dynamic interplay between insight and many attributes of recovery. Insight may have undesirable effects on self-esteem and motivation and could hinder recovery [21]. There may be unintended consequence of insight, with a tragic outcome such as suicide [22].

Approach to Complete Recovery

We outline here 10 elements needed for a successful complete recovery approach.

1. *Developing the Model*: An important initial step is the full development of the complete recovery model. Complete recovery has not been the target of any of the current approaches. While secondary and tertiary prevention as traditionally defined in Medicine focus on reducing morbidity through physical, vocational, and social rehabilitation, the recent recovery-based approaches focus on finer psychological aspects such as illness education (psychoeducation), stress management, social skills, and fellowship, as well as encourage providers to be patient-centered and allow/encourage patient autonomy. However, none of the current approaches include acceptance and restoring dignity as the central goals. This is indeed hard to achieve in the current care delivery systems, especially in Western countries. These systems are reimbursement-based, and payers do not ascribe any relative value units (RVU) to helping one feel human. The focus is often on diagnosis and treatments to reduce symptoms and prevent hospitalization. For example, a 30-minute walk in the park between the therapist and the "patient" as between friends is not reimbursable, yet such an activity is crucial to complete recovery. To a limited extent, activity coaches are available and focus on specific daily activity; peer counselors aim to improve illness understanding and acceptance of treatment; therapists strive to enhance stress management and coping, crises management, adaptation to the illness, etc.; and doctors focus on reducing core

symptoms, achieving behavioral stability, and reducing hospitalization. Nowhere do we hear in lectures, classes, treatment algorithms, or outcome measures the words dignity, respect, esteem, and humanity. Only in patient satisfaction reviews and first-person accounts do we see these phrases: "I did not feel respected." "I was judged." "The police treated me like an animal." "I was lost, who am I?" "I am a shadow, not a real person." "Everyone was looking at me like I was an alien," etc. Therefore, the complete recovery model needs to be embraced by the profession, researched, and promoted. Resources and reimbursements will need to be aligned with the model.

2. *Development of Instruments*: This is a key step in implementing the model. There are sufficient scales to assess clinical recovery, but very few for personal recovery. Thirteen instruments that include elements of personal recovery in the context of schizophrenia or schizoaffective disorder were reviewed in a study which concluded that the Recovery Assessment Scale (RAS) was thought to be the best currently available measure of personal recovery [23]. It has 38 items covering personal confidence, hope, goals, mastering illness, being connected, and the sense of belonging [23]. There are also other instruments to assess recovery [24] that especially focus on subjective awareness of symptoms.
3. *Identifying Basic QOL Needs*: While we have focused on the personal losses and clinical losses, not to be forgotten is the material losses. Many persons with schizophrenia just do not have the basic necessities of life, and any attempt at recovery that does not address these basic needs will fail. Numerous studies across the world have documented housing and employment needs of persons with schizophrenia. As many as 75% of such persons go without social supports and/or access to employment. Monetary support, social engagement, and employment are the most important needs for people with psychotic illness, as well as good physical and mental health. These are to be the foundational elements of the CR approach [25–28].
4. *Utilizing Current Knowledge and Evidence-Based Therapies*: There is no inherent conflict with biologically based knowledge of the illness and therapies and the principles of recovery. In fact, they can build on each other. It has been recommended that the latest knowledge of the neuroscience of schizophrenia be utilized in developing a new bio-psycho-socio-behavioral model for treatment [29]. Such a model would recognize the limitations and gaps in current knowledge, for example, a poor understanding of the biology of negative symptoms and lack of treatments for the same [29]. It is beyond the scope of this chapter to list effective biological or psychosocial therapies. Making such therapies accessible and available is also a required part of the CR model. We only mention here that cognitive remediation techniques in particular may help address the metacognitive impairments and allow better participation by the patient in all aspects of his/her care. Other psychosocial therapies currently with adequate evidence base and/or promising include assertive community treatment (ACT), cognitive behavior therapy (CBT), family psychoeducation, social skills training, cognitive adaptive therapy, and social skills training [30, 31].
5. *Use of Patient-Centered Terminology/Language*: Before proceeding too far in developing the recovery approach, it is to be emphasized the art of appropriate communication is critical to this approach. No matter how good the intentions might be, if the person with schizophrenia does not feel invited as a participant through the use of appropriate, sensitive, and respectful language, our attempts are likely to fail. Sometimes, such language has been termed "person-first language" [32].
6. *Recovery Settings*: The recovery approach needs to be practiced in all settings and not just the counselor's office. This is especially important in inpatient settings. While engaging the person when he/she is most unwell

seems challenging, however studies indicate it can be accomplished. The risk of not engaging the person actively in the recovery process during the acute stages of illness is that recovery-oriented dialogues will not have any credibility. Engaging with former inpatients, role-play, mentorship, and learning recovery processes go hand in hand with specific symptomatic treatments [33].

7. *Consumer Perspective and Subjective Assessments*: Assessments, scales, interventions, and outcome measurements need to have a strong consumer perspective. Prior studies indicate consumers are more interested in personal well-being, social inclusiveness, and self-management and less in clinical recovery measures [34, 35]. However, it is likely that there are relations between subjective measures of personal wellness and objective elements relating to observable symptoms [36].
8. *Role of Peers*: While peer counseling has been accepted as a valuable tool in reaching the person with psychosis, it remains severely underutilized for various reasons, most importantly reimbursement. Both direct peer support and peer-led family education as well as peer-operated services should be integral parts of a recovery-based approach [37]. Peers can provide mutual support/self-help and consumer-operated services. Also see item 7 in the section *Implementing a Program for Complete Recovery* for more on peer counseling.
9. *Autonomy and Shared Decision-Making*: Another key element of a successful recovery approach is the practice of shared decision-making (SDM). We have referred to loss of control as a key loss in schizophrenia and its consequences. While many illness/therapy models acknowledge this, care delivery systems have largely ignored the process of SDM. In part, it is due to the nagging concern that a person with schizophrenia is not capable of such decisions. However, such a concern is not empirically validated. Further, interventions exist such as metacognitive training to enable the sufferer to overcome cognitive impairments and actively participate in SDM [38]. In fact, psychosocial programs have been developed with a curriculum to assist the patient with illness management [39]. Also see the section *Implementing a Program for Complete Recovery* for more on illness management.
10. *Recovery as a Right*: Finally, in developing and implementing the complete recovery model, it should be recognized that recovery with all its individual elements is the right of the person with schizophrenia. This includes both recovering the clinical, functional, personal, and material losses.

Challenges to Implementing a Complete Recovery Program

Implementation of the above CR model faces many challenges. These can be systematically overcome by a thoughtful plan with the participation of all the stakeholders. Several challenges have already been alluded to, such as the rigidity of the reimbursement systems and disincentives to personalizing care. Unfortunately, there are more ingrained challenges to overcome. Some are beyond the scope of this chapter, such as the historical roots and misunderstandings of the nature of mental illness. We list below 10 challenges that create barriers to complete recovery. This is a selective list and is not exhaustive.

1. *Lack of Education*: A lack of understanding of the basics of mental illness among health professionals and community stakeholders including leadership, and most importantly the person with schizophrenia, is a critical weakness. Ignorance or outdated knowledge among our own colleagues is painful and embarrassing. In health profession schools, mental illnesses and their treatment are either inadequately taught or stigmatized. Trainees may even be discouraged from choosing careers in the mental health field. A strong reorientation of the educational curriculum, and continuing education of the educators and school leadership, is needed. While

medical and other schools are incorporating human values in the curriculum, we have moved too far in the direction of laboratory and radiological studies, short hospital stays, high throughput, and defensive medical practices to seriously consider giving a central place in our curriculum to human suffering and patient respect. As said above, these are not reimbursable. For this and other reasons, personal losses are mostly ignored in medical school and other education. That chronic illness takes away something more than health and (material) productivity needs to be seriously recognized.

There is also a very significant lack of education within the community, including within the leadership, as to the nature and enormity of mental disorders and their consequences to the individual and the family/community. This knowledge deficit acts as a major barrier in making resources available to improve access, create an appropriate workforce, and provide a continuum of services that address the losses mentioned in the earlier section. Mental health professionals need to join with patients and their families in understanding that schizophrenia is not a malignant disease that inevitably deteriorates over time but rather one from which most people can achieve a substantial degree of recovery [40].

While educating professionals and community is critical, such knowledge will lead to limited results unless the consumer is well informed of the nature of his/her own condition. Most persons with schizophrenia simply experience and suffer while not knowing the basics pertaining to their illness and its impact on their lives [41]. Stigmatizing perceptions may be reduced by receiving information about symptoms, diagnosis, medications, therapies, etc. Therapies like CBT serve both educational and therapeutic purposes [42, 43].

2. *Stigma*: Stigma puts a choke hold on recovery. While stigma is a complex and multilevel challenge, it has a direct negative effect on any attempt to recover the personal losses necessary for complete recovery. As long as society does not fully understand or believe that schizophrenia is a brain disease and no different from any other chronic major medical illness, the challenges to complete recovery will remain. In a study of 16 countries, with regard to stigma concerns with childcare, perceived potential for violence, fears of unpredictable behavior, reservations about marrying into the family, and children's access to education emerged as common concerns resulting from stigma [11]. Stigma discourages from seeking care, impedes access, and enables noncompliance, but most importantly, the false basis of stigma begins to appear real to the afflicted person. This seriously challenges recovery. It is almost impossible to genuinely recover if family, friends, and/or the community at large believe that mental illness is a personal weakness; a made-up, imaginary, or fake condition; an attention-seeking manipulation, etc. Under such beliefs, it is difficult to make a case for empathy or convince that the victim of schizophrenia is deserving of the same respect that all human beings deserve. Also see prior discussion on the toxic role of stigma in the section *Lost in Schizophrenia*, item 5.
3. *Access*: Any progress in understanding the nature of schizophrenia and the losses suffered is negated if there is no access. Less than 50% of persons with a mental disorder seek help, less than 50% of those seeking help have access to such help, and less than 50% of those having access get the full range of services needed. Without a warlike effort to improve access, our hopes for recovery will remain only that. Both stigma and shame hinder access. Shame discourages help seeking and often leads to depression, isolation, and alienation. Guilt forms another dimension of this quadruple challenge. The quad of stigma, shame, guilt, and depression soon lead to loss of hope and further alienation and often end in suicide [44]. Sense of belonging and hope have been identified as vital for recovery [9].

4. *Human Resources*: A very significant challenge with relevance to all other aspects discussed here is the absence of qualified workforce, both medical and nonmedical. For complete recovery to be realistic, access, support, and understanding are needed from providers. The notion that assessment, medication, and supportive therapy complete a quality program is seriously flawed. While these are certainly key ingredients of a quality service, they are but ultimately an inadequate answer to the challenges of schizophrenia. A workforce that is educated and trained in the full spectrum of losses suffered in schizophrenia is needed. Each discipline needs to transform its curriculum to adequately understand the trauma and loss inflicted by this mental illness. To achieve this requires significant resources and possibly a reorientation of our health education priorities and curricula.
5. *Media*: We now live in a very different world than 50 years ago. The mentally ill person no longer lives hidden in a basement. However, the public at large is just as mystified and terrified of schizophrenia as it was then. This is unfortunate, and the blame may be squarely laid at the foot of the various health professions and media for this. Review of media continues to show significant negative, dramatized, and ill-informed coverage. Understandably, this directly impacts on what/how the public, community, and leadership understand mental illness to be. It negates any effort the professions may make in correctly informing the public about serious mental illnesses. There may be light at the end of this tunnel, and there is some indication that media articles now are becoming less stigmatizing [44].

   The personal losses mentioned earlier are by themselves significant challenges and are discussed below. However, in order to restore them, the above listed more tangible challenges need to be addressed first.
6. *Metacognitive Impairments*: We have alluded to impaired metacognition in schizophrenia. Such impairment limits the ability to be self-aware emotionally, cognitively, and socially and thus have a pervasive negative influence on attempts at recovery. Motivation is dulled. It is not uncommon to hear persons with schizophrenia say they do "nothing" with their time. Whether such a mental state itself perpetuates positive symptoms of hallucinations or paranoia, or so-called internal stimuli, is a good question [6, 46, 47]. Also see prior discussion on this topic in the section *Lost in Schizophrenia*, item 1, and in the section *Challenges to Implementing a Complete Recovery Program*, item 7.
7. *Impaired Empathy*: Impairment in the ability to empathize is a significant challenge. Among other things, this ability allows the individual to be connected, to be trusted, and to put in perspective one's suffering with that of others. Studies indicate deficits in empathy for persons with schizophrenia. For example, interpersonal reactivity index may be blunted, albeit less so in females with schizophrenia [5].
8. *Loss of Control*: Earlier, it was indicated that loss of control is one of the unfortunate end products of the consequences of schizophrenia. Loss of volitional control is a central feature of the Jasperian and Schneiderian criteria for the psychotic experiences of schizophrenia. However, over and above these fundamental experiences, lack of understanding of the nature of the disease, misunderstanding its impact, and maladaptation by patient, family, and society all contribute to the creation of loss of control in the individual. Persons with schizophrenia often identify an external locus of control. Both psychotherapeutic and psychosocial recovery approaches are necessary to restore some degree of control within the individual. Adherence/compliance and recovery approaches are likely to fail if this loss is not adequately addressed [7].
9. *Loss of Faith, Religion, and Spirituality*: Yet another critical factors in ensuing progress toward complete recovery are faith, religion,

and spirituality. These provide a foundation for connecting with fellow beings, in having a sense of structure, and in creating a sense of higher purpose. Persons with schizophrenia often lose faith in fellow human beings and in God and may feel working toward a higher purpose in life is beyond them. They may feel cheated of the basic freedoms of life and conclude that their family does not love them, that God does not love them, that they are lesser beings who could not possibly aspire for higher goals in life, etc. Caregiver love, nurturance, and love of God are reported as very important in continuing to live and recover [8, 56].

10. *Maladaptive Coping*: As unfortunate and challenging as the disease might be, it is the inability to cope with the impact of the disease that actually determines the outcome and eventually extent of recovery. Well-intentioned but ineffective coping strategies result in frustration, disappointment, negative emotions, and burnout. Both culture and education and health-care organizations influence how people cope with schizophrenia and other major illnesses. It is likely that the finding from WHO studies that less developed and more rural countries have a better prognosis in schizophrenia may very well be a result of both acceptance and more natural coping styles [48].

Implementing a Program for Complete Recovery

The future for implementing programs to achieve complete recovery is bright. This is despite the challenges and limitations listed above. In part, this optimistic view is made possible by increasing knowledge in psychiatric neuroscience, neuropsychology, and social psychology; by increasing awareness of recovery; and, most importantly, by increasing advocacy. We list below 10 elements of a successful recovery program. This list is selective and not exhaustive or complete.

Utilizing Advances in Neuroscience and Psychosocial Sciences for Education and Treatment Development

Our best opportunities are coming both from neurosciences and psychological sciences such as personal psychology, trauma psychology, etc. The former is shedding light on the pathophysiology of hallucinations and delusions, on the neural basis of the chaos that the person with schizophrenia has to endure and struggle through, and in the development of biological therapies, for example, new glutamatergic agents, theta burst magnetic stimulation, etc. The psychosocial sciences help us understand impairments in working memory, social cognition, metacognition, etc. as well as the personal losses of self-esteem, hope, faith, respect, dignity, etc. that were listed in the earlier sections. These developments will enhance our knowledge of the challenges a person with schizophrenia faces and the treacherous road they are traveling on and offer some solutions. Rather than get lost in a black hole of symptoms and behaviors that appear odd and irrational, providers will be able to appreciate the underlying neurophysiology and psychology of the symptoms and behaviors of psychosis and the personal struggles of the sufferer. Such understanding should serve as the foundation of a complete recovery program.

Other sciences that are contributing to a better understanding of what it takes for a complete recovery include personal psychology, trauma psychology, and human ethics. These are informing us of the uniqueness of each individual, styles of cognition, perception, interaction and behavior, experience, and vulnerabilities of the traumatized individual. Another source of learning will be through recent innovations in psychosocial approaches to serious mental illness including patient autonomy, patient centeredness, first-person language, peer counseling, etc. These are compelling us to think beyond symptoms, diagnosis, and prescription or mere verbal support. (See prior discussion of this topic in the section *Approach to Complete Recovery*, item 4.)

Ethical studies help us understand that every individual has a right to recovery and to be treated with respect and dignity. There will no doubt be a positive fallout on both societal leaders and community stakeholders from such new knowledge. This, it is hoped, will transform their views of mental illness and lead to better resources. More importantly, it is hoped this will change society's reaction to the individual with schizophrenia. Increased awareness and better understanding within all stakeholders could translate into more resources, more research, better treatments, better access, and less stigma, setting the stage for true and full recovery of the individual with schizophrenia.

Creating Therapeutic Alliance

Another fundamental characteristic of a strong recovery program is the therapeutic alliance. While not a new concept by any means, creating therapeutic alliances, incorporating the approach of patient autonomy and patient centeredness can be challenging to traditional practitioners and systems. However, studies indicate that a greater degree of recovery orientation, reduced stigma, and more awareness of these on the part of the client and therapist help create better therapeutic alliances [49]. Strong therapeutic alliance allows the therapist to substitute his/her ego resources for the impairments of the person with schizophrenia and creates the platform to effectively address the other personal losses.

Treatment Setting

The terms *recovery*, *approaches to recovery*, and *recovery programs* seem to be more associated with outpatient/community care. While clearly the bulk of recovery should happen in such settings, the seeds have to be sown in all settings, and especially in acute and step-down programs, crisis stabilization centers, partial hospitalization, and other day programs. While this appears daunting because of the severity of the condition and perceived lack of readiness for recovery, as well as limitations of short length of stay, multiple studies have demonstrated the feasibility and the value of implementing recovery approaches in such settings. Marked improvements in symptom management, functioning, social connectivity, and self-confidence have been noted [50].

Vocational Rehabilitation, Employment, and Housing

Another critical aspect of a complete recovery program is the attention and emphasis on vocation. The material and psychological impacts of not having a vocation and job contribute heavily to personal loss, especially control and self-esteem. Access to vocations is not simply a matter of providing a referral or performing an intake. Appropriate psychological and hands-on support is needed throughout the vocational process [51]. Clearly, vocational rehabilitation not only provides a job and income but also improves self-care, reduces social isolation, creates a sense of autonomy, and has a cascading positive effect on the ability to overcome other impairments such as in planning and budgeting. Mapping one's time is another critical need for many persons with schizophrenia, and having a vocation is one way of achieving this [4]. There had been significant hindrance to recovery from the practice that one ought to be clinically stable before housing could be obtained/provided for a person with schizophrenia. Housing First initiatives have done away with such mistaken notions and are imperative in a successful CR program. Cross mapping of resources within a catchment area goes a long way in identifying all the available resources, helps decision-making in where to put resources, and avoids duplication.

Technology

A major source of support for recovery is coming from developments in technology. Technological tools help in all aspects of recovery, from access (tele-psychiatry), compliance (smartphone reminders), self-help blogs and online support

groups, easy access to mental health videos and films, etc. Use of technology can be an integral part of illness education and management [52].

Mobile Services

Meeting the patient where he/she is both literally and functionally is a central principle of recovery. From the older concept of house calls to the recent intensive or assertive community treatment methods, mobile services can be helpful in improving access, treatment compliance, transportation challenges, crisis intervention, relapse, and hospitalization prevention as well as address personal losses of isolation/alienation. Clinicians working with mobile services can also help clients manage their own illnesses better and develop healthier lifestyles [53].

Peers

Reference has been made to the emerging role of peers in the recovery process. This appears to benefit both the index patient and the peer counselor. It is now well established that peers add a unique new value toward engagement, adherence, improvement, and recovery of a person with serious mental illness. We have not yet tapped the full potential of this resource. Both paid and volunteer peer services are now becoming available. Several aspects of such services need continued study and refinement, such as confidentiality/privacy, conflicts of interest, individual bias, supervision of the peer counselor, etc. Nevertheless, studies supporting the role and value of peer services are growing and indicate the value and benefits of such services [54]. (Also see prior discussion in the section *Approach to Complete Recovery*, item 8.)

Self-Reflectivity

Impaired metacognition including self-reflectivity poses significant challenge in achieving recovery goals. The ability to learn about oneself including past experiences is a critical element toward complete recovery. Techniques are being developed to improve or overcome this handicap. For example, both cognitive remediation techniques and manualized narrative psychotherapy have been shown to produce specific improvements in persons with schizophrenia. (Also see prior discussion on this topic in the section *Lost in Schizophrenia*, item 1, and *Challenges to Implementing a Complete Recovery Program*, item 6.)

Illness Management

While traditionally clinicians have directed the management of psychiatric illness, it has become more evident that illness management by the patient with schizophrenia is both feasible and highly desirable and contributes significantly to progress toward more complete recovery. Such management is a joint effort between providers and patients. Patients are encouraged to learn to identify symptoms and behaviors, manage them, and learn techniques to cope with triggers, benefits of compliance, relapse prevention, etc. Peer support and counseling are especially important in this regard [55]. (Also see the section *Approach to Complete Recovery*, item 9, for prior discussion of this topic.)

Spirituality

We have earlier described the role of spirituality in the recovery process. There is no single method of incorporating spirituality into a recovery program. Faith- and religion-based services, nondenominational services, yoga, and other meditation practices are all available. The critical element is not any one method but the realization that such practices instill a sense of hope, connectivity, and a higher sense of being—elements that are often severely hurt in schizophrenia. Clients may regard spirituality as a source of giving and receiving love and care, and professionals may regard it as a means of receiving support and managing symptoms [31, 56]. Such differeing

goals may easily be reconciled to optimize the benefits.

In this chapter, we have provided a model for complete recovery and examples of evidence-based methods of implementing such a model. However, it is acknowledged that many more significant topics that impact recovery are not addressed here. These include, but are not limited to, the role of substance use, medical comorbidities, challenges around behaviors of aggression and violence, and self-injurious and suicidal behaviors. Also not addressed in the model building is legislative advocacy. Lastly, we have not included the burden on families and supports needed, which are also part of a total recovery program. A comprehensive model would certainly include these challenges and current recommendations and evidence-based interventions to address them.

Conclusion

Schizophrenia is a devastating chronic disease afflicting at a young age and robbing the person of what every other person takes for granted—a healthy, productive, and satisfying human life. Attempts over the last 100+ years have been to understand the biology and psychopathology of this disease and mitigate its symptoms, reduce hospitalization, and improve function. Largely forgotten in these otherwise worthwhile and appropriate efforts is a range of personal losses suffered by the individual. The disease and society together rob the individual of his/her dignity and humanity. Complete recovery involves the identification, understanding, and recovery of the full range of losses suffered by the person with schizophrenia, especially the personal losses. We have presented the range, scope, and nature of these losses, and challenges and opportunities in creating an approach and a model to recover them, and outlines of a program with the goal of complete recovery. Continued research into the neuroscience of schizophrenia, major changes in our educational curricula and field training, war-like effort against stigma, and a thorough understanding of the personal losses are needed to achieve this goal. All measures and targets of outcome and all approaches to recovery need to continue vigorously, but always with the understanding that it is about our fellow human being, and not just a patient or client. It is just as important to foucs on who and what is recovered as on how much is recovered. Complete recovery is very possible if such transformative changes can be accepted and implemented.

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9 Biological Markers for Outcome and Recovery in Schizophrenia

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Introduction

Diagnosing and monitoring the progress of psychiatric disorders including schizophrenia are primarily based on subjective experiences of the patients. Advancement of the scientific field in schizophrenia needs to rely on objective measures to enhance understanding pathophysiology and invent new therapeutics. Biomarkers are the biological markers which help in diagnosing, prognosticating, and monitoring the therapeutic outcomes. They are defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic process, or pharmacological responses to a therapeutic intervention." [1] Biomarkers denote the presence or the severity of the biological process linked to a particular disorder [2]. Endophenotypes are related concept best considered as the stable trait markers of presumed inherited vulnerability to a disease [2]. Biomarkers can be classified into three types [3]:

1. Screening biomarkers – to identify high-risk states.
2. Diagnostic biomarkers – to verify the presence of a disease.
3. Prognostic biomarkers – helps in predicting course/response/outcome.

Biomarkers can be measured with various techniques from macro level such as brain imaging and electrophysiological techniques (EEG, eye tracking) to micro systems like genomics (DNA), transcriptomics (mRNA), metabolomics (metabolites), and proteomics (proteins) evaluated in different tissues of the body ranging from CSF to blood (serum, plasma, cells) to saliva and urine. Literature is emerging in "theranostics" [4] that uses biomarkers to identify the patient who would benefit from personalized treatment and possibly thereby predict treatment response. They will also help in predicting adverse effects and risks of relapse on a certain treatment. This new conceptualization is specifically aimed at clinical conditions like schizophrenia, which are heterogeneous in presentation, and outcomes with effectiveness of treatments possibly limited to specific stage of disease process [5]. Current evidence in utility of such biomarkers in schizophrenia is preliminary and indicates that we indeed need to go a long way [3].

Characteristics

Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Cognitive Neuroscience Treatment Research to

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Improve Cognition in Schizophrenia (CNTRICS) were initiated to identify the cognitive markers in schizophrenia which brought together a panel of members from various industries and had provided a consensus on desired measurement characteristics for cognitive tests battery. These apply to neurophysiological markers as well and are recommended as follows [1, 6]:

1. High reliability.
2. Usefulness as a repeated measure.
3. Meaningful link to functional outcome.
4. Response to pharmacological agents.
5. Practicability/tolerability.
6. Construct validity.
7. Plausible links to neural circuits/cognitive mechanisms.
8. An available animal model.

Putative Markers

Clinical Markers

Poor premorbid adjustment and severity of symptomatology had been consistently shown to be predictors of unfavorable course and outcome. Other clinical measures like young age at onset, nonadherence to treatment, and comorbid substance use are reported to predict poor response [7, 8].

Neuroimaging Markers

Reduced cortical gray matter volume, enlarged lateral ventricles, reduced hippocampal and parahippocampal volume, dorsolateral prefrontal cortex volume, decreased neuronal and glial density [9, 10], and reduced prefrontal cortex activation during working memory tasks in functional magnetic resonance imaging (fMRI) [11] are some of the noticeable imaging markers in schizophrenia envisaging poor outcome.

Neurodevelopmental Markers

Neuromotor markers (poor coordination/balance, involuntary movements, poor muscle tone) and minor physical anomalies (adherent earlobes, epicanthus, steepled palate, widened toes, etc.) [9] show the presence of stronger impact of the biosocial factors on the developing brain, thereby negatively influencing the course of illness.

Neurocognitive Markers

Working memory, processing speed, attention, verbal and visual learning, reasoning and problem-solving, and social cognition [12] are accessible through neuropsychological tools. Some of these neurocognitive deficits are demonstrated to be the major measures correlating with the functional outcome of an individual [9].

Neurophysiological Markers

Event-related potentials such as P50, N100, mismatch negativity (MMN), P300, and prepulse inhibition (PPI) represent the deficits in the information processing system. Sleep spindles, smooth-pursuit eye movement (SPEM) abnormalities, and anti-saccade have been used as surrogate markers in diagnosing and treating different symptoms of schizophrenia. Cortical plasticity measured by transcranial direct current stimulation (tDCS)/repetitive transcranial magnetic stimulation (rTMS) [13] is emerging as an interventional modality of investigational research.

Neurotrophic Markers

Brain-derived neurotrophic factor (BDNF) regulates the GABAergic signalling in cortex and other areas and had been postulated to play an important role in neuroplasticity. Many studies had shown lowered BDNF level in serum of patients diagnosed with schizophrenia versus healthy controls [14, 15].

Neurotransmitter Markers

Along with dopamine, serotonin (5-HT), acetylcholine (ACh), glutamate, and gamma-aminobutyric acid (GABA), neurotransmitter systems are hypothesized to be involved in the pathogenesis of schizophrenia. Biomarkers have been identified in relation to these neurotransmitters using various techniques. DNA analysis of catechol-*O*-methyltransferase (*COMT*) gene which codes for dopamine-regulating enzyme, serotonin receptor genes

5-*HTR2A* and *5-HTR2C* polymorphisms, and hypermethylation of *HTR1A* gene have shown to determine response to antipsychotics and brain stimulation techniques [5].

Studies using peripheral blood cells like DA uptake by platelets, increased lymphocyte tyrosine hydroxylase, elevated lymphocyte DAT mRNA, and reduced DRD2, *DRD3*, *DRD5, and* α-7 acetylcholine receptor mRNA levels in lymphocytes have been associated with differential outcomes [5]. Altered neurotransmitter metabolite levels in body fluids like plasma/CSF homovanillic acid (a metabolite of dopamine), 5-HT concentrations in plasma and platelets, and 3-methoxy-4-hydroxyphenylglycol (the metabolite of norepinephrine) in plasma were observed in poor responders to antipsychotic drugs [16].

Few of these markers have attempted to predict the effectiveness of specific antipsychotics. Molecules associated with glutamatergic system like plasma D-serine and D−/L-serine ratio are reduced in patients resistant to non-clozapine antipsychotics. It is also shown that clozapine treatment increases glycine and glycine/L-serine ratio [5, 17]. Some markers could suggest differential presentation and improvement in symptom domains of schizophrenia. GABA density of benzodiazepine receptors in platelets predicted aggressive behavior, and D-serine plasma levels predicted improvements in positive [18], but not in cognitive, symptoms.

Inflammatory Markers

Various inflammatory markers had been reported to be elevated in schizophrenia. IL-1β, IL-6, and TGF-β are state-dependent markers, and they decrease after antipsychotic treatment, whereas IL-12, IFN-γ, TNF-α, and sIL-2R are considered as trait markers. Major histocompatibility (MHC) gene with area coding for complement 4 (C4) has been found to be the most prominent among all genetic variations in GWAS in schizophrenia [19]. An initial evidence suggests addition of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin with antipsychotics in treatment-resistant patients with elevated C-reactive proteins would be of therapeutic benefit [5, 20].

Neuroendocrine and Metabolic Markers

Markers for outcome and recovery depend not only on factors involved in pathophysiology/vulnerability but also on factors involved in resilience against stress. Individual HPA axis components like increased cortisol level, dexamethasone suppression test (DST) nonsuppression, altered diurnal cortisol rhythm, and reduced cortisol response to acute physiological stressors are postulated to be the neuroendocrine biomarkers. Corticotrophin-releasing hormone receptor 1 (*CRHR1*) and its binding protein (*CRHBP*) are associated with suicidal behavior in schizophrenia [5].

Metabolic disorders are more prevalent in schizophrenia compared to healthy controls. Elevations of insulin, prolactin, pancreatic polypeptide, progesterone, and low growth hormone are reported in patients with schizophrenia [5]. The chronic elevation of insulin could contribute to neuroinflammation and adversely impact the brain and its function. Reduced thyroxine, triiodothyronine, and thyroid-stimulating hormone are proposed as markers representing oxidative stress [21]. Neurosteroid dehydroepiandrosterone (DHEA) has plausible neuroprotective effects but reportedly is altered in patients with schizophrenia. They have been used as an augmenting agent in small trials with positive effects on somatic and metabolic parameters [5]. Thus these endocrinal/metabolic markers would have a role in personalized medicine.

Among the above-stated putative markers, it is interesting to discuss and review the outcome markers that might shed light on the course, required antipsychotic dosage for treatment response, possibility of side effects, and recovery in a given individual. Though not a single measure might be able to predict a clinically relevant outcome, combining various abovementioned markers might be the promising way ahead [22]. Event-related potential mismatch negativity (MMN) had been shown to be sensitive in predicting response to various pharmacological/non-pharmacological agents and clinical, cognitive, and psychosocial functioning [6]. A recent quantitative review had suggested that out of all

available markers, only a single nucleotide polymorphism in HLA-DQB1 region had a clinically meaningful utility in predicting the risk of serious agranulocytosis with clozapine administration [23]. Given the complexities of schizophrenic psychoses, identification of reliable biomarkers had been elusive. However recent developments in this field might pave the way for more meaningful interpretation of the above-described markers [9].

Limitations

Given the vast research enquiring the biomarkers in schizophrenia, it is disheartening to note the translation to regular clinical practice has not been successful. Major drawbacks withholding the expansion of the field are as follows:

(a) Nosological system is based primarily on symptom clusters and not on biological abnormalities on which biomarkers are to be validated.
(b) The methodological limitations of the existing studies on biological abnormalities restrict generalizations and clinical utility, as well as small sample sizes, low-powered studies, difficulty in replicating findings and selecting single-modality parameter, small effect size, lack of rigorous study designs, and, most importantly, the risk of publication bias.
(c) There is a lack of valid in vitro models due to the difficulty in conceptualizing or developing unique animal models for multidimensional psychopathological nature of schizophrenia which is postulated to have heterogeneous causality.
(d) Conceptualization of pathogenetic paradigms is immature given the multilevel interactions of multiple biological systems. The neurotransmitters and neuroimmune, neuroendocrine/neurotropic, and neuroplasticity systems have complex interaction at distal evolutionary, neurodevelopmental, and pathophysiological phases.

Future Directions

Studies focusing on clinical utility-based markers research, adopting consistent terminologies, registering biomarker trials, and unbiased reporting of the findings are the need of the hour to reduce the uncertainties existing in this field of research. Cost-effectiveness and clinical significance are the parameters to be taken into consideration while designing such studies. Combining multimodal strategies involving multiple study centers appears promising in the way forward toward personalized medicine.

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10 Outcome Measurement in Schizophrenia: Challenges and Barriers

Sandeep Grover and Swapnajeet Sahoo

Introduction

Schizophrenia is a complex neuropsychiatric disorder, which ranks among the top ten chronic disabling disorders worldwide. Initial evaluation of schizophrenia mainly focused on symptom resolution. However, in the present-day scenario, lack of symptoms is not considered to be an effective outcome. Many outcome measures other than the lack of symptoms have been defined. Over the years different domains of life of an individual which can reflect the impact of ongoing interventions among patients with schizophrenia have been evaluated as the outcome measures. However, the basic problem lies on the evaluation of various outcome measures and how these measures have been defined [1].

Outcome is now considered as a construct, which besides symptomatic remission, includes constructs like overall psychosocial functioning, social reintegration, quality of life, satisfaction with treatment, medication adherence, treatment-related side effects, economic outcome, disability, personal recovery, and so on [2]. It has been reported and frequently observed that there exists a discrepancy in outcome measurements when the evaluation is obtained from patients, caregivers, and clinicians. Outcome measures in schizophrenia have different perspectives and vary across the studies. Some of the outcome variables apply to patients, and others are related to the services.

In this chapter, we will be focusing on the different outcome measures being used currently and discuss the various limitations and barriers in their use.

Evolution of the Concept of Outcome Measurement in Schizophrenia and Present Status

The psychiatric nosology began with the Kraepelinian dichotomy. He categorized major mental disorders as "dementia praecox" and "manic-depressive psychosis." Bleuler later named dementia praecox as schizophrenia. Kraepelinian dichotomy was based on the course and outcome of these disorders, and according to Kraepelin, recovery was very rare or impossible in patients with schizophrenia. This has resulted to the persistence of an excessively gloomy estimate of the outcome of schizophrenia in psychiatric textbooks [3].

However, ever since the introduction of antipsychotics, the outcome of schizophrenia and expectation from treatment has changed remarkably. Over the years, the concept of outcome has shifted from the viewpoint of just symptomatic

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control to attainment of clinical remission, recovery, and improvement in functionality.

The current viewpoint of outcome of schizophrenia is not that gloomy, and multiple outcome measures have been included across various studies.

Different Domains of Outcome Measures

As the concept of outcome is too vast to include a single dimension/domain of an affected individual with schizophrenia, researchers have conceptualized outcome as multidimensional concept [4]. Some of the commonly used domains in assessment of outcome measures include:

Symptom Control/Remission First and foremost measure of outcome is symptom control or achievement of remission in an individual with schizophrenia. There is ample evidence to suggest that change in the dimensions of psychopathology influences other broader aspects of outcome [5]. Several structured rating scales have been designed to assess the symptoms of schizophrenia. These have been widely used to assess the influence of various therapeutic interventions. Further, ratings on these scales have also been used to define clinical remission in schizophrenia [6].

Cognitive Functions Although both Kraepelin and Bleuler considered cognitive decline as an inherent feature of schizophrenia, it is only since the last two to three decades that the assessment of cognitive functions had come to the limelight [7]. Neurocognitive and social cognitive deficits have now been identified as main reasons of social and functional impairment in the long run after symptomatic remission. Hence, neurocognition and social cognition have been included as outcome measures in schizophrenia.

Patient-Reported Variables Apart from clinician-reported outcome measures, several patient-reported factors have also been evaluated as outcome measures. Patient-reported outcomes place the patient as a "consumer" of the care provided by the mental health services, and its assessment has a definite role in treatment protocols. Some of these variables include satisfaction with treatment, unmet needs, empowerment, self-esteem, therapeutic relationships, and personal recovery. Several scales have been developed to evaluate these variables [8].

Treatment-Related Variables Despite the benefits of symptom control, it is not unknown that treatment with antipsychotics poses several health hazards like metabolic syndrome, obesity, extrapyramidal side effects, menstrual problems, etc., which cause a significant distress and impair the quality of life of an individual with schizophrenia. These side effects have been associated with poor medication adherence, stigma, and subsequent relapse [9]. Often these treatment-related variables are not given due attention while assessing outcome [4].

Social Functioning Social functioning or social outcome is now regarded as an important outcome variable, and many interventions in the form of vocational rehabilitation have been developed to improve the social functioning of the affected individual after symptomatic remission to reintegrate the patient into the society. The social outcome measures which have been identified include quality of life, social integration, social adaptation, etc. [10].

Societal Outcomes The impact of the illness on other members of society has been understood as societal outcome, and it includes variables like violence, suicide, self-harm, substance abuse, homelessness, unemployment, etc. These variables are thought to be of public concern [11]. These outcomes have led to setting up of various public agenda and have led to the increased attention of various mental health-care reforms. Some of these outcomes like employment and homelessness lie outside the purview of psychiatric services, but these involve governmental policies and hence are regarded as societal outcome measures. Though there are no standardized tools to assess these outcomes, these are of important concerns to service-related outcomes.

Economic Outcomes Due to the chronic nature of schizophrenia, it invites several economic adversities. While the overall care of an individual with schizophrenia is dealt by the government in developed/high-income countries, the same is not true in case of developing countries, and the entire wrath of expenditure is dealt by the caregivers. Economic outcome analyses like cost minimization, cost of illness, and cost-benefit analyses have been used to link costs with outcomes in schizophrenia when any new intervention is planned [12]. Studies on the economic outcomes of schizophrenia are important, as these try to draw the attention of the policymakers toward prioritizing treatment facilities and service improvement [4].

Cultural Factors The course and outcome of schizophrenia in developing countries vary in different dimensions from developed countries, as evident from previous studies in this regard [13]. This suggests that the pattern as well as the outcome is influenced by cultural factors in the two settings. Roles of family, marriage, and society have been found to be significant but are usually overlooked in the West [4].

Classification of Outcome Measures

The main use of outcome measures clinically and in research settings has been to judge the level of improvement in an affected individual with schizophrenia with any specific intervention (pharmacological/non-pharmacological) [4]. Researchers had tried to categorize these outcome measures in several ways. Some authors have also classified outcome measures based on duration of treatment as described in Table 10.1 [14].

However, for better understanding, the outcome measures can be broadly divided into patient-related outcomes, caregiver-related outcomes, and service-related outcomes. Patient-related outcomes include symptom resolution, remission, recovery, quality of life (QOL), disability, socio-occupational functioning, neurocognitive functioning, insight, medication adherence, side effects experienced, satisfaction with treatment, needs, and stigma. Caregiver-related outcomes include burden, QOL, experience of caregiving, stigma, etc. The service-related outcomes include orientation of the services, such as recovery orientation, unmet service needs, etc.

Table 10.1 Types of outcome measures

Type of outcome	Duration of treatment	Outcome measures
Proximal outcomes	6–12 weeks	Symptomatic improvement on rating scales, medication side effects
Intermediate outcomes	3–12 months	Response to drugs – remission, treatment adherence, quality of life, treatment satisfaction, unmet needs, stigma
Distal outcomes	>12 months	Recovery, socio-occupational functioning

In this chapter, we will discuss various assessment instruments used to assess each of these outcome measures and highlight the challenges while using them.

Patient-Related Outcomes

Patient-reported outcomes as defined by the US Food and Drug Administration (USFDA) are "any report coming directly from patients about a health condition and its treatment." It is also defined as "any outcome based on a patient's perception of a disease and its treatments, scored by the patient, without any interpretation by a clinician or researcher" [8]. Usually, such outcome measures are assessed by single item or multi-item measures.

Patient-related outcomes in schizophrenia have been used since the 1970s for evaluation of treatment/interventions. These are supposed to be better means to evaluate outcome measures because of various reasons such as the following: psychiatric symptoms are usually not accompanied by physical observable signs, and these are "felt" by the patients and cannot be measured by

observers/caregivers/professionals; clinical improvement may not always correlate with patient's perspectives of improvement; patient's self-reported/rated scales are presumed to be more reliable due to lack of inter-rater bias; and these outcome measures place the importance of consumer care in the hands of service providers. Overall, patient-related outcome measures have been successful in shifting the focus of treatment from symptomatic management to enhancement of patient's QOL, self-esteem, and recovery. A discussion of some of the patient-related outcomes follows.

Symptom Rating Scale

Symptom rating scales in schizophrenia were the first to be used as outcome measures in various treatment trials. These are structured clinician-rated scales, with rating done by a trained clinician by using an interview and observation of the patient along with information collected from the caregivers. The first instrument used in this regard was the Present State Examination (PSE) [15], but it was soon replaced by more structured rating scale to measure symptoms of schizophrenia and thereby evaluate outcome. The most extensively used structured rating scales in various trials till date are the Scale for Assessment of Positive Symptoms (SAPS) [16], Scale for Assessment of Negative Symptoms (SANS) [16], Positive and Negative Syndrome Scale (PANSS) [17], Brief Psychiatric Rating Scale (BPRS) [18], and Clinical Global Impression (CGI), as described in Table 10.2 [19].

The BPRS and PANSS have been further analyzed to factor structures based on various symptom dimensions of schizophrenia. To assess depression in patients with schizophrenia, a specific scale has been developed named as Calgary Depression Rating Scale for Schizophrenia (CDSS) [20]. CDSS is different and more specific to detect depression from the commonly used scales to assess depression like Hamilton Depression Rating Scale (HDRS) [21], as it has been found that the factor structure of CDSS overlaps less with the positive and negative symptoms of schizophrenia as compared to the factor structure of HDRS [22].

Studies which have evaluated the concordance of these scales suggest that apparently there is no linear relationship between BPRS and CGI, though a roughly logarithmic relationship and rough correlation have been found between these scales [23]. Further, it has been shown that an absolute reduction of the BPRS/PANSS by approximately 10–15 points corresponds to a change of one severity step in the CGI severity score [24]. In terms of relationship of PANSS and BPRS, evidence suggests that the improvement in the PANSS is around 5% lower than BPRS improvement under same treatment protocol probably because of more number of PANSS items [25].

Some of the authors suggest that evaluating outcome of schizophrenia only on the basis of symptom reduction fails to provide a complete assessment of global outcome in schizophrenia [2]. These are helpful to diagnose patients and to assess clinical change over a period of time with any specific interventions. Accordingly researchers recommend development of more well-structured scale evaluating functioning, and patient's perspectives need to be developed for more comprehensive assessment.

Remission

A common approach in studying outcome in schizophrenia has been to measure the resolution of symptoms on structured rating scales. A lasting resolution of symptoms and signs over a particular period of time is called remission. Remission in schizophrenia has been standardized by the Remission in Schizophrenia Working Group (RSWG) led by Andreasen et al. in 2005 [6] based on three best well-established syndromes of schizophrenia (disorganization, reality distortion, and negative symptoms) and the five DSM-IV criteria for schizophrenia (hallucinations, disorganized speech, delusions, negative symptoms, and disorganized or catatonic behavior). These items are measured by eight items on PANSS, and each of these item's score should be

Table 10.2 Structured symptom rating scales used for outcome measurements

Scale	Description	Subscales	Usefulness	Drawbacks
BPRS [18]	16/18-item rating scale Each item rated on 7 points (0–7) Highly sensitive with excellent inter-rater reliability [30] Translated into many languages and have been modified for use in children [31] Expanded version also available with 24 items [32]	5 subscales [33] Affect Positive symptoms Negative symptoms Resistance Activation	Broad coverage of all typical symptoms of schizophrenia: positive, negative, and disorganization Extensively used in clinical drug trials Used in epidemiological studies [34] Can be used easily by nursing staff [35]	Poor coverage of negative symptoms; only 3 negative syndrome items (blunted affect, emotional withdrawal, motor retardation)
SAPS [16]	34-item rating scale to assess only positive symptoms 4 domains, each of which has separate symptoms rated on a 0–5 scale along with global rating of each domain separately	4 domains assessed are hallucinations, bizarre behavior, positive formal thought disorder, and delusions	Assess all types of positive symptoms in a comprehensive manner	Only assess positive symptoms Does not assess other symptoms of psychosis like cognitive, depressive, and somatic symptoms
SANS [16]	25-item rating scale to assess negative symptoms 5 domains, each of which has separate symptoms rated on a 0–5 scale along with global rating of each domain separately	5 domains assessed are affective flattening, attention, alogia, avolition/apathy, and anhedonia/asociality	Assess all types of negative symptoms in a comprehensive manner	Only assess negative symptoms Does not assess other symptoms of psychosis like cognitive, depressive and somatic symptoms
PANSS [17]	Derived from BPRS Has 30 items, 7-point rating scale (1–7) Items grouped under 3 subscales: positive, negative, and general psychopathology subscales All subscale scores are normally distributed and are not dependent on each other Scores have been found to have strong correlations with the effect of chronicity, mood, cognition, and medication side effects [36]	Many studies have evaluated the factor structure of this scale; 5-factor structure model is widely used 5-factor structure [37] includes positive, negative, depression disorganization, and excitement	Sensitivity and specificity well established with pharmacological treatment in both positive and negative symptoms Consistency in scoring patients over illness course and time Has been used to determine remission criteria of schizophrenia [6]	Some ambiguous symptom items like lack of judgment and insight have multiple domains in patients with schizophrenia and cannot be measured accurately by these items Depression subscale (PANSS-D) is not powered enough to distinguish between depression, negative symptoms, and extrapyramidal symptoms [38]

(continued)

Table 10.2 (continued)

Scale	Description	Subscales	Usefulness	Drawbacks
CGI–Scheme [39]	Derived from original version of CGI which was used to rate the overall severity of any mental disorder [19] Rates both severity of illness and global improvement Severity is rated on a scale from 1 (healthy, not ill) to 7 (among the most severely ill) Global improvement rated on another 7-point scale from baseline to the current condition	–	Used in a large number of clinical trials Well-established reliability and validity in the evaluation of severity of all almost all symptoms of schizophrenia Sensitive to change and correlates well with scores of other scales [24, 39] Recommended for use in research as well as for clinical practice	Lacks standard definitions

Table 10.3 Remission criteria as outcome measure [2, 6]

Broad areas of psychopathology	DSM-IV criteria	DSM-5 criteria	ICD-10 criteria	PANSS items and item no. Score ≤3
Reality distortion	Delusions Hallucinations	Same as DSM-IV	Delusions Thought echo, insertion or withdrawal; thought broadcasting Hallucinations	P1 – Delusions G9 – Unusual thought content P3 – Hallucinatory behavior
Disorganization	Disorganized speech/thinking Disorganized behavior/catatonic behavior	Same as DSM-IV	Breaks in train of thoughts; incoherence or irrelevant speech Catatonic behavior	P2 – Conceptual disorganization G5 – Mannerisms/posturing
Negative symptoms	Negative symptoms	Same as DSM-IV	Negative symptoms	N1 – Blunted affect N4 – Passive/apathetic social withdrawal N6 – Lack of spontaneity and flow of conversation

≤3 for a period of 6 months so as to be included under remission (see Table 10.3). The symptom-based criterion can also be assessed using the SANS/SAPS (severity ≤2 points). However, if BPRS (severity ≤3 points) is used to assess for remission, then it needs to be additionally supplemented by either PANSS or SANS as it does not contain adequate representation of negative symptoms (mainly the items "social withdrawal" and "lack of spontaneity"). Hence, the BPRS has a limited use for assessment of remission [26].

The definition of remission has been found to be theoretically feasible, along with easy implementation in scientific trials and clinical practice [3]. This remission criteria has been used across several studies to test efficacy of pharmacological agents [27]. Evidence also supports the use of remission criteria as a meaningful measure of outcome and correlates well with CGI-SCH scores, and better functioning and quality of life [28]. However, there are certain limitations to this widely used remission criteria. It is still not clear whether remission assessment is valuable to patients or not. The service providers are usually unfamiliar with assessment of PANSS remission criteria as a measure of their service effectiveness. Additionally, the remission criteria can only be applied to those who have been previously diagnosed using the defined criteria. Further clinical remission is not equivalent as

personal recovery, which is a long-standing goal [2, 3, 29]. Surprisingly, in contrast to remission, relapse has not yet been operationally defined.

Recovery

In recent times, the patient-led groups have proposed the concept of recovery which takes patient's perspective into account while evaluating the outcome. This is understood as personal or psychological recovery and is conceptually different from clinical recovery. Clinical recovery is understood as "an improvement after an episode of mental illness, including an absence of symptoms and deficits and a return to a premorbid level of functioning" [40]. The concept of personal/psychological recovery does not infer that the suffering has wiped out, all the symptoms have cleared off, and/or the functioning is completely reestablished [41].

Personal/psychological recovery from mental illness is superior to recovery from the illness itself. Individuals with mental illness may have to overcome from the internalized stigma which they have integrated into their very existence, from the iatrogenic effects of management, from lack of recent instances for autonomy, and from being socially backward. Therefore, recovery is often agreed as a multifaceted and laborious process [41]. Accordingly, personal or psychological recovery is understood as an individual striving process [42, 43]. In contrast to the clinical definition, the importance of this definition is not focused upon the resolution of problematic symptoms but on the process of assimilation, whereby persons with schizophrenia develop self-identity to live outside their mental illness [42]. Different dimensions of recovery which have been described include symptom remission, independent living, vocational functioning, and social functioning [44, 45]. The commonly described stages in recovery process include stage of acceptance, development of hope, self-redefinition, development of self-autonomy, overcoming difficulties and stigma, and reconnection with the environment [46].

There are at least 22 instruments to assess personal psychological recovery, and 11 instruments have been designed to assess recovery orientation of the psychiatric services [47]. The most commonly used and psychometrically tested instruments for assessment of personal recovery include Recovery Process Inventory (RPI), Illness Management and Recovery (IMR) scales, Stages of Recovery Instrument (STORI), Recovery Assessment Scale (RAS), and Functional Recovery Scale in Schizophrenia (FROGS), as described in Table 10.4. Studies which have evaluated recovery using these instruments have found that supportive family, meaningful activity, and economic support act as facilitators of recovery, while stigma and life burdens are considered as obstacles for recovery. Further, it has been suggested that less isolation and greater perceived social support can lead to a better sense of personal recovery [48].

Quality of Life (QOL)

Quality of life is defined by the World Health Organization (WHO) as the "Individuals' perceptions of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns" [49]. QOL as an outcome measure has been well established across several studies in schizophrenia. Several instruments have been used to assess QOL in patients with schizophrenia. Some of these are generic instruments and have been validated in patients with schizophrenia. These include the World Health Organization Quality of Life Assessment (WHOQOL), the EuroQoL-5 Dimensions (EQ-5D), and the 36-Item Short-Form Health Survey (SF-36). Some of the instruments have been specifically developed to assess QOL among patients with schizophrenia such as the Quality of Life Interview (QoLI), the Quality of Life Scale (QLS), the Sevilla Quality of Life Questionnaire (SQLQ), and the Quality of Life Questionnaire in Schizophrenia (S-QoL). Table 10.5 highlights some facts about these instruments. However, some limitations should always be kept in mind while using these instruments to

Table 10.4 Commonly used instruments to measure personal recovery from client's perspective

Instrument	Description	Advantages	Limitations
Recovery Assessment Scale (RAS) [65]	Assess various domains of recovery from individual's perspectives with special focus on self-determination and hope 41 items – original scale and shorter version has 24 items; each item rated on a 5-point Likert scale	Has 5 five domains: personal confidence and hope, goal and success orientation, willingness to ask for help, reliance on others, and no domination by symptoms Good internal consistency and reliability Total score correlates positively with QOL and empowerment, negatively with psychiatric symptoms [8]	A lengthy 41-item scale to use and has overlapping items to measure a same item [66] Sensitivity to change has not been tested [67]
Illness Management and Recovery Scale (IMR) [68]	Designed to promote advancement toward personal goals and illness management 2 versions (client version) and clinician version (both having 15 items), each rated on a 5-point Likert scale	Assess a number of aspects of illness management and recovery	Does not purport to measure interrelated domains Sensitivity to change has not been tested [67]
Stages of Recovery Instrument(STORI) [69]	Developed from the findings of the studies related to psychological recovery 50 items, each rated on a 6-point Likert scale based on the 5 stages of recovery, i.e., moratorium, awareness, preparation, rebuilding, and growth	4 components of recovery – finding and maintaining hope, finding meaning in life, re-establishing identity, and taking responsibility for recovery Good internal consistency (0.88–0.94) and moderate to good concurrent validity Self-reported scale Most commonly used and has been translated and validated in Hindi [70], Chinese, Italian, French, Greek, Spanish, and Persian [71]	Reliability of STORI has not been tested adequately Sensitivity to change has not been tested [71]
Recovery Process Inventory (RPI) [72]	Measures the domains of recovery from an individual's perspective, i.e., anguish, connectedness to others, others care/help, confidence/purpose, living situation, and hopeful/cares for self 22 items, each rated on a 5-point Likert scale	Has good internal consistency and concurrent validity Has positive correlation with quality related outcomes and has fair to moderate test-retest reliability [72]	Sensitivity to change of RPI has not been tested [71]
Functional Recovery Scale in schizophrenia (FROGS) [73]	Designed to measure functional remission in schizophrenia 19 items with 5 responses	Assess five domains: daily life, relationships, quality of adaption, activities, health, and treatment Takes into account all functional domains linked with behavioral aspects Does not include any item which reflect clinical symptoms Has been used in clinical outcome studies and patient evaluations	Sensitivity to change, acceptability, predictive validity, and stability of the factor structure of the FROGS have not been studied yet [73]

Table 10.5 Instruments to assess QOL as an outcome measure

Instrument	No of items	Domains assessed	Usefulness	Remarks
Generic				
World Health Organization Quality of Life (WHOQOL) [49]	Original scale: 100 items structured in 24 facets – takes 45 min Shorter version (WHOQOL-BREF) – 26 items and takes 15 mins [49]	6 domains for the 100-item version (physical, independence, psychological, environment, social, and spirituality) along with one overall general quality of life and health scale 5 domains for 26-item version: general, physical, psychological, environmental, and social	Items are formulated in terms of "perceived objective" questions and "self-report subjective" questions Good internal consistency – alpha −0.94 [74] Correlates well with BPRS depression/ anxiety and negative symptoms scale of PANSS	Sensitivity has not been evaluated in large follow-up studies [50] Recently WHOQOL-BREF validated in patients with schizophrenia [75]
SF -36 [76]	36 items grouped into 8 scales and summed up into 2 broader dimensions of physical and mental health Takes 15 min; score range 0–100	8 domains: physical functioning, physical role limitations, general health, bodily pain, vitality, social functioning, mental health, and emotional role limitations	Good reliability with Cronbach's alpha (0.71–0.89) Current mood correlates significantly with QOL [77]	Psychopathology, duration of illness, and demographic variables do not correlate with QOL [77] Limited use
EuroQoL-5 Dimensions (EQ-5D) [78]	3 sections – first section is descriptive system (243 health states) to assess health-related QOL, second section is a visual analogue scale which reflects individual's self-report health on the day of administration, and third section is EQ-index which denotes a series of societal preferential values for the full set of 243 health states with the states of perfect health and death	5 dimensions assessed in first system along with severity of impairment in the domains of mobility, self-care, pain/ discomfort, anxiety/ depression, and usual activities Second and third system are expressed as cardinal numerals on a continuous scale of measurement	Has good construct validity [79] Identifies differences on QOL among patients with schizophrenia with varying degrees of severity	Difficult to execute and takes a long time for assessment
Specific designed QOL scales for schizophrenia				
Quality of Life Scale for Schizophrenia (QLSS) [80]	21 items, semi-structured, clinician-rated interview Takes 45 min	Takes into account four categories: intrapsychic foundations, instrumental role, interpersonal relations, and common objects and activities	Specifically designed to assess deficit syndrome of schizophrenia	Does not incorporate subjective view of patient (clinician rated) Limited use

(continued)

Table 10.5 (continued)

Instrument	No of items	Domains assessed	Usefulness	Remarks
Quality of life Interview (QoLI) [81]	143 items, takes 45 min to complete Based on information on personal characteristics, subjective satisfaction with current predicament and objective life conditions	8 domains (living situation, family relations, daily activities, social relations, job, finances, safety, and health) along with a global measure of life satisfaction	Assess general life satisfaction along with QOL	Limited use
Sevilla Quality of Life Questionnaire (SQLQ) [82]	59 items measuring favorable aspects of life (13 items) and unfavorable aspects of life (46 items); takes 20 min	12 dimensions assessed – 3 in favorable aspects of QOL and 9 in unfavorable aspects of QOL	Developed in Spain Assess patient's own view of their QOL in context of their expectations, cultural surroundings, and personal interests Good psychometric properties [82]	Limited use
Quality of Life Questionnaire in Schizophrenia (S-QoL) [83]	41 items grouped into 8 subscales Based on Calman's approach on cancer patients [84] Takes 15 min, self-reported	8 subscales: psychological well-being, family relationships, self-esteem, resilience, relationship with friends, physical well-being, sentimental life, and autonomy	Provides global QOL index Good psychometric properties [83]	Currently being used in many research studies

assess QOL as an outcome measure. First, there are probable confounding elements between symptoms and functioning with quality of life. Second, some of the authors suggest that there is lack of a theoretical basis to consider QOL as an outcome measure. Third, data on various psychometric properties of such measures as treatment outcome is lacking. Fourth, self-assessment of QOL is criticized, because many researchers are of the opinion that patients with schizophrenia are not very capable of self-assessment of their QOL due to lack of insight and existing cognitive deficits [50].

Disability

According to the International Classification of Impairment, Disability, and Handicap, disability is interference with activities of the whole person in relation to the immediate environment [51]. Disability in schizophrenia affects several domains of the individual's personal (self-care and self-management), social (relationships and interpersonal activities), and occupational/vocational functioning [52]. Disability in schizophrenia has been related to almost all the symptom dimensions of schizophrenia, namely, positive symptoms, cognitive impairment, negative symptoms, and affective symptoms [53]. It has been found across several studies that the negative symptoms strongly correlate with disability in socio-occupational and family function [54, 55]. The most widely used instrument to measure disability is the second version of the World Health Organization Disability Assessment Schedule (WHODAS 2.0) [56].

The WHODAS 2.0 has been based on the theoretical framework of International Classification of Functioning, Disability and Health (ICF) and measures an individual's level of functioning in six domains of life: cognition, mobility, self-care, getting along, life activities, and participation in society. It has 36 items and has been used in various population surveys and for monitoring patient outcomes in clinical trials. It has been validated, modified, and used across different countries for assessing disability in many disorders including schizophrenia [57–60]. However, the limitation of WHODAS 2.0 is that it does not take into account various environmental factors and covers mainly activities and participation domains of the ICF, and it has only been validated for use in adult population [56].

Some of the countries have developed their own disability assessment scales for certification purposes. One such instrument includes Indian Disability Evaluation and Assessment Scale (IDEAS) [61], which has been designed in India. It evaluates disability in four areas (self-care, interpersonal activities, communication and understanding, and work) and has been found to have satisfactory psychometric properties [62–64].

Socio-occupational Functioning

Socio-occupational functioning as assessed by the disability scales has limited application. To overcome this limitation, many other instruments have been designed to assess socio-occupational or social functioning (Table 10.6). Social functioning has been shown to be associated with functional remission and improvement, and this has been shown to be associated with rapid reintegration and resocialization and a better quality of life in patients with schizophrenia [85].

Cognitive Impairment

Neurocognitive deficits are now regarded as core feature of schizophrenia and have been shown to be associated with significant impairment in functional status in patients with schizophrenia across several cross-sectional and longitudinal studies. Based on the consistent findings across the various studies, cognitive impairment was proposed to be included as separate diagnostic criteria in DSM-5. However, it was later dropped, because most cognitive outcome measures have low face validity and it is very difficult to debate that improvements in performance on these batteries would make a difference to the patient's QOL. Still these neurocognitive and social cognitions as outcome measures have changed the traditional view of schizophrenia and are being used for designing more effective interventions. Neurocognitive deficits have been linked with poor professional skills. Recent evidence supports that improvement in the neurocognitive domains leads to improvement in the overall functional status in patients with schizophrenia [93].

Social cognitions are special cognitive abilities, which are regarded as an important mediator between neurocognitions and functional outcome [94]. Poorer social cognition leads to social discomfort on the job, leading to poorer socio-occupational outcomes. Accordingly, both neurocognitions and social cognitions have been considered as outcome measures.

Specific neurocognitive batteries and social cognitions batteries have been developed for assessment of these deficits in patients with schizophrenia. Some of the widely used neurocognitive batteries include MATRICS Consensus Cognitive Battery (MCCB), Schizophrenia Cognition Rating Scale (SCoRS) and Brief Assessment of Cognition in Schizophrenia (BACS) battery.

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Project has developed the MATRICS Consensus Cognitive Battery (MCCB) [95], specially designed to assess the effect of various pharmacological and non-pharmacological interventions on the cognitive functions of patients with schizophrenia. It assesses seven cognitive domains: processing speed, working memory (verbal and nonverbal), verbal and visual learning, attention/vigilance, reasoning, problem-solving, and social

Table 10.6 Instruments to assess socio-occupational functioning as outcome measure

Instrument	Description	Usefulness	Limitations
The Social and Occupational Functioning Assessment Scale (SOFAS) [86]	Derived from Axis–V of DSM Rated from 0 to 100 by clinician on information derived from patient and caregiver	Rates the level of functioning at the time of the evaluation	Has no clear operational instructions to rate severity of disability
Personal and Social Performance scale (PSP) [87]	Developed from SOFAS 100-point single-item rating scale, subdivided into 10 equal intervals Clinician administered	Ratings are based on four main areas: (1) socially useful activities, (2) self-care, (3) personal and social relationships, and (4) disturbing and aggressive behaviors Adequate psychometric properties and face validity [88] Is a quick, valid, and acceptable instrument to measure patients' social and personal functioning Reliability and validity demonstrated in patients with schizophrenia during both acute and stable phases of illness [89, 90]	Does not incorporate psychopathological aspects of illness [87]
Schizophrenia Outcomes Functioning Interview (SOFI) [91]	Measures community functioning related to cognitive impairment and psychopathology Clinician administered	Covers 4 domains – living situation, productive activities, instrumental activities of daily living, and social function Good reliability and construct validity and takes into account the functioning of patients in the real world	Newly developed tool based on small sample size Not yet used in clinical trials
The Social Occupational Functioning Scale (SOFS) [92]	Developed specifically for schizophrenia patients Observer rating scale 14 items scale to be rated from 1 to 5 based on levels of impairment noted/reported	Simple 3-factor structure model – comprising of adaptive living skills, interpersonal skills, and social appropriateness Brief and comprehensive scale and does not require any formal training for administering Has been found to be suitable for use in outpatient, inpatient, and rehabilitation settings Adequate psychometric properties in terms of reliability and validity	Stability of the factor structure not yet replicated on larger samples

cognition. It has been demonstrated to have minimal practice effects, excellent reliability, and significant correlations with measures of functional capacity across several studies. Studies have also found significant association between the scores on the MATRICS cognition battery, negative symptoms, and aspects of functional outcome in stable patients with schizophrenia. Disadvantage of MCCB is that it is very lengthy and many of its domain scores are based on performance on one test [7].

The Brief Assessment of Cognition in Schizophrenia (BACS) [96] is a brief cognitive battery and assesses different the aspects of cognition and requires about 30 min to complete. It has high reliability and is currently being widely used for assessing cognition in clinical trials. Disadvantage of BACS is that it lacks domain-level analysis [7].

The Schizophrenia Cognition Rating Scale (SCoRS) was developed precisely to assess aspects of cognitive functioning found in each of

the seven cognitive domains of the MATRICS battery and has 20 items. It has excellent test-retest reliability and has been found to be strongly associated with cognitive performance as measured by the MCCB with sensitive to treatment. Its limitations include its dependence on informant's reporting, which is not available for some patients and may vary by region [7]. Various region-specific modifications and validations of SCoRS are now available and are being widely used not only for assessment of neurocognition but also for planning cognitive remediation strategies across different phases of illness and treatment settings [97–99].

Social cognition includes a person's perception, causal attribution concerning self and others, and bringing social judgments to decision-making, among other elements [100]. The social cognitive impairment in schizophrenia – which includes substantial and persistent impairments in a range of social cognitive domains, including emotion processing, social perception, attributional bias, and theory of mind (ToM) – has been found to be linked with, but quite distinguishable from, impairments in (nonsocial) neurocognitions such as attention, memory, and problem-solving [101]. In terms of its function, social cognition acts as a mediator between basic nonsocial cognition and social functioning [94], and in this context, schizophrenia has been described as an interpersonal disorder in which problems result from defective constructions of the social environment and one's habitation in that environment [102].

The basic domains of social cognitions include ToM, emotional processing (EP), social perception, and attributional styles. ToM is defined as ability to infer intentions, dispositions, and beliefs of others [103]. It refers to the ability of a person to represent the mental states and/or to make inferences about another's intentions and includes understanding false beliefs, hints, intentions, deception, metaphor, irony, and faux pas [103]. Emotional processing is the ability to perceive emotions expressed by others and includes both facial expression and affective prosody. Emotional processing has been found to have four components: identifying emotions, understanding emotions, facilitating emotions, and managing emotions [104]. Social perception involves the early stages in the processing of information that terminates in the precise analysis of the dispositions and intentions of others [105], and it includes the perception of social cues. It is also conceptualized as a part of larger domain of cognitive skills which includes ToM, emotion recognition, lip reading, understanding body language, and social attention, all of which are related with deriving inference intentions of others [106]. Attributional styles have been defined as "the pervasive tendency to explain the cause of social actions in terms of oneself or others or the context of the event" [104] and include the clarifications people generate regarding the cause of both progressive and undesirable events in their life. Table 10.7 below lists the various instruments/tools used to assess different domains of social cognitions.

Apart from the four major domains of social cognitions, two additional domains are also assessed: social metacognition and social reciprocity [121]. Social metacognition refers to the ability to evaluate thinking, including both one's own thoughts and those of others. This allows for the formation and modification of ideas about oneself in the present and about one's identity and characteristics over time. Social reciprocity is defined as engaging in emotionally and socially appropriate turn-taking interactions with others and requires awareness of the interpersonal cues of others, appropriate responding to those cues, awareness of others' reactions to themselves and their behaviors, and emotional engagement.

Social Cognition Rating Tools in Indian Setting (SOCRATIS) [122] is a battery of tests designed to assess social cognitions in Indian patients. It assesses three social cognition constructs: theory of mind, social perception, and attributional bias. It has been found to have good content validity, good internal consistency, and concurrent validity.

Satisfaction to Treatment

Earlier it was presumed that patients with schizophrenia need not be asked if they are satisfied with their treatment or not. But studies

Table 10.7 Tools to measure the domains of social cognition

Domain of social cognition	What the tasks assess	Name of the tests
Theory of mind (ToM)	The tasks assess false beliefs or deception task; intention-inferencing task; indirect speech such as irony, banter, metaphor, and hint; use of animated geometric shapes; and eye tasks	*First-order ToM* Sally-Anne task [107] Smarties task [108] *Second-order ToM* Ice-cream man task [109] Intention-inferencing task [110] Indirect speech tasks – metaphor-irony stories [111] Faux pas recognition test [112]
Emotion processing	Identification of six basic human emotions: sad, fear, surprise, anger, happiness, and disgust with set of black-and-white photographs of posed emotions restricted in ethnicity and age	FEEL task [113] Facial discrimination task [114] Penn Emotion Recognition Test [115]
Social perception	The tasks assessing social perception involve looking at the interaction patterns of others and making inferences from the same	Social cue recognition test [116] Profile of nonverbal sensitivity [117]
Attributional styles	The explanations people generate regarding cause of positive and negative events in their life are	Internal, Personal, and Situational Attributions Questionnaire [118] Attributional Style Questionnaire [119] Pragmatic Inference Test [120]

have proved that treatment satisfaction in schizophrenia needs to be assessed for better treatment outcome as it is central to treatment adherence [123]. Thus, treatment satisfaction in patients with schizophrenia should not be neglected while assessing outcome, as it can adversely affect other measures like functioning, remission, etc.

Treatment satisfaction is governed by many factors, but most important of all are treatment-related side effects and therapeutic relationship. Few scales have been developed and used in patients with schizophrenia to assess their satisfaction with treatment. These include Verona Service Satisfaction Scale (VSSS) [124], Client Assessment of Treatment [125], and Client Satisfaction Questionnaire (CSQ) [126].

VSSS [124] is an 82-item questionnaire which takes into account seven dimensions: overall satisfaction, professionals' skills and behavior, information provided, access, efficacy, types of intervention, and relative's involvement. Most of the studies have found that the dimension of professional skills and behavior play a significant role in treatment satisfaction and there is very less evidence that treatment satisfaction is influenced by treatment variables [127].

Therapeutic relationship has been regarded as an important aspect of good psychiatric practice. Scales have been developed primarily to assess therapeutic relationship mainly in the context of psychotherapy. However, few scales like the Scale to Assess the Therapeutic Relationship (STAR) [128], the Therapist-Patient Relationship Scale with Schizophrenic Patients [129], and the Helping Alliance Scale (HAS) [125] have been developed and used in patients with psychosis in research setting to evaluate therapeutic relationship.

Health-Care Needs

From the health care, prospective need is considered to be present when the subject's level of functioning falls below, or threatens to fall below, some minimum specified level (i.e., there is distress from symptoms or disablement), and this is due to some potentially remediable or preventable cause [130]. Planning and formulating a structured treatment plan need an

assessment of an individual's needs, as it is fundamental to community care [130]. Studies have differed on the needs of care as reported by patients and mental health professionals [131]. Unmet needs of patients and caregivers have been linked with poorer QOL [132]. Assessment of needs involves collection of information from the patients, carers, and physicians with respect to what can be done to improve the overall outcome of the patients. Needs assessment has been found to be helpful in understanding the mismatch between the demands of patients and their caregivers and the services provided to them [133]. Healthcare needs can be assessed at three levels: (1) the problems experienced by the patients, (2) the interventions required for alleviating or containing the problems, and (3) the services required to provide these interventions.

The assessment of need is multifaceted, and many different instruments have been developed that differ in their content, format, and aims. At the practical level these instruments also differ in the time required to complete them, their user friendliness, and the ease with which the resulting data on "need" can be integrated and analyzed. The instruments which have been designed specifically to assess mental health-care needs are the Avon Mental Health Measure (AMHM) [134], the Cardinal Needs Schedule (CNS), the Camberwell Assessment of Needs (CAN) [135], the Camberwell Assessment of Need Short Appraisal Schedule (CANSAS) [132], and the Camberwell Assessment of Need-Research version (CAN-R).

The AMHM was designed by a multidisciplinary group which also included the service users, for use in clinical practice rather than the research. The aim of the instrument is to empower the users and assist them in identifying and articulating their own needs. However, one of its limitations is that it encourages the users to give "open responses"; hence the data gathered can't be aggregated to a population prospective.

The CNS has a "service-oriented approach" and was specifically designed for use in research settings. It has a comprehensive battery of assessment scales to gather information from users, professionals, and lay carers and measures the extent to which mental health services are failing to provide suitable care. However, the assessment process requires a lot of involvement, and hence it has not been used quite frequently in research settings.

The CAN was designed to be used in both clinical and research settings. It recognizes the subjective nature of "need" and emphasizes the importance of gathering information from both service users and staff carers. It is brief and simple to use and can be completed by a member of staff without training. It is one of the commonest scales used to assess the needs of the patients with schizophrenia.

The CAN-R assesses perceived needs in 22 different areas of life (e.g., accommodation, self-care, daytime activities, and intimate relationships) and whether patients are currently receiving any effective help with these difficulties. It has been used for assessing the perceptions of the patient, their caregivers, and a member of staff working with them. The CANSAS is a shortened version of the CAN covering the same areas. Researchers have reported that people with schizophrenia can estimate their needs, and better executive functioning may be associated with the ability to get one's needs met, increased awareness of needs, better ability to communicate needs, or more needs in certain areas [136]. Studies which have compared unmet needs of patients with schizophrenia with other severe mental illnesses like bipolar disorder and obsessive compulsive disorder have found no significant difference between the groups but have revealed that welfare benefits, psychological distress, information about the condition, money, and company to be the top needs identified by all groups of patients [133, 137, 138]. Additionally, a high level of correlation has been found between the needs as reported by the patients, caregivers, and the mental health professionals [132, 133]. All these studies put forward the importance of assessment of needs in patients with schizophrenia, and hence needs assessment should be considered as a valid outcome measure.

Insight

Simply speaking, understanding about one's illness has been regarded as insight. As per David [139], insight has three dimensions: awareness of illness, the capacity to relabel psychotic experiences as abnormal, and treatment compliance. Insight is mostly rated with insight scales which are usually clinician rated (Table 10.8). However, a few self-rated insight instruments are also available, as shown in Table 10.8 The self-rated insight scales have broadened the concept of insight as they not only measure the person's knowledge about how the disorder affects them but also how it affects their interaction with the world [140]. It has been found that patients with greater insight have more positive attitudes toward their treatment [141] but at the same time have greater risk of developing depression and poorer subjective quality of life [142].

Medication Adverse Effects

Treatment with antipsychotics has been associated with a number of side effects, and the measure of these adverse side effects has been regarded as outcome measures in many studies. Existing literature on adverse side effects of antipsychotics are available from randomized controlled trials, post-marketing surveillance, and naturalistic studies [9]. Several scales have been developed to assess these side effects and have been used in clinical trials so as to evaluate adverse side effect as an outcome measure. Some adverse side effects like metabolic syndrome are assessed using definite criteria rather than on scales. Some of the commonly used scales to assess side effects associated with use of psychotropic medications are listed in Table 10.9.

Stigma

Stigma has been defined historically as a deeply discrediting attribute which reduces the bearer/sufferer from a whole and usual person to a tainted discounted one [172]. The stigma experienced by patients with mental illnesses has been classified into public stigma and personal stigma. The personal stigma consists of perceived stigma, experienced stigma, and self-stigma. Stigma in patients with schizophrenia has been associated with several negative consequences including social exclusion, unsatisfactory housing, restricted opportunities for employment and education, and a poorer quality of life [173]. Studies have found strong association between perceived/experienced stigma and depression, social anxiety, low QOL, poor self-esteem, and poor social functioning [174]. Various scales (as mentioned in Table 10.10) have been developed to measure various types of stigma among patients with mental disorders.

Caregivers' Related Outcome Measures

The role of caregivers in overall management of an individual with any mental disorder is very important as they become partners in care and decision-making. Mental health professionals have to pay more attention to the expectations and needs of the caregivers for a better outcome. The same holds true for schizophrenia, too. Schizophrenia has been shown to have significant negative impact on the caregivers. It has been found that there occurs a significant change in the QOL and restriction in roles and activities of family caregivers. The caregivers also experience significant psychological morbidity in the form of psychosomatic, anxious, or depressive symptoms [194–196]. Further, their negative experiences can affect their ability to care for the patients [197]. Hence, it is essential to estimate outcome of schizophrenia by taking into account various caregivers' variables. In this regard, a number of outcome measures for caregivers have been developed and have been evaluated in research settings. The measures commonly evaluated among the caregivers include caregiver burden, caregiving experience, coping, distress, quality of life, and stigma.

Table 10.8 Scales to assess insight in schizophrenia

Instrument	Rated by	Number of items	Psychometric properties	Description
Insight and Treatment Attitudes Questionnaire (ITAQ) [143]	Clinician rated in an open-ended interview	11 items	Good inter-rater reliability of 0.82	Scored from 0 to 2 (0 = no insight, 1 = partial insight, or 2 = good insight) on the basis of interview
Insight Scale [140]	Self-rated	32 items	Re-standardization has been done, and the new scale has good reliability, internal consistency, and concurrent validity [144]	The scale includes patients' perception of changes within themselves and within their environment, their recognition of being ill, and their acknowledgment of needing help Requires a semi-structured interview for qualitative assessment of insight without numerical rating
Scale to Assess Unawareness of Mental Disorder (SUMD) [145]	Clinician rated	74 items	Good reliability and validity, has been validated and translated and adapted in different languages [146, 147], and shorter version (9 items) also available	Comprehensive instrument that has 6 general items and 4 subscales with 17 items each
Insight Scale (IS) [148]	Self-rated	8 items	Adequate internal consistency (Cronbach's alpha 0.75)	3 subscales which assess awareness, relabel, and need for treatment
Lack of Insight Index (LII) [149]	Clinician rated	3 items	Inter-rater reliability has not been evaluated and validity not well established	Each item is rated on 4-point scale then summed to give a global index
The Schedule for Assessment of Insight-Expanded (SAI-E) [150]	Clinician rated	4 items	Reliability and validity well established across several studies	Comprises of questions to assess three dimensions of insight (awareness, relabeling of symptoms. and adherence), plus a "hypothetical contradiction" item added to evaluate the person's capacity to consider another's perspective [151] Each dimension comprises two or three questions which are scored on a 3-point scale from 0 (no insight) to 2 (good insight), with a maximum total score of 24
The Beck Cognitive Insight Scale (BCIS) [152]	Self-rated	15 items	Adequate reliability and validity well established, translated, and adapted in many languages across the world	2 subscales – self- reflective and self-certainty Assess how individuals evaluate their own judgment
The Knowledge About Schizophrenia Questionnaire (KASQ) [153]	Self-administered	25 items	KASQ has sound psychometric properties (reliability and validity) and support its use as an outcome measure	Multiple choice questionnaire; assesses patient's knowledge about illness and its management Used in assessing outcome of psychoeducation in schizophrenia

Caregiver Burden and Caregiving Experience

The caregiver of an individual with schizophrenia often assumes an unpaid and unanticipated responsibility for his/her patient. This caregiving experience of handling day-to-day problems of the patient requires a substantial amount of patience and care. Authors have referred this concept of caregiving to be a burden and have tried to assess the same through validated scales and interviews. Family burden or caregiver burden has recently evolved as an important health-related outcome measure in schizophrenia. These scales take into account the various effects of the patient's illness on family interaction, family routine, leisure, work, social life, finance, time spent in caregiving/supervising/encouraging patient, distress due to problematic behaviors of the patient, and perceived stigma/shame/guilt due to schizophrenia [198]. Some of the commonly used instruments to assess caregiver burden are shown in Table 10.11.

The concept of burden is limited by the fact that it attributes all the negative consequences in the caregiver's life to patient's illness without taking into consideration factors like normal life changes, the personality of the caregiver, and his/her social life. Some studies have shown that caring for their relative with mental illness can be a source of positive transformation in a person's life and can provide caregivers with a sense of inner strength and satisfaction [199, 200]. This has been regarded as experience of caregiving. The existing literature on experience of caregiving suggests that the caregiving experience, as

Table 10.9 Scales to assess adverse side effects associated with psychotropic medications

Adverse side effect	Instrument	Rated by	Number of items	Psychometric properties
Tardive dyskinesia	Abnormal Involuntary Movements Scale (AIMS) [19]	Clinician	12 items (10 items rated on 5-point anchored scale and 2 items on yes/no responses)	Some items (2 and 4) have good inter-rater reliability, but some items (1, 6 and 7) show high variability [154] Rating is influenced by the experience of raters in using this scale [155]
	The Abbreviated Dyskinesia Scale (ADS) [156]	Clinician	13 items; derived from Simpson Tardive Dyskinesia Rating Scale	Has been used in clinical trials and shown good reliability and validity Less detailed and complicated than other scales More suited for screening procedures and individual patient ratings in clinical practice
Akathisia	Barnes Akathisia Scale [157]	Clinician	4 items (assess objective akathisia, subjective awareness of restlessness, and subjective distress related to restlessness along with global clinical assessment of akathisia)	Validity and reliability has been established, and it has been used extensively in clinical studies worldwide [158]
Parkinsonism symptoms	Simpson-Angus Scale (SAS) [159]	Clinician	10 items (assess pseudo-parkinsonism; grade of severity of each item is rated using a 5-point scale)	In clinical trials, treatment-emergent parkinsonism has been defined as a SAS score≥3 Reliability and validity well established [160]

Table 10.9 (continued)

Adverse side effect	Instrument	Rated by	Number of items	Psychometric properties
Sexual dysfunction	Arizona Sexual Experiences scale (ASEX) [161]	Clinician and patient	5 items	Internal consistency is very good (0.90) Test-retest reliability not yet studied [162] Sensitivity, specificity, and positive and negative predictive values have been described Does not cover all stages of sexual cycle and may also lead to increased concerns in patients who are experiencing a decreased or absent ejaculatory volume, lubrication problems, or orgasm problems [162]
	Changes in Sexual Function Questionnaire-14 (CSFQ-14) [163]	Self-rated/ reported	14 items	Useful when self-report is desired but contains more items Cover all stages of sexual functioning Sensitivity, 93%; specificity, 63%; positive predictive value, 74%; and negative predictive value, 87%
	Antipsychotics and Sexual Functioning Questionnaire (ASFQ) [164]	Clinician	7 items for males and 9 items for females	Assesses improvement as well as deterioration of sexual functioning and includes items about hyperprolactinemia; more appropriate for use in research and intervention studies Cover all stages of sexual functioning All aspects of reliability have been described only for ASFQ [162]
	Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) [165]	Clinician	7 items	Helps in measuring change and sexual functioning related to medications; more appropriate for use in intervention studies [162] Internal consistency, 0,68 Cover all stages of sexual functioning Convergent validity is good and internal reliability satisfactory [162]
Extrapyramidal symptoms – drug-induced movement disorders	The Extrapyramidal Symptom Rating Scale (ESRS) [166]	Clinician	12 items; involves physical exam and 12 questionnaire items that assess abnormalities both subjectively and objectively	Its sensitivity and validity had been established through clinical trials with oral antipsychotics, depot antipsychotics, various antiparkinsonian drugs, antimanics, various CNS drugs, and placebo [167]

(continued)

Table 10.9 (continued)

Adverse side effect	Instrument	Rated by	Number of items	Psychometric properties
Global side effects	UKU Side Effect Rating Scale [168]	Clinician rated and self-rated version available [169]	48 items; the time needed for conducting the interview varies from 10 to 30 min depending on the number of symptoms reported, their complexity, and the patient's ability to provide good report	Available in most major languages in the world and all Nordic languages The potential psychometric reliability of the scale has been found to be acceptable to good Reliable and valid use of the scale requires trained mental health professionals
	Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS) [170]	Self -rated	51 items; total score may vary from 0 to 204 for females and 0 to 196 for males	Enables case managers to establish baseline measures for individual clients and evaluate changes in medication and other nonmedical strategies for reducing unwanted side effects [171] Less frequently used

Table 10.10 Scales used to measure stigma in patients

Scale/instrument	Rated by	Number of items	Number of domains	Psychometric properties	Translations/ adaptations available
Internalized Stigma of Mental Illness Scale [175]	Self-rated	29 items answered with 4 answering options (1–4)	5 domains: Alienation, stereotype endorsement, perceived discrimination, social withdrawal, and stigma resistance	Internal consistency coefficients range from alphas 0.84 to 0.96, and test-retest reliability coefficients range from 0.61 to 0.9	Has generic application and can be used in different health conditions like leprosy Has been used in Indian population Hindi [176], Tamil, and Bengali language adapted versions available [177]
Explanatory Model Interview Catalogue Stigma Scale [178]	Self-rated	15 items with 4 answering options (0–3)	Patterns of distress, perceived causes, preferences for help-seeking and treatment, and general illness beliefs	Internal consistency ranges from 0.76 to 0.83 [179] and cross-cultural validity well established [180]	Has been used for different health conditions like in cases with tuberculosis, leprosy, and HIV/ AIDS English and Tamil language versions available [181]
Questionnaire on Anticipated Discrimination Scale [182]	Self-rated	14 items rated on a 4-point Likert scale	Addresses areas of anticipated discrimination	Good internal consistency (alpha = 0.86) and good test-re-test reliability (0.81) [182]	–

Table 10.10 (continued)

Scale/instrument	Rated by	Number of items	Number of domains	Psychometric properties	Translations/ adaptations available
Stigma Scale [183]	Self-rated	28 items	Discrimination (12 items), disclosure (11 items), and positive aspects of mental illness (5 items)	Good internal consistency ($\alpha = 0.87$) and adequate test-retest reliability (k, 0.49–0.71)	Translated, adapted, and validated in French [184] and Chinese [185]
Self-Stigma of Mental Illness Scale [186]	Self-rated	10 items rated on a 5-point Likert scale	Stereotype awareness, stereotype agreement, self-concurrence, and self-esteem decrement	Strong reliability and all forms of validity well established [187]	Has been translated and adapted in Chinese language [188]
Participation Scale [189]	Clinician rated	18 items with a 2-step, 5-point response scale	Focus on restrictions in functioning due to stigma	High Cronbach's coefficient (0.9), intra-tester stability 0.83, and inter-tester reliability 0.80	Has generic application and can be used for different health conditions Developed in seven languages, with generic and cross-cultural adaptations In India, has been translated in Hindi and Tamil language [190]
Discrimination and Stigma Scale [191]	Clinician rated	36 items	Evaluates discrimination domain	Has good reliability, validity, and acceptability	–
Perceived Devaluation Discrimination Scale [192]	Self-rated	12 items rated on a 6-point Likert scale	Evaluates discrimination domain	Internal consistency reliability ranges from 0.82 to 0.86	–
Community Attitude towards the Mentally Ill (CAMI) scale [193]	Self-rated	40 items rated on a 5-point Likert scale	Measures public stigma on 4 domains: authoritarianism, benevolence, social restrictiveness, and community mental health ideology	Adequate reliability well established [193]	Has been translated and adapted in many languages

compared to the burden of care, is a better predictor of the psychological well-being of caregivers of patients with schizophrenia [201, 202]. Various instruments have been developed to assess the caregiving experience (both negative and positive) as listed in Table 10.11.

Coping

Coping is understood as the process of managing demands (external or internal) that are appraised as taxing or exceeding the resources of the person [223]. It is seen as a process involving at least two stages: primary appraisal (is this something to bother about?) and secondary appraisal (what can I do about it?) [223]. It is proposed to serve two distinct purposes, i.e., to do away with the problem (i.e., problem-focused coping) and to regulate emotional reactions (emotion-focused coping) [199]. While problem-focused coping is considered as adaptive behavioral coping and involves dealing with the problem, emotion-focused coping basically

Table 10.11 Instruments used for assessing carer burden in schizophrenia

Instrument	No of items	Rated by	Psychometric properties	Dimensions assessed
Caregiver burden				
Perceived Family Burden Scale [203]	24 items, 3-point Likert scale	Self-rated	Adequate validity and reliability demonstrated and has greater predictive power for early symptomatic relapse	2 dimensions: relatives' reactions to active/aggressive behaviors and to withdrawn/passive behaviors
Behavior Disturbance Scale [204]	16 items, 3-point Likert scale	Self-rated	Adequate test-retest reliability has been reported	2 dimensions: positive symptom behaviors and negative symptom behaviors
Subjective Burden Scale [205]	22 items, 4-point Likert scale	Self-rated	Internal consistency – for the total score was 0.86 [206]	No dimensions
Objective Burden Scale [205]	18 items, 3-point Likert scale	Self-rated	Good internal consistency (α −0.96 to 0.99) and good test-retest reliability [207]	3 dimensions: negative consequences for children, negative consequences for primary caregiver, and negative consequences for other adult family member
Care Burden Scale for Relatives [208]	10 items	Structured clinician interview	Good psychometric properties	3 dimensions: relatives' practical burden, aspects regarding own health, and emotional burden
Involvement Evaluation Questionnaire (IEQ) [209]	31 items, 5-point Likert scale	Self-rated	Internal consistency for four subscales ranges from 0.74 to 0.85	4 dimensions: tension, supervision, worrying, and urging
Family Burden Interview Schedule [210]	100 items	Telephonic and personal structured interview	Internal consistency – alpha coefficient for global objective burden (0.82) and for global subjective burden (0.92)	Multiple aspects of caregiving
Family Burden Interview –Indian version [211]	24 items	Clinician interview	Inter-rater reliability of each item ranged from 0.87 to 0.99; internal consistency, 0.90 [212]	6 dimensions: financial burden, disruption of routine family activities, disruption of family leisure, disruption of family interaction, effect on physical health, and effect on mental health
Zarit Burden Scale [213]	22 items, 4-point Likert scale	Clinician interview	Has been adapted in several languages, and the internal consistency ranged from 0.85 to 0.94 [214]	5 dimensions: sacrifice, loss of control, embarrassment/anger, self-criticism, and dependency
Burden Assessment Schedule [215]	40 items, 3-point Likert scale	Clinician interview	Reliability (k, 0.80) and criterion validity well established	9 dimensions: spouse related, physical and mental health, external support, caregiver's routine, support of patient, taking responsibility, other relationship, patient's behavior, and caregiver's strategies
Montgomery Borgatta Caregiver Burden Scale [216]	14 items; 5-point responses	Self-rated	Internal consistency ranges from 0.60 to 0.90 and test retest stability, 0.92	3 dimensions, objective burden, subjective burden, and demand burden

Table 10.11 (continued)

Instrument	No of items	Rated by	Psychometric properties	Dimensions assessed
Caregiving experience				
Experience of Caregiving Inventory (ECI) [217]	66-items, 5-point Likert scale	Self-report	Good reliability and validity, acceptability to and appropriateness for caregivers	10 dimensions of relatives' appraisal of caregiving: eight negative and two positive; various countries have validated it in their own regional languages [218, 219]
The Caregiver Response Scale (CRS) [220]	24 items, rated on a 5-point Likert scale	Self-report	Internal consistency relatively high alpha, 0.81	4 negative dimensions: impact on schedule, impact on health, negative emotional reactions, and role responsibility
Caregiver Appraisal Scale (CAS) [221]	47 items, rated on 5-point Likert scale	Self-report	Internal consistency ranges from alpha −0.65 to 0.87 for different subscales	5 subscales: negative (impact and burden), positive (satisfaction, mastery, impact), and neutral (cognitive reappraisal)
Caregiver Reaction Assessment (CRA) [222]	24 items, rated on 5-point Likert scale	Self-report	Internal consistency for subscales ranges from 0.62 to 0.86	5 subscales: negative (disrupted schedule, financial problems, lack of family support, health problems) and positive (care-giver self-esteem)

involves the management of emotions that accompany the perception of stress so that the distress can be minimized, reduced, or prevented [224]. Studies in coping in caregivers of schizophrenia have mainly focused on its relationship with other variables like burden, psychological distress/psychological morbidity, expressed emotions, and psychopathology in patients, social support, sociodemographic variables of patients and caregivers, and clinical variables and illness perception.

Ways of coping questionnaire developed by Folkman and Lazarus (1980) is the most commonly used scale to assess coping. It is a 66-item scale which has eight types of coping: confrontive coping, distancing, self-controlling, seeking social support, accepting responsibility, escape-avoidance, planful problem-solving, and positive reappraisal. Each type of coping is expressed as a percentage that ranges from 0 to 100 [225]. Coping has also been assessed by using the Family Coping Questionnaire [226] which is a 27-item self-rated questionnaire which is rated on a 4−/5-point Likert scale. It provides information about seven dimensions of caregiving, including positive communication, social interests, coercion, avoidance resignation, and patient's social involvement. Coping Checklist by Rao et al. [227] is another commonly used scale which is a 70-item scale in a yes/no format and covers a wide range of cognitive, behavioral, and emotional responses that are used by the carers to handle stress. It has seven subscales which include problem-solving, positive distraction, negative distraction, acceptance, religion/faith, denial/blame, and social support. It has a good test-retest reliability of 0.74 and adequate internal consistency of 0.86.

A modified Hindi version of the coping checklist of Scazufca and Kupiers [228] has been developed by Nehra et al. [229] and consists of 14 items, divided into 5 domains (problem-focused, avoidance, seeking social support, collusion, and coercion). It has been found to correlate well with most of the items of the original English version with an acceptable level of internal consistency (alpha-0.62) [229]. Other instruments available to evaluate coping in caregivers are carers' coping style questionnaire [230], strategic approach to coping scale [231], and brief cope [232].

Studies have also shown that family members' religiosity may also interact negatively with their experiences of coping in general with mental illness. While collaborative forms of religious coping are often associated with better psychological adjustment to stress [233], adopting self-directing

or deferring styles of religious coping may be associated with negative consequences such as feelings of less competence. The religious coping methods included religious or spiritual beliefs, religious or spiritual practices, and religious or spiritual community participation [234]. The Brief RCOPE [235] is the most commonly used measure of religious coping. It is a 14-item measure of religious coping with major life stressors and has good reliability, concurrent validity, and internal consistency (alpha-0.94).

Expressed Emotions

Expressed emotion (EE) refers to caregiver's attitude toward a person with a mental disorder as reflected by comments about the patient made to an interviewer. The construct of EE comprises the following factors/behavioral patterns: criticism, hostility, and emotional over-involvement (EOI) [236]. It is now an established psychosocial predictor of relapse in patients with schizophrenia, and researchers have positioned EE within the diathesis-stress model of psychopathology, characterizing it as an environmental stressor that can potentially precipitate/cause relapse of psychosis among people with a genetic vulnerability [237]. Various scales have been developed to assess EE. They are the Camberwell Family Interview [236], Five-Minute Speech Sample [238], Level of Expressed Emotion Scale [239], Perceived Criticism Scale [240], and Family Attitude Scale [241]. All these scales have been found to adequately express reliability and validity across many studies [242, 243].

Psychiatric Morbidity in Caregivers

Caregivers of patients with schizophrenia are vulnerable to develop several psychiatric disorders due to ongoing stress due to their affected relative. Symptoms of depression and psychosomatic complaints were more prevalent among caregivers of schizophrenia [244]. Studies have demonstrated that the caregivers of persons with severe mental illness suffer from a number of stresses and high level of burden [245, 246]. Studies have generally used General Health Questionnaire-12 [247] which has a sensitivity of 68% and a specificity of 70% and good internal consistency (0.93). There is evidence of high rates of depression in caregivers of schizophrenia [248, 249].

Quality of Life (QOL)

The impact of caring for a relative with a mental disorder on the quality of life (QOL) of family caregivers has been studied by several researchers [250, 251]. Existing literature suggests that caregivers of patients with schizophrenia score low on QOL as compared to caregivers of patients with other psychiatric disorders [249, 252]. It may be due to the stress of coping with the problematic/abnormal behaviors of their near ones, emotional reaction to the nature of illness of their relative, stigma experienced leading to restriction in their social life, and economic difficulties. Most of the studies have linked poor QOL of caregivers with female gender, state of health, positive appraisal of their role, subjective burden, and time spent in caregiving [249, 250]. QOL of caregivers is an essential domain to assess and has been regarded as an outcome measure, too [253, 254]. The instruments developed to assess QOL in patients have been used to assess QOL in caregivers. Some of the generic instruments which have been used include WHOQOL and WHOQOL-BREF. Another important aspect of QOL in caregivers of schizophrenia which is assessed in several studies is the spirituality, religiousness, and personal beliefs (SRPB) facets, of WHOQOL (WHOQOL-SRPB) [255].

Stigma Experienced by Caregivers

Stigma experienced by caregivers of patients with mental illness is called associative stigma and affiliate stigma. Associative is a process in which a person is stigmatized by virtue of his or her association with another stigmatized individual [172, 256]. Affiliate stigma occurs when the people affiliated with a stigmatized individ-

ual such as caregivers, family members, and friends are personally affected by the public stigma that prevails in the society. Caregivers may develop affiliate stigma and thus feel unhappy and helpless about their affiliation with the stigmatized individual and tend to conceal their status from others. Affiliate stigma thus includes both self-stigma and subsequent psychological responses of the associates [173]. Stigma in caregivers of patients with schizophrenia can adversely affect the outcome of the affected individual.

Instruments have been developed to assess stigma experienced in caregivers. Some of these instruments are Stigma Scale for Caregivers of People with Mental Illness [257], Stigma Experience Scale [258], Stigma Impact Scale [258], and Discrimination-Devaluation Scale [259].

Another important domain of stigma is public stigma, which is also prevalent in caregivers and relatives of patients with mental illness. A specially designed scale has been developed to evaluate it, i.e., Community Attitude toward the Mentally Ill (CAMI) scale [193], so that appropriate steps can be taken to reduce the same. CAMI is a self-rated, 40-item scale which measures public stigma on four domains: authoritarianism, benevolence, social restrictiveness, and community mental health ideology. It has adequate and well-established reliability [193] and has been translated into many languages.

Critique of Outcome Measures and Recommendations to Overcome Barriers

Though there are several studies which have evaluated the patient-related and caregiver-related outcome measures in patients with schizophrenia, there are many shortcomings. These pose a barrier to the effective use of these measures and hence lead to difficulty in their interpretation, too. One of the frequently encountered difficulties in using outcome measures is choosing a particular tool for evaluating a specific outcome. Some of the tools have generic application, and few are developed specifically for schizophrenia. Problems arise in interpreting and comparing similar studies evaluating these outcome measures by using different types of tools in the same domain.

The studies which have evaluated the patient-related outcome measures have tried to assess more than one outcome at a time, and this had resulted in finding low discriminant validity due to an empirical overlap of measures designed to assess different outcomes [138]. Authors have suggested recommendations on careful use of these outcome measures as per the aim of the service provided, to avoid use of several outcome measures at a time unless each outcome measure addresses a different and distinct domain and to use outcome measures with previously well-established good psychometric properties [138].

With respect to the caregiver-related outcome measures, the classical psychometric properties such as reliability, validity, acceptability, feasibility, and interpretability have not been evaluated in all aspects [197]. Some have reported that many of these tools have been considered irrelevant by the caregivers themselves [260]. Additionally, most of these tools have been designed based on expert opinions, without taking input from the caregivers, and many have not been tested on caregivers of patients with mental disorders. This is important, as many tools rarely examine positive aspects of caregiving. This suggests that the actual validity of these tools is doubtful. The ideal recommendation is to carry out interviews and focused group discussion of caregivers in defining outcomes and design measuring tools that will be better adapted to the expectations and perceptions of caregivers.

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11 Suicide and Schizophrenia: Factors Affecting Recovery

Avinash De Sousa and Pragya Lodha

Introduction

Schizophrenia is a complex neuropsychiatric disorder which has multiple domains of symptomatology that span from affective to cognitive and has a long, drawn-out course and outcome [1]. Many patients with schizophrenia may die unnaturally and early due to various causes. Suicide is a common cause of death in schizophrenia. It has been noted that 20–30% of patients suffering from schizophrenia may attempt suicide and 10% successfully complete it [2]. There are multiple factors that herald the onset and affect the occurrence of suicide in schizophrenia. Suicide attempts and suicidal behavior are known to affect the course of schizophrenia and also affect the outcome and recovery from the disorder. The course and prognosis of the disorder are directly proportional to suicidal behavior that may be seen in the patient, and this behavior also determines the treatment patterns that may be used in the long-term management of the disorder [3]. The current chapter looks at suicide in schizophrenia from the point of view of how suicide and suicidal behavior may affect recovery from schizophrenia.

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Suicide and Recovery from Schizophrenia

Suicide and schizophrenia are closely related to each other. A high number of people who attempt or commit suicide suffer from schizophrenia, and a high number of patients suffering from schizophrenia exhibit suicidal behavior. Suicide and suicidal behavior are observed throughout the course of schizophrenia and seen in the prodromal stage, during acute phase of remission, in residual phase, in chronic schizophrenia, and even after recovery during reintegration into society [4]. It may also be a symptom that marks relapse. A number of times, patients with schizophrenia show an improvement in positive symptoms, while negative symptoms and suicidal behavior persist [5]. Many patients with schizophrenia actually get hospitalized post a suicide attempt. Repeated suicide attempts in patients with schizophrenia are always two to three times more than initially, and the severity of the attempt also may be greater [6]. There is a strong interplay of factors that affect recovery from schizophrenia and affect suicidal behavior in patients with schizophrenia.

Many patients in the West seek treatment for schizophrenia early due to health insurance, unlike in Asia where it may be hidden due to stigma, leading to many patients being ill for years and treatment being sought only after a severe suicide attempt. Suicide in schizophrenia

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is a part of the illness but is not often considered as an outcome criterion [7]. Outcome of any illness is measured on parameters of clinical remission, quality of recovery, level of functioning, quality of life, rehospitalization, impact on key relationships, economic cost and utilization of health system, global burden of disease, and loss of productivity. Suicidal behavior correlates with the clinical and social outcome to a consistent and proportionate degree. Whenever schizophrenia has poor outcome, suicide behavior also recovers poorly and vice versa [8].

It is generally accepted that we are yet far away from finding out accurate measures of deciding the level of recovery in schizophrenia. Many patients are hospitalized due to a suicidal attempt or crisis. Prevalence of suicide behavior is two to three times higher in comorbid disorders (where more than two or three mental disorders coexist), for example, schizophrenia with depressive and obsessive compulsive features and schizophrenia with substance abuse [9]. It is important to understand that while suicide is a part of the disorder in schizophrenia being a symptom, it is also on its own an independent psychopathological construct that affects the outcome and recovery from many psychiatric disorders [10]. Stigma in schizophrenia also increases once the patient attempts suicide, and this fact is known to people in the patient's family and those around him [11]. We must include suicidal behavior in the list of factors that affect recovery from schizophrenia to have a better understanding of how it affects functioning, quality of life, chances of rehospitalization, and rate of mortality [12].

Suicidal behavior contributes significantly as "all causes of death" in schizophrenia. Since suicidal ideation is a strong predictor of attempted/completed suicide, an accurate identification of suicidal ideation may help prevent these attempts. This may finally prove to be lifesaving and improve recovery from schizophrenia. Since suicide is responsible for a large number of rehospitalizations in schizophrenia, by keeping suicide in recovery and outcome criteria, a better assessment and probability of relapse will be estimated. It is not clear whether persistent ideas of suicide or risk of suicide contributes to poor social function. By identifying suicide behavior as a predictor of outcome (good or bad), level of recovery can be increased by providing appropriate treatment for risk of suicide [13].

In the last 15 years in schizophrenia research, there has been a strong focus in conceptualizing response, remission, and recovery in order to better understand the influence of schizophrenia on the overall life of a person. During this period, research has come out with significant conclusions. Sophisticated predictors have been defined, outcome is multidimensional, and by clearer understanding of outcome status, a better understanding has been sought about how an illness progresses and originates. It is imperative that suicide and suicidal behavior be considered as one of the predictors of the same [14].

Factors That Affect Suicide in Schizophrenia

There have been multiple studies that have looked at various facets of schizophrenia and suicide as well as suicidal behavior related to it. The current section shall look at the various factors that interplay in the occurrence of suicide in schizophrenia and how suicide thus becomes an important parameter in recovery from schizophrenia.

When Is Suicide Risk Highest in Patients with Schizophrenia?

The risk for suicide in patients suffering from schizophrenia is considered to be highest in the early course of the illness and usually within the first year of illness [15]. The same may be said of patients with first-episode psychosis. In fact, patients with first-episode psychosis have higher estimates of mortality from suicide than studies with longer periods of follow-up in patients with schizophrenia. Suicide has been noted in our clinical experience in all phases of schizophrenia. There is the acute phase where suicide and suicidal behavior occur in the context of psychosis and command hallucination that may prompt the patient to end his life. Suicide also occurs in chronic untreated patients when they act upon their symptoms. There is also a chance of

depression setting in the post-psychotic phase where the patient realizes that he has been through an episode of psychosis. The stigma of psychosis and recovery from it while trying to return to normalcy may prompt the patient to end his life, as he may not be able to cope with the fact that psychosis has in fact happened. Negative symptoms in schizophrenia may have depressive variants, and these may induce suicidal ideation and behavior as a part of the symptom makeup. Most studies of suicide in schizophrenia have been retrospective in nature, and there is a need for prospective data [16].

Suicide and Demographic Factors of the Patient in Schizophrenia

The age of the patient and the age of onset are very important factors in recovery for schizophrenia. There has always been a debate about whether younger-onset patients versus later-onset patients show differences in recovery. It has been shown that late-onset schizophrenia after the age of 35 has poorer prognosis [17]. Educational level is another factor that plays a role in recovery. However, educated patients think more and tend to develop depressive features far more than non-educated subjects and increase their risk for suicide and suicidal behavior [18]. Younger subjects below the age of 30 and older subjects above the age of 45 are more prone to suicidal behavior in schizophrenia. Presence of severe hallucinations is another determinant of suicidal behavior in schizophrenia. Marriage and sound social support with good family environments serves as a protective factor from suicide in schizophrenia [19]. Patients with good insight are more likely to develop affective features and are more prone to suicide as well.

Suicide and Hospitalization in Schizophrenia

The suicide risk in schizophrenia is especially high in relation to hospitalization, which stresses the importance in clinical practice of paying extra attention during all phases of the illness. It has been reported in literature that 33–35% of suicides among patients with schizophrenia occur during admission or within 1 week after discharge from the hospital [20]. There is a peak of suicide risk during these periods, and there is a need for an immediate assessment of suicide risk after admission and proper follow-up and outpatient treatment immediately after discharge from the hospital. The suicide risk for schizophrenia was relatively constant during the first year following discharge. The total number of psychiatric admissions and duration of hospitalization has also been associated with a higher risk of suicide and is a measure of the severity of the illness [21].

There has been a study linking the relationship between post-discharge suicide in schizophrenia and the age and gender of the treating psychiatrist, stressing the need for quality care and assessment among mental health professionals. There has been a decline in inpatient psychiatric care in the last decades, with the advent of better medications and early treatment. These changes have been proposed to be a cause of the rising mortality seen in patients with schizophrenia, as outpatient treatment is not as effective as inpatient care in many cases [22].

Suicide Attempts in Patients with Schizophrenia

A history of deliberate self-harm or suicide attempt and the presence of active suicidal ideation are the strongest risk factors for suicide in patients with schizophrenia. A history of attempted suicide significantly increases the risk of suicide among patients with schizophrenia and is the single most commonly reported clinical risk factor for suicide. It is well known that schizophrenia as an illness influences the overall risk and temporality for completed suicide [23]. More male patients with schizophrenia may attempt suicide, while more female patients attempt it. The estimates of attempted suicide range from 15% to 40% in schizophrenia. Many patients may use methods which are far more violent and lethal than when compared to patients with depression [24].

Depression is an important risk factor for attempted suicide in schizophrenia. Depression affects recovery in schizophrenia as well. Depression may be seen as symptom of the illness, as a part of negative symptoms; it may

also been in the recovery phase as a part of post-psychotic depression and may be seen sometimes as an antipsychotic-induced depression when typical antipsychotics are used. Studies have shown that past or recent suicide ideation, previous deliberate self-harm, past depressive episodes, and a higher mean number of psychiatric admissions increase the risk of suicide in schizophrenia. This is coupled with suicidal ideation of a past and recent nature [25].

Suicide, Substance Abuse, and Recovery from Schizophrenia

Substance abuse has been associated with impulsiveness and suicidal behavior as a disorder, and it increases when the substance abuse is present in a patient with schizophrenia. Alcohol dependence is a common disorder—along with nicotine dependence—seen in schizophrenia, and this is often used by the patient to cope with the distressing symptoms associated with the disorder [26]. Cannabis is another commonly abused drug among patients with schizophrenia and more so seen in patients with first-episode schizophrenia, and the age of onset of schizophrenia appears to be lower among cannabis abusers compared with both cannabis non-abusers and alcohol abusers [27]. Presence of substance abuse in schizophrenia leads to noncompliance with medication, irregular follow-up, violence and aggression, depression, and suicide risk, along with financial difficulties. Cannabis use has been reported as a risk factor for nonadherence to medication and to treatment dropouts [28]. There have, however, been no differences in symptom profiles of psychosis between patients who abuse and do not abuse cannabis. Patients with schizophrenia who had substance abuse spent more days in the hospital, reported higher anxiety and depression levels, and were more likely to indulge in aggression or hostile behavior or crime [29].

Biomarkers of Suicide in Schizophrenia

Multiple studies have looked at various blood parameters at an attempt to elucidate viable blood biomarkers that may serve as indicators of suicidal behavior in schizophrenia and first-episode psychosis. Low levels of cholesterol have been described in suicide behavior, including among those individuals who have an increased tendency for impulsivity. Violent suicide-attempt patients show significantly lower cholesterol levels than those with nonviolent suicide attempts [30]. In a study of 60 patients with suicide attempts and schizophrenia, lower cholesterol levels were correlated with severe suicidal behavior and female patients [31].

Thyroid hormones have been implicated in both depression and suicide. Elevated and normal total T4 levels are seen in drug-naive patients with acute psychotic episodes, and these levels are known to normalize or decrease in response to treatment with different drugs. A positive correlation between circulating free T4 and free T3 with the severity of schizophrenia has been reported across studies. In a study of 60 cases of first-episode psychosis, a higher level of TSH and an inverse correlation with suicide potential in patients suffering from schizophrenia were noted. There is a high suicide risk and possibility of hypothyroid states in these patients. The study argued that careful screening for suicide in patients with schizophrenia was a must along with estimation of TSH levels [32].

Brain-derived neurotrophic factor (BDNF) has gained the most attention in suicide research, and several studies consistently show that expression of BDNF is reduced in blood cells of suicidal patients and in brains of subjects who have committed suicide. A large number of studies have shown an evidence of the role of BDNF in suicide, and a strong association of suicidal behavior with BDNF functional polymorphism has been noted. Reports indicating lower levels of BDNF in subjects suffering from schizophrenia with suicide attempts suggest that serum BDNF levels may be a potential marker of suicidal behavior in schizophrenia. Literature reviews indicate that abnormalities in neurotrophic expression in schizophrenia exist. BDNF reductions have been noted in the early phase of the disorder and improve as the disorder improves. BDNF is a survival factor for CNS neurons, and a deficit in the production and utilization of BDNF leads to neuronal integrity and synaptic dysfunction

in schizophrenia. This may have implications for suicide in schizophrenia as well [33, 34].

Many other studies have looked at parameters like neutrophil-lymphocyte ratio (NLR) [35], C-reactive protein [36], and serum testosterone levels [37] but have remained inconclusive.

Neuroimaging and Suicide in Schizophrenia

Magnetic resonance imaging studies have shown differences between prodromal patients who convert to schizophrenia or psychosis and those who do not, based on the fact that converters have less gray matter in the cerebral cortex, and magnetic resonance spectroscopy studies have shown changes in different brain metabolites in these patients, but no studies specific to suicide in schizophrenia have been conducted [38]. It is established that the early stage of schizophrenia is associated with progressive changes in brain structure and function, and there is a need to investigate the "transition" to psychosis from an "at-risk" stage using functional brain imaging [39]. Structural brain changes have been noted in the prodromal phase as well as in first-episode psychosis within drug-naive and drug-medicated patients. These brain changes have been implicated clinically in symptoms like impaired cognitive control of mood, pessimism, reactive aggressive traits, impaired problem-solving, over-reactivity to negative social signs, excessive emotional pain, and suicidal ideation, finally leading to suicidal behavior [40].

Hypothesis for Suicide as an Important Factor in Recovery from Schizophrenia

Suicide is an important factor in the recovery of patients from schizophrenia, as there are biopsychosocial implications of suicide in schizophrenia. Some of the reasons why it is an important factor are as follows:

Suicide attempts have devastating effects on both the patient and the caregivers. The recovery from a suicide attempts adds to the recovery period from schizophrenia, and this adds to days of hospitalization and also increases the chances of rehospitalization. This is so because suicide attempts may very often be forerunners of future attempts and rehospitalization [41].

Suicide attempts may also serve as an indicator that there are a preponderance of depressive features and negative symptoms. This increases the number of add-on medications, and thus compliance may be affected, leading to relapse and impaired recovery [42].

Suicide attempts also affect a patient from a neurobiological perspective. Depletion of positive neurotransmitters and protective neurotrophic factors has been reported in schizophrenia. This worsens in the wake of suicide, and thus makes the patient weaker biologically, thereby preventing full recovery [43].

Suicide attempts may also impair cognition and recovery from a neuropsychological perspective, as many neurocognitive parameters are known to be impaired in suicide [44].

The increased days of hospitalization may cause loss of employment and income and impair treatment compliance and follow-up, causing impairments in the recovery process [45].

The stigma associated with schizophrenia increases when there is a suicide attempt, and this, too, adds to the burden during recovery [46].

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12 Resilience as a Measure of Outcome and Recovery in Schizophrenia

Reetika Dikshit, Pragya Lodha, Amresh Shrivastava, and Avinash De Sousa

Introduction

Resilience is the capacity and dynamic process of overcoming stress and adversity while maintaining normal psychological and physical functioning and bouncing back to earlier levels of function [1]. Each individual shall experience stress, and everybody is exposed to trauma at some point of time in their lives. Resilience has now been implicated as a psychobiological construct as an important factor in the maintenance of remission, in the prevention of relapse, and during recovery from psychiatric illnesses [2]. The role of resilience has been explored across research in all psychiatric disorders like post-traumatic stress disorder, affective disorders, depression, and schizophrenia. The understanding of resilience is of great relevance in building effective coping styles, dealing with maladaptive coping, and understanding the stress response in psychiatric illnesses [3]. Resilience has huge psychological, social, biological, and neuroendocrine underpinnings that affect the outcome of psychiatric disorders. Mechanisms that include genetic, epigenetic, developmental, psychological, and neurochemical factors that play a role in resilience development and promotion have been identified with respect to psychiatric disorders [4]. Resilience plays a very important role in the response and recovery of schizophrenia as well as in the prevention of relapse and also matters when we look at how the family of a patient with schizophrenia copes with the illness. This chapter aims to present an overview of the role of resilience in promoting recovery and positive outcomes in schizophrenia.

The Concept of Resilience

Within the field of psychology, early inquiry examining resilience represented a paradigm shift from looking at risk factors that led to psychosocial problems to the identification of strengths of an individual [5]. Resilience is the ability to adapt successfully in the face of stress, adversity, or any situation/event that leads to a negative emotional experience. As formally defined, resilience is the ability of individuals to bounce back after trauma and return to their previous psychological selves [6]. Resilience is a

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construct with inherent biological and psychological factors that affect it [7] and consequently lead to substantial ramifications. It is also implicated as a marker of psychopathology in various disorders and plays a role in the recovery from trauma and stressful events [8]. It is crucial to note that in the definition of resilience, psychological and physical functioning are maintained in the face of adversity. Although the understanding of resilience is nascent, recent investigations have identified several mechanisms encompassing genetic, epigenetic, developmental, psychological, and neurochemical factors that underlie the development of and enhancement of resilience and factors that predict vulnerability to stress and susceptibility to psychiatric disorders in the face of stress and trauma [9].

Resilience is an individualistic and contextualized construct that builds, depending on the experience that one goes through. The extent of level of resilience also varies depending on the internal and external sources of support and protection available to the individual. The individual traits that allow the more flexible outcomes undoubtedly depend upon a foundational capacity of that individual that is built upon experiences in the life course, particularly early, that promote the development of healthy brain architecture supporting cognitive flexibility that allows the brain to continue to change with ongoing experiences. There is no single agreed-upon definition of resilience, but the construct is understood under various lenses depending on the context of study [10].

Resilience as a Psychobiological Construct

With the paradigm shift in understanding the concept of resilience, the construct (of resilience) is increasingly being understood as a psychobiological one, especially in the context of psychiatric disorders. Quintessential to remember is that resilience can be a protective factor against the development of mental disorders and also be a risk factor for a number of clinical conditions [11]. It has been well established that resilience is lower in individuals suffering from a psychiatric condition or disorder and that higher levels of resilience may prevent the development of an illness or minimize the severity of illness [12]. Trauma, its intensity, and the number of traumatic incidences are inversely proportional to resilience. The lesser the frequency and intensity of trauma, the higher the resilience and vice versa. However, this is a simplistic understanding to the relationship between trauma and resilience, and there are multiple variables including the personality organization, available support, nature of protection in environment, and several other factors that influence the interplay [13]. Having suffered trauma once is enough to influence the way in which the brain functions and is structured to manage trauma. This brings us to an understanding that every individual who has suffered trauma reacts to and manages it differently—even if the nature of trauma has been similar. Therefore, their brains undergo differential functional and structural changes. This functional and structural change is markedly different between individuals who have, and those who have not, undergone traumatic experiences [14]. Resilience helps to minimize the extent of pathogenesis in developmental process or transition from health to disease or wellness or illness by facilitating or arresting conversion to illness.

There is a strong argument which claims that response to trauma develops through resilience, and although some neurobiological changes correlate with resilience and trauma, it is unclear whether the nature and degree of response to trauma are dependent on the extent of neurobiological changes alone. The level for resilience protection and modification also depends on other complex factors that shape the influence of resilience on individuals experiencing trauma [15]. The capacity to which resilience is able to act as a preventative measure seems to have a strong correlation to ingrained psychosocial factors. Human cognitive factors have been recognized as potential possible factors that may help determine the level of resilience in an individual, depending on the way an individual responds to trauma. The cognitive factors that act to maintain and uphold resilience are active coping, cognitive flexibility,

and social support [16]. Research claims that resilience is mediated by adaptive changes in several neural circuits involving numerous neurotransmitter and molecular pathways [2]. Along with psychosocial factors, it is also the interplay with neurobiological factors that determines resilience as an outcome in psychiatric illnesses.

Linked with the concept of resilience is the concept of allostasis. The active process of responding to challenges and adaptive changes is called allostasis. This process involves multiple mediators such as the autonomic nervous system, cortisol, immune and inflammatory markers, metabolic factors, and neuromodulators within the brain that interact in a nonlinear fashion with each other and promote adaptation in the short run as long as they are turned on efficiently when needed and turned off promptly when no longer needed [17]. Neurobiological research has implicated several brain structures and molecular models that are involved in the stress and trauma reaction/coping. Of all, the cortical and limbic structures are most involved. The mechanism of trauma can be simply understood by the activity of the cortical and limbic structures on the hypothalamic–pituitary–adrenal (HPA) axis and their influence on glucocorticoid-mediated negative feedback that acts as major trigger for the fearful memories (stress/trauma) [18]. Neurochemical and neuroendocrine changes occurring in response to trauma may lead to neuronal loss and functional disconnectivity. Changes in neuroplasticity, HPA axis response to stress, and neurotransmissions of dopamine, serotonin, and norepinephrine play an important role in maintaining homeostasis of resilience plasticity [3].

Resilience is increasingly being studied in the phenomenon of mental illnesses and more so recently with patients suffering from schizophrenia [19]. Evidence says that 80% of patients with first episode of schizophrenia will have another episode in the span of 5 years. Social and clinical recovery in these patients is low. The state of transition from illness to wellness has grown with the revolutionary interventions for disorders like schizophrenia [20]. Cognitive dysfunction is one of the earliest signs of the illness, which begins with deteriorating memory functions, learning, and social cognition and finally impairment. Cognitive dysfunction further leads to socio-occupational and functional impairments. Due to this, an individual's psychosocial responses to stressors inevitably come down. Thus, resilience as a phenomenon is directly impacted in outcome of the illness. Though there is no clearly explained association between cognitive impairment and poor outcomes in schizophrenia, several neurobiological and psychobiological processes explain the mechanism of a pathway for poor outcomes from cognitive impairment [21, 22].

Critical Aspects of the Neurobiology of Resilience Relevant to Outcome and Recovery in Schizophrenia

In last few years, there has been increasing interest in the active, adaptive coping mechanisms of resilience, with a lot of work focusing on the neurobiological correlates that are associated with resilience. The human brain exhibits a remarkable degree of resilience in the face of extreme stress, resisting the development of neuropsychiatric disorders. The brain perceives potential threats and determines the response, thus acting as a central organ of stress [23]. Moreover, the brain is a plastic organ that changes its architecture, gene expression, and function through internal neurobiological and hormonal mechanisms when faced with stress. The goal is to recognize those biological changes that underlie flexible adaptability, and to recognize these factors that indicate resilience, particularly when the individual is challenged by new circumstances [24]. This is governed by early life experiences that determine individual differences in such capabilities by laying down the brain architecture that determines the flexible adaptation or the lack thereof [25].

Genetics

Genetic factors contribute to the risk, as well as resilience, of the psychiatric disorders. Huge research work has been done to identify the

candidate genes with relatively weak associations. The field is now pivoting increasingly to genome-wide studies on large numbers of people to parse the complex genetic contributions to psychiatric disorders [26].

Hypothalamic–Pituitary–Adrenal Axis-Related Genes Regulation of the HPA axis is affected by genetic factors. Functional variants of the brain mineralocorticoid receptor (MR) and glucocorticoid receptor (GR), which are respectively involved in setting the threshold and regulating the termination of the HPA axis response to stress, have also been identified in humans [27]. Interestingly, four SNPs of FKBP5 (rs9296158, rs3800373, rs1360780, and rs9470080), a gene that codes for a "chaperone" protein that regulates GR sensitivity, were found in patients with PTSD [28]. Many such genes are now being investigated for schizophrenia.

The Human Serotonin Transporter Gene (5-HTTLPR; aka SLC6A4) The short allele is associated with decreased serotonin transporter availability and a resulting lower reuptake of serotonin from synaptic clefts, leading to risk for depression when exposed to stressful life events. An association between the long allele of 5-HTTLPR and emotional resilience has been found [29].

COMT Val158 Met gene polymorphism that codes for COMT is linked to resilience. Individuals with the low-functioning Met158 allele have higher circulating levels dopamine and noradrenaline. Thus, they tend to exhibit higher anxiety levels, increased plasma adrenaline levels in response to stress, and lower resilience to negative mood states [30]. Recent research has focused on the implications of the COMT gene in schizophrenia [31].

Neuropeptide Y The level of neuropeptide Y mRNA expression showed an inverse correlation with trait anxiety, as well as a direct correlation with levels of stress-induced endogenous opioid release, which is implicated in the suppression of pain and stress responses [32]. Neuropeptide Y has also been implicated in the neurobiology of schizophrenia as per new research [33].

Brain-Derived Neurotrophic Factor (BDNF) A single nucleotide polymorphism (G196A, Val66Met) in the gene that encodes BDNF in humans significantly impairs BDNF's intracellular trafficking and activity-dependent release Met66 allele. This leads to reduced BDNF function with greater anxiety-like behavior and impaired hippocampus-dependent learning, but resilient to chronic stress [34]. BDNF genes play a role in the pathogenesis of depressive features and negative symptoms that may be seen in schizophrenia [35].

Gene–Gene and Gene–Environment Interactions Evidence of gene–gene and gene–environment interactions underlying interindividual variability in stress responses have been postulated. An interaction of 5-HTTLPR-COMT genes and stressful life events leads to the risk for depression [36]. Researchers have reported gene–environment interactions that influence the risk for depression in maltreated children. They reported that social support seems to mitigate the effects of the short allele of 5-HTTLPR61 and the 5-HTTLPR and BDNF Val66Met genotypes that cause risk of depression when exposed to stressful life events [37].

Epigenetics Good environment for nurturing and rearing practices shows attenuated corticosteroid responses to stress and expresses higher levels of glucocorticoid receptors (GR) in the hippocampus. This enhanced GR expression is mediated by nerve growth factor-inducible protein A (NGFI-A; also known as EGR1). However, little nurturing and poor rearing practices show increased methylation of the GR gene promoter at the NGFI-A binding site in the hippocampus, an epigenetic change that is associated with reduced GR expression [38, 39]. This difference in methylation emerges in the first week of life and persists into adulthood and is passed on to their offspring. Epigenetic changes that occur during brain development are an additional means by which behavioral variability is generated in indi-

viduals, better preparing the species for a host of possible environmental challenges [40].

Neurotransmitters

Hypothalamic–Pituitary–Adrenal (HPA) Axis Stress leads to activation of the HPA axis, which results in widespread hormonal, neurochemical, and physiological alterations in the body. Glucocorticoids thus released interact with steroid receptors, leading transcription factors to regulate cellular function. Glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) are expressed at high levels in the hippocampus, amygdala, prefrontal cortex (PFC), and other limbic and midbrain structures, where they modulate the neural circuitry and neuroendocrine systems that underlie behavioral responses to stress [40].

Norepinephrine and Dopamine Hyperresponsiveness of the locus ceruleus-norepinephrine system may result in chronic anxiety and fear. The norepinephrine transporter (NET) and receptors (α- and β-adrenoreceptors) involved in norepinephrine signaling have been implicated as biological mediators of stress-related psychiatric disorders and resilience. Dopamine release upon stress is increased in the PFC and inhibited in the nucleus accumbens, an area mainly associated with the reward pathway. Some studies have found decreased levels of circulating dopamine in depression [41]. There have been many research reports on the role of norepinephrine in the genesis of negative symptoms in schizophrenia [42].

Dehydroepiandrosterone (DHEA) DHEA is a precursor for the synthesis of anabolic steroids and is co-released with cortisol in response to stress. Reports have shown that blood DHEA levels increase under acute stress and that a higher level of DHEA, or a higher DHEA to cortisol ratio, is associated with less dissociative symptoms and superior performance in healthy subjects undergoing military survival training [43]. The role of DHEA in schizophrenia is currently being investigated [44].

Serotonin Acute stress leads to increased serotonin turnover in multiple brain areas. Serotonin affects the regulation of stress response and emotional behavior through 5-HT1–7 receptors [45]. Literature abounds with data on the role of specific serotonin receptors in the genesis of certain symptoms and in the psychopathology of schizophrenia [46].

Testosterone Testosterone has been strongly linked to social rank and aggression. It serves as a pro-resilience factor by promoting positive mood and social connectedness [47]. There are reviews on the role of testosterone as a treatment option in the long-term management of schizophrenia. Low testosterone levels have been linked to negative symptoms in schizophrenia [48].

BDNF Hippocampal BDNF expression contributed critically to resilient adaptations to chronic stress. BDNF acts through its two main receptors Trk-B and p75 [49]. Central administration of BDNF has antidepressant-like effects and can enhance hippocampal neurogenesis. Evidence from animal and human studies shows that administration of antidepressants can lead to increase of BDNF and TrkB expression in the hippocampus and PFC, suggesting a role of BDNF-TrkB signaling in the behavioral effects of antidepressants. Nevertheless, there is also evidence for antidepressant effects without changes in BDNF or neurogenesis [50].

Glutamate, GABA, and endocannabinoids Glutamate, GABA, and endocannabinoids have also been widely studied and implicated in the stress response, resilience, and pathophysiology of mood and anxiety disorders. The dysregulation of these systems can lead to profound deficits in successful adaptation to acute and chronic stress. Pharmacological studies targeting these systems in psychiatric disorders have begun to show promising results in achieving therapeutic effects [51–53]. The endocannabinoids have been extensively studied in the pathogenesis and treatment of schizophrenia, and their relation to the genesis of psychosis is also under investigation [54].

Glutamatergic Signaling and Synaptic Connectivity Animal models have been used to understand circuit-level synaptic changes in glutamate systems with far greater precision. The literature supports the idea that chronic stress reduces dendritic arborization and glutamatergic dendritic spine density of pyramidal neurons in the PFC and hippocampus and reduces hippocampus neurogenesis while increasing dendritic spine number or branching in amygdala and NAc [55]. Studies have shown greater degree of c-Fos, FosB, or ΔFosB expression in glutamatergic neurons of mPFC (infralimbic, paralimbic PFC) of resilient mice following chronic predator or social defeat stress [56]. Increased expression of these immediate early genes would suggest increased neuronal activation within this brain region, which might represent a pro-resilience adaptation.

Neural Circuits of Resilience

Animal and human studies have identified functional neural circuits and interactions among multiple brain regions, such as the amygdala, PFC, and nucleus accumbens, that are involved in the regulation of adaptive psychobiological responses to stress and adversities. Reduced insular activation under stress has been linked to greater non-reactivity to inner experience, a key component of trait mindfulness which may protect against negative bias and reduce depression vulnerability [57]. By potentially targeting the top-down and bottom-up regulation of these neural circuits, psychotherapeutic interventions including cognitive behavioral therapy with cognitive reappraisal, positive emotion exercises, coping skill training, well-being therapy, and mindfulness meditation can be efficacious approaches to build and enhance resilient psychosocial responses to stress [58].

Resilience and Schizophrenia

The clinical expression of schizophrenia is diverse, and this significant heterogeneity is still unexplained. Schizophrenia is not a single disease entity, and there are several etiological factors and various pathophysiological mechanisms involved, with the most recent concept being a neurodevelopmental disorder [59]. Schizophrenia has a profound impact on the individual life and may lead to several adversities. Resilience represents positive adaptation in the face of adversity and has received increasing attention as a factor contributing to recovery in individuals with schizophrenia. Resilience is thus becoming an important topic as there is evidence that it increases the probability for long-term recovery [60]. This section shall look at important studies at the intersection of resilience and schizophrenia.

Resilience and Schizophrenia: Long-Term Follow-up Studies

Follow-up studies reveal that patients who have fully recovered from schizophrenia have the ability to endure setbacks without giving up hope. This quality of recovery is referred to as resilience, a construct which means "bouncing back" from difficult experiences [61]. A Norwegian study describes patients with fully recovered schizophrenia who were followed up for a period of 15 years. It consisted of 17 subjects interviewed with semi-structured interview and Connor-Davidson Resilience Scale (CD-RISC) to assess resilience. The results showed that nearly half the participants maintained full recovery. These subjects did not use any neuroleptic medication and had not done so for about 17 years. The findings represent potentially important clinical and research implications. The possibility of being cured of schizophrenia instilled hope in patients and helped reduce stigma about the disease, showing that persons with schizophrenia are not doomed to a life of disability. The results demonstrated the importance of separating the person from the disease when studying recovery in schizophrenia [62]. Optimism and willpower are personal attributes that characterize the recovered individuals in this study, which was reflected in their high scores on

the resilience scale [63]. The data from this study indicate that there are important relationships between symptom severity and recovery process variables. The fully recovered participants had significantly higher resilience scores and significantly lower symptom scores than participants in remission, and there was a significant negative association between resilience and the PANSS negative subscale scores [62]. Other researchers decided to study the transcultural attributes in resilience across schizophrenia between Austria and Japan. Another objective was to examine transcultural differences in internalized stigma, self-esteem, and hopelessness, which can be expected to be relevant in this context, as well as the interrelations between these subjective elements of recovery and symptom severity. Notably, it was detected that a significant country effect with markedly lower resilience and self-esteem scores as well as higher hopelessness scores among Japanese subjects in general. In addition, both Austrian and Japanese patients indicated significantly lower degrees of resilience, self-esteem, and hope compared to healthy control subjects. This suggests that schizophrenia patients from Western European and Japanese cultures may have different needs to achieve recovery. In conclusion, it will be critical to develop culture-specific psychosocial programs and to examine their feasibility and effectiveness among these patients [63]. Kim and others described psychosocial functioning to be comprised among participants prone to ultrahigh risk [UHR] of psychosis; this dysfunction was associated with negative symptoms, adaptive coping, and resilience. In addition, baseline resilience was lower among those in the UHR group who converted to frank psychosis than among those who did not. Resilience has been shown to be lower among ultrahigh-risk individuals who convert to full-blown psychosis compared to those who do not [64]. In another study, patients meeting the full diagnostic criteria for schizophrenia were studied with resilience as the capacity to cope with and to gain insight into the illness, and resilience was shown to have a beneficial effect on the course of the illness [65].

Resilience and Schizophrenia: Developmental Studies

The parent–infant relationship is an important context for identifying very early risk and resilience factors as targets for the development of preventative interventions [66]. Authors systematically reviewed studies investigating the early caregiver–infant relationship and attachment in offspring of parents with schizophrenia. There was some evidence to support disturbances in maternal behavior among those with a diagnosis of schizophrenia, and there was more limited evidence of disturbances in infant behavior and mutuality of interaction, thus exhorting the need to investigate both sources of resilience and risk in the development of offspring of parents with a diagnosis of schizophrenia and psychosis [67]. Another study attempted to explore resilience and its correlates among the offsprings of parents with schizophrenia. The findings of the study showed that majority of the offspring reported medium resilience. High and medium resilient group had internal locus of control; engaged in coping mechanisms such as acceptance, religious coping, problem solving, and seeking social support; had positive self-concept such as likeability, task accomplishment, giftedness, and morality; had more satisfaction with emotional support; and had less non-utilization of support compared to low resilient group. The study highlights that majority of the offsprings were resilient and that the factors associated with resilience are presence of good support system, use of problem-focused coping strategies, and having positive self-concept [68].

Neuroimaging Studies

Researchers investigated the neurobiological underpinnings of resilience to self-stigma using neuropsychological and functional magnetic resonance imaging (fMRI) data. In a sample of 20 patients with schizophrenia, association strengths between social inferiority and schizophrenia were negatively correlated with activation

strengths of the rostral-ventral medial prefrontal cortex (mPFC). Moreover, the mPFC activation strengths correlated negatively with activation in the right amygdala, suggesting that resilience to stigma is associated with emotion regulation [69]. There is a dearth of neurobiological and neuroimaging data on the interactions between resilience and schizophrenia, and further research in this area is warranted.

Psychological Studies

Henderson and Cock took a qualitative approach (i.e., grounded theory method) to study how ten patients experienced recovery after first-episode psychosis. Based on unstructured interviews, two styles of resilience were identified: "tenacity," requiring effort over a period of time, and "rebounding," springing back. In addition, internal and environmental resources including self-pacing and support from others were described as mechanisms of "harnessing resilience" [70]. Other research studied another relevant concept that potentially contributes to resilience in a sample of 74 non-remitted chronic schizophrenia patients, namely, "happiness." While happiness was assessed using four items of the Center for Epidemiologic Studies-Depression (CES-D) scale , "trait resilience" and "event resilience" were measured using the Connor-Davidson Resilience Scale 10-item version and the Hardy-Gill Resilience Scale, respectively. Compared to healthy controls, lower levels of happiness were found in the schizophrenia group; higher levels of happiness were associated with higher resilience, along with lower perceived stress, higher optimism, and higher personal mastery [71].

Resilience and Suicide in Psychosis

Recent years have seen growing interest into concepts of resilience, but minimal research has explored resilience to suicide among psychosis. One study aimed to examine whether a proposed resilience factor—positive self-appraisals of the ability to cope with emotions and difficult situations and the ability to gain social support—could buffer against the negative impact of hopelessness among individuals with psychosis-spectrum disorders when measured cross-sectionally. Positive self-appraisals were found to moderate the association between hopelessness and suicidal ideation. For those reporting high levels of positive self-appraisals, increased levels of hopelessness were significantly less likely to lead to suicidality. These results provide cross-sectional evidence suggesting that positive self-appraisals may buffer individuals with psychosis against the pernicious impact of a well-known clinical risk factor, hopelessness. Accounting for positive self-appraisals may improve identification of individuals at high risk of suicidality and may be an important area to target for suicide interventions [72].

Critical Clinical Aspects of Resilience in the Outcome and Recovery from Schizophrenia

If one has to understand how resilience may impact outcome and recovery in schizophrenia, the understanding has to be multidimensional. Studies that involve resilience and schizophrenia have been multimodal and of different types.

Some studies have focused on resilience and psychopathology, while others have focused on resilience and the impact of schizophrenia years after the illness has set in. There are other studies that focus on resilience groups which are at risk for the development of schizophrenia, i.e., offspring of patients who suffer from schizophrenia and nonpsychotic siblings of these patients. Many studies have been done using psychological rating scales, but very few studies using biomarkers or neuroimaging exist.

There are some confounding factors when various studies of resilience and outcome in schizophrenia are analyzed. There are no standard scales for the measurement of resilience, and various studies have used different measures. There is a dearth of longitudinal follow-up studies of resilience during the entire course of an illness like schizophrenia from prodrome to maintenance phase.

There are also no studies that look at interventions and treatment methods to promote resilience. Many studies have focused on protective factors associated with benign outcomes, while others have looked at dynamic processes leading to positive adaptation following psychosis.

Most studies in realm of resilience, outcome, and recovery in schizophrenia have been cross-sectional. Many findings warrant confirmation via prospective studies. Longitudinal studies must look at resilience as a dynamic process . Development of treatment programs to enhance resilience and their incorporation in schizophrenia relapse prevention treatment algorithms must be given due consideration in the coming years.

One must understand that resilience does not have a specific role, but plays an important role in every stage of schizophrenia, from the at-risk state to the prodromal state. Resilience determines the conversion of prodromal and at-risk states into full-blown psychosis.

Resilience determines how the patient and his or her family members cope with a diagnosis of schizophrenia and their positive attributes that determine recovery from the illness. Resilience also helps the patient cope with distressing symptoms of schizophrenia, enhances understanding of the illness, and improves compliance to medication and psychosocial treatments.

Resilience also plays a role in enhancing the effectiveness of psychotherapeutic treatments used in the management of schizophrenia and is a paramount patient variable in determining treatment outcome and recovery.

Conclusion

The relationship between resilience and recovery as well as outcome in schizophrenia is multipronged and complex. Resilience is a protective factor for various psychiatric disorders in both the development and recovery phases. The same holds true for serious mental illnesses like schizophrenia. Resilience is vital in the prevention, pathogenesis, recovery, and symptom alleviation in schizophrenia. Research into resilience and its role in schizophrenia are still in a nascent stage. There is need for further long-term prospective studies that look at neurobiological substrates, biomarkers, and neural circuitry that play a role in recovery from schizophrenia using resilience as a mediating mechanism. This shall go a long way toward our understanding of recovery as a process in schizophrenia and the role of resilience in mediating that process

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Stigma: A Clinical Risk Factor for Psychopathology and Recovery

13

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Introduction

Mental health is an essential component of a person's capacity to live a fulfilling life, with an ability to form and maintain relationships; to study, work, and pursue leisure interests; to contribute to responsibility-taking; to contribute to the society; and to make day-to-day decisions about education, employment, housing, and other choices. Disturbances to a person's mental well-being can adversely compromise this capacity, leading not only to decrease in functioning at the individual level but also to broader welfare losses for the household, society, and nation. Despite the high prevalence of mental illness, most people do not access by choice, or do not have access to, professional healthcare for mental health problems; hence, psychiatric illnesses frequently remain undiagnosed and untreated. Larger populations do not access mental healthcare by choice as a consequence to the stigma attached to mental health, where talking about it alone is considered taboo.

The key barriers to seeking help are the following: public, perceived, and self-stigmatising attitudes to mental illness; difficulty identifying the symptoms of mental illness; concern about the characteristics of the provider; poor knowledge about mental health services; lack of accessibility (e.g. time, transport, cost); difficulty or an unwillingness to express emotion; and worry about effect on career and other aspects of daily life [1].

The causes of stigma are manyfold, one of which is the undue importance to the label of mental illness in our society. It is not surprising that the majority of patients, when being asked about strategies for stigma coping, recommend keeping mental illness a secret or even avoiding contact with other people [2]. This is more so in girls and females for fear of difficulty in getting married. Also, stigmatising views about mental illness are not limited to uninformed members of the general public; even well-trained professionals from most mental health disciplines, including medicine, have stereotypes about mental illness.

Although such attitudes are not limited to mental illness, the public seems to disapprove of persons with psychiatric disabilities significantly

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more than persons with related conditions such as physical illnesses. Different illnesses arouse different kinds of emotional reactions from people, for example, illnesses like heart disease or cancer arouse a feeling of sympathy, communicable diseases garner a fear of getting infected from the sufferer, and other disfiguring conditions may lead to feelings of disgust. Unfortunately, emotional reaction to mental illness is usually more than all these; it is perceived as something strange, mysterious, or dangerous. Such discrimination is usually based on unfounded irrational misconceptions and stereotypes about mental disorders. Unlike physical disabilities, persons with mental illness are perceived by the public to be in control of their disabilities and responsible for causing them [3].

Stigma and Its Types

Stigma is a Greek word which means "mark" or "tattoo" that was cut or burnt into the skin, to identify criminals, traitors, and slaves as morally polluted and shunned by the public [4]. Stigma can occur in many different forms and most commonly deals with culture, race, gender, body appearance, illness, and disease. Stigma may also be described as a label that associates a person to a set of unwanted characteristics that form a stereotype and is affixed. Once a person gets labelled with stigma, others will assume that is just how things are, and the person will remain stigmatised until the stigmatising attribute is addressed. However, the attributes that society selects differ according to time and place [5].

Stigma may affect the behaviour of concerned persons. They start acting in a way that is not expected of them, which affects their emotions and beliefs. The stigmatised individual/social groups often face prejudice that causes depression leading to identity crisis and low self-esteem [6].

Erving Goffman describes stigma as an "attribute, behaviour, or reputation which is socially discrediting in a particular way". Goffman also defined the meaning of the word "stigma" as a special gap between vital social identity and actual social identity. Goffman's meaning on "vital social identity" relates to the way we represent ourselves with people we don't see, and for his take on "actual social identity", he explains it as the way we deal with people in real life [7]. According to Goffman, there are three types of stigma, which is a discrepancy between actual and virtual social identity that causes us to alter our estimation of others negatively [8].

Goffman divides the individual's relation to a stigma into three categories:

- *The Stigmatised*—those who bear the stigma. The stigmatised are rejected and shunned. They experience discrimination and prejudice and are also associated with negative physical and mental health outcome.
- *The Normal*—those who do not bear the stigma.
- *The Wise*—those among the normal who are accepted by the stigmatised as "wise" to their condition.

A recent study showed empirical support for the existence of the own, the wise, and the normal as separate groups; but the wise appeared in two forms: active wise and passive wise. Active wise encouraged challenging stigmatisation and educating stigmatisers, but passive wise did not [9].

The Six Dimensions of Stigma

Jones and others added the "six dimensions" and correlated them to Goffman's two types of stigma, discredited and discreditable [10]. There are six dimensions that match these two types of stigma:

1. *Concealable*—extent to which others can see the stigma
2. *Course of the mark*—whether the stigma's prominence increases, decreases, or is terminated
3. *Disruptiveness*—the degree to which the stigma and/or others' reaction to it impedes social interactions
4. *Aesthetics*—the subset of others' reactions to the stigma, comprising reactions that are positive/approving or negative/disapproving but

represent estimations of qualities other than the stigmatised person's inherent worth or dignity
5. *Origin*—whether others think the stigma is present at birth, accidental, or deliberate
6. *Peril*—the danger that others perceive (whether accurately or inaccurately) the stigma poses to them

Stigma in Psychiatric Disorders with a Focus on Schizophrenia

As an underlying condition, stigma prevails across all mental illnesses. However, the severity of stigma increases with severe mental illnesses such as schizophrenia and psychotic disorders. It is difficult to clearly demarcate the difference between the causes and consequences of stigma due to an overlapping phenomenon that exists among the two processes. However, stigma continues to exist as a clinical situation that poses clinical risks along with a bundle of problems that deteriorate the outcome of treatment in schizophrenia [11, 12].

The global state of mental illnesses has battled an extreme form of stigma to reach its current state. From institutionalised mental healthcare to the deinstitutionalised movement and the rehabilitative care model approach, mental health has barely ever been taboo-ridden. While it is not possible that stigma may ever be off the mental health approach, the dynamics and nature of stigma are always changing. Research has shown that there is relatively greater stigma toward severe mental illnesses such as schizophrenia and psychotic disorders [13, 14]. Stigma can have three dimensions: (i) perceived stigma or the way in which an individual believes they are seen by society; (ii) experienced stigma or instances of experience where an individual has faced discrimination/ostracisation; and (iii) self-stigma or when an individual internalises societal public stigma [13]. There is an alternative way to categorise stigma that includes (a) internalised or negative stereotypes and views of permanent flaws accepted by labelled individuals; (b) interpersonal or labelled individuals socially categorised facilitating discrimination; and (c) institutional or labelled individuals excluded by institutional policies and practices [15].

As mentioned, stigma is a clinical condition. It is associated with the symptom constellation and phenomenology of an illness [13]. Stigma is a universal condition. It is one of the leading causes for mental health treatment gap [15]. The burden of mental illnesses climbs above the mere symptom presentations—it is about the first-hand denial of illness severed by stigmatisation of the condition.

Narrowing down the focus on stigma in schizophrenia, there are several aspects that hold a significant value with respect to the treatment outcomes of the illness. There are multiple components of stigma with respect to schizophrenia as an illness: (1) labelling of socially important differences such as hearing voices (hallucinations) or having delusions; (2) linking labelled people with negative stereotypes like saying that people with schizophrenia are violent and unpredictable; (3) categorising people to facilitate social exclusion with labels of "psychotic" or "schizophrenic"; and (4) socioeconomic status loss for and discrimination toward labelled people that includes employment and healthcare inequalities, incarceration, homelessness, and retaliatory violence [16].

There are multiple facets to stigma in schizophrenia that can be understood as the following:

In general, stigma is said to be associated with illnesses that manifest as behavioural disturbances or socially odd behaviours, with schizophrenia being one of the more severe ones as opposed to the less stigmatised perception of somatic complaints.

Following the dimensions of stigma as mentioned above, stigma originates from various sources such the society, general public, infrastructure and resources, policies, familial acceptance, and personal attitudes of an individual. Research shows that a greater share of stigma associated with schizophrenia arises due to societal stigma and least due to self-stigma [13, 15].

Stigma as a condition is seen at all phases of schizophrenia—from onset/prodrome phase of the disorder to illness course, treatment, and

rehabilitation. Research claims that the most stringent effects of stigma are seen during the prodrome and acute phase as the behavioural changes become frank due to socially unacceptable behaviour [13].

The nature of illness of schizophrenia is a debilitating one and is itself stigmatising due to the behavioural oddities (hallucinations, delusions, frank negative symptoms, catatonia) that present as illness symptomatology [17].

Perceived social norms are a crucial contributor to an individual's social distance with those who suffer from a mental illness. Lack of awareness and low levels of education/literacy are reasons that lead to negative stereotypes and prejudiced attitude of the society. People generally have misperceptions that individuals suffering from schizophrenia are violent and sabotaging. Public attitudes and public prejudice are the chief causes of stigma around schizophrenia.

Individuals who have had no contact with mental illness before are also potential sources of stigma.

Attitudes of family members toward schizophrenia determine the stigma that an individual faces in the closest circle of interpersonal relationships and influence the quality and quantity of care/support they receive and the recovery process from the illness [18].

Poor resources, inadequate national mental health policies and programmes, and lack of mental healthcare are institutional deficiencies that encourage stigma to sustain.

The greatest devitalising effect of stigma is observed as delayed intervention or poor early intervention as individuals deny treatment, prolong to harbour stigmatised views of the public and self, and thus, lose on the quality of life that could persist with intervention at an earlier stage. This further accentuates stigma in the treatment process, which not just involves delayed treatment but also noncompliance of medication, wearisome recovery, and overall treatment dropout, which increases the stigma. Public prejudice may also impact treatment where the individual may absolutely deny treatment or end treatment prematurely.

Stigma also emanates among primary healthcare and mental healthcare professionals, in their attitudes toward the patients in the treatment phase of schizophrenia, which may aggravate the stigmatised outlook to schizophrenia among the general community.

Stigma around schizophrenia is also an outcome of work environment and colleagues'/coworker attitudes who are reported to make fun and outgroup those with schizophrenia. It is an unpleasant situation that further increases self-stigma in suffering individuals.

Criminalisation of mental illnesses is another institutionalised source of stigma that involves growing intolerance of forensic issues and general human rights issues [13].

Poverty is another stigmatising factor that deters effective mental health treatment and social inclusion. The association is stronger in lower- and middle-income countries. There are increased social stressors as a resultant of poverty and various other factors, such as impoverished nutritional state and poor affordability.

Media representations such as those in movies, radio broadcasts, and other media are also reported to be stigmatising, especially for illnesses such as schizophrenia [15].This instigates further taboo related with illnesses in the society.

Stigma is also medication-induced, where side effects of drugs may cause discomfort to the individual and lead to internalisation of stigma. Frequent hospitalisations are also one of the reasons for stigmatisation and early and repetitive relapse.

Research has shown that being a female and being young as a patient of schizophrenia led to relatively higher stigma than in the counterparts [17].

Low self-esteem, low mood, depression, self-isolation, and post-hospitalisation suicide are common after the treatment of schizophrenia and bear a link with the attached stigma.

The consequences of stigma, though not very distinguishable, are exhausting. It can be life-threatening and humiliating, can deprive an individual of their basic needs, marginalises them and leads to poorer psychosocial support and low self-esteem which affects interpersonal relationships and marriage prospects, and can lead to ostracisation from the society. These consequences of stigma are seen across the duration of illness, from the onset to the course and treatment of illness. The nature, determinants, and conse-

quences of stigma vary with socio-demography and cultures.

Stigma and Recovery: An Indian Perspective

Stigma has been shown to lead to complete social devaluation of a person who suffers from psychiatric disorders [19]. This discrimination leads to disadvantages in many aspects of life including personal relationships, education, social life, and work. Psychiatric patients may lose self-esteem and harbour feelings of shame, social withdrawal, guilt, and a sense of alienation after experiencing stigma [20]. Many patients with psychiatric disorders feel that they may be treated in a discriminatory way and hence hide their illness or refrain from taking up opportunities for treatment and recovery.

Across nations, the meaning, society attitudes, and outcome of stigma differ, even when we find stigmatisation to be a powerful and most likely response to illness and disability [21]. A large body of stigma and mental health research has been done in the West, and there is a dearth of research to understand the experience of stigma and how it may be burdensome in the Indian context [22].

Studies on stigma in India started over 30 years ago, but recent research has reported severe levels of stigmatising attitudes toward patients with mental illness among community members and healthcare workers [23]. The effects of stigma on seeking help, treatment compliance, and recovery have been shown to be high. A study reported that patients with psychiatric problems were ridiculed, avoided, or looked down upon by society. They were also starved or given stale food, kept home bound, chained, tied up, and beaten or hit with stones. They were subject to ridicule, insults, and lack of respect from family members [24]. Male psychiatric patients experienced stigma with regard to employment, work place, and earning, while female patients experience the same in relation to marriage, childbirth, and purely out of their belonging to the female gender [25].

Many studies have shown that stigmatising reactions were often expressed by family members and neighbours [26]. In a study that had 76 women with schizophrenia whose marriages had broken, qualitative methods were used to assess and gather information about stigma. The majority were abandoned by their husbands and very few received financial support, while others experienced beating, domestic violence, emotional torture, and neglect. Many felt themselves a burden to their own parents and received hostility from family members and their spouse [27].

There are few studies on the determinants of subjective experiences of stigma in India, and very little qualitative research is available. Indian research on stigma in mental illness across diverse income groups is poor and yields no conclusive evidence [28]. The nature of the mental illness, symptoms, diagnosis, and aggression or violent behaviour in determining social reactions has been studied [29]. Stigma in India must be understood in transcultural contexts and with what is at stake [30].

Hindu philosophy, in Indian society across different religious groups, holds that doing one's duty in life (living in accordance with "Dharma") is central to a moral life and that living by the ways of conduct described by Dharma (i.e. meeting social role expectations and codes of behaviour) shall lead to purification of mind and, ultimately, Moksha (liberation) [31]. Furthermore, employment holds added importance in India, with minimal state government welfare provisions, and loss of income from mental illness affects families existentially. Many patients in India are sole income generators, and cost-effective treatment with minimal days of loss at work may not always be possible due to the nature of mental illness itself [32]. Unemployment poses huge threats to a man's social status, while remaining unmarried is a huge stigma for women and plays a vital role in recovery from psychiatric illnesses like schizophrenia [33].

Marriage and schizophrenia in Indian society are looked at as a desired outcome, an economic necessity, a social role expectation, and a potential "cure" for the illness [34]. In a recent study, women with schizophrenia and broken marriages perceived the loss of social status associated with a broken marriage as more burdensome than even the stigma associated with their mental illness, affecting long-term recovery and treatment compliance [35].

Mental health professionals are aware of the harmful effect of stigma against mental illness. One of the earliest scales questionnaires developed was culture specific, valid, and reliable, along with the development of socioculturally relevant vignette stories [36, 37]. In an early review on the subject, it was stated that "The general trend of the studies carried out in India indicate that the lay public, including the educated urban groups, are largely uninformed about the various aspects of mental health. The mentally ill are perceived as aggressive, violent, and dangerous. There is a lack of awareness about the available facilities to treat the mentally ill, and a pervasive defeatism exists about the possible outcome after therapy. There is a tendency to maintain social distance from the mentally ill and to reject them" [38].

An early review on stigma mentions that "Mental illness is usually perceived as something strange, mysterious, and also dangerous. It is probably due to the difficulty in communicating with persons having mental illness and a certain unpredictability about their behaviour. Such discrimination is usually based on unfounded irrational misconceptions about mental illness" [39]. The common man has a general concept of mental illness where mental illness is equated with being mad or insane, and this thus affects recovery from illnesses like schizophrenia [40]. Research reports maximum prejudice faced in India faced by patients with schizophrenia [41].

Mental illness has always been reported as something to ridicule, something to laugh at, which is bizarre, disgusting, or frightening. But the current trends point toward the opposite, with media being supportive of mental health and the mentally ill in recent years [42].

Summary of Research Findings on Stigma and Recovery

Reviews on attitudes toward mental illness summarised some recent findings: People are currently better informed about mental illness. The public's ability to label a broader range of behaviour as mental illness has also increased. However, even though mental illness seems to be accepted as an illness like any other, people's feelings about it are not consistently shaped by this cognitive awareness. This shall aid faster recovery in illnesses like schizophrenia [43].

Factors in the patients with schizophrenia and other disorders that influence public attitude include frequency of actual or anticipated behavioural events; extent to which violence is an issue; intensity of the behaviour; visibility in the open community and geographic location; the degree of unpredictability; and the loss of accountability [44].

Increasing age, lower socioeconomic status, and lower educational level are associated with greater intolerance and rejection in patients with schizophrenia. Among the relatives, the lower the socioeconomic class, the greater the feelings of fear and resentment, whereas the higher the socioeconomic class, the greater the feelings of shame and guilt [45].

Even taking into account the inadequacy of delivery of mental healthcare services in many countries, there is still general reluctance in seeking psychiatric care. People would choose friends, family doctor, relatives, or clergymen before resorting to professional psychiatric services. This delays recovery from illnesses like schizophrenia [46].

Stigma may be real or perceived (i.e. fear of stigmatisation by the patient and family). Fear of rejection, self-doubts, concealment, and withdrawal can be far more significant barriers to full social reintegration than the stigma associated with negative public attitudes. This has been reported widely to affect recovery in patients with schizophrenia [47].

There exist more supernatural, religious, moralistic, and magical approaches to illness and behaviour. While they may confer strong stigma in some cultures, they may not in others (e.g. the sufferer may not be blamed for an external cause and the course is expected to be brief). Engaging in these forms of treatment for respite rather than scientific approaches may affect recovery from schizophrenia [48].

Assessment of Stigma

Stigma is an invisible, clinical component of mental health. Several assessment tools have been developed to make an attempt to quantify stigma in order to make it a measurable entity and, thus, address it appropriately. There are various ways to assess stigma in an individual or in a group to understand their attitude and acceptance. Some of them are as follows:

Social Distance One of the most commonly used measures is that of social distance. This assesses a person's willingness to interact with a target person in different types of relationship. It has good to excellent internal reliability and good construct validity. There are two main limitations to its validity—social desirability bias and difference between reported intentions and behavioural responses [49].

Semantic Differential and Related Measures This provides a direct assessment of stereotyping. This also has the limitation of social-desirability bias.

Opinions About Mental Illness (OMI) This scale was developed by Cohen and Struening. OMI has a wide spectrum of coverage of issues, and it also measures changes in attitudes over time [50].

Community Attitudes Toward the Mentally Ill (CAMI) The scale includes 40 items. It measures attitudes toward community mental health treatment facilities [51].

Emotional Reaction to Mental Illness Scale It is developed by Angermeyer and Matschinger. It has three dimensions: aggressive emotions, prosocial reactions, and feelings of anxiety.

A brief self-report scale to measure the stigma related to mental illness is available. The scale measures both felt and enacted stigma and consists of 42 questions. The questionnaire takes 5–10 min to complete. This scale is similar in content to that the Internalised Stigma of Mental Illness scale developed by Ritsher and others [52].

A Stigma Quantification Scale has been developed that can help to identify individuals having severe stigma. It consists of 49 items and 3 subscales: self-experience, illness-related consequences, and coping strategies. Some believe that this scale can also change stigmatisation levels [53].

Assessment of knowledge, attitudes, and emotions regarding stigma is also a way of measurement of stigma itself. Measuring knowledge about mental illnesses is a good predictor of readiness for treatment, compliance, and long-term maintenance in treatment. Knowledge measures are relatively easy to administer and score. Attitudes can be measured using behavioural intention, which can be done by direct observation. Behavioural intentions, which are proximal to the time when the behaviour will occur, are more likely to reflect actual change. Emotional reactions are measured using self-report instruments [54].

Stigma and Its Role in Recovery from Schizophrenia

Stigma cripples the recovery process of an individual suffering from any illness. With the abovementioned factors that contribute to stigma, a vicious cycle gets created that prolongs stigma, further disabling the outcomes of mental illnesses (Fig. 13.1). The outcome of treatment of schizophrenia can be understood from the similar standpoint.

The stigma faced by individuals suffering from schizophrenia is doubled, taken the nature and course of illness. The problems begin right from delayed early intervention due to stigma and continue to rehabilitating individuals after treatment process [55].

To begin with, there is a stigma of the diagnosis itself. Stigma prevents early intervention during the onset of schizophrenia that only promises a debilitating course of the illness with poor psychosocial adjustability. With growing symptoms and lack of awareness (and consequent lack of sensitivity), schizophrenia becomes a matter of targeted discussion, and the individual ends up feeling further stigmatised. Feelings of low mood and sometimes depression are likely consequent.

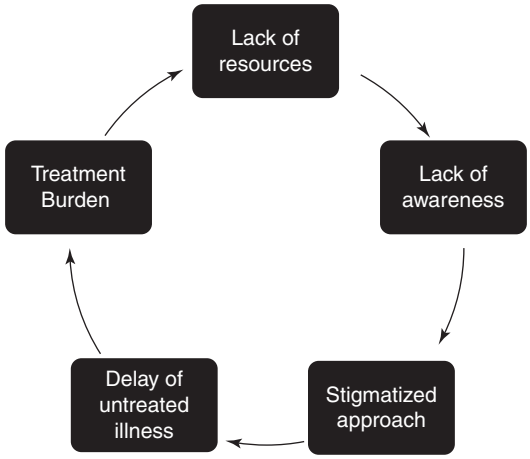

Fig. 13.1 A cycle of events reinforces stigma. (Original figure by co-author Pragya Lodha; used with permission)

Violence and aggression are also likely seen to spurt. The availability of resources, infrastructure, and the policy of provisions also play a crucial role in aiding the illness or further deteriorating its status [56].

The course, nature, and treatment of the illness, medications being taken—and their side effects—can be an additional cause of stigma apart from the society's prejudiced understanding about the illness. Thus, stigma during the treatment phase of the illness is one of the stronger factors when an individual internalises stigma or when the self-stigma strengthens (see Table 13.1). This impacts the potential recovery rate and relapse prevention in the illness of an individual. Going to work during the treatment phase or in the recovery phase is further stigmatised with institutional stigma, self-stigma, and lack of inclusion/acceptance in the workplace and among peers [57].

Anti-stigma Interventions

Stigma is a clinical risk that deters recovery and treatment process in schizophrenia. Being a clinical condition, it must be treated in a similar way in order to make the outcomes in schizophrenia treatment more resilient. There have been both broad-based and specific-focused interventions to address stigma, however, with a spectrum that addresses the problems faced by the patient and the caregivers. There has been a long-standing public health perspective to stigma [13]; however, the present need of the hour is to address stigma from a clinical standpoint in order to target prevention and intervention for stigma.

The following would contribute toward effective anti-stigma interventions, aiding better care and treatment for schizophrenia [58]:

- Psychoeducation to the patient and his/her family to inform about the nature and course of illness, preventions to be taken, and adherence to treatment.
- Psychoeducational programmes must also address sensitivity toward the burden caused to the patient and the caregivers during the course of the illness.
- Effective early intervention can reduce stigma, delay relapse, and ensure a prolonged quality of life.
- One-on-one and face-to-face sessions with the patient are a prime recommendation for higher retention in treatment.
- Increasing public and community awareness to make mental health and mental illnesses a sensitive issue and part of colloquial narration with reduced attached stigma.
- Increasing the overall mental health literacy.
- Imparting the knowledge of mental illness from a biological-psychological-sociological model of understanding vs only a biological explanation.
- Addressing stigma straightforwardly rather than avoiding the topic.
- Encouraging treatment of mental disorders is one of the most progressive and direct ways of attacking stigma.
- People may not choose to speak about their mental health condition, but approaching for treating silently also is a step forward.
- Comorbid conditions of depression and suicidal ideation should be directly addressed as part of the treatment.
- Enhancing access to care, relapse prevention, and early identification are some of the other measures.

Table 13.1 Various causes and consequences of stigma at different phases of schizophrenia

Phase of schizophrenia	Causes of stigma	Consequences
Onset/prodrome	Lack of awareness, lack of education, denial due to interpersonal/societal stigma, stigma of diagnosis	Delayed early intervention
Acute phase	Due to socially unacceptable behaviour and behavioural disturbances, role of media representations	Considered violent and dangerous to society, socially isolated
Treatment phase	Medication induced stigma due to side effects, internalised/self-stigma	Noncompliance, premature termination, early relapse, debilitating condition, suicide, lack of self-care, violence
Rehabilitation phase	Public stereotypes, self-doubt and low self-esteem, self-denigration	People are made fun of especially at work, social isolation, compromised psychosocial abilities, suicide

- Completion of treatment, risk management, relapse prevention, and rehabilitative facilities are one of the stronger markers to deal with stigma attached with outcomes in schizophrenia.
- Improving access to mental healthcare by bridging the treatment gap and providing new and more services.
- Individualised and tailored treatments to best suit the needs of the patients are also a promising intervention.

An integrated approach of public health and clinical practice for addressing the stigma around schizophrenia is an ideal one. Stigma may never be eradicated from the face of mental illness, but we, as a community, can always work toward reducing it and normalising mental illnesses in order to facilitate care.

Conclusion

After an extensive discussion, it is evident that stigma in mental illness leads to adverse outcomes. It is due to stigma that patients with mental illness avoid seeking treatment. This leads to increase in the symptoms and exacerbation, which in turn causes further stigma. As stigma affects the line of treatment, we need more systematic ways to manage stigma and improve the outcome. An evidence-based approach is required to understand what to change and how to make this change possible.

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Part IV

Challenges for Good Outcome and Recovery

Attenuated Psychosis Syndrome

14

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Introduction

Schizophrenia is a neurodevelopmental disorder characterized by psychosis (e.g., delusions, hallucinations, and disorganized communication), negative symptoms (motivational deficits and decreased emotional experience/expression), cognitive deficits (e.g., processing speed and verbal memory), and impairment in social and academic/vocational function. As schizophrenia is associated with significant morbidity and cost, for both patients and their families [1–3], and is as yet refractory to cure, there has been an effort to identify at-risk individuals before the onset of psychosis and provide preventive intervention to improve outcomes [4, 5].

Psychosis onset in schizophrenia is typically preceded by a prodromal stage, characterized first by social withdrawal and nonspecific affective symptoms of anxiety and depression, and then the emergence of psychotic-like symptoms such as unusual thought content, suspiciousness, perceptual disturbances, and subtle disturbance in language [5–7]. This prodromal period typically has its onset between the ages of 12 and 35 [8] and can last from months to years [9–13].

Research into the putative schizophrenia prodrome began in the early- to mid-1990s as researchers sought to gain insight into schizophrenia before psychosis onset [9–11, 14]. This work inspired the development of criteria to identify individuals during a putative prodromal state, comprising the clinical or ultra-high-risk (CHR/UHR) syndrome for psychosis [15]. The main goals of clinical psychosis risk research have been early identification and intervention to prevent psychosis onset and improve clinical and functional outcome. Over the past two decades, there has been a significant increase in the number of early detection and intervention programs worldwide and several efforts to design and test preventive intervention strategies.

The main operationalized criteria to identify the CHR/UHR syndrome is the presence of

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clinically significant attenuated or subthreshold psychotic symptoms in the absence of any prior threshold psychosis, which cannot be attributable to medical illness or exposure to drugs of abuse. These criteria were first described in the Comprehensive Assessment of At-Risk Mental States (CAARMS) [16]. There is a second and very similar measure that has been used in North America, the Structured Interview for Prodromal Syndromes (SIPS)/Scale of Prodromal Symptoms (SOPS) [17], adapted from the positive and negative syndrome scale (PANSS) [18]. These two measures have overall agreement in the identification of CHR/UHR [19]. Individuals identified as at CHR/UHR for psychosis typically meet criteria for the Attenuated Positive Symptom Syndrome (APSS), though a few also (or exclusively) meet criteria for Brief Intermittent Psychotic Syndrome (BIPS), and/or Genetic Risk and Decline (GRD), comprised of familial risk or schizotypy in the context of a significant decline in function.

In developing preventive interventions for CHR/UHR individuals, investigators have focused on positive symptoms as a primary outcome measure (e.g., psychosis onset and/or the proxy of worsening positive symptoms over a shorter timeframe). Other outcome measures in studies have included improvement in negative symptoms, cognition, and function.

Approaches for Intervention to Prevent Psychosis

Treatment for the putative prodrome is still a nascent field, with no evidence base for intervention yet established. The first manuscripts describing studies of preventive intervention for CHR/UHR individuals were published in 2002, including an open-label trial of risperidone to assess efficacy and safety [20] and two larger RCTs of cognitive behavioral therapy (CBT), one alone [21–23] and the other in combination with risperidone (Table 14.1) [24]. An RCT of olanzapine vs. placebo in CHR/UHR individuals was published in the following year [25], suggesting efficacy in psychosis prevention but at the cost of significant weight gain. The rationale for testing antipsychotics was that their efficacy in treating threshold psychosis might extend to earlier, more attenuated, or subthreshold psychotic symptoms. A similar rationale existed for CBT, with the additional advantage of not having problematic adverse effects such as weight gain and akathisia, but its efficacy has been less clear. The combination of CBT with risperidone showed both efficacy and safety in an RCT in CHR individuals [24], as compared with treatment as usual (TAU), though has not yet been replicated (see Table 14.1). In the ensuing years, other preventive interventions have been tested, including pharmacological strategies, such as omega fatty acids, lithium, and D-serine; psychological approaches, including additional CBT studies, cognitive remediation, and family therapy; and studies that combine both pharmacological and psychological strategies.

Pharmacological Interventions

Antipsychotics

Antipsychotic medications are an established effective treatment for acute psychosis [26]. Antipsychotics are based on the dopamine model of psychosis and inhibit dopamine activity at D2-type dopamine receptors [27–29]. Second-generation antipsychotics (SGA) have typically been tested in CHR/UHR cohorts, as serious adverse effects like tardive dyskinesia are far less common than for first-generation antipsychotics (FGA) [30, 31].

One of the first studies examining the efficacy and tolerability of antipsychotics in a CHR/UHR sample was an open-label trial of risperidone [20]. The mean dose of risperidone was 1.04 mg/day (SD = 0.12). The primary outcome, symptom severity, was assessed using the Child Behavior Checklist (CBCL) [32] in a CHR/UHR sample (n = 5; mean age = 15.6; SD = 0.8) and the PANSS in a first episode psychosis (FEP) sample (n = 11; mean age = 23.9; SD = 5.5). In the CHR/UHR sample, follow-up was at 12 weeks, and thought disorder (t = −5.9; p = 0.01) and attention symptoms (t = −40.6; p = 0.0001) decreased

Table 14.1 Randomized clinical trials in clinical high-risk cohorts

Authors	Active treatment	Comparison treatment	Duration	Outcome	Findings
McGorry et al. [24]	Combined CBT and Risperdal ($N = 31$)	Supportive treatment ($N = 28$)	6 months with 6-month follow-up	Transition to psychosis and overall functioning	Active treatment reduced the risk of transition to psychosis
Morrison et al. [22]	CBT ($N = 37$)	Monitoring ($N = 23$)	6 months with 12-month follow-up	PANSS and DSM-IV criteria for psychotic disorders	Active treatment reduced the risk of transition to psychosis
McGlashan et al. [40]	Olanzapine ($N = 31$)	Placebo ($N = 29$)	12 months with 12-month follow up	Transition to psychosis and overall functioning	Active treatment reduced the risk of transition to psychosis (but substantial weight gain)
Ruhrmann et al. [97]	Combined needs-focused intervention and Amisulpride ($N = 65$)	Needs based intervention only ($N = 59$)	12 weeks	Prodromal symptoms, global functioning and extrapyramidal side-effects	Active treatment led to symptomatic and functional improvement (with prolactin side effects)
Amminger et al. [46]	ω-3 PUFA ($N = 41$)	Placebo ($N = 40$)	12 weeks with 12-month follow-up	Transition to psychosis and overall functioning	Active treatment reduced the risk of transition to psychosis and led to symptomatic and functional improvement
Addington et al. [74]	CBT ($N = 27$)	Supportive therapy ($N = 24$)	6 months	Transition to psychosis and symptoms	Active treatment did not reduce the risk of transition to psychosis (low rates in both groups with general improvement)
Morrison et al. [75]	Combined cognitive therapy and monitoring of mental state ($N = 144$)	Monitoring of mental state only ($N = 144$)	6 months	Transition to psychosis, psychotic symptoms, and quality of life	Active treatment did not reduce the risk of transition to psychosis (low rates in both groups with general improvement)
Van der Gaag et al. [76]	CBT focusing on normalization and awareness of cognitive biases ($N = 98$)	Treatment as usual (TAU) ($N = 103$)	6 months with 18-month follow up	Transition to psychosis, and symptoms of depression/anxiety, quality of life, social functioning	Active treatment reduced the risk of transition to psychosis and led to symptomatic and functional improvement
Bechdolf et al. [86]	Integrated psychosocial intervention ($N = 63$)	Supportive counseling ($n = 65$)	12 months	Transition to psychosis	Active treatment reduced the risk of transition to psychosis
Woods et al. [62]	Glycine ($N = 4$)	Placebo for double blind ($N = 4$)	12 weeks	Changes in psychotic and depression symptoms	Active treatment led to symptomatic improvement
McGorry et al. [98]	Combined cognitive therapy and risperidone ($N = 43$)	A) Combined cognitive therapy and placebo ($N = 44$) B) Combined supportive therapy and placebo ($N = 28$)	12 months with 12-month follow up	Transition to psychosis, symptoms, psychosocial functioning, and quality of life	No group differences; all 3 groups improved

(continued)

Table 14.1 (continued)

Authors	Active treatment	Comparison treatment	Duration	Outcome	Findings
O'Brien et al. [80]	Family-focused therapy (FFT-CHR) providing psychoeducation, communication and problem-solving training ($N = 66$)	Enhanced care (EC): three psychoeducation therapy sessions ($N = 63$)	6 months with 6-month follow-up	Prodromal symptoms, family tension and communication	FFT-CHR individuals and family members showed greater increases from baseline to 6 months in active listening and calm communication and greater decreases in irritability and anger, complaints and criticism, and off-task comments compared to participants in EC
Holzer et al. [87]	Computer-assisted cognitive remediation (CACR) ($N = 18$)	Computer games ($N = 14$)	8 weeks	Cognitive abilities, psychotic symptoms and psychosocial functioning	Superior improvement in CACR group for visuospatial abilities, and improvement in both the control and treatment group for attention, immediate and delayed memory, and general psychopathology, as well as social-occupational functioning
Kantrowitz et al. [63]	D-serine ($N = 20$)	Placebo ($N = 24$)	16 weeks	SOPS scores (negative primary, all secondary) and cognitive abilities	D-serine produced significant improvement in negative symptoms and total symptoms compared to placebo
Loewy et al. [88]	Neuroadaptive cognitive training (Posit Science) ($N = 50$)	Commercially available computer game ($N = 33$)	8 weeks (1 hour/day; 5 days/week)	Cognition (MATRICS)	Significant improvement in verbal memory (but attrition high at 42%)
McGorry et al. [48]	ω-3 PUFA and cognitive behavioral case management (CBCM) ($N = 153$)	Placebo and cognitive behavioral case management (CBCM) ($N = 151$)	6 months with 6-month additional CBCM as needed follow-up period	Transition to psychosis, general levels of psychopathology and functioning	Although ω-3 PUFAs were well tolerated, they did not demonstrate an advantage over placebo in the prevention of psychosis at 6- or 12-month follow-up evaluations Secondary outcome measures of psychiatric symptoms and functioning tended to favor the placebo group
Choi et al. [89]	Processing speed training (PST) ($N = 30$)	Active training treatment (matched for training format and same dose and duration of treatment) ($N = 32$)	3.5 to 4 hours per week for 2 months	Processing speed and social functioning	The PST group showed faster motoric and nonmotoric processing speed at post training and 2-month follow-up and reported better overall social adjustment

significantly from baseline, as did average CBCL scores (t = −3.6; $p = 0.04$). Although the sample was small, there was no placebo group, and the CBCL was used (as opposed to a more psychosis-specific measure, like the PANSS), this study encouraged the development of RCTs to more rigorously evaluate the promise of antipsychotic medications in CHR/UHR.

Risperidone RCTs conducted since Cannon's open-label trial have combined the medication with CBT (see the section "Interventions Combining Psychological and Pharmacological Strategies" and Table 14.1) [33, 34]. Other open-label pilot studies have evaluated antipsychotics such as aripiprazole [35] and perospirone [36]. In an 8-week aripiprazole (5–30 mg/day) trial ($n = 15$), SOPS scores significantly improved from baseline ($p < 0.001$), but more than half of the participants experienced akathisia ($n = 8$). No participants transitioned to psychosis. In a preliminary open-label trial of perospirone for 26 weeks ($n = 11$), the mean changes of total SOPS score from baseline were significant in the CHR/UHR sample ($p < 0.05$). No adverse effects were noted, and none of the participants developed psychosis.

The largest antipsychotic monotherapy RCT to date aimed to evaluate the efficacy and safety of olanzapine in decreasing positive symptoms severity and potentially preventing psychosis onset (see Table 14.1) [37–40]. In a double-blind placebo-controlled RCT conducted at the Prevention through Risk Identification Management and Education (PRIME) clinic, 60 CHR/UHR participants were randomized to olanzapine 5–15 mg/day ($n = 31$) or placebo ($n = 31$) for 1 year, with psychosocial treatment held constant [37–40]. Participants who did not develop psychosis were followed for 1 year, whereas those who transitioned stopped the study drug and were able to participate in an open-label trial of olanzapine 5–20 mg/day. The researchers used the presence of psychotic symptoms (POPS) criteria in the SIPS/SOPS to determine the primary outcome of psychosis onset. Secondary efficacy measures included prodromal symptoms, schizophrenia symptoms, and functioning, changes in which were assessed using the SOPS, PANSS, Clinical Global Impression (CGI) Severity of Illness Scale [41], Montgomery-Asberg Depression Rating Scale (MADRS) [42], Young Mania Rating Scale (YMRS) [43], and Global Assessment of Functioning (GAF) scale [44].

The authors found a trend difference in psychosis onset between groups (16.1% for olanzapine and 37.9% for placebo; $p = 0.08$) in intent-to-treat analysis and a nonsignificant decrease in positive symptoms at follow-up as compared to baseline (SOPS positive symptom score change from baseline = 0.31) in the olanzapine group. Low acceptability of the study medication was reflected in high dropout rates (45%) and dramatic weight gain in the olanzapine treatment arm (8.8 (SD 9.1) kg vs. 0.3 (SD 4.2) kg).

Omega-3 Polyunsaturated Fatty Acids

Another strategy was to test neuroprotective agents for preventive intervention in a CHR/UHR cohort. Omega-3 polyunsaturated fatty acid (PUFA) acts as an anti-inflammatory agent and antioxidant and is thought to counteract the pro-inflammatory reactions and oxidative stress associated with symptoms of schizophrenia [45]. RCTs of PUFA in schizophrenia have had mixed results, though some studies suggest it may be effective earlier in the course of the disorder. Therefore, an RCT of omega-3 fatty acids was completed in a cohort of CHR/UHR individuals (see Table 14.1) [46]. In this 12-month double-blinded RCT of 81 CHR/UHR individuals, administration of four capsules of omega-3 PUFA supplements (1.2-g/d) was given daily for 12 weeks, as compared to placebo, and was associated with a lower rate of transition to psychosis at 12 months (4.9% vs. 27.5%; $p = 0.007$), as well as improvement in positive symptoms ($p = 0.01$), negative symptoms ($p = 0.02$), and general symptoms ($p = 0.01$), and improved functioning ($p = 0.002$), assessed at 1, 2, 3, 6, and then 12 months, as compared to placebo. The primary outcome was measured using the severity thresholds on the PANSS, and the secondary outcomes were measured by the PANSS, MADRS, and GAF. Dropout was low at 6%. Of note, the difference in psychosis onset between the two treatment arms persisted for up to 7 years, suggesting

lasting neuroprotective effects of PUFA [47]. However, despite this early promise, the results of this study have yet to be replicated.

A subsequent study of PUFA vs. placebo in the context of comprehensive care, including evidence-based psychosocial treatment, was inconclusive in that low conversion rates (11.2% for control vs. 11.5% for PUFA) were found for the two groups [48]. In this multicenter RCT, 304 patients were given a daily dose of 1.4 g of omega-3 PUFA or placebo, along with cognitive behavioral case management (CBCM) for 6 months. The outcomes were measured using the Brief Psychiatric Rating Scale (BPRS; [49]), Scale for the Assessment of Negative Symptoms (SANS), MADRS, YMRS, Social and Occupational Functioning Assessment Scale (SOFAS; [50]), and the Global Functioning Scale (GFS) [51]. While only a handful of studies that directly examine the efficacy of omega-3 PUFA in delaying onset of psychosis exist as of now, further study is indicated (see Table 14.1).

Modulators of NMDA Receptors

Amphetamines can elicit psychotic-like symptoms [52, 53]. But phencyclidine (PCP) and ketamine, N-methyl-D-aspartate-type (NMDA) receptor antagonists, have been found to elicit both psychotic-like and negative symptoms, as well as cognitive deficits, similar to those seen in schizophrenia [54]. Given the wide range of symptoms (positive, negative, and cognitive) associated with schizophrenia, medications that target the glutamatergic pathway via NMDA receptors provide an alternative for treating negative symptoms and neurocognitive deficits that are resistant to dopamine-receptor antagonist antipsychotics [55, 56].

As of now, there is no clear evidence base for treatment of negative symptoms or cognitive deficits in schizophrenia. Recent findings from clinical trials using compounds targeting NMDA receptor sites, such as glycine, D-serine, D-cycloserine, and high-affinity glycine transport inhibitors, show promise in alleviating not only positive symptoms but more notably in negative symptoms, especially early in the course of psychotic illness, without significant side effects [55–61].

The first clinical study on the efficacy of glycine in CHR/UHR patients was a two-part study, first using an 8-week open-label design and subsequently followed by a 12-week double-blind, placebo-controlled pilot study [62]. Subjects were outpatients ages 14–35; the Criteria of Prodromal Syndromes (COPS) and a minimum Scale of Prodromal Symptoms (SOPS) score of 20 were used to determine eligibility. Glycine dosage started at 0.2 g/kg once daily, ending at 0.4 g/kg twice daily, for both pilot studies. There were large and significant effect sizes in the open-label phase for changes in SOPS scores (total –1.39, positive –1.10, negative –0.74, disorganized –1.05, general –1.12). Effect sizes in the second phase were less pronounced and were not significant for the glycine group (total –0.71, positive –0.82, negative –0.60, disorganized –0.15, general –0.74). No specific concerns for treatment-emergent adverse events were found using the Systematic Assessment For Treatment Emergent Events (SAFTEE), and there were no significant endpoint changes in vital signs and weight. While the strength of these findings is bolstered by having a representative cohort group of risk syndrome patients (who were adolescents with poor function, 70–75% male, and with a baseline SOPS total score in the high 30s), both studies had very small sample sizes (pilot 1: $n = 10$, pilot 2: $n = 4$ each for glycine and placebo groups) that led to a lack of statistical power (see Table 14.1).

The first study to assess the efficacy of D-serine in CHR/UHR individuals showed markedly improved negative symptoms [63]. Forty-four participants (with assessable data from 15 D-serine and 20 placebo treatment assignments) participated in a double-blind, placebo-controlled, multicenter, parallel-group RCT. Inclusion criteria were similar to the previous Woods et al. study [62], with a minimum severity score of 20 for the total SOPS score and age range of 13–35. D-serine dosage was set at 60 mg/kg per day, divided into two 30 mg/kg oral doses, which was taken daily for 16 weeks. Assessments took place weekly for the first 6 weeks and then biweekly thereafter. The primary outcome was the SOPS score for negative

symptoms, for which D-serine led to a 35.7% reduction, which was significant versus placebo (F 1231 = 4.4, p = 0.03 d = 0.68). Secondary measures such as MATRICS consensus cognitive battery (MCCB) scores did not show significant differences from placebo. The reduction of negative symptoms in this D-serine trial is promising, but requires further replication (see Table 14.1).

Other Pharmacological Interventions

Antidepressants, mood stabilizers, and nonsteroidal anti-inflammatory drugs have also been explored as alternative pharmacological intervention strategies for CHR/UHR, primarily in three pilot studies.

In a naturalistic (non-randomized) study, participants ascertained as CHR/UHR using the SOPS were prescribed one of two types of medications, antidepressants (n = 20) or SGAs (n = 28) [64]. Onset of psychosis was the primary outcome measure: there were 12 cases of psychosis onset in the total sample of 48 (25%), all of whom had been prescribed SGAs. However, 11 of these 12 were nonadherent to the prescribed SGA medication, which suggests the prescription of SGAs was a marker of symptom severity. The high noncompliance rate shows that SGAs are not an acceptable treatment for CHR youths themselves. The study is inconclusive as to the efficacy of antidepressants as there was no randomization to a comparison treatment, such that an RCT of antidepressants in CHR/UHR individuals remains warranted.

Lithium has known neuroprotective properties [65, 66] and so has also been studied as a potential treatment in CHR/UHR patients, in a longitudinal MRI/MRS pilot study of low-dose lithium (n = 21) [67]. Eleven CHR/UHR participants in the experimental group received low-dose lithium, and 10 CHR/UHR participants in the comparison group received treatment as usual (TAU). Primary outcome measures were proton magnetic resonance spectroscopy (1H-MRS) and hippocampal T2 relaxation time (HT2RT) measures. Changes in metabolite concentrations were not significant, but HT2RT was significantly less in the experimental condition compared to control group (p = 0.018), suggesting that low-dose lithium may protect the hippocampus in CHR/UHR.

Inflammation and oxidative stress are potentially important in the development of prodromal and psychotic symptoms [68, 69], and trials with anti-inflammatory drugs are therefore indicated. According to clinicaltrials.gov, there has been an RCT of aspirin 1000 mg/day vs. placebo, with a plan to test inflammation markers and genetic samples. However, results of this RCT have not yet been published.

Psychological Approaches

Cognitive Behavioral Therapy (CBT)

CBT for psychosis emerged consequent to observed partial effectiveness of antipsychotics, challenges for patients in adhering to antipsychotic medication regimens, symptom relapse despite medication adherence, and the limited scope of symptoms that antipsychotics target [70]. In contrast, CBT for psychosis offers a side effect-free, structured, flexible, and time-limited intervention [71]. The cognitive model of psychosis centers around the impairing impact of negative appraisal of psychotic symptoms [72]. For instance, negative appraisals of symptoms and oneself are linked with depressed mood [73] and persistence of delusions in schizophrenia populations. Since its inception, CBT for psychosis has been extended to CHR/UHR and is a growing field of study. To date, there are four CBT monotherapy RCTs in CHR/UHR, which have assessed efficacy of CBT for psychosis in reducing psychosis onset and decreasing positive symptoms.

The earliest CHR/UHR psychological intervention study was a single-blind RCT of CBT vs. mental state monitoring with individuals at high risk for psychosis from the early detection and intervention evaluation (EDIE) program [22]. The primary aim of the intervention was to determine if CBT could significantly reduce the rate of transition to psychosis as compared with TAU in help-seeking CHR/UHR individuals. Transition to psychosis was operationalized in three ways: PANSS-defined psychosis scores, meeting DSM-IV criteria for a psychotic disorder, and/or the prescription of antipsychotic medication.

Sixty high-risk participants were randomly assigned to the TAU control group (monitoring only; $n = 23$) or the experimental group (up to 26 CBT sessions plus monitoring; $n = 37$) for 6 months. Randomization was stratified by gender and family history of psychosis. In this 3-year study, there were monthly follow-ups in the first year and then follow-ups every 6 months for the next 2 years, with PANSS used to measure symptoms. Low attrition rates (14%) suggest that both conditions were tolerable (see Table 14.1).

At 1-year follow-up, the researchers reported a significant main effect of CBT for PANSS-defined transition ($p = 0.03$) and antipsychotic prescription ($p = 0.01$). At 3-year follow-up, the main effect of CBT was not significant ($p = 0.24$). Taken together, the results of this study were inconclusive. Certain elements of the monitoring component in both conditions incorporated case management, rendering it difficult to identify CBT-specific aspects of intervention as the main ingredient of psychosis prevention. Furthermore, the authors' conclusion that the 6-month CBT treatment was effective in reducing transition to psychosis over a 12-month period is based on a post-hoc exclusion of two participants because they were discovered to meet criteria for psychosis after randomization into the experimental group. In addition, the small sample size and broad operationalization of conversion to psychosis make interpretation of the results less clear. Depending on the criteria used to determine transition to psychosis, transition rates ranged from 14% to 20% in the experimental group and 22% to 35% in the control group. Although this study had limitations, it did offer the promise of using nonpharmacological interventions to treat attenuated psychosis symptoms and prevent psychosis onset, spurring a movement in CBT RCT research.

The second study was a single-blind 6-month trial of CBT vs. supportive therapy that entailed monitoring at 6, 12, and 18 months [74]. Ascertainment methods differed from the previous CBT study, as the SIPS/SOPS was also used to measure the severity of attenuated positive symptoms over time. Randomization was stratified by gender and prodromal symptom severity, and participants were assigned to either a 20-session CBT treatment ($n = 27$) or supportive therapy treatment ($n = 24$). Supportive therapy did not include CBT techniques and was considered treatment as usual (TAU). The SIPS/SOPS was also used to determine conversion to psychosis.

The sample size was modest ($n = 51$), and there was a high dropout rate (25%; see Table 14.1). Additionally, only 5% of the sample developed psychosis. Further, only 60% of the participants completed the 18-month follow-up. SOPS positive symptoms significantly decreased over time in both groups ($p < 0.001$), without any significant difference in improvement between them. Raters were blind and treatment fidelity was high (91% of the treatment tapes were rated correctly). This RCT suggests that there are nonspecific factors in psychotherapy that may offer benefit to patients. Alternatively, in the absence of a comparison "follow-along" group, it is unclear if the low conversion rate was due to ascertainment of participants for this RCT or nonspecific effects of clinician contact. Overall, it is difficult to draw conclusions about the efficacy of CBT from this study.

A third single-blind multisite RCT evaluated 26-session CBT plus mental state monitoring vs. mental state monitoring only [75]. Both conditions were in addition to TAU, which was routine clinical care that varied by treatment site; therefore, randomization was stratified by site. CAARMS scores were a primary outcome measure and were ascertained at baseline and then at 6, 12, 18, and 24 months. Rater blinding was moderately successful (22.2% of the participants had treatments that featured blind breaks). Although this RCT was the first CBT study with a large sample ($n = 288$), there were no significant differences in conversion to psychosis between the experimental ($n = 144$) and comparison ($n = 144$) groups. However, there was a within-group effect in that frequency and intensity of psychotic experiences were significantly reduced in the experimental group ($p = 0.02$; see Table 14.1).

A fourth RCT, the Dutch Early Detection and Intervention Evaluation (EDIE-NL), implemented a single-blind multisite intervention comparing 26-session CBT plus TAU ($n = 97$) vs. TAU ($n = 104$) with 18-month follow-up [76].

Randomization was stratified by site and assessors were blinded. The primary outcome for the CHR participants (n = 201) was transition to psychosis, as measured by the CAARMS at baseline, and then at 2, 4, 6, 12, 15, and 18 months. Treatment fidelity is challenging to gauge, as therapy sessions were not recorded, but the authors did report therapists' competency ratings on the Revised Cognitive Therapy Scale. This study is the most promising in terms of efficacy in preventing psychosis onset: significantly fewer ($\chi 2$ (1) = 5.575, P = 0.03) CHR/UHR participants in the experimental group (n = 10) transitioned to psychosis than in the comparison group (n = 22) (see Table 14.1) [76].

The CHR/UHR CBT studies to date have had particularly low conversion rates, suggesting potential methodological concerns (e.g., ascertainment of healthier individuals at lower risk), or perhaps the influence of a nonspecific efficacious element in psychological treatment. Future RCT studies could parse out this question by including a follow-along group.

Family-Focused Therapy

Most treatments for CHR/UHR focus on the individual. However, family dynamics also play a role in the prodrome and FEP [77, 78]. Families play a role in help-seeking and treatment, as well as in social and role functioning. Family-focused therapy adapted for CHR/UHR (FFT-CHR) is a psychosocial intervention that aims to address the individual in the context of his or her family. Thus far, there has been one RCT of family therapy in CHR/UHR. This 6-month multisite RCT (n = 129) used the SIPS/SOPS to ascertain CHR/UHR status and compared 18 sessions of FFT-CHR to 3 sessions of general family psychoeducation [79, 80]. Both treatment assignments were in addition to TAU, which included concurrent antipsychotic, antidepressant, psychostimulant, anxiolytic, and mood stabilizer medication use. FFT-CHR involved 1-hour family sessions that focused on psychoeducation, communication enhancement training, and problem-solving. The intervention mirrored CBT in the assignment of homework between therapy sessions. Independent evaluators were blinded.

The primary outcome measures in this FFT-CHR RCT were SOPS positive and negative symptoms. Attenuated positive symptoms improved more in the experimental than in the control group (F[1,97]=5.49, P = 0.02). Negative symptoms improved for both groups, but improvement was not significantly related to treatment group assignment. Transition to psychosis using SIPS/SOPS criteria and psychosocial functioning was also an outcome measure. Twenty-seven participants dropped out (20.9% attrition). Six of 102 (5.9%) participants who completed baseline and 6-month follow-up developed psychosis. Psychosocial functioning was measured using GAF and GFS Role and GFS Social. Global and role functioning changes were found to be age dependent. Participants between the ages of 16 and 19 in the experimental group showed relatively more improvement than in the comparison group, whereas participants over 19 years of age improved more in the comparison group. Improvement in social function was independent of treatment assignment (see Table 14.1).

Overall, relatively high attrition rates suggest that the intervention may require modification before it is implemented more widely. Furthermore, it would be useful to compare family intervention to individual therapy with respect to efficacy. As with the CBT studies, low transition rates suggest the need for a follow-along group to rule out nonspecific benefits of a therapeutic setting or ascertainment effects. The authors also argued that the short duration of the study may have had an impact on rates of psychosis onset. Overall, this study is promising and FFT-CHR warrants further study.

Cognitive Remediation

Cognitive deficits exist in clinical high-risk patients, typically around a half standard deviation below the norm [81]. These deficits have been associated with both functional impairment and also risk for psychosis. Slowing of processing speed is a predictor of psychosis outcome [82], as is verbal memory impairment [81, 83]. Hence, there has been an effort to test cognitive remediation (CR) in these domains in CHR/UHR patients

to improve function and prevent psychosis onset. Early open-label trials suggested that CR might improve the prognosis of CHR/UHR individuals by addressing some of the cognitive deficits present in both people with schizophrenia and those at CHR. One such study found that CR may have greater efficacy in CHR/UHR in improving long-term memory and function, as compared to individuals with schizophrenia. Training CR regimens like Lumosity and Socialville may enhance processing speed and role functioning in CHR/UHR individuals [84]. In open-label studies, Posit Science Brain Fitness Training, a training program focused on remediating auditory processing deficits, has also shown some promise in improving processing in CHR/UHR individuals [85].

Thus far, there has been one study of CR as part of a combined intervention and three RCTs of CR alone in CHR/UHR patients. In the combined intervention, CR was part of a combined treatment intervention that included CBT, skills training, CR, and psychoeducational multifamily groups [86]. The first CR RCT used computer-assisted cognitive remediation (CACR), developed by Captain's Log® software, which was previously shown to have efficacy in schizophrenia [87]. A second RCT used auditory-based processing tasks as part of a neuroadaptive cognitive training program to improve verbal memory in CHR/UHR individuals [88]. The most recent, and possibly the most promising, trial used neurofeedback during a processing speed task (PST) program to remediate processing speed deficits in CHR/UHR individuals with the aim of improving their long-term social functioning [89]. Each of these is reviewed in more detail in the following paragraphs (see the section "Integrated Psychological Treatments" for more detail about the combined intervention).

In the first CR RCT study, 32 adolescents were randomly assigned to either train with computer-assisted cognitive remediation (CACR) or to play a nontargeted computer game. Only 12 of the participants were considered to be at CHR; the rest had a psychotic disorder. After 8 weeks of training, participants in the CACR group showed significant improvements specifically in visuospatial abilities, but not in other domains [87]. However, it was not clear if this improved performance could be accounted for by increased psychological support, practice effects, activities at the day clinic, or other nonspecific factors, all of which can be clarified in future research. Of note, there were low rates of attrition (12.5%) in the study and high ratings of acceptability (mean of 4.3/5 on motivation rating survey) for the CACR, which makes this training regimen a potentially promising one (see Table 14.1).

In a double-blind RCT targeting verbal and working memory deficits in (n = 83) CHR/UHR individuals, auditory-based processing tasks were used in a CR treatment intervention [88]. This study used neuroadaptive cognitive training with neuroplasticity-based software created by Posit Science Corporation, which aimed to improve accuracy of perception of and response to verbal targets [88]. Outcomes included changes in neurocognitive functioning, measured using the MATRICS, and changes in symptoms as assessed in clinical interviews. All healthy volunteers received the neuroadaptive cognitive training, while CHR/UHR subjects were randomly assigned to neuroadaptive cognitive training, or to a commercially available computer game. Individuals assigned to the neuroadaptive cognitive training significantly improved their verbal memory, as compared to those assigned to the commercially available computer games. However, attrition rates were high (42%), which may have been due to the amount of work involved, which included training at home for an hour each day, 5 days a week, for 8 weeks, a training that was repetitive and entailed tone discrimination [90]. While this study was promising with respect to remediating verbal learning and memory deficits in CHR/UHR, the high attrition rate highlights the importance of creating engaging tasks to make them more acceptable for memory deficits in individuals at CHR/UHR (see Table 14.1).

Processing speed deficits are associated with social impairment in CHR/UHR individuals [91]. In an RCT, a novel CR program called processing speed task (PST) was compared to nonspecific computer games, with respect to its efficacy in improving processing speed and concurrent

social impairment in CHR/UHR individuals ($n = 62$) [89]. The intervention was administered for 2 months, and evaluations of cognition were done before the intervention, immediately after the intervention, and 2 months after the completion of the intervention. Of note, PST uses pupillometry as a form of biofeedback that allows the task to personalize the training module for each participant, making it more engaging. The program tracks pupil dilation to appropriately adjust the difficulty level of the practice session. Because pupil dilation increases with activation of the sympathetic nervous system, the task is programmed to decrease difficulty level when dilation surpasses a given threshold (indicating that the person is becoming less engaged in the task) and decreasing the difficulty if the pupils are constricted beyond threshold [92]. This led to fewer errors throughout the intervention, which enhances self-efficacy in participants, according to proponents of errorless learning [93]. As hypothesized, a robust relationship between processing speed (as defined by WAIS-III) and social functioning (as defined by SAS-SR) was found in CHR/UHR individuals, and both improved in tandem with treatment, with enhanced social functioning evident even 2 months beyond end of treatment. The treatment was acceptable to participants, with only 10% dropout, likely because PST was specifically designed to simulate a computer game, with fantasy contexts that increase intrinsic motivation [94]. Given its acceptability and efficacy for both cognition and function, this is particularly a promising treatment that warrants more study (see Table 14.1).

Future studies of CR in CHR/UHR cohorts can explore whether other forms of neurofeedback can be incorporated into CR and if CR would be an important component of a treatment package.

Integrated Psychological Treatments

Prior to the use of CR as an isolated intervention in an RCT, CR was used as part of an integrative psychological intervention (IPI) that included individual CBT, modified social skills training, and multifamily psychoeducation (see Table 14.1) [86]. The CR involved computerized tasks that were based on cognitive tasks used in COGPACK software (Marker Software, 1992) to address thought and perception deficits. During each session, patients repeatedly practiced exercises targeting attention, memory, and executive functioning. Task progression to more difficult levels was based on performance errors [86]. Compared to the participants ($n = 65$) who received only supportive counseling, participants who also received the IPI ($n = 63$) had lower rates of psychosis transition, an effect that remained throughout the 2 years of the study. By the end of the treatment phase, 2 of 63 patients in the IPI group and 11 of 65 patients in the supportive counseling group had transitioned to psychosis, with an additional 2 transitions in each of the treatment groups during the posttreatment period [86]. The role of the individual components of the IPI is not clear and bears further study to identify active ingredients.

Interventions Combining Psychological and Pharmacological Strategies

Across the board, in studies combining psychological and pharmacological strategies, the effects of medication versus nonpharmacological intervention are confounded. However, aggregate treatment is promising for preventing psychosis onset, as well as reducing symptoms and improving function.

A landmark single-blind 12-month RCT combining psychological and pharmacological strategies compared 6 months of specific preventive intervention (SPI; $n = 31$), with needs-based intervention (NBI; $n = 28$) [24]. NBI involved supportive psychotherapy, case management, and psychoeducation, with potential concurrent antidepressant or benzodiazepine use. SPI was comprised of NBI in addition to low-dose risperidone (mean dose = 1.3 mg/day) and CBT. Follow-up occurred at 6 months and 12 months. Attenuated positive symptoms were the primary outcome, as measured by the Brief Psychiatric Rating Scale (BPRS). Functioning and mood symptoms were secondary outcomes, assessed by the GAF and

Hamilton Rating Scales for Depression and Anxiety (HRSD). Treatment adherence for risperidone was an issue, with 14 participants in the SPI group (45%) adhering to the medication regimen.

Another early integrated treatment RCT examined transition to psychosis in individuals diagnosed with schizotypal disorder (n = 79) [95]. The intervention lasted for 2 years. The integrated treatment included a multidisciplinary treatment team conducting a modified assertive community treatment model, social skills training, and patient and family psychoeducation. The standard treatment consisted of treatment at a community mental health center with a physician, nurse, and, in some cases, also a social worker. Antipsychotic medication treatment differed between participants as it remained the decision of the psychiatrist responsible for treatment. Transitions to psychotic disorder was the primary outcome as measured by the SCAN 2.0, the Scale for the Assessment of Positive Symptoms (SAPS), and Scale for Assessment of Negative Symptoms (SANS). Secondary outcome measures were psychotic, negative, and disorganized symptoms based on SAPS and SANS interviews.

Thirty-six integrated-treatment patients and 29 standard-treatment patients participated in the 2-year follow-up conducted by independent assessors who were psychiatrists, psychologists, or psychiatry residents. Of this group, nine participants (25.0%) randomized to integrated treatment and 14 participants (48.3%) randomized to standard treatment converted to psychosis. A multivariate analysis found that male sex was a significant risk factor for transition (relative risk = 4.47 (CI = 1.3–15.33), but integrated treatment reduced the risk (relative risk = 0.36 (CI = 0.16–0.85). Previous work has suggested that cannabis use can be a risk factor for developing psychosis [96], but a univariate analysis in this study indicated that the use of cannabis at least monthly at baseline did not predict transition to psychosis (relative risk = 1.80 (CI 0.66–4.88), $P = 0.2$).

An open-label, randomized parallel-group study with a 2-year observation period put putatively prodromal participants (n = 124) in one of two conditions; both conditions involved needs-focused interventions which included psychoeducation, crisis intervention, family counseling, and assistance with education or work-related difficulties according to individual need [97]. In the experimental condition (n = 65), participants were also given a second-generation antipsychotic, amisulpride, ranging in dosage from 50 to 800 mg (daily mean = 118.7 mg) and increased if attenuated or brief limited intermittent positive symptoms were present (mean dose at endpoint = 169.5 mg). At baseline and at 12-week follow-up, participants were given a basic and positive psychotic spectrum symptoms score (ERI–BAPPSS) split into two subscores: one for the assessment of threshold psychotic symptoms and attenuated positive symptoms (ERI-PPS) and one for basic symptoms (ERI-BS). Participants were also assessed with the positive, negative, and general psychopathology subscales of the PANSS, as well as the MADRS, GAF, Extrapyramidal Symptom Rating Scale (ESRS), and UKU Side Effect Rating Scale (UKU).

At the 12-week follow-up, the 58 combined protocol participants and 44 control participants who remained were analyzed. The combined treatment produced a significantly superior effect on ERI–BAPPSS scores (F (1,98) = 7.49, $P < 0.01$), with significant improvement observed in both groups (amisulpride, t = 6.88, d.f. = 57, $P < 0.001$; controls t = 2.87, d.f. = 43, $P < 0.01$), ERI–PPS scores (F (1,98) = 7.42, $P < 0.001$; amisulpride, t = 7.35, d.f. = 57, $P < 0.001$; controls t = 2.57, d.f. = 43, $P < 0.05$), and ERI–BS scores (F (1,98) = 6.30, $P < 0.05$; amisulpride, t = 6.88, d.f. = 57, $P < 0.001$; controls, t = 2.87, d.f. = 43, $P < 0.01$). A significant effect of treatment with amisulpride also emerged regarding the PANSS positive subscale (PANSS–P) score (F (1,98) = 7.83, $P < 0.01$); paired t-tests revealed a significant decrease of baseline scores only in the group with amisulpride (t = 5.50, d.f. = 57, $P < 0.001$). Analysis of PANSS negative subscale (PANSS–N) scores by ANCOVA also yielded a significantly better effect of amisulpride (F (1,98) = 4.85, $P < 0.05$). Within-group comparisons revealed a significant effect only for amisul-

pride (t = 4.56, d.f. = 57, $P < 0.001$). A superior effect for amisulpride was also observed for GAF scores (F (1,98) = 5.70, $P < 0.05$), and paired t-tests showed a significant change in the amisulpride group only ($t = 4.56$, d.f. = 56, $P < 0.001$). No significant difference between groups emerged regarding MADRS scores. General psychopathology improved significantly in the amisulpride group (F (1,98) = 4.63, $P < 0.05$; amisulpride: $t = 5.02$, d.f. = 57, $P < 0.001$; controls, $t = 2.11$, d.f. = 43, $P < 0.05$). The strongest effects were observed for attenuated and brief limited intermittent positive symptoms. Remission occurred more than twice as often in the amisulpride group.

An RCT randomized CHR/UHR participants into three groups: one received CBT, consisting of stress management, strategies for dealing with depression/negative symptoms, positive symptoms, and other comorbid conditions, in conjunction with risperidone (2 mg if tolerated); another group received CBT with a placebo medication; and the third received supportive therapy, providing them with emotional support and problem-solving skills and a placebo medication [98]. There was also a follow-along group not randomized for treatment but simply monitored. The primary outcome measure was transition to psychosis (criteria defined a priori), assessed using the CAARMS. Secondary outcome measures were psychiatric symptoms, psychosocial functioning, and quality of life which were assessed respectively using the CAARMS, Brief Psychiatric Rating Scale (BPRS), SANS, Hamilton Depression Rating Scale (HDRS), GAF, and Quality of Life Scale (QLS).

At 6-month follow-up, 2 of the 43 subjects (4.7%) in the CBT and risperidone group, 4 of the 44 subjects (9.1%) in the CBT and placebo group, and 2 of 28 subjects (7.1%) in the supportive therapy and placebo group had transitioned to a psychotic disorder. These were not significant differences (log-rank test, $p = 0.92$). In the monitoring group, 4 of 78 (5.1%) developed psychosis, also not significantly different from the randomized groups (log-rank test, $p = 0.93$). All three randomized groups and the monitoring group showed significant improvement in BPRS total, BPRS psychotic subscale, and HDRS scores. All groups except the combined CBT and risperidone significantly increased in functioning. The supportive therapy and placebo group and the monitoring group showed significant improvement in total negative symptoms. Only the monitoring group showed significant increases in QLS scores. Poor adherence was prevalent in this study: 23 participants in the CBT and risperidone group (53.5%) had poor adherence (less than 50% of doses taken), 18 (41.9%) had partial adherence (50–89% of doses taken), and only 2 (4.7%) had full adherence to risperidone (≥ 90% of doses taken). Of the two subjects in the CBT and risperidone group who were known to have developed psychosis by the 6-month assessment, both belonged to the <50% adherence group. However, this was not statistically significant (log-rank test, $P = 0.57$). There were no significant differences in symptoms or level of functioning between the groups, although there was a trend for those who were poorly adherent to show greater improvement in functioning and quality of life (GAF, $P = 0.095$; QLS, $P = 0.089$).

At a 12-month follow-up [98], seven participants in the CBT and risperidone group, seven in the CBT and placebo group, six in the supportive therapy and placebo group, and five in the monitoring group had transitioned to psychosis. The estimated 12-month transition rates were 10.7 ± 5.0% for the CBT and risperidone group, 9.6 ± 4.6% for the CBT and placebo group, 21.8 ± 8.8% for the supportive therapy and placebo group, and 8.7 ± 3.8% for the monitoring group. There were no significant differences in the rate of transition between the randomized groups (log-rank test $P = 0.60$) or the four groups (log-rank test $P = 0.59$). Poor adherence to medication was also high at the 12-month follow-up. In the CBT and risperidone group, 27 subjects (62.8%) showed poor adherence, 16 (37.2%) showed partial adherence, and none showed full adherence to risperidone. All groups showed improvement on the secondary outcome measures, and there was no significant difference between the groups.

In an RCT study, adolescents and young adults (initially ages 14–30) who had previously partici-

pated in a combined treatment study were reevaluated [99]. CHR/UHR participants either received up to 2 mg risperidone as well as cognitively oriented psychotherapy (specific intervention: SPI, $n = 31$) or supportive psychotherapy only (needs-based intervention: NBI, $n = 28$). During the study, neither participants nor clinicians were blind to treatment, but research interviewers were. Thirteen SPI participants were partially or nonadherent to their medication, and 11 were fully adherent. At a medium-term follow-up, 17 from the original NBI group and 24 from the SPI group consented to be interviewed again and were assessed using symptomatology and functioning measures such as the Brief Psychiatric Rating Scale (BPRS), SANS, Quality of Life Scale (QLS), the Hamilton Rating Scales for Anxiety (HRSA) and Depression (HRSD), and the Mania Rating Scale (MRS). There was no significant difference in follow-up ratings between the two groups ($\times 2(1) = 1.94$, $p = 0.164$). There was also no significant difference in probability of developing psychosis between the SPI and NBI groups. However, both the SPI and NBI groups had significantly higher Mania Scale ($t(22) = 3.06$, $p = 0.006$ and $t(16) = 2.41$, $p = 0.029$, respectively) and QLS ($t(23) = 2.716$, $p = 0.012$ and $t(17) = 3.86$, $p = 0.001$, respectively) scores at the 3–4-term follow-up compared to baseline.

Future Directions

Overall, there is no clear evidence base for treatment of CHR/UHR individuals. With respect to pharmacological strategies, the use of second-generation antipsychotics is greatly limited by adverse effects that interfere with adherence. Glutamatergic strategies appear to have efficacy specifically for negative symptoms and cognitive deficits. Among psychological treatments, cognitive behavioral therapy holds promise, but such studies have been limited by low conversion rates to psychosis, such that there may be a nonspecific effect of clinical contact that is the operative ingredient. Cognitive remediation is particularly promising, as it has shown efficacy in improving cognition, with concomitant improvement in functioning. There are now clinical trials underway for exercise, which may be effective. Further, neurostimulation has not yet been tried, but a circuit-based approach to treatment, alone or in conjunction with cognitive remediation, may hold particular promise.

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15 Outcome Determinants and Parameters in Late-Life Schizophrenia

Nitin Gupta and Subhash Das

Introduction

Schizophrenia is a complex disorder of thought, perception, cognition, emotion, and behavior which usually manifests in the second or third decade of life [1]. However, it is not uncommon for the disease to have an onset in extremes of age, i.e., childhood as well as old age [2, 3], and has even been described in a 100-year-old individual [4]. Eugen Bleuler's son, Manfred Bleuler, demonstrated that schizophrenia can manifest for the first time in later life and even suggested a clinical subdivision based on age at onset [5, 6]. Though Kraepelin initially conceptualized schizophrenia as "dementia praecox" in order to suggest that this disorder had a dementia-like pattern, but which emerged earlier, later on he found that some of the older people may develop schizophrenia for the first time during old age [1].

Concept, Types of Presentation, and Classification

Schizophrenia in the elderly tends to present in different manners:

(a) Schizophrenia is generally diagnosed quite early in the individual who then continues to live with the disorder through middle age and subsequently old age [7]. These are the older people with schizophrenia having an onset before the age of 40 years, the so-called early-onset schizophrenia (EOS) [8].
(b) Individuals who have onset of schizophrenia after the age of 40 years. As per the consensus statement by the International Late-Onset Schizophrenia Group, these individuals with schizophrenia should be called as "late-onset schizophrenia (LOS)" [1].
(c) Lastly, a group of people in whom schizophrenia-like psychosis may be present for the first time with onset after age 60 years. This group has been labeled as "very-late-onset schizophrenia-like psychosis (VLOSLP)" [1].

It needs to be borne in mind that the term "late-life schizophrenia" is usually used for all older persons with schizophrenia without taking into consideration whether it is EOS, LOS, or VLOSLP; but principally it more often than not includes the first two entities [5].

However, it needs to be mentioned here that a clear delineation of schizophrenia as per onset of age is neither included nor emphasized in the most recent (DSM-IV) or current (DSM-5 or ICD-10) classificatory systems. Only DSM-III-R classificatory system mentioned LOS as those who had onset of symptoms after the age of 44 years, and it

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is seen that about 15–20% of all patients with schizophrenia fall in this category [7].

Schizophrenia in the elderly also needs to be differentiated from "paraphrenia," a late-onset delusional disorder in the elderly with prominent persecutory delusions without any association with dementia [9]. It should be noted that delusional disorder in the elderly has often been referred to as paranoia, paranoid reaction, paraphrenia, paranoid psychosis, paranoid condition, paranoid state, and paranoid disorder [5]. Unfortunately, it has been observed that this only generates more ambiguity, and hence the usage of the term "paraphrenia" is best avoided for any particular entity.

All throughout this text, only EOS and LOS will be discussed, mostly because they are the ones which can be considered as "late-life schizophrenia" in the true sense. Both EOS and LOS have some similarities as well as some differences.

Similarities Between EOS and LOS

(a) Positive symptoms are present in both [1].
(b) 10–15% may have a family history of schizophrenia [1].
(c) History of clinical maladjustments is present in both groups [1].
(d) Both show response to antipsychotics, though dosages used may differ [1, 11].
(e) Cognitive dysfunction is prevalent in both groups [7].
(f) Neuroanatomical findings on CT scan and MRI reveal enlargement of lateral and third ventricles (suggesting tissue loss) in both groups [7]; focal structural changes are present in both groups [5].
(g) Both have a chronic course and similar severity of global psychopathology [5].
(h) Both have two to three times greater mortality rates in comparison to various groups [5].

Differences Between EOS and LOS

(a) Gender: LOS has a preponderance for the female gender, a finding which has been consistently reported [5, 10, 11].
(b) Phenomenology: There is relative absence of thought disorder in LOS. Affective blunting is absent or found in lesser degree compared to EOS [12, 13]. LOS may have partition delusion (the belief that people, animals, objects, or radiation can pass through structures that in usual circumstances would have been a barrier to such passage) [14], persecutory delusions [14, 15], and phantom boarder (that guests are living in the person's house when actually no one was there) [5]. Studies have reported that LOS have less severe negative symptoms, though evidence to the contrary also exists [5]. Presence of paranoid symptomatology is more common in LOS [5, 10]. Visual, tactile, and olfactory hallucinations are present with greater frequency in LOS individuals in comparison to those with EOS [5].
(c) Cognition: LOS individuals were better than EOS when abstraction/flexibility of thinking, semantic memory, and speed of processing were considered [5]. On the other hand, EOS individuals had less impairment on auditory and visual attention compared to those with LOS [16].
(d) Functioning: LOS individuals were found to have better premorbid functioning than those having EOS [10] when their socio-occupational history was considered [17, 18], and LOS individuals were likely to have been married at some point in time [5]. When the daily functioning as well as health-related quality of life was assessed, it was found that LOS individuals fared better than those with EOS [19].

Outcome Parameters

To track the course and outcome parameters of late-life schizophrenia is very challenging. This is due to innumerable reasons like:

(a) There are hardly any follow-up studies [20].
(b) Even when studies are present, findings may vary depending upon the methodology used like the nature of sample selected, whether there is presence of comorbid con-

ditions (which are often present in elderly), age at which psychotic symptoms first appeared, etc. [8].
(c) Defining the exact age at onset itself might be challenging, as this information is often gathered from the elderly patient or from his caregivers who are also his contemporaries; thus the information could be inaccurate, as it will be based on recall which may be compromised due to potential cognitive impairment in the elderly [3].
(d) Follow-up of LOS patients is arduous due to limited social support of these patients, comorbid medical conditions that may interfere with treatment follow-up, presence of sensory deficits which may limit patient's mobility, and various other factors [3].
(e) Presence of ethical considerations for this vulnerable group may restrict the investigators to exclude the elderly from research.
(f) Symptoms of psychosis in the elderly may often be attributed to organicity or due to age-related changes.

Despite these abovementioned limitations, various reviews and studies have been able to throw some light on the course and outcome of late-life schizophrenia.

Risk Factors

Despite some confusion, many studies and reviews have hinted at some of the risk factors for late-onset psychosis. These are:

(a) Sensory deficit, especially hearing impairment, has been found to be a potential risk factor in the elderly [20, 21].
(b) Social isolation is another risk factor for the development of psychosis in the elderly [20, 21]. However, it has been suggested to be a phase that just precedes the onset of psychosis and may not be a risk factor [22].
(c) As there is a preponderance of females in LOS, so this gender factor has also been postulated as a putative risk factor for the development of psychosis in the elderly [23]. However, this has been refuted in a review [24].
(d) Presence of cognitive deficits has also been suggested to be a risk factor [21, 24].
(e) Other risk factors that have been suggested are history of psychotic symptoms [24], poor health [24], and use of polypharmacy [21].

Age of Onset and Its Relation to Outcome in Schizophrenia

The relationship between age of onset and outcome has been lucidly portrayed in a very recent review [25]. This review highlights the following:

(a) Age of onset does not have any effect on remission; if at all there is any effect, it is very modest.
(b) Similar was the situation with relapse, though there were studies which highlighted that onset of illness above the age of 25 years increased the chances of relapses.
(c) Earlier age of onset resulted in more hospitalization. Those above 60 years had decreased risk of rehospitalization when compared to those who had their first admission before the age of 20 years. In addition, lower age was associated with a more negative outcome.
(d) Overall, there was no statistically significant relationship between age of onset and employment status, but lower age at onset predicted poorer socio-occupational functioning, though two studies reported the opposite as well.
(e) Overall lower age of onset was associated with poor global outcome.

Outcomes of EOS

Outcome of EOS is likely to be the same as that of schizophrenia in general. Overall, the remission rate varied from as low as 3% to as high as 64% [7]. This was mainly due to the way the sample was selected and even how remission itself was defined.

More interesting information regarding the course was garnered from those cases with schizophrenia which were followed up on a longitudinal basis. While 20% of patients were able to achieve remission, 20% worsened over time, while the course of the remaining 60% remained unchanged [11, 26]. There was initial fluctuation in the course of illness, usually in the first 5–10 years followed by a somewhat stable period or even improvement in symptoms as the individual with schizophrenia aged [11]. Though it appeared that older persons with schizophrenia remained asymptomatic and positive symptoms decreased over time, one thing that needed to be looked into is that there could be an increase in negative symptoms and cognitive decline which resulted in a picture of a calm and improved patient from the caregivers' perspective. This may be likely, as researchers have found out an age-related increase in negative symptoms and cognitive decline, as well as a positive correlation between these two domains [8]. Also a possibility exists that the older patients may not be reporting their positive symptoms [8]. Though there is cognitive impairment in individuals with schizophrenia, as reported in some studies, overall cognitive performance remains stable in older persons with schizophrenia [8, 11]. However, it has also been reported that there is cognitive decline in about a third of institutionalized patients [11].

Thus, there may be different outcomes related to cognitive deterioration. Outcome in EOS could vary considerably, including recovery, in a substantial proportion of individuals, depending upon the dwellings of the individuals, i.e., institution versus community [8].

Functional Outcome

When it comes to recovery itself, depending on whether the patients with EOS lived in a community or institutional setting, a review mentioned that significant improvement was noted in the range of 46–84% for clinical recovery and 21–77% for social recovery [8]. However, the same review mentions that recent short-term follow-up studies suggested that many elderly patients with EOS had substantial level of impairment [8]. A review of the same has also suggested that EOS need not necessarily have a poor cognitive and functional outcome [27].

Outcomes of LOS

As highlighted earlier, due to various reasons, it is very difficult to follow up patients with LOS. There is a dearth of literature in this regard, and this makes it very challenging to track the outcome in LOS.

In terms of symptomatology, over the course of time, positive symptoms diminish, and there are hardly any new symptoms. There may be an increase in negative symptoms or the negative symptoms itself may reduce over time [27].

Though cognitive impairment is supposed to be a possible risk factor for development of LOS, a study in a community setting which compared individuals of EOS, LOS, and Alzheimer's disease (AD), regarding the change in cognitive functioning (changes at 1 and 2 years), found that EOS, LOS, and normal subjects had a relatively stable cognitive functioning, whereas those with AD had greater decline. Thus, there was no deterioration in the cognitive functioning in those with LOS [28]. However, some previous studies have reported an increase in, as well as intermediate rates of, deterioration in cognition as well [29].

An insight into the outcome of LOS has been provided by a 5-year follow-up study of Brodaty et al. [29] which found that overall patients had a worse outcome after 5 years in comparison to controls on several parameters like instrumental ADL and ADL scores, cognitive decline assessed with CDR, and cognitive decline scale, as well as decline in the score on MMSE (by 6.5 points over 5 years). Though three individuals out of ten (who were alive) in this study at the end of the 5-year period could not be interviewed, all seven individuals interviewed had symptoms of psychosis, and one even fulfilled the criterion A of DSM-IV for schizophrenia. This study also found that out of 19 cases that were assessed (including nine who had died and information as gathered from the informant), almost 50% had dementia

(five had met DSM-IV criteria for dementia). These perspectives thus bring into focus the existence of dementia in those with LOS, and clinicians need to be aware of this as it can be easily overlooked. However, the individuals with LOS and controls in this study did have significant differences in the presence of neurological abnormalities at the end of the 5-year period [29].

Functional Outcome in LOS

The social decline in those suffering with LOS may be less than that of those with EOS, as those with LOS may have already attained some developmental maturity [30], and this could be also the reason why better socio-occupational functioning is usually expected in those with LOS [20]. In fact, the 5-year outcome study mentioned previously commented that despite decline in several areas, global functioning (as assessed by GAF score) did not decline much in the LOS group, though it was somewhat lower than those of the controls [29].

Conclusions

Late-life schizophrenia is not entirely a homogenous entity, comprised of EOS and LOS. The similarities between these types tend to outweigh the differences. Numerous risk factors have been identified related to the outcome. Structural and functional outcome tends to be better for EOS than for LOS. Nevertheless, these are tentative statements, as the amount of longitudinal evidence and literature available in this particular aspect of late-life schizophrenia is not robust enough to draw definitive conclusions.

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Behavioural and Psychological Symptoms Occurring in Dementia

16

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Introduction

Behavioural and psychological symptoms of dementia (BPSD), also known as neuropsychiatric symptoms, represent a heterogeneous group of non-cognitive symptoms and behaviours occurring in subjects with dementia [1]. Behavioural and psychological symptoms of dementia (BPSD) are an integral part of dementia syndrome. Decline in emotional control or motivation, or a change in social behaviour manifesting as emotional lability, irritability, apathy, and coarsening of social behaviour, has been a part of diagnostic criteria for dementia [2].

BPSD constitute a major component of the dementia syndrome irrespective of its subtype. They are as clinically relevant as cognitive symptoms, as they strongly correlate with the degree of functional and cognitive impairment. BPSD include agitation, aberrant motor behaviour, anxiety, elation, irritability, depression, apathy, disinhibition, delusions, hallucinations, and sleep or appetite changes. It is estimated that BPSD affect up to 90% of all dementia subjects over the course of their illness and is independently associated with poor outcomes, including distress among patients and caregivers, long-term hospitalization, misuse of medication, and increased health-care costs [1].

Behavioural and Psychological Symptoms in Dementia (BPSD)

The BPSD have several domains which show differences among the various types of dementia, with studies showing predominance of hallucinations in dementia with Lewy bodies (DLB); of depression and apathy in vascular dementia (VaD); of apathy, disinhibition, elation, appetite, or eating changes in frontotemporal dementia (FTD); and of apathy, agitation, depression, anxiety, irritability, and sleep disorders for Alzheimer's disease [3]. The most frequent BPSD in a study by Mukherjee et al. are apathy and agitation, followed by irritability, sleep and night-time behaviour disorders, depression, appetite and eating disorders, and anxiety, whereas disinhibition and elation/euphoria were least frequent. This study demonstrated that caregiver distress increased with increasing number of BPSD, and elation/euphoria was the only individual domain of BPSD

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not significantly predicting caregiver distress [4]. These non-cognitive abnormalities which increase the morbidity of patients and burden of caregivers are mostly treatable. Their assessment and management are essential components of the treatment of dementia [5].

BPSD have myriad manifestations. There has been attempt to conceptualize these symptoms in various ways. Clusters comprising a psychotic syndrome and an affective syndrome have been frequently suggested. Other major manifestations are in the areas of motor behaviour, social interactions, speech, personality changes, and somatic symptoms.

Inappropriate behaviours have been divided into four main subtypes: physically aggressive behaviour, such as hitting, kicking, or biting; physically non-aggressive behaviour, such as pacing or inappropriately handling objects; verbally non-aggressive agitation, such as constant repetition of sentences or requests; and verbal aggression, such as cursing or screaming [6].

Motor Behaviour

Agitation manifests with restlessness, pacing, complaining, repetitive sentences, negativism, requests for attention, cursing and verbal aggression, etc. Reported frequencies are between 24% and 48% [7].

Physical violence and hitting occur in approximately 30% in Alzheimer's dementia (AD). Premorbid history of aggression, troubled premorbid relationship between caregiver and patient, and multiple problems are predictors of aggressive behaviour [8].

Mood Disturbances

Depression is common; however, it may not have a typical presentation—often there is a lack of sad or depressed affect or mood. The aphasic patient may not be able to articulate the subjective experience of being depressed [9]. Depressive cognitions and death wishes are common. Other predominant mood disturbances are anxiety, fear, irritability, anger, etc. Emotional lability, explosive emotional outbursts, weeping, and laughing are also seen [10].

Personality Changes

Changes in personality are noticed with increasing passivity, coarsening of affect, decreased spontaneity, inactivity, feelings of insecurity, and less cheerfulness and responsiveness. There are blunted individual characteristics or exaggerated premorbid traits. Loss of socialization, companionship, self-centred behaviour, and irritability are also seen. Social behaviour is marked by reduced initiative and drive, grossly insensitive behaviour, lack of restraint, disinhibition, sexual misadventure, indolence, and foolish jokes and pranks [10].

Psychotic Features

Psychotic features in patients with dementia are usually paranoid in nature. Some common ideas have been that someone is stealing things, being present in the room, living inappropriately in the home (phantom boarder), mishandling personal finances, planning to harm physically, etc. Other psychotic features are delusions of infidelity, hypochondriasis, zoopathy, dead relatives being still alive, erotomania, Capgras syndrome, believing television images are real, personal images in a mirror are a different person, and misidentifying own home [11].

Aetiology of BPSD

Various theoretical models have been proposed to understand BPSD, which basically guide the non-pharmacologic intervention. They are unmet needs model, a behavioural/learning model, and an environmental vulnerability/reduced stress-threshold model [12]. Often the needs are not apparent to the observer or the caregiver, or the caregivers do not feel able to fulfil these needs. Unmet biological, social, and psychological needs lead to discomfort and distress, and in a back-

ground of impaired cognitive state and ineffective communication, these often manifest as BPSD.

Many problem behaviours are learned through reinforcement by caregivers or staff members, who provide attention when problem behaviour is displayed. BPSD may arise possibly from the intensive approach to care where patients are stressed beyond their cognitive capabilities. It is assumed that dementia process results in greater vulnerability to the environment and a lower threshold at which stimuli affect behaviour. Persons with dementia progressively lose their coping abilities and therefore perceive their environment as more and more stressful [13]. Premorbid personality has also been linked to BPSD. Dementia accompanied by florid paranoid or affective symptoms is associated with abnormal personality earlier in life; persons with simple downward course were found to have been more stable [10]. Underlying neurobiology of BPSD is still unclear. Agitation has been linked to dementia severity, brain-damaged state, specific psychiatric syndromes or symptoms, or specific types of psychopathology implicating frontal lobe dysfunction [14]. An imbalance of different neurotransmitters (acetylcholine, dopamine, noradrenaline, serotonin, GABA) has been proposed as the neurochemical correlate of BPSD [15]. In FTD, increased activity of dopaminergic neurotransmission and altered serotonergic modulation of dopaminergic neurotransmission are associated with agitated and aggressive behaviour, respectively [16].

The onset and trajectory course of BPSD is often unpredictable, unlike the cognitive symptoms. This often leaves the caregivers unprepared, leading to resentment and anger towards the persons with dementia. The presence of BPSD is also associated with more rapid disease progression, accelerated functional decline, and reduced quality of life and has been associated with early nursing home placement and the usage of restraints [17]. BPSD are now accepted as an important therapeutic target in dementia. Mild forms of BPSD may respond to simple environmental and psychosocial interventions. Although non-pharmacologic interventions should be the first line of treatment, drug therapy is often required for the more severe psychotic, aggressive, and agitated presentations [18]. Evaluation of BPSD includes a thorough diagnostic investigation, careful consideration of the aetiology of the dementia, and the exclusion of other causes, such as drug-induced delirium or adverse effects of treatments for comorbid conditions [19].

Pain is often underdiagnosed in patients with dementia and can manifest itself by behaviour changes (such as agitation and increased confusion) and decreased mobility [20]. Language difficulties associated with dementia interfere with the patient's ability to express pain. In addition, the autonomic activation in response to pain may be blunted in AD patients. A number of pain scales have been developed to evaluate pain in patients with dementia. Some are self-report (for milder dementia); others, such as the PAIN-AD (Pain Assessment in Advanced Dementia), measure nonverbal signs such as breathing, vocalization, facial expression, and body language [21].

Sleep disturbances may be associated with and part of BPSD. Circadian rhythms may be altered in AD. Patients with Lewy body dementia have a high incidence of REM sleep disorders, acting out their dreams. Clinicians should evaluate medications that may disrupt sleep. Other common medical causes of confusion and agitation in the elderly include infections, endocrine disorders, fluid and electrolyte imbalances, and constipation [22]. A careful medication review should be performed, paying particular attention to any recently introduced medications. Elderly patients may be more vulnerable to the cognitive effects of drug interactions or to what may be considered therapeutic blood drug levels in younger patients [23]. Care of patients with BPSD involves a broad range of psychosocial treatments for both the patient and family. Caregiver education, support, and behavioural training are integral parts of the intervention for these patients [24]. Environmental adjustments, such as lifestyle support, are generally first-line interventions; however, many cases of aggression, agitation, and psychotic symptoms may require pharmacotherapy [25].

Individualized music therapy, bright light treatment (BLT), and aromatherapy have been

found to improve certain problematic behavioural symptoms [24]. Good sleep hygiene, avoidance of caffeine and alcohol, and adequate daytime physical activity can be beneficial, particularly for patients who have sleep disturbances and depression. Teaching caregivers techniques to minimize behaviour problems can make the home environment less stressful for both the family and the patient [26]. The evidence base for drug treatment of the behavioural and psychological symptoms of dementia is poor, considering the size of the problem and the distress these symptoms cause. Over the years, drug prescribing for BPSD has evolved in a haphazard and anecdotal way. Although there are multiple classes of drugs in use for neuropsychological symptoms, including antipsychotics, anticonvulsants, antidepressants, anxiolytics, cholinesterase inhibitors, and NMDA modulators, there is no consensus nor clear standard of care, and treatment is often based on local pharmacotherapy customs [18]. In elderly patients, it is possible that any medication could help and/or harm, and the safety of a drug must be considered in the context of its known efficacy [27].

If drug therapy is to be instituted, two approaches are recommended. One is to identify the target symptom and choose a drug that is known to treat symptoms most closely related to the one the patient is exhibiting (as mentioned above). An alternative approach is one guided by current evidence in combination with the goal of minimizing side effects. Begin with a cholinesterase inhibitor if the patient is not already on one, because they are well tolerated and may benefit cognition and function. It is important to remember that titration speed and target dosage of psychoactive drugs are substantially reduced in the elderly [22].

In psychotic, behaviourally disturbed elders, an ideal medication should have rapid onset, sustained action, and minimal somatic and cognitive side effects. Conventional antipsychotics, such as haloperidol, have been used effectively to control the behavioural and psychological symptoms of dementia. Other drugs, such as valproate and carbamazepine, have shown some efficacy in controlling behavioural symptoms in elderly patients. However, only the atypical antipsychotics risperidone and olanzapine currently have the best evidence of efficacy in treating neuropsychiatric symptoms. Trials of cholinesterase inhibitors have had consistent, yet small, positive effects as well [18].

Antipsychotics are the drugs of choice in the treatment of intrusive delusions and hallucinations. Coexisting nonpsychotic symptoms including sleeplessness, excitability, hostility, belligerence, emotional liability, restlessness, agitation, aggression, and irritability may also show improvement with antipsychotics. Other symptoms such as hypersexuality, apathy, and withdrawal do not generally improve. Since antipsychotics have such a narrow therapeutic window, they should be prescribed and dosage adjusted with the expectation of clinical improvement within a certain timeframe [28]. The goal of antipsychotic therapy must be the improvement in a specific target behavioural syndrome without impairing other aspects of dementia such as cognition, function, and quality of life [24]. The American Academy of Neurology recommends the use of antipsychotics to treat agitation and psychosis in patients with dementia where environmental manipulation fails, and guidelines state that atypical antipsychotics may be better tolerated than older conventional antipsychotics [29]. Anecdotal reports have suggested that anticonvulsants such as carbamazepine, valproic acid, and gabapentin may be effective in the treatment of BPSD. Gabapentin has shown some benefit when treating aggressive behaviour in patients with dementia, but it has not been well studied [30].

Carbamazepine has been investigated in several trials and was found to reduce agitation, restlessness, and anxiety [31]. Depression is common in patients with dementia. As many as 40% of patients with dementia have significant depressive symptoms at some stage. Reducing symptoms such as irritability may aid in the treatment of BPSD [32]. Selective serotonin reuptake inhibitors (SSRIs) may have “neuroleptic” effects by reducing dopaminergic outflow, and dysregulation in serotonergic neurotransmission may play an important role in the psychotic symptoms of dementia patients [33]. Trazodone is widely used for agitation, sleep disorders, and

disruptive behaviour because of its sedative effect and negligible anticholinergic activity. A comparison of trazodone with haloperidol for treatment of agitation in 28 patients with dementia showed similar overall efficacy of both drugs and a lower rate of adverse effects in the trazodone group [34]. Cholinesterase inhibitors are licenced for the treatment of mild to moderate AD. In some studies, donepezil had no effect on neuropsychiatric symptoms, while in one study, anxiety, depression/dysphoria, and apathy were significantly improved compared with placebo [32]. Medications such as memantine, buspirone, beta blockers, benzodiazepines, and thiothixene have been evaluated for their use in treating BPSD. Adding memantine to donepezil resulted in better outcomes (than placebo) for dementia patients on measures of cognition, ADLs, global outcome, and behaviour. It showed a significantly beneficial effect compared with placebo in relation to agitation and aggression [35].

Conclusion

BPSD are the common presenting problems in dementia. The course varies depending on the type of dementia, and also there is a variable course, highly individualistic. The research suggests that anticholinesterase agents do alter BPSD, and other molecules have differing evidence that ultimately the course can be modified. The last words have not yet come on the effective management of BPSD. But the future is going to see better pharmacological agents to help the BPSD.

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17 Objectives of Recovery from Schizophrenia

Avinash De Sousa, Nilesh Shah, and Pragya Lodha

Introduction

Recovery from an illness like schizophrenia is a difficult construct to establish. It has been a source of debate for years to determine the parameters that would constitute recovery from a complex neuropsychiatric disorder like schizophrenia. In general, recovery may be defined as "a deeply personal, unique process of changing one's attitudes, values, feelings goals, skills, and/or roles. It is a way of living a satisfying, hopeful, and contributing life, even with the limitations caused by illness. Recovery involves the development of new meaning and purpose in one's life as one grows beyond the catastrophic effects of mental illness" [1]. Recovery may also be an attempt to reinstate the premorbid lifestyle for an individual, though it may not always stand true to achieving the same.

Recovery is about individualized approaches and is about having a satisfying and fulfilling life, as defined by each person. Recovery does not necessarily always mean "clinical recovery" (usually defined in terms of symptoms and cure), but it does mean "social recovery"—building a life beyond illness without necessarily achieving the elimination of the symptoms of illness. Recovery is often described as a journey, with its inevitable ups and downs, and people often describe themselves as being in recovery rather than recovered [2]. Recovery is like being in a "healing process."

Recovery can be seen as a process and can be most helpfully defined by three core concepts:

1. *Hope*. Hope is a central aspect of recovery, and recovery is probably impossible without hope. It is essential to sustaining motivation and supporting expectations of an individually fulfilled life [3].
2. *Agency*. This refers to people gaining a sense of control and service users taking control over their own problems, the services they receive, and their lives. It is concerned with self-management, self-determination, choice, and responsibility [4].
3. *Opportunity*. This links recovery with social inclusion and, thus, peoples' participation in a wider society. People with mental health problems wish to be part of communities; to be a valued member of, and contribute to, those communities; and to have access to the opportunities that exist within those communities [5].

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Apart from the componential essence of recovery as discussed above, it is important for mental health professionals to ponder over the effectiveness of rapport building that may be the first prelude to recovery. It is a core aspect of drawing treatment and therapy goals to encompass personal goals of a patient in order to build the spirit toward recovery. The patient's belief in recovery is prime for an effective treatment/therapeutic plan (though it is true that complete recovery may be difficult for mental illnesses, especially so for schizophrenia, it is helpful to have a belief in working toward recovery, as it keeps the treatment and management process going).

The objective of recovery from any mental illness is to reinstate quality of life, return to personal and social responsibilities, and build resilience for the future. Recovery may also contribute to stronger belief in hope and optimism.

Principles of Recovery from Any Mental Illness

The basic principles in recovery from any mental illness, e.g., schizophrenia, include the following [6]:

- Recovery is about building a meaningful and satisfying life, as defined by the individual, whether or not there are ongoing or recurring symptoms or problems.
- Recovery represents a movement away from pathology, illness, and symptoms to health, strengths, and wellness.
- Hope is central to recovery and can be enhanced by each person seeing how he or she can have more active control over their lives ("agency") and by seeing how others have found a way forward.
- Self-management is encouraged and facilitated. The processes of self-management are similar, but what works may be very different for each individual. There is no "one size fits all."
- The helping relationship between clinicians and service users moves away from being expert/patient to being coach/partner on a journey of discovery. Clinicians are there to be "on tap, not on top."
- People do not recover in isolation. Recovery is closely associated with social inclusion and being able to take on meaningful and satisfying social roles within local communities, rather than in segregated services.
- Recovery is about discovering—or rediscovering—a sense of personal identity, separate from illness or disability.

The language used and the stories and meanings that are constructed have great significance as mediators of the recovery process. These shared meanings either support a sense of hope and possibility or invite pessimism and chronicity.

The development of recovery-based services emphasizes the personal qualities of staff as much as their formal qualifications. It seeks to cultivate their capacity for hope, creativity, care, compassion, realism, and resilience.

Family and other supporters are often crucial to recovery, and they should be included as partners wherever possible. However, peer support is central for many people in their recovery.

Objectives of Recovery in Schizophrenia

Most of mental health treatment is recovery oriented; however, in the management, we are clear that recovery is not an intervention. It is not what professionals do to people, but rather it is a description of processes underlying the struggle of people with mental health problems to live meaningful and satisfying lives [7]. Recovery is a person-centered approach that completes the well-being approach in the mental health paradigm. We aim to specify certain conditions that help us understand the need for recovery in schizophrenia and that impinge upon what most people agree would be a recovery approach. We shall examine these factors as recovery relevant outcomes in schizophrenia and discuss various factors that determine what we may call recovery in schizophrenia.

Employment of Patients with Schizophrenia

Studies all over the world have demonstrated the efficacy of Individual Placement and Support (IPS), a specific approach to vocational rehabilitation in patients with schizophrenia and other major psychiatric disorders. The patient needs employment based on his education, abilities, and level of social desirability. It is not only employment but also a job that interests the patient and where employment is maintained [8]. The IPS approach is superior to sheltered workshops and daycare centers for schizophrenia. The aim of employment is not only merely work but also building self-esteem, good pay, and better job tenure. The higher rates of employment help maintain treatment compliance and foster recovery with reduced mental health service usage and improved confidence in patients with schizophrenia [9]. Employment is far better for recovery in schizophrenia than even social skills training and psychotherapy, as shown by some studies.

Treatment Compliance and Follow-Up

Advances in the psychopharmacology of schizophrenia have led to the advent of second- and soon third-generation antipsychotics that have substantial efficacy in the management of schizophrenia. Treatments for schizophrenia must effectively treat both positive and negative symptoms of schizophrenia and must also prevent symptom exacerbation during an acute episode or in the residual phase of the illness [10]. Many patients with schizophrenia, after considerable improvement, reject prescribed treatment regimens and end up in a relapse. For this reason, patient evaluation in schizophrenia must have an understanding of factors affecting treatment compliance that impede or promote patient continuation with the prescribed treatment, and this would help determine further psychosocial treatment pathways. Many factors like the basic psychopathology and mistrust in schizophrenia, medication-induced side effects, social support and family unity, substance abuse, and the quality of the therapeutic alliance between patients and psychiatrists affect treatment adherence and compliance that in turn determine recovery in schizophrenia [11]. There is a need for an individualized plan for treatment compliance and regular follow-up to be determined for each patient, including interventions that target specific factors thought to be operative in the individual patient. A psychoeducation model that is individualized for every family also needs to be developed when we aim to foster recovery in schizophrenia. Recovery, in a way, is an outcome of treatment compliance in any mental illness, and importantly so in schizophrenia, given the necessity of pharmacological intervention for betterment. Follow-up, on the other hand, is not just a crucial part of the treatment, but also leads the way to recovery as it ensures the strength of recovery in a patient. Though relapse of illness may nevertheless be inevitable, adherence to follow-up leads to better symptom management, early identification of relapsing episode, and smoother recovery [12].

Empowerment of Patients

Empowerment means the involvement of service users in key decisions regarding their treatment and management. This may be difficult in patients with schizophrenia where insight into the illness may not always be present. Patients with good insight in schizophrenia must become decision-makers in their treatment along with their caregivers [13]. This helps boost self-esteem, lowers the sense of stigma, improves quality of life, and prevents negative outcomes. Shared decision-making models with caregivers and patients for their benefit are important to foster recovery. This may not always be possible but must be done if possible. With the advent of advance directives in mental health care, one must have crisis plans in place to cover admissions to a hospital when needed, reducing involuntary admissions. There is a need for psychoeducation to boost self-esteem of patients and caregivers and focus on an educational- rather than treatment-based approach. Personal recovery goals must be part

of the program (along with clinical recovery), and steps to be taken toward the same must be chalked out. The benefits of an increased knowledge of their illness and better coping skills with personal goal identification help them feel more on the road to recovery in partnership with the treating psychiatrist [14].

Family and Peer Support

In schizophrenia, large number of studies supports family and peer support interventions that help the patient on the road to recovery. The family can help the patient expand their social networks, gain hope, and become more involved in their own care. Families need to rally around their patients, and any hostility toward the patient needs to be dealt with. Family support is known to reduce the length of hospital admissions, promote earlier discharge, and prevent rehospitalizations [15].

Families must be educated about schizophrenia as an illness. The primary goal of family psychoeducational interventions consists of finding a common denominator between the objective textbook medical knowledge with regard to background information of the disorder and treatment measures and the subjective viewpoint of the afflicted patient. Carrying out this requires an extremely differentiated behavioral approach, supported by a basic humanistic orientation [16]. The goal for good recovery is to make families resilient and capable of handling small problems when they arise in the course of treatment, on their own, and foster faith in the patient. Family can be an important external agency, instrumental in the recovery from schizophrenia, allowing the patient to return to fundamental daily functioning, socializing, and developing hope for the future [17].

Self-Management in Schizophrenia

Self-management aims to enable people to develop practical tools of everyday living in order for them to make daily decisions that will maintain or improve their mental health. There are two forms of mental health self-management: condition-specific self-management [18] and generic self-management [19, 20]. There is a need to train patients with schizophrenia in self-skills like social skills, living skills, and self-care. Schizophrenia as an illness with its enduring psychopathology and neurocognitive deficits may sometimes hinder the training, but it is important that patients be trained to the maximum ability they have. In fact, the training must help patients overcome the cognitive and information processing deficits that may be present in schizophrenia. This would include overcoming anergia, abulia, and social withdrawal and improving the blunted affect that may be present. This would help in the recovery process and bring about a huge boost to self-esteem of the patient. Such work is still in its infancy, and there remains a need for more systematic research in this area. The participation of a patient in the management/treatment of his or her illness is an empowering step toward recovery [20, 21].

Marriage and Recovery in Schizophrenia

In schizophrenia, there is severe psychopathology in terms of clinical symptoms and psychological and social deficits, which could be expected to hinder the person from entering and managing social roles, especially marital or spousal roles. Studies have reported that patients who suffer from schizophrenia have lower marriage rates than the normal population and also lower than those with other psychiatric disorders [21]. It has been a topic of debate whether marriage may promote recovery in schizophrenia. In countries like India, a myth prevails that marriage, with the responsibilities it brings, may serve as a means to help the patient recover, and so marriage is sought as a cure for mental illness. This is never true [22].

Patients with schizophrenia have multiple deficits in various areas that may lead to marital dissatisfaction in terms of relationship and marital obligations. Marital quality is compromised, and violence and aggression seen in schizophrenia may also become part of the marital relationship,

with reports of domestic violence being high in women married to someone suffering from mental illness. The emphasis on getting the patient married is more for women than men in India, and it is stigmatic to have a female in the house who is unmarried and suffering from a psychiatric disorder. This stigmatizes the entire family and other women of the family and their marital prospects. Many a time, patients with schizophrenia are married off without having their mental illness disclosed to their partner. Marriage of patients with schizophrenia needs to be planned based on highly individual biopsychosocial factors and then tailor-made based on the needs of each patient [23].

Wellness Initiatives for Recovery in Schizophrenia

There are many areas of schizophrenia treatment that may immensely benefit from the addition of wellness initiatives. Wellness initiatives may prevent patients with schizophrenia from moving toward substance use and may give them alternative ways of dealing with their stress and anxiety [24]. Factors like lack of exercise, overeating, and sedentary lifestyle on the part of the patient may increase the likelihood of development of antipsychotic-induced metabolic side effects. Wellness enhancement in the form of a healthy lifestyle, a daily exercise, and a regular fitness regimen may prevent or delay the onset of these side effects and thereby improve the quality of life (QOL) of the patient [25]. When taught by a trained professional, wellness enhancement focuses on planning, skill building, social support, and confidence enhancement. This shall promote autonomous motivation for attitudinal and behavioral changes that lead to recovery [26].

We also assume that wellness enhancement shall lead to the development of other positive factors like resilience, optimism, better perception of social support, and positive attitudes toward one's own illness and recovery. It is also noteworthy to mention that wellness enhancement may not be possible in the acute stage of the illness where the patient may be uncooperative and/or has poor insight. Rather, wellness enhancement shall be a part of the long-term rehabilitation in cases of schizophrenia. It is also important to understand that wellness programs cannot be generalized and may have to be tailor-made to suit the needs of individual patients [27]. Wellness programs may also differ for impatient and outpatient populations. Wellness models focused on positive lifestyles and enhancement of social support and social skills may be more relevant for patients with schizophrenia who reside with family and friends or live independently. The aim of wellness enhancement in schizophrenia should be recovery, accompanied by a positive mindset, happiness, and positive lifestyle. There is a need in the current paradigm of treatments within schizophrenia to expand the scope beyond just the management of positive or negative psychopathology and cognitive remediation. As stated by some authors, wellness within the illness is an attainable goal in schizophrenia [28].

There is a need for wellness on the road to recovery as a means of cultivating self-reliance and hope, as well as preventing relapse whenever stress or turmoil may occur in the life of a patient with schizophrenia. It is vital that interventions that enhance self-confidence and build self-esteem be a part of the recovery program in schizophrenia [29]. Today we are in an era where psychiatry and rehabilitation have progressed from medical- and treatment-based to a recovery-based and positive psychiatry model, where the focus is on cultivating all those factors that shall enhance the well-being and improve the QOL of the individual [30]. There is a need for the positive psychiatry movement to be incorporated into long-term management programs and the treatment of schizophrenia.

There have been isolated studies on various aspects of wellness in schizophrenia. In a systematic review, it was noted that walking is beneficial in schizophrenia and reduces the incidence of medical morbidity over time. Walking must be encouraged in patients with schizophrenia, and they must be motivated to adhere to a walking regime [31]. Psychosocial weight management programs have also been shown to be beneficial in schizophrenia, both in reducing medical mor-

bidity and preventing weight gain as a result of psychotropic drugs [32]. Indian researchers have come up with a six-module yoga program that may be beneficial to patients with schizophrenia, and this module may enhance wellness when incorporated into both inpatient and outpatient treatment programs [33]. Emerging evidence suggests that mindfulness-based treatments may help in the management of negative symptoms associated with schizophrenia. A recent study documented that mindfulness-based training was associated with more adaptive emotion regulation (greater reappraisal) and beliefs (lower dysfunctional attitudes). It also helped in increasing self-reported motivation. Further studies in the direction of those done above are warranted [34].

Recovery in Schizophrenia: Critical Issues

It has been repeatedly argued that recovery should be assessed on multiple parameters. However, no consensus has evolved regarding the minimum requisite number of parameters. It is desirable to have broader parameters to capture as much information as possible in terms of domains. A survey of people with schizophrenia, their family members, and health professionals reported seven categories of recovery. This study represents collecting understanding of recovery. The common denominators in various expressions of schizophrenia were reported as "recovery being a process" and refer to recovery, which is "gaining broader meaningful goals for individuals" [35].

There has been reasonable debate defining recovery. It is reported as a process as well as recovery from illness, which gives an indication of cure. Recovery connotes complete absence of the disease. Current studies also emphasize outcome as "return to normal function." The other meaning is a broader dynamic process, wherein an individual has learned to cope with the illness, recognizes the limitations, and makes attempts to define goals to pursue a meaningful life. Both these theorems are unrealistic and impractical. Both disregard scientific evidence of neurobiological changes and their irreversibility and the psychological impact of the illness, which is also irreversible.

The emphasis on the range of improvement in specific areas should allow clinicians to communicate more effectively on current scientific evidence and goals of treatment. A more pragmatic finding emerges from a Chinese study, which reports that full recovery could not be said to have been achieved until patients stop medication and have a steady job [36]. Traditional medical paradigm looks at recovery as resolution of symptoms or syndrome. The Westernized definition is more of a narrative account of experience. These two views continue to remain conflicting.

Few facts about outcome of schizophrenia have been repeatedly replicated. Symptomatic remission, low hospitalization, less time spent during psychosis, and low relapse rate are perhaps the most reported expressions. The term "favorable outcome" which has been widely used though appears technically vague has more rich descript. The "science of recovery" has moved away from this descript to strategic quantification of domains. Though this paradigm shift is evidence-based, it leaves a wide scope and vacuum while bringing objectivity in selection of parameters. For example, if cognitive function is an independent outcome measure and it also mediates social and functional improvement, why it's being a measurement of end point is not enough for all three components [37].

Conclusion

The concept "central theme: recovery is only a sweet dream" appears more realistic. It states that recovery is an ideal position where there is (a) no need for medication, (b) higher psychosocial functioning, and (c) satisfying interpersonal relationships. The concept of full recovery is different for patients and for medical professionals. The latter can accept continuation of medication and still call it recovery if psychosocial functions are better. It is prudent that as clinicians we work toward a recovery from complex illnesses in schizophrenia rather than just symptom reduc-

tion. Though recovery may be scientifically understood as categorized concepts of clinical and personal recovery or an understanding of the clinician and patient, it is an individualized concept from a process point of view. There are various factors that play a role in determining the process and extent of recovery for every individual patient.

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18 Metabolic Syndrome in Bipolar Disorder

Renee-Marie Ragguett and Roger S. McIntyre

Introduction

Obesity and its associated risk factors are synonymous with bipolar disorder (BD). Underscored by the presence of cardiovascular diseases (CVD) as a leading cause of premature mortality for those with BD, accounting for approximately 38% of early deaths in this population, the impact on quality of life is evident [1, 2]. In addition to physical health concerns, poor mood disorder prognosis has been positively associated with metabolic symptomatology [3].

Toward rectifying, targeting, and monitoring these negative metabolic traits, they must first be identified. Metabolic syndrome (MetS) has been introduced as a diagnostic term used to characterize the identification of risk factors which increases the likelihood of developing major metabolic diseases (e.g., heart disease, diabetes, and stroke). Screening for MetS is often applied to high-risk groups such as those with BD in order to introduce a metabolic monitoring system in an effort to control adverse symptomatology.

Metabolic syndrome refers to the presence of specific risk factors associated with the development of CVD or type 2 diabetes (T2D). The importance of monitoring MetS is underscored by its overall prevalence of ~35% in the United States and can vary worldwide between 4% and 84%, depending on a wide range of factors including age, sex, and ethnicity [4, 5]. Given the ever-increasing prevalence of MetS and its positive association with cardiovascular events and death (RR 1.78, 95% CI 1.58–2), those typified into high-risk populations for MetS are correspondingly subject to increased risk for premature death [6].

Homologies exist between risk factors for MetS and the lifestyle of those with BD. Table 18.1 enumerates the factors that contribute to the increased rate of MetS in BD [7–10]. For example, those with BD generally have a sedentary lifestyle which can contribute to weight gain and CVD risk [11]. In addition, the presence of MetS can be emphasized in the BD population due to psychotropic mediations which have shown to induce weight gain [12]. Ultimately, these poor metabolic effects resulting in MetS are contributing to poor health and functional outcomes, making MetS a target for management in order to improve the associated poor symptomatology. These management approaches can be noninvasive such as behavioral changes (e.g., diet

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Table 18.1 Factors contributing to increased rate of metabolic syndrome in BD

Factor domain	Components
Social determinants [8]	Poverty Insufficient access to primary/preventative healthcare
Lifestyle and behavioral factors [7]	Habitual inactivity Sleep disturbances Poor food choices (i.e., high empty calorie consumption) Smoking Substance use disorders Opposition to seeking healthcare
Environmental exposures [9]	Childhood trauma (e.g., sexual abuse)
Intrinsic biological factors [7, 10]	Proinflammation **** HPA and HPT axis dysregulation Glucose and insulin regulation Hemostasis and sympathetic nervous system regulation
Treatment [7]	Pharmacological agents (e.g., psychotropic medication)

and exercise) or, in contrast, invasive (e.g., bariatric surgery), both with their own benefits and limitations.

Background of Metabolic Syndrome

The criterion used for determining the presence of MetS can be categorized in an overarching fashion by insulin resistance, obesity, and dyslipidemia. The aforementioned cluster of characteristics has shown positive associations with the occurrence of CVD and T2D [13]. Coincidently, these aspects of metabolic health are often targets of medical interventions due to their association with illness symptomatology and poor prognosis [14]. For example, a systematic review and meta-analysis on intentional weight-loss and depressive symptomatology demonstrated that obesity interventions provided reductions in symptoms of depression [15].

The National Institutes of Health has subdivided MetS into five diagnostic criteria: (1) large waistline, (2) high triglyceride level, (3) low high-density lipoprotein (HDL) cholesterol level, (4) high blood pressure, and (5) high fasting blood sugar [16]. The application of diagnostic criterion can vary, insofar as a variety of organizations have created their own variation on definitions of MetS, and there exists a disaggregation toward the way in which the cluster of MetS symptoms are characterized to determine the presence of the syndrome. Table 18.2 outlines the different definitions of MetS per association [17–20]. In short, the different definitions vary based on the metabolic components (e.g., central obesity, abdominal obesity) and/or the measurements needed to meet the criterion of MetS [21].

It is evident there exists a lack of consensus surrounding the particular cutoff points per MetS criterion measurement and the criterion itself. Contributing to this discord is likely the heterogeneity of MetS. For example, it has been demonstrated that there are metabolic differences between the sexes and race/ethnicity; as such, the differences seen in metabolism should be reflected in the definition of MetS [22, 23]. Almost all frequented definitions of MetS provide gender-specific guidelines; however, only the International Diabetes Federation Global Consensus definition additionally takes into account country/ethnic group. Given the rising prevalence of obesity and novel associations with many life-threatening conditions, it is likely that the definition of MetS will continue to evolve, for example, to include both endogenous population differences and further widen its definition criteria across a multitude of CVD risk measures.

Pharmacology: Potential Contribution to Metabolic Risk

Pharmacological agents commonly in use with BD (e.g., psychotropics) have been positively associated with weight gain, which as a result can contribute to the metabolic burden characterized by MetS. These effects are characteristic of the medication themselves, as changes in metabolism can be seen in various populations (e.g., BD, schizophrenia, and mentally healthy) both endogenously (e.g., increased leptin levels) and exogenously (e.g., weight gain) [24–26]. Metabolic effects present with psychotropic agents are dependent on a variety of factors, including the metabolic properties of the agent itself, the

Table 18.2 Definitions and criterion of MetS by association

Association	Definition
World Health Organization [17]	Glucose intolerance, impaired glucose tolerance or diabetes mellitus and/or insulin resistance paired with 2 or more of the following: Impaired glucose regulation or diabetes Insulin resistance (under hyperinsulinemic euglycemic conditions) Raised arterial pressure ≥140/90 mmHg Raised plasma triglycerides (≥1.7 mmol 1–1; 150 mg dl-1) and/or low HDL-cholesterol (<0.9 mmol l–1, 35 mg dl-1 men; <1.0 mmol 1 = 1, 39 mg dl-1 women) Central obesity (Male waist to hip ratio >0.9; Female wait to hip ratio >0.85) and/or BMI >30 kg/m^2 Microalbuminuria (urinary albumin excretion rate ≥20 ug/min or albumin: Creatinine ration ≥30 mg/g)
European Group for Study of Insulin Resistance Definition [18]	Nondiabetic individuals Insulin resistance or fasting hyperinsulinemia (upper 25th percentile) and 2 or more of the following: Hyperglycemia (nondiabetic, fasting plasma glucose ≥6.1 mmol/l) Hypertension (systolic/diastolic blood pressure ≥140/90 mmHg or treating hypertension) Dyslipidemia (triglycerides >2.0 mmol/l or HDL-cholesterol <1.0 mmol/l or treated for dyslipidemia) Central obesity (waist circumference Male ≥94 cm and Female ≥20 cm)
National Cholesterol Education Program Adult Treatment Panel III [19]	Presence of 3 or more of the following: Waist circumference >40″ Male or 35″ Female Blood pressure >130/85 mmHg Fasting triglyceride >150 mg/dl Fasting high-density lipoprotein (HDL) cholesterol level <40 mg/gl (Male) or 50 mg/dl (Female) Fasting blood sugar over 100 mg/dl
International Diabetes Federation Global Consensus Definition [20]	Central obesity, based on provided country/ethnic group and gender specific cutoffs Raised triglyceride ≥150 mg/dl or history of specific treatment for lipid abnormality Reduced HDL cholesterol <40 mg/dl Male and <50 mg/dl Female Raised blood pressure 130/85 Raised FPG ≥100 mg/dl or T2D

amount being used, and physiology of the user (e.g., gender) [12, 27].

The effect that pharmacological agents have on metabolic factors can be described in terms of a metabolic burden or metabolic liability. Strides have been taken toward reducing the metabolic burden associated with psychotropics, for example, the introduction of "third-generation" antipsychotics, which have a different mechanism of action, in efforts to overcome limitations of second-generation antipsychotics (SGAs), such as metabolic effects [28]. In particular, SGAs olanzapine and clozapine have been positively associated with severe weight gain. Table 18.3 outlines the antipsychotics and mood stabilizers in relation to their metabolic burden [29, 30]. In

Table 18.3 Risk of metabolic effects (weight gain) of pharmacological agents often used in BD

Pharmacological agents	Metabolic risk with antipsychotic (none, low, medium, high) [29]
Clozapine	High
Olanzapine	High
Risperidone	Medium
Quetiapine	Medium
Aripiprazole	Low/none
Ziprasidone	Low/none
–	Metabolic risk with mood stabilizers (present/absent) [30]
Lithium	Present
Valproic acid	Present
Carbamazepine	Absent
Lamotrigine	Absent

contrast, aripiprazole, a third-generation antipsychotic, while still undergoing trials has initial evidence that suggests there are less metabolic effects while still continuing to maintain positive treatment effects [25]. Despite the introduction of new psychotropics, older psychotropics are still widely used for their treatment effects regardless of their known metabolic effects.

Polypharmacy also introduces a method by which the risks for MetS can be amplified. For example, there is evidence which suggests the amount of psychotropics taken concurrently appear to have additive effects, insofar as taking more than one pharmaceutical agent with poor metabolic associations has a larger effect than taking one agent alone [31]. Given the increasing use of use of polypharmacy in BD (almost 70% of the population is prescribed two or more medications), it is essential to explore the relation between polypharmacy and MetS [31]. Same- and/or multi-class polypharmacy in BD can be used in order to treat complex symptomatology [32]. Unfortunately, due to complex symptomatology, it is difficult to elucidate the relationship between the risks for MetS associated with polypharmacy and those with disease prognosis, as very poor metabolic symptoms could be complications of psychological symptoms and not medication [31].

Health and Functional Impact

Despite the characterization of MetS as a cardiovascular disorder and representative of diseases associated with obesity, there exist non-CVD-related disease phenotypes, specifically concurrent with BD.

Illness Prognosis

Illness prognosis, including depressive symptomatology and overall remission, has shown to be influenced by metabolic health. The effects of obesity on illness prognosis have been studied in detail, demonstrating that obesity is linked to poor BD prognosis [3, 33]. This phenomenon has been further explored in attempts to include the effects of MetS; however, current studies of MetS in BD in relation to patient outcomes are inconsistent with older literature, which focused primarily on obesity in BD and illness prognosis. In particular, there is unawareness around whether MetS or specific components of MetS, such as obesity, are mediating the poor effects seen in BD [34].

Contrasting evidence is present in the literature regarding the effects of MetS on BD symptomatology and prognosis. For example, a modest amount of studies have demonstrated that MetS concurrent with BD is associated with a greater burden of illness [10]. These effects can be seen in increased suicide attempt, increased mood symptoms such as depressive episodes, and overall poor global functioning [35–37]. In contrast, in a recent longitudinal study of BD, individuals with metabolic disturbances (i.e., obesity, abdominal obesity) and not MetS were associated with poor global improvement (e.g., mood symptoms, functioning, and life satisfaction). In particular, BMI increases were directly correlated to decreased global improvement [34].

The mechanism by which MetS could be influencing illness prognosis is unknown. Additionally, why obesity in some cases, and not MetS, is associated with poor outcomes is also unknown [34]. This paucity in the literature continues to be an area for research. It is possible that individual components of MetS such as obesity are acting as a mediating factor for illness outcome.

Cognition

Patients with comorbid BD and MetS have shown more severe cognitive impairments than those with BD alone [36]. In addition, the cognitive impairment profile associated with poor metabolic symptomatology in BD patients has been shown to reflect both clinically (e.g., through standardized cognitive testing) and structurally (e.g., reduced brain volume with increased BMI) [38]. Physiologically, MetS-induced inflammatory responses are likely one of the contributing factors to the clinical cognitive presentation, and other factors include oxidative stress, lipid metabolism, and vascular reactivity [39].

The profile of cognitive function in BD and MetS presents as a dysfunction across multiple cognitive domains. Significant differences between BD patients with MetS and those with-

out can be seen in the Winconsin Card Sorting Test (BD – MetS 34.2 +/− 12.5 in contrast to BD + MetS 41.4 +/− 11.7, $p = 0.007$), which relies on a variety of cognitive domains and often reflects frontal lobe dysfunction [36].

Neurologically, MetS has been known to modify the brain in a variety of ways, which could contribute to cognitive dysfunction. For example, the presence of microstructural white matter abnormalities has been significantly associated with poor cognitive performance over a variety of domains [40]. Furthermore, MetS has also been significantly associated with the presence of silent lacunar infarctions, which contribute to both neurodegeneration and cognitive impairment [41, 42]. In addition, MetS is known to induce inflammatory responses throughout the body, and there is evidence suggesting increased levels of inflammatory markers in those with BD and MetS [43]. Elevated levels of pro-inflammatory markers have been positively associated with cognitive dysfunction in the BD population [44]. It is also possible that inflammation and metabolic syndrome behave in a cycle, where inflammation activates the hypothalamic-pituitary-adrenal axis, which can lead to metabolic dysfunction, and metabolic dysfunctions (e.g., MetS) in turn activate inflammatory pathways [44–46].

Prevention, Treatment, and Management

Management and treatment of metabolic symptoms is crucial in high-risk populations such as those with BD. Given the associated effects of MetS in BD (e.g., poor illness prognosis), and prevalence intensification in the population due to shared risk factors, it is possible that targeting metabolic symptoms could improve the quality of life of this population [10, 47, 48]. Toward improving both overall health of those with BD and psychiatric prognosis, it has been suggested that this population's metabolic symptoms be monitored [36].

Prevention of MetS can include prescribing medication that has less of a metabolic impact than those with a large metabolic impact, for example, aripiprazole instead of olanzapine [25, 49]. However, changing pharmaceutical agents is a complex task and could be unfavorable, resulting in worsened psychiatric symptoms [50]. In addition, the use of pharmaceutical interventions for weight control is also a short-term option, for example, topiramate and reboxetine have both shown that taken in conjunction with psychotropic medication may control metabolic symptoms and/or result in weight loss [51].

Lifestyle changes are another approach for control of metabolic symptoms. This change, however, may prove to be challenging, as the lifestyle of patients with BD is conducive of elements which are associated with obesity (e.g., sedentarism and poor diet). Life-changing interventions can include increases in activity and nutrition monitoring [11]. It is also possible that exercise could have a benefit for mood symptomatology. This phenomenon is present in depression, and there have been attempts in literature to extend it to BD. Thus far, there is conflicting evidence of the effect of exercise on BD symptomatology; however, some studies have shown positive associations. For example, Ng F et al. (2007) demonstrated that BD patients who attended a walking group over a 24-month period showed lower Depression Anxiety Stress Scales ($p = 0.005$) [52, 53].

Bariatric surgery (BS) has been used as a long-term weight-loss solution for those who are unable to maintain weight loss following traditional behavioral methods (e.g., diet and exercise) and given their weight are at risk for CVD. Those with BD account for 1.4% to 35.6% of people requesting BS [54]. Not only does BS serve to lower weight and reduce traditional weight-associated comorbidities (e.g., CVD); BS is also associated with long-term improved cognition in a variety of domains (e.g., executive function and memory) shown to be maintained 3 years after surgery [55, 56]. Unfortunately, while BS is one of the most effective treatments for morbid obesity, there are some limitations surrounding its use in those with BD. There exists conflicting evidence surrounding the psychiatric effects around the use of BS with BD, as it is possible that this population could have poor metabolic outcomes and exacerbated psychiatric

symptoms post procedure; however some studies have shown that BS did not affect psychiatric symptomatology and resulted in a successful weight-loss trajectory [57, 58].

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19 Comorbid Psychiatric and Physical Disorders

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Comorbid Psychiatric Disorders with Schizophrenia: Introduction

Schizophrenia remains a major burden on patients and society. No two patients with schizophrenia present with the exact same constellation of symptoms. Even in the same patient, symptoms can show a drastic variation over time, and there is significant interlink between different sets of symptoms. Psychiatric comorbidity is recognized as an important clinical problem in the diagnosis, treatment, and prevention of mental illness. More than half of all patients with schizophrenia experience at least one co-occurring psychiatric disorder [1]; moreover, such disorders often have a detrimental effect on the course of schizophrenia and can complicate the clinical picture. Detection and optimal treatment of such co-occurring disorders in this patient population are essential if patient outcomes are to be optimized.

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Substance Use Disorders

Nearly half of the people suffering from schizophrenia also present with a lifetime history of substance use disorders [2], a rate at least three times as high as seen in the general population [3]. Alcohol, cannabis, and cocaine are the most common substances of abuse.

There are several demographic characteristics that influence the probability that a schizophrenic patient will have a substance use disorder. Younger age and male gender especially increase the likelihood of abuse of drugs and alcohol among those with schizophrenia [4]. Earlier age of onset of schizophrenia is also associated with increased substance abuse [5].

Several hypotheses have been proposed to try to account for the high comorbidity of schizophrenia and substance use. These include:

1. The self-medication hypothesis suggests that individuals with schizophrenia may use substances to alleviate distressing psychiatric symptoms [6] or the uncomfortable neurologic side effects of antipsychotic medications [7]. Despite the initial allure of this explanation, studies that have tried to confirm this hypothesis

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have failed to do so [8–13]. Thus, while patients with schizophrenia report that use of substances subjectively lessens social problems, insomnia, and low mood similar to people with primary substance use disorders, the self-medication hypothesis does not appear to be an adequate causal explanation for the elevated rates of substance use disorder in schizophrenia.

2. That substance use leads to schizophrenia. Several groups have proposed that substance use can trigger the onset of schizophrenia in vulnerable individuals [14–16]. Several reports suggesting that patients with schizophrenia with a history of substance use disorder may have an earlier age of onset of schizophrenia would appear consistent with this possibility [17, 18].
3. That substance use and schizophrenia have a common origin (share a genetic basis). A family history of substance use disorder may increase the risk for substance use disorders in patients with schizophrenia [19], but family history alone does not explain the overall increased prevalence of substance use. Family, twin, and genetic studies thus far point toward the fact that the biological/genetic vulnerability for one disorder is different from the vulnerability for the other. Thus, the presence of schizophrenia in a family member does not appear to increase the risk for substance use disorder in other family members without schizophrenia, and conversely, the presence of a substance use disorder in a family member does not increase the rest of the family's risk for schizophrenia [20].
4. That the increased rate of substance use results from multiple risk factors, including affect dysregulation and poor coping skills. This theory has been explained by an affect regulation model that focuses on stable personality traits that affect long-term risk for substance abuse [8]. The suggestion is that if longstanding traits of individuals are implicated in the onset of substance abuse, then onset of substance abuse can occur independent of the onset of symptoms of schizophrenia.
5. That the substance use is a response to reward circuitry dysfunction. This formulation, based on a series of animal studies [21], suggests that the dysregulated dopamine-mediated mesocorticolimbic brain pathways that are thought to underlie the symptoms of schizophrenia are also the basis of a brain reward circuit deficit in these patients. It is proposed that substances of abuse transiently lessen this deficit and thus allow patients with schizophrenia to enjoy normal activities while, unfortunately, they also worsen the course of schizophrenia [22, 23].

Although the increased vulnerability to substance use disorders in people with schizophrenia is most likely to be multifactorial, most of the findings from neuroanatomical, neuropsychological, and neuropharmacological studies are consistent with the reward system dysfunction model [22, 24].

Effects of Substance Use on Course of Illness

Substance use disorder comorbid with schizophrenia is associated with greater morbidity than schizophrenia alone. They have higher rates of relapse, decreased employment, and increased homelessness [25–27]; increases in suicidal ideation, risk of victimization, and violence; and risk of incarceration [28–30].

This dual diagnosis is linked with increased risk of medical disorders, including hepatitis B, hepatitis C, HIV, purified protein derivative (PPD) reactivity, and traumatic injury [31–33]. Chronic use of cocaine or cannabis may also lead to a higher risk of tardive dyskinesia [34, 35]. The increased prevalence and intensity of smoking among schizophrenic patients can be expected to lead to increased morbidity from conditions for which smoking is a known risk factor.

Studies also suggest a significant association between schizophrenia and potomania, defined as the ingestion of beverages in large quantities, on the order of 8 to 10 liters per day. In cases of water intoxication, severe metabolic imbalances can occur, leading to hyponatremia, convulsions, and coma [36].

Management

Clinicians must remember that even relatively small amounts of substances can lead to larger than expected effects in persons with schizophrenia [37]. Therefore, it is essential to explore the possibility of substance use in each patient. For this, multiple sources of information can be used to aid in identifying substance abuse, such as patient interviews, chart reviews, and collateral information from family members and from other clinicians involved in the treatment of the patient.

Standardized questionnaire that clinicians can use as screening tools include the Alcohol Use Disorder Identification Test (AUDIT), the Drug Abuse Screening Test (DAST), the Michigan Alcohol Screening Test (MAST), and the Dartmouth Assessment of Lifestyle Inventory (DALI), an instrument developed for use specifically in persons with mental illness [38, 39].

Urine and blood toxicology tests can be used for objective assessment of substance abuse.

An ideal treatment practice would involve use of an integrated program that combines the treatment of substance abuse and schizophrenia. Treatment includes both psychosocial treatments and pharmacotherapy.

Psychosocial Management

The initial aim is to assist the patient with primary needs, such as housing, and to establish regular contact. The focus should be on building rapport, and as the patient moves forward in treatment, motivational techniques should be utilized to gradually increase the patient's awareness of the problems and risks associated with substance use until a desire to change develops. This initial phase should be followed by active treatment. These approaches include cognitive–behavioral strategies and 12-step programs. There is little evidence demonstrating the superiority of any one particular program over the other. Family psychoeducation should also be used to supplement these treatment strategies.

Pharmacotherapy

General measures include use of longer-acting oral medications so that the frequency of dosing can be minimized and possible use of depot neuroleptics.

Of the atypical agents, the one most thoroughly studied for use in this population is clozapine. Several studies of clozapine have shown it to be associated with reduction not only of psychotic symptoms but also of substance abuse [40].

The strong dopamine-2 (D2) blockade of conventional antipsychotic agents does not improve the function of the mesocorticolimbic reward system, unlike clozapine, which, with its reduced D2 blockade, decreases the dysfunction of this reward system in schizophrenic patients, leading to reduction in substance abuse [22].

The medications used for reducing use of alcohol and other substances in the general population include naltrexone, disulfiram, and acamprosate, which can also be tried.

Techniques to promote smoking cessation include nicotine replacement therapy and use of oral medications such as bupropion and varenicline. Both nicotine replacement therapy and sustained-release bupropion have been tested in patients with schizophrenia. Nicotine replacement appears to be effective in reducing smoking cessation rates, although less effective than in patients without schizophrenia [41, 42].

Anxiety Disorders

There is an increased prevalence of anxiety disorders among patients with schizophrenia compared with that of the general population [43]. These include panic disorder, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), generalized anxiety disorder, and social anxiety disorder (SAD).

In schizophrenia patients with anxiety, there is evidence of an underactive fear circuitry during anxiety-provoking stimuli but increased autonomic responsiveness and increased responsiveness to neutral stimuli. Recent findings implicate the serotonin transporter (SERT) genes, brain-derived neurotrophic factor (BDNF) genes, and the serotonin 1a (5-HT1a) receptor but are preliminary and in need of replication [44].

A few of the significant diagnostic issues complicating the study of anxiety in schizophrenia are that symptoms may occur spontaneously or might be intermittent presentation, in direct response to psychotic symptoms, and/or as a side effect of antipsychotic medications.

OCD

The prevalence rate of OCD is 1–2% in the general population [45]. In comparison, patients with schizophrenia have a risk of about 25% for comorbid obsessive-compulsive symptoms (OCS), and about 12.1% also fulfill the criteria for an obsessive-compulsive disorder (OCD). On the other hand, primary OCD patients carry a relatively low risk (1.7%) to develop comorbid psychotic symptoms [1, 46, 47].

OCD and schizophrenia share some epidemiological and clinical similarities – both disorders develop in early adulthood, have an equal gender ratio with earlier onset in males, have high prevalence rates of comorbid disorders, and have a chronic course. However, there is no evidence of a clear familial relationship or shared genetic aetiology between OCD and schizophrenia [48].

The obsessions and compulsions in patients with schizophrenia are similar to those in patients without psychosis and include, namely, obsessions of contamination, sexual, somatic, religious, and aggressive themes with or without accompanying compulsions and intrusiveness. One of the challenges faced by the psychiatrist is in differentiating between delusions, preoccupations, and obsessions in patients with formal thought disorders.

Delusions are false, firm, fixed beliefs that are ego-syntonic, whereas obsessions are ego-dystonic and recognized as pathological intrusions by the patient [49]. However, this differentiation does not always hold good in some patients with primary OCD or in patients with psychosis. About 15% of the patients with primary OCD have poor insight [50]. Also, in some patients, there may be an overlapping of obsessions and delusions [51]. Earlier psychiatrists such as Bleuler, Westphal, and Kraepelin considered obsessive-compulsive symptomatology as a prodrome of psychotic illness and suggested that the presence of OCS in schizophrenia is a predictor of better clinical outcome. Recent studies [52], however, suggest greater neurobiological dysfunction and worse clinical course and long-term outcome in patients with OC schizophrenia, but at the same time, several studies concur that obsessive-compulsive symptoms predated psychotic symptoms in more than half of the patients with schizophrenia [53, 54].

Onset of obsessive-compulsive symptoms can occur at different stages during the course of psychotic illness:

1. Before psychosis as a prodrome.
2. Prior to psychotic manifestation as comorbid independent disorder.
3. Simultaneously as a part of psychosis.
4. After the psychotic episode during the course of chronic schizophrenia, either during recovery or remission.
5. As de novo OCS following the initiation of antipsychotic treatment.

Neurobiological Basis

The current evidence suggests dorsolateral prefrontal cortical dysfunction in schizophrenia and a corticostriatal–thalamic–cortical circuitry abnormality in OCD. Neuroimaging studies of patients with schizophrenia have shown significant degenerative changes in the orbitofrontal cortex, cingulate, and caudate nucleus; however, despite the implication of these areas in OCD, no gross anatomical changes have been found in patients with OCD [55].

Functional neuroimaging studies have revealed differences between OCD and schizophrenia; hyperactivity in the orbitofrontal cortex, caudate nucleus, and thalamus has been often observed in OCD patients, whereas dorsolateral prefrontal cortex dysfunction is a dominant finding in schizophrenic patients [56]. This diversity in the neurobiological abnormalities in these two disorders suggests that schizophrenia and OCD constitute two distinct disorders with significantly unique pathogenesis, however, with some overlap in pathogenesis that might explain common clinical features.

Neuropsychological studies in recent years have demonstrated greater prefrontal cortex functional impairment in the OC subgroup compared with non-OC schizophrenia patients [57].

Role of Antipsychotics in Etiology

Some atypical antipsychotics have been known to cause de novo OCS or exacerbate preexisting OCS [58–63]. These include clozapine, olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone. Among all of the above, clozapine therapy has been most commonly associated with the emergence of de novo OCS [64]. This is attributed to their antagonist effect on 5-HT2a receptors, whereas D2 receptor blocking activity of antipsychotics is thought to be related to their antiobsessional effect [65]. Clomipramine and fluoxetine with mild indirect dopamine blocking properties are highly effective antiobsessional agents [66].

The current evidence suggests that changing to an antipsychotic treatment with a minimal 5-HT2a receptor affinity and antidopaminergic (D2/D3), such as amisulpride and haloperidol, can offer a treatment option for antipsychotic-induced OCS in schizophrenia [66].

Management

The Yale–Brown Obsessive-Compulsive Scale can be used to detect the obsessive-compulsive symptoms in these patients. Management strategies include:

1. The OCS that develop as a part of the psychotic episode might successfully resolve along with overall improvement in psychosis with the use of antipsychotics alone.
2. If the OCS is exacerbated or newly developed after use of atypical antipsychotics, then a dosage adjustment or switch in antipsychotic medications to a strong antidopaminergic properties and a negligible 5-HT2 receptor affinity should be considered. Amisulpride seems to be promising in the management of neuroleptic-induced OCS [64].
3. Use of the adjunctive anti-OCD medications such as clomipramine and SSRI seems to be effective, but clinicians must be aware of their potential pharmacokinetic and pharmacodynamic interactions with antipsychotic medications. There are also a few reports that use of anti-OCD agents in some acutely psychotic schizophrenic patients may increase the risk of symptom exacerbation [49].
4. Patients receiving clozapine should be carefully assessed to determine the role of clozapine therapy on OCS. If the OCS seem to have started or worsened with clozapine treatment, clinicians should consider switching to another antipsychotic after weighing the benefits derived from clozapine against the morbidity caused by an increase in OCS. If clozapine is to be continued, its dosage may be adjusted, or SSRI should be considered as an antiobsessional treatment of choice, given the significant adverse effects associated with combined clozapine and CMI regimen. The novel antipsychotic drug amisulpride may offer a new treatment prospect in OC schizophrenia.
5. Finally, pharmacotherapy should be combined with the cognitive-behavioral psychotherapy in treating obsessive-compulsive symptoms in schizophrenia once the patient is clinically stable or able to participate in the therapy.

Panic Disorder

The prevalence rates for panic attacks in patients with schizophrenia have been found to be very variable, between 7.1% and 47.5% [53] in some studies, while 4.2% to 35% [67] meet criteria for panic disorder. This is in comparison to a lifetime prevalence rate of 1.2% in the general population [68].

Schizophrenia patients with panic symptoms exhibit some differences in clinical presentation that set them apart from other schizophrenia patients. Studies suggest that panic attacks are more common in patients with paranoid schizophrenia, compared to other schizophrenia subtypes [1], and it has been proposed that panic may be directly related to delusional fears and to auditory hallucinations in some patients [67, 69].

Patients with schizophrenia and panic attacks or panic disorder also exhibit higher rates of

depression, suicidal ideation, and lifetime substance use [70, 71]. Trembling, feelings of unreality, and fear of dying are particularly prominent symptoms. Patients with schizophrenia and panic are more likely to seek mental health and medical treatment than are patients with schizophrenia who do not have panic symptoms.

Cognitive–behavioral therapy (CBT) is effective for the treatment of panic disorder in the general population and has been modified for use in treating schizophrenia [72].

Social Anxiety Disorder

Social anxiety disorder (SAD) is reported to affect 10% to 20% of patients with schizophrenia [73]. One possible explanation for this comorbidity is that dopaminergic dysfunction may be involved in the development of both disorders. Clinical significance is that, when SAD is also present, schizophrenic patients are even more likely to withdraw socially and have greater difficulty functioning in social situations. They are also more likely to have a history of alcohol and substance abuse. They are more likely to attempt suicide and also use more lethal means than a schizophrenia patient who does not have SAD [74].

Social anxiety and fear of social situations may be confused with the avoidance and withdrawal associated with psychotic symptoms and must be carefully differentiated from paranoia, withdrawal, and apathy. The prominent features of social phobia include fear of social situations in which the individual might be scrutinized by others and avoidance of those situations or endurance of them only with intense anxiety. Evidence of embarrassment regarding scrutiny in these situations, rather than fear of persecution, will help identify patients with schizophrenia and social anxiety.

CBT usually includes education, cognitive restructuring, social skills training, and gradual exposure to feared social situations. Social skills training and other rehabilitation efforts for patients with schizophrenia and social anxiety should incorporate education and gradual exposure to feared social situations [75].

Posttraumatic Stress Disorder (PTSD)

Patients with schizophrenia may be at increased risk for exposure to trauma, due to illness-related features, environmental influences, and/or comorbid substance use. A history of trauma is common in patients with schizophrenia, and especially, childhood trauma is a risk factor for psychosis [76]. Most patients with schizophrenia who have experienced one trauma report experiencing multiple traumas [77]. Many factors complicate the diagnosis and investigation of co-occurring PTSD and schizophrenia, including the presence of psychotic symptoms within the context of PTSD or PTSD symptoms – such as reexperiencing the trauma – these flashbacks might mimic psychotic symptoms.

The presence of PTSD has also been shown to be associated with more severe psychopathology, especially including cognitive impairments, higher rates of suicidal ideation and suicidal behaviors, and more frequent outpatient physical health visits and hospitalizations in patients with schizophrenia. A history of PTSD is associated with worse role function, substance abuse, homelessness, lower quality of life, and less employment [78–80].

Depression

Around a quarter of people with schizophrenia meet criteria for a depressive disorder at some time in their lives [1]. Significant depressive features are common in schizophrenia and are often interfaced with core psychotic symptoms, as well as being a significant mediator of disability and potentially driving suicidality. Studies of individuals at high risk for developing schizophrenia have generally demonstrated a significant degree of depressive symptoms prior to and during the emergence of psychotic symptoms [1].

Depressive symptoms in schizophrenia may be associated with significant distress, particularly around themes of loss, grief, and hopelessness, and can occur throughout all phases of the illness, including the prodrome, acute psychotic episodes, and the post-psychotic phase. There is

an increased risk of psychotic relapse when these symptoms persist in the chronic phase of schizophrenia [81].

Risk assessment is crucial for anyone with schizophrenia comorbid with depression, as suicide is a leading cause of death among people with schizophrenia. Other risks such as self-neglect and poor oral intake must also be assessed, as many patients are socially isolated and do not have adequate social support.

Suicide is about 13 times more likely in people with schizophrenia than in the general population [82]. Although the precise nature of the link between suicide and depressive symptoms in schizophrenia has not been firmly established, depression remains the most significant mediator of suicide in the general population, and this is likely to also apply to people with schizophrenia. Hopelessness and demoralization are pointers of increased risk of suicide, as well as social isolation and substance use.

Schizoaffective disorder is the co-occurrence of a mood disorder (episodes of depressive, manic, and/or mixed types) with schizophrenic symptoms in the same episode of illness. Schizoaffective episodes of the depressive type are often less florid than schizoaffective episodes of the manic type, but they usually tend to last longer, and the prognosis is less favorable [83].

Management

Psychiatrists, along with the general practitioner, have a very important role to play in schizophrenia patients with comorbid depression because depressive symptoms may be a presentation of general medical issues. Some of these include thyroid dysfunction or malignancy. Poor diet might be associated with anemia, another potential cause of depressive symptoms. Obstructive sleep apnea can also herald fatigue and depression. Prescribed psychotropics or medications for other medical conditions like antihypertensives might also precipitate depressive symptoms.

It is also important to determine whether a substance use disorder is present or not, as it might be contributory.

Psychosocial Management

Demoralization, with feelings of hopelessness, helplessness, an external locus of control, and lowered self-esteem, can be a component of comorbid depression in people with schizophrenia. It needs particular interventions, including meaning-based, cognitive behavior, interpersonal, and family therapies, as clinically appropriate.

Pharmacotherapy

The weight of evidence is that antidepressants can play an important adjunctive role in treating depression in patients with schizophrenia and may reduce suicide risk. Potential downsides include the complexity of the medication regimen, which may negatively affect adherence, and exacerbation of the side effects of prescribed antipsychotic medications – for example, SSRIs and serotonin–noradrenaline reuptake inhibitors can induce akathisia and sexual side effects, and mirtazapine can cause somnolence and weight gain [84, 85].

Eating Disorders

Eugen Bleuler described disturbances in eating behavior as a feature of schizophrenia in the early nineteenth century [86]. The various disturbances in eating behaviors seen in patients with schizophrenia include pica, gorging, anhedonic displeasure from food, and starvation associated with paranoid delusions.

Pica is defined as the repeated ingestion of non-nutritive substances (pebbles, hair, small metal objects, etc.) [87]. This disorder is common in children (and is found more rarely in adulthood) with developmental disorders (e.g., autism) or mental retardation. In schizophrenia, it can be defined as an impulsive consumption associated with delusions. Many cases of coprophagia, defined as the ingestion of feces and considered a variant of pica, have been associated with schizophrenia [88].

Anorexia Nervosa

The frequency of anorexia nervosa in schizophrenia has been approximated to be between 1% and 4% [89]. This disorder can occur as a symptom on the spectrum of manifestations of schizophrenia and overlapping symptoms in the psychopathology of schizophrenia. Symptoms such as distortion of body image and fear of being fat are frequently observed. Anorexia nervosa may precede or follow schizophrenia. For example, many male patients who are diagnosed with anorexia nervosa are found to have schizophrenia several years after the initial diagnosis (sometimes even 6 years later) [90, 91].

Additionally, various clinical features of schizophrenia can lead to anorexia. For example, a depressive disorder associated with schizophrenia can lead to losses of appetite and weight. Secondly, due to paranoid delusions, the patient may believe that their food or drink is being poisoned or contaminated and refuse to eat it. Finally, auditory hallucinations can be perceived as ordering a complete food refusal.

Antipsychotic-Related Appetite Changes

The mechanisms of weight gain and increased food intake associated with antipsychotics include:

1. Direct effects on antipsychotic receptors.
2. Direct or indirect effects on the neuronal circuits (hypothalamus) controlling food intake and satiety.
3. Disruption of the hypothalamic–pituitary–adrenal axis.
4. Direct effect on insulin sensitivity and insulin secretion.
5. Effects on gastrointestinal hormones involved in food intake.
6. Decreased physical activity and decreased basal metabolism.

Blockades of dopamine (D2 and D3), serotonin (5-HT2c), histamine (H1) [61], and muscarinic (M2 and M3) receptors have all been shown to increase appetite [62, 63].

Other studies suggested a relationship between the increased food intake induced by an antipsychotic drug and changes in leptin, melatonin, opioid, and endocannabinoid signaling [92]. Additionally, by endocrine/metabolic mechanisms, antipsychotics can directly induce the activation of the hypothalamus–pituitary–adrenal axis [93], deficits in insulin secretion [94] leading to changes in appetite.

Sexual Dysfunction in Schizophrenia

Sexual dysfunction (SD) is estimated to affect 30–80% of patients with schizophrenia and is a major cause of poor quality of life. Dysfunctions such as erectile dysfunction, decreased libido, or disturbances in ejaculation/orgasm are more frequent in both men and women suffering from schizophrenia [95].

Sexual dysfunction in patients with schizophrenia may be related to the disease itself (attributable to the negative symptoms, decreased initiative, and motivation), psychosocial factors, somatic health, and the use of psychotropic medications [96].

Cigarette smoking is known to occur with greater prevalence among patients with schizophrenia and is also a contributory factor for sexual dysfunction.

Antipsychotic medications are also known to be commonly associated with sexual dysfunction. The mechanisms by which they cause sexual dysfunction include histamine receptor antagonism, dopamine receptor antagonism, dopamine D2 receptor antagonism, cholinergic receptor antagonism, and alpha-adrenergic alpha receptor antagonism [97, 98].

Risperidone and olanzapine have the highest likelihood of causing SD [99]. More than 50% of the patients treated with olanzapine experience SD. Clozapine, another antipsychotic, has been considered as having one of the lowest associations with SD with respect to the first-generation antipsychotics but produces higher rates of erec-

tile and ejaculatory problems than other atypical antipsychotic medications. Furthermore, quetiapine seems to be associated with SD rates of about 50–60% [100], but the severity of such dysfunction may be lower than in patients treated with risperidone or olanzapine.

Being bound to histaminergic receptors could impair arousal by directly increasing sedation. Dopaminergic receptor antagonism may decrease the libido by inhibiting motivation and reward. Blockade of D2 dopamine receptors in the tuberoinfundibular pathway by antipsychotics may decrease the libido, impair arousal, and impair orgasm indirectly, by leading to elevated prolactin levels. Cholinergic receptor antagonism may induce erectile dysfunction by reducing peripheral vasodilation. Alpha-adrenergic alpha receptor antagonism can reduce peripheral vasodilation, resulting in erectile dysfunction in men and decreased lubrication in women [101]. Additionally, abnormal ejaculation is correlated with the antiadrenergic effects of treatment.

Measures of Sexual Dysfunction

Several questionnaires are available to evaluate sexual function before and during psychotropic treatments. These include the Arizona Sexual Experience Scale, the Changes in Sexual Functioning Questionnaire, and the Sex Effects Scale. The Sex Effects Scale is a brief 13-item clinician-administered or self-report scale that has been used to compare sexual adverse effects of different antidepressants. It is a gender-specific measure designed to assess changes in three dimensions: desire, arousal, and orgasm [102–104].

Management

General principles of management include:

1. Gradually reducing the dosage of the implicated antipsychotic.
2. If subsequently there is no improvement in symptoms, switch to other antipsychotics that have a better sexual profile.
3. If the symptoms still persist, use of phosphodiesterase inhibitors like sildenafil can be considered.

Other approaches, such as drug holidays and psychological interventions, have all been tried with mixed, unconfirmed results [105].

Physical Comorbidities in Schizophrenia: Introduction

Schizophrenia is a highly debilitating disease that affects ~1% of the world's population [106]. Patients with schizophrenia not only have increased standardized death rates but also a life expectancy 10–25 years lower than that of the general population [107–109]. On an average, men with schizophrenia die 20 years earlier and women die 15 years earlier than people without a major mental illness [110, 111]. Although death due to suicide is a contributing factor, approximately two-thirds of this premature mortality and poor physical health outcomes are attributable to physical illness, namely, cardiovascular disease, smoking-related lung disease, and type 2 diabetes [112, 113].

Schizophrenia is a complex disorder that impairs multiple aspects of cognitive, perceptual, emotional, and behavioral functioning. Improved detection and treatment of medical illness in schizophrenia will have significant benefits for their psychosocial functioning and overall quality of life [114, 115]. On the other hand, unrecognized physical diseases may exacerbate the symptoms of psychiatric illness by affecting brain function or by affecting multiple organ systems.

Atypical antipsychotics have offered patients many benefits, such as alleviation of positive and negative symptoms, cognitive deficits, and mood symptoms, and a lower risk of extrapyramidal symptoms, compared with traditional first-generation antipsychotics [116]. However, evidence is beginning to suggest that these agents, though significantly beneficial, in some cases can also potentially exacerbate comorbid medical conditions. One of the major challenges faced by a consultation-liaison psychiatrist treating

patients with comorbidity is to determine which medications are safest in which medical conditions.

Higher rates of morbidity in patients with schizophrenia result in a high financial burden [117]. Patients who have schizophrenia also face barriers in receiving prompt and appropriate medical health care. The social withdrawal associated with schizophrenia is a factor that could prevent self-care and treatment-seeking behavior for physical complaints and comorbidities.

The comorbidity of physical and mental illnesses has implications for the treatment in terms of health-care utilization and cost, quality of life, and understanding of the pathophysiology of those disorders. Medical comorbidity can either cause or exacerbate the psychotic illness [118]. Studies suggest that persons with schizophrenia who have at least one medical problem also had worse perceived physical health status, more psychosis, more depression, and a greater likelihood of a suicide attempt [119]. Therefore, medical conditions that may go unrecognized in this population can contribute to prolonged hospitalizations and treatment failure. This section discusses the various physical comorbidities in schizophrenia and their management, the models of development of these disorders, and the barriers to their prevention and early detection.

Models of Comorbidity

Four models were used to explain the higher rate of substance use comorbidity in schizophrenia [120]. These same models have been applied by Dixon et al. to explain the somatic comorbidities in schizophrenia. These include:

1. In the secondary disorder model, the presence of schizophrenia leads to an increased vulnerability to substance abuse for either self-medication, social facilitation, or pleasure enhancement and to an increased risk for somatic comorbidities, either through medication side effects or through behavioral inclinations. Risk of diabetes, for example, could be increased by antipsychotic drugs or by poor dietary habits or decreased physical activities.
2. In the secondary psychiatric disorder model, the psychiatric presentation is a result of the comorbid condition like how partial seizures or systemic lupus erythematosus could lead to psychotic symptoms, mimicking schizophrenia.
3. In the common factor model, the increased rate of schizophrenia and other comorbidities is the result of a shared etiological factor. The third factor could be either a common genetic vulnerability or a shared environmental risk factor. For example, some have hypothesized a shared genetic risk between diabetes and schizophrenia, given the increased family history of diabetes.
4. In the bidirectional model, schizophrenia and the comorbid conditions interact in such a way that either disorder influences the occurrence of the other. An example of this model is when patients with schizophrenia use psychoactive substances to counter symptoms and experience worsening of psychotic symptoms as a result of the substance use.

Diabetes

The recent literature is consistent in showing a prevalence rate of diabetes of about 15% in patients with schizophrenia or a risk of two- to three-fold compared with the general population [121]. There is an increased risk in people with schizophrenia of developing glucose regulation abnormalities, especially insulin resistance [122]. Lifestyle factors such as poor diet, sedentary behavior, and cigarette smoking tend to maintain and further exacerbate the problem. All antipsychotic agents increase the propensity to develop diabetes. This risk is more with atypical antipsychotics than typical agents. Among the atypical antipsychotics, clozapine, quetiapine, and olanzapine seem to be associated with an increased risk for developing diabetes [123].

The mechanisms for illness susceptibility in schizophrenia remain unclear but could be attributed to the thrifty phenotype hypothesis which proposes that the epidemiological associations

between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose–insulin metabolism. Other possible explanations include autonomic hyperactivity and potential cellular and genetic links [124]. Social health determinants, such as income, housing, and food insecurity, could also be contributory factors.

Presence of psychotic symptoms, as well as cognitive disturbances, poor social support, and poor treatment adherence, affects the outcome of diabetes in persons with schizophrenia. Those patients with comorbid diabetes mellitus are also prone to develop macrovascular and microvascular complications. These long-term complications include retinopathy, nephropathy, peripheral neuropathy, and autonomic neuropathy which could, in turn, increase the risk of ulcers and Charcot's joints. Stroke, myocardial infarction, and peripheral vascular disease are also associated with poor diabetic control.

These lifestyle factors, along with the atypical antipsychotic, can increase the risk of development of metabolic syndrome, which is characterized by obesity, insulin resistance, dyslipidemia, impaired glucose tolerance, and hypertension [125].

For all these reasons, it is important to initiate schizophrenia treatment with antipsychotics that have low metabolic risk whenever possible and reserve more potent agents with high metabolic liability for patients who do not respond adequately.

Hyperlipidemia

Antipsychotic medications have been associated with the development of hyperlipidemia. Typical antipsychotics like haloperidol have no effect on lipids, but phenothiazines like chlorpromazine tend to raise triglyceride levels and reduce levels of high-density lipoproteins [126]. Dibenzodiazepine group of atypical antipsychotics like clozapine and olanzapine is linked with increased levels of fasting glucose and lipids compared with risperidone [126]. Development of glucose intolerance also seems to be involved, as insulin resistance is a key factor in the pathophysiology of hyperlipidemia [127].

Cardiovascular Disease (CVD: Hypertension, Cardiac Arrhythmias)

Mortality due to ischemic heart disease, cardiac arrhythmias, and myocardial infarction is higher in people with mental illness [128]. Cardiovascular disorders have been attributed as a major determinant of increased mortality reported in patients with schizophrenia [129, 130]. Hypertension, which is a strong independent risk factor for CVD, affects approximately 9–27% of patients with schizophrenia [131]. Antipsychotic agents contribute to metabolic syndrome, which is also a significant risk factor for development of cardiovascular disease [132]. Lifestyle factors like smoking, alcoholism, poor diet, and a lack of exercise contribute to increased risk of cardiac problems.

Introduction of psychotropic medications in this population should be followed by a periodic monitoring of changes in the various risk factors for cardiovascular disease [132]. Subsequently, any detection of an increase in these risk factors, especially those occurring early after start of medication, should further intensify the monitoring [133].

Obesity

40–62% of people with schizophrenia are obese or overweight [134]. Typical and atypical antipsychotics can both induce weight gain. Dibenzodiazepine-derived atypical antipsychotics like clozapine and olanzapine cause rapid increase in weight in the short term. Long-term differences between agents are, however, less clear [135]. The Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) study, funded by the National Institute of Mental Health, examined 1493 patients diagnosed with chronic schizophrenia and treated with risperidone, olanzapine, quetiapine, ziprasidone, or perphenazine for up to 18 months. Weight gain was most noted with olanzapine [136]. Lifestyle factors and poor

ability to modify behavior in schizophrenia also influence obesity.

Treatment compliance is an important aspect of schizophrenia management. A factor that can have a negative impact on treatment compliance is negative self-esteem. Overweight and obesity may negatively influence self-esteem, which can increase stigma and social discrimination and have a negative influence on treatment compliance. A threefold enhanced risk of drug treatment discontinuation in patients experiencing AP-induced overweight or obesity and consequent increasing risk of relapse has been observed [137].

Autoimmune Conditions in Schizophrenia

A role for autoimmune dysfunction in psychiatric illness has been actively investigated since at least the 1930s, when autoantibodies were first reported in a schizophrenia patient [138]. Schizophrenia patients or their relatives have been reported to have either higher or lower than expected prevalence of some autoimmune disorders, including rheumatoid arthritis [139], type 1 diabetes [140], thyroid disorders [140, 141], and celiac disease [142].

Systemic Lupus Erythematosus (SLE)

Prevalence of neuropsychiatric syndromes in SLE is estimated to be up to 90% [143]. Neuropsychiatric lupus can present with various neurologic and psychiatric symptoms and signs, including psychosis resembling schizophrenia [144].

Celiac Disease

Patients with schizophrenia were placed on a gluten-free diet with improvement of symptoms, but their symptoms worsened with reintroduction of gluten. Higher levels of antigliadin IgA were observed in schizophrenia patients [145].

Malignant Neoplasms

People with schizophrenia are not more likely to develop cancer overall but, in the event of cancer, have a 50% lower chance of survival [146]. Differences exist for individual cancers in people with mental illness (e.g., increased risk of breast cancer for women; reduced risk of lung cancer for men) [147].

Neurotropic Viruses and Schizophrenia

Crow was one of the first to postulate an infectious aetiology of schizophrenia. He hypothesized that schizophrenia may be due to infection with a virus that becomes integrated in the genome and is sometimes passed from one generation to the next.

Recent studies have indicated an increased activity of human endogenous retroviruses (HERVs) in plasma, CSF, and brain tissues in patients with schizophrenia [148].

Infections like encephalitis lethargica, prion diseases, toxoplasmosis, retroviruses, cytomegalovirus, Epstein–Barr virus, and Borna disease virus are also known to cause psychotic manifestations resembling schizophrenia [149]. Herpes simplex virus has been associated with the cognitive deficits seen in schizophrenia [150]. An increased prevalence of hepatitis C has been noted in people with schizophrenia compared with the general population [151].

HIV/Aids

Onset of schizophrenia is typical in late adolescence and early adulthood in both men and women, during the developmental period where sexuality and sexual behaviors typically increase in frequency and importance.

Various studies estimate the incidence of HIV/AIDS in patients with schizophrenia to be around 4–23% which is higher than in the general population [152, 153]. Associated risk factors include poor judgment, impulsivity, “unsafe sex,” drug injection, and non-injected drug use. Women with schizophrenia are at particularly high risk for HIV infection – the male-to-female ratio is 4:3, in contrast with the 5:1 ratio that is reported

in the general population. Literature clearly establishes the comorbidity between HIV, mental illness, and substance use [154]. Recent evidence suggests that patients with schizophrenia and comorbid substance abuse were at markedly greater risk for HIV infections, but in the absence of a substance use diagnosis, patients with schizophrenia alone were actually at lower risk for HIV infections [155, 156].

Epilepsy

Kraepelin in 1919 was the first to suggest an association between schizophrenia and epilepsy. In his landmark paper on schizophrenia, he made the following note about the relationship between the two conditions: "As in dementia praecox epileptiform seizures occur, the malady may be taken for epilepsy…" [157]. Then in 1952 Gibbs and Gibbs reported an increased frequency of interictal psychoses in patients with complex partial seizures. They suggested that schizophrenia and epilepsy might share some common pathology of the medial temporal lobe, where epileptiform potentials that underlie complex partial seizures most often originate [158]. Subsequently, a number of studies have consolidated the link, and patients with schizophrenia are reported to have an 11-fold increase in the prevalence of comorbid epilepsy [159].

On the other hand, patients with epilepsy were also found to be at increased risk of schizophrenia and schizophrenia-like psychosis [160, 161]. A shared biological liability could be the reason behind the significant overlap of these two disorders. Prominent examples include the ventricular enlargement seen in both conditions and the leucine-rich glioma inactivated (LGI) family gene loci overlap in both conditions [159]. There are also suggestions that LGI genes associated with partial epilepsy with auditory features might also represent genes of interest for schizophrenia, especially among patients with prominent auditory hallucinations and formal thought disorder [159].

Dementia

Mounting evidence supports a neurodegenerative origin for schizophrenia [162, 163]. It has been proposed that individuals with schizophrenia experience an "accelerated aging" that contributes to their reduced life expectancy.

Various studies have compared the risk of dementia among persons with and those without schizophrenia using clinical dementia diagnoses, and their findings ranged from a 2.4-fold to a 16-fold higher risk of developing dementia [164]. However, further studies are needed to substantiate these results.

Persons with schizophrenia may be at higher risk of developing dementia for several reasons. First, persons with schizophrenia are at increased risk of developing several chronic conditions, which are also well-established risk factors for dementia, including diabetes mellitus, ischemic heart disease, congestive heart failure, atrial fibrillation or flutter, peripheral vascular disease, and cerebrovascular disease [165–167]. Additional studies are warranted to elucidate the pathophysiologic factors of the link between schizophrenia and dementia.

Osteoporosis

The increased rates of osteoporosis in people with schizophrenia have been attributed to the following [168–170]:

1. Antipsychotic-induced decreases in estrogen and testosterone.
2. Reduction in calcium levels due to smoking and alcoholism.
3. Polydipsia as well as hyperprolactinemia and hypercortisolemia.
4. Dietary and behavioral features associated with schizophrenia.

Therefore, a decrease in bone mineral density (BMD) in patients with schizophrenia may be disease-related or drug-induced. However, decreased BMD and osteoporosis are multifacto-

rial processes, and abnormal bone structure and functions can be a result of multiple dynamic processes leading on to impairment of bone homeostasis and eventually bone abnormalities. So other medical causes of osteoporosis should also be ruled out, as many of them may go untreated in patients with schizophrenia.

Hyperprolactinemia

High doses of typical antipsychotics as well as atypical antipsychotics, especially risperidone and amisulpride, raise prolactin levels and can present with galactorrhea, amenorrhea, oligomenorrhea, sexual dysfunction, and reduced bone mineral density, predisposing to cardiovascular disease [171].

Polydipsia

The prevalence of polydipsia in patients with mental illness is estimated to be between 5% and 20% [172] and is most commonly associated with schizophrenia. Before a diagnosis of psychosis-induced polydipsia is reached, other causes of polydipsia should be ruled out, such as diabetes mellitus, diabetes insipidus, chronic renal failure, malignancy, pulmonary disease, hypocalcemia, and hypokalemia.

Respiratory Disorders

Persons with schizophrenia have a higher prevalence of respiratory diseases, including asthma, emphysema, and chronic bronchitis [173]. A part of this association is likely to come from the higher rates of cigarette smoking.

A commonly encountered challenge is respiratory suppression with psychotropics in patients who have already compromised respiratory function. Respiratory suppression can be a serious side effect in patients who have impaired pulmonary function [174]. Benzodiazepines and sedative-hypnotics, if used as adjuncts in schizophrenia, have been known to worsen or precipitate sleep apnea in patients who have COPD [175]. However, one advantage is that their use will allow the clinician to lower the dosage of antipsychotics in agitated patients.

Other Physical Illnesses

Incidence of irritable bowel syndrome in people with schizophrenia is 19% (versus 2.5% in the general population) [176]. Prevalence of *Helicobacter pylori* infection is significantly higher in people with schizophrenia [177]. Life expectancy for people with schizophrenia is estimated to be about 15–20 years shorter than for the general population [128], and a particular cause for concern is that the mortality gap between the general population and those with schizophrenia seems to have increased during the last decade [178, 179]. Death from unnatural causes appears to be 10–20 times higher in schizophrenia than in the general population [180]. Suicide and accidents accounted for about 40% of the extra deaths, while 60% were from natural causes [167, 181].

Influence of Risk Factors

- Smoking-related morbidity and mortality are significantly higher in people with schizophrenia than in the general population. Smoking is a good example of how behavior and treatment interact to increase morbidity at a number of levels. It is a risk factor for respiratory and ischemic heart disease and stroke, and by reducing available plasma levels of antipsychotics (especially olanzapine and clozapine), it may have a negative influence on the treatment outcome.
- Diet. The cognitive and social deficit symptoms of schizophrenia may make patients liable to be choosing easily obtainable "fast" foods that are high in saturated fats as a major component of their diet. The same deficits are also often associated with low levels of moti-

vation that deprive the patient of any intent to keep physically active. This is further complicated by extrapyramidal symptoms especially Parkinsonism, antipsychotic-related sedation, and cognitive deficits.

- Substance misuse is a major contributor to both mortality and morbidity in people with schizophrenia. Persons with schizophrenia who have a coexisting substance use disorder often have many negative outcomes, such as more frequent and longer periods of hospitalization, more pronounced psychotic symptoms, more severe cerebral gray matter volume deficits [182], poorer treatment adherence, more depressive symptoms, higher risk of suicide, violence, legal problems, incarceration, severe financial problems, family burden, housing instability, and increased risk for HIV infection [183] and hepatitis infection, particularly hepatitis C [151].

Barriers to Recognition and Management of Medical Illness in People with Schizophrenia

Barriers to Recognition: Patient-Related Factors

- Poor treatment compliance [184].
- Unawareness that physical problems might arise owing to the cognitive impairments associated with schizophrenia [185].
- Avoidance or neglect of contact with general practitioners or primary health-care facilities [186].
- In general, patients might have difficulty in communicating their physical symptoms.
- Physical symptoms unreported/masked because of high pain tolerance in some patients and reduction in pain sensitivity associated with use of antipsychotic drugs [185].
- In some patients, reluctance to discuss problems or volunteer symptoms and/or general uncooperativeness [186].
- Patients' difficulty in comprehending health-care advice and carrying out required changes in lifestyle.

Doctor-Related Factors

- Hesitation of nonpsychiatrists to treat people with serious mental illness.
- Lack of adequate follow-up of patients with mental illness, due to patients' itinerancy and lack of motivation [184].
- Persons with schizophrenia may be less likely to receive a detailed physical examination.
- Changes of treating doctor, with the result that many patients do not have a longitudinal history available [186].
- Perception by specialist psychiatrists that physical health matters should be the province of referring doctors [186].
- Specialists' attention focused principally on patients' psychiatric problems [186] with physical examination conducted infrequently.
- Physical complaints regarded by psychiatrists as psychosomatic symptoms [185].
- Time and resources for physical/medical examinations not available in current mental health service settings.

Management of Weight Gain, Diabetes, and Other Metabolic Abnormalities

- Weight should be routinely monitored in all patients with schizophrenia. BMI can be used as a reliable indicator to monitor weight gain.
- Waist circumference can be used as a measure to supplement BMI, as it indicates visceral adiposity, which is associated with particularly high rates of type 2 diabetes, dyslipidemia, hypertension, and metabolic syndrome.
- Psychoeducation is an important part of management of weight gain. Patients who are receiving an antipsychotic that is associated with significant weight gain and their caregivers should be informed of the risk of weight gain and the health risks associated with excessive weight. This is especially significant for patients who have a family history of obesity or diabetes and those who are overweight or obese at the start of therapy itself. Advice should be focused on dietary modifications,

including reducing high-caloric intake, and exercising to prevent initial weight gain, as subsequent weight loss is more difficult to achieve.
- Various studies have shown that regular physical activity is effective in prevention and treatment of hypertension, obesity, IGT, diabetes, and dyslipidemia [187, 188].
- Some risk factors are modifiable. A reduction of 10% in cholesterol levels results in a 30% reduction of CVD risk, a lowering of blood pressure of 4% to 6% decreases CVD risk by 15%, and smoking cessation would result in a 50% to 70% lowering of CVD prevalence. Maintaining a BMI less than 25 lowers CVD risk 35% to 55%, and having an active lifestyle (20-minute walk a day) results in a similar decrease of risk [128].
- Given that cardiovascular risk assessment has been shown to be acceptable to many people with psychosis [189], a more systematic use of such screening in both primary and secondary care may improve early detection and treatment of hypertension, hypercholesterolemia, diabetes, and smoking.
- Although it is not common to be detected during routine monitoring, the psychiatric team should be aware of and inquire about the symptoms of diabetic ketoacidosis. Symptoms include rapid onset of polyuria, polydipsia, weight loss, nausea/vomiting, dehydration, rapid respiration, and visual disturbance, especially in patients with poor compliance to hypoglycemic drugs. Diabetic ketoacidosis is a life-threatening condition that requires emergency treatment but is preventable with good glycemic control.

HIV and Viral Hepatitis

- Clinicians should educate about safe sexual practices, including the use of contraception, as well as needle use.
- Just like how antipsychotics are associated with an increased risk of development of metabolic syndrome, similarly, use of protease inhibitors for treatment of coexisting HIV can lead to development of symptoms similar to that of metabolic syndrome [190] such as weight gain, hyperglycemia, and hyperlipidemia. Therefore, monitoring of weight, fasting blood glucose, and lipid profiles is integral to treatment for people taking any of these medications.
- Health-care providers should also address the issue of substance abuse.

Hyperlipidemia

- Psychiatrists should be aware of the lipid profiles for all patients with schizophrenia.
- As a group, individuals with schizophrenia should be considered to be at high risk for coronary heart disease, and regular screening should be done at follow-ups.

Chronic Lung Disease

- Mental health providers should assess level of cigarette smoking and consider an intervention.
- Clinicians should inquire about possible respiratory symptoms such as chronic cough and breathlessness at each follow-up.
- Reducing the risk of lung infections through vaccinations like pneumonia vaccinations can be considered in high-risk populations.
- Encourage patients to participate in physical activity that can slow lung function decline [190].
- Stress the importance of adhering to prescribed medications in those patients with an already-diagnosed pulmonary disorder to prevent further exacerbation of the primary psychiatric illness.

QT Prolongation

- Clinicians should refrain from prescribing thioridazine, mesoridazine, or pimozide for patients with cardiovascular disease, especially a family history of sudden death at an

early age (younger than 40, especially if both parents had sudden death), or a diagnosed prolonged QTc syndrome [191].
- If ziprasidone is prescribed for patients with the abovementioned risk factors, an electrocardiogram should be used for evaluation at baseline, and a subsequent ECG is indicated if a patient presents with symptoms such as syncope [192].

Management Strategies

- Collection of a standard checklist and core information data concerning physical health should be a routine procedure for every patient [185].
- Psychiatric services should be adequately equipped to carry out basic physical medicine tasks.
- Refresher training should be regularly provided for psychiatrists and key members of multidisciplinary community psychiatric teams. This could encompass elements of detection, management, and preventive counseling.
- Targeted patient education regarding physical health, medication, and side effects may help to increase awareness of medical comorbidity in schizophrenia patients and help make them better advocates for themselves.
- Increasing clinician awareness of comorbid conditions that may have an impact on patient compliance can lead to closer monitoring of patient characteristics that may signal noncompliance and ultimately will lead to improved care of schizophrenia patients.
- Education of the mental health team should not be forgotten. Many psychiatrists, nurses, and other health professionals may be unfamiliar with the notion of metabolic risk and the means of assessing and treating it. These topics should be included in continuing professional development programs.
- Pharmacogenomic studies certainly would be extremely valuable for clinicians to identify individuals at high risk, but although some interesting findings have been produced by genetic association studies and whole-genome and linkage studies, no conclusive data have been provided so far. Therefore, more studies are needed to cope with weight gain and other metabolic abnormalities of people suffering from schizophrenia.
- Smoking cessation programs have been shown to be effective for schizophrenia patients [193] and need broader utilization to reduce the substantial health effects in this population.
- Consider the use of oral and injectable depot preparations as an option to ensure better compliance in suitable patients [194].
- Even though adequate facilities for physical activities are available, and diet and smoking cessation programs are conducted, patients do not necessarily take advantage of them. Motivation is needed for a change in behavior. Many patients are ambivalent or lack motivation to increase their physical activity.
- Health-care professionals are thus challenged to assist patients in their motivational process. The cognitive technique of motivational interviewing is increasingly being used in areas of medicine where change in the patients' behavior is important, and the results of pilot studies in cardiology are promising. The Transtheoretical Model of Change describes the motivational process and seems applicable in physical activity programs in severe mental illness populations [195].

Conclusion

Schizophrenia is complicated by medical disorders such as obesity, diabetes mellitus, cardiovascular and pulmonary diseases, HIV infection, and cancer. Early detection and treatment of these disorders can reduce the high rates of premature death seen in this population as well as improve their overall quality of life. Left untreated, they can also exacerbate the psychotic illness further hampering the patient's morbidity. These comorbidities pose substantial challenges to the clinical team and require an integrated approach between a psychiatrist and a general physician, with the use of rigorous monitoring in high-risk groups and timely interventions that might help patients with schizophrenia live longer and healthier.

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Recovery in Severe Mental Disorder and Comorbidity

20

Shailesh V. Pangaonkar

Introduction

The concept of recovery in schizophrenia has evolved significantly since the initial identification of this psychiatric condition. The initial views were pessimistic in nature and emphasized on the inevitability of deterioration of the disease. The term recovery also had different connotations for different people, and its ambiguity led to a lot of debates. There are certain conceptual constraints, and that further accentuates the ambiguity regarding the recovery and application of recovery principles for different persons having schizophrenia with comorbid or co-occurring diseases. There are challenges for the interpretations of "clinical" and "personal" recovery, and authors find it difficult to integrate commonalities and effectiveness in clinical as well as social practices of schizophrenia management [1–5].

This chapter is thus an integrated and interpretative study of recovery principles in schizophrenia with comorbid conditions and tries to answer the above questions using certain hypotheses which would further critically evaluate factors that affect the management principles, measurements, and recovery principles in comorbid schizophrenia:

1. Comorbidity poses a bigger challenge in understanding the management of schizophrenia.
2. Recovery-oriented model for severe mental illnesses can be very well applied for comorbid schizophrenia.
3. Tools for measuring recovery in severe mental illness can be applied to measuring of recovery of comorbidity in schizophrenia.
4. The barriers and threats in recovery of comorbid schizophrenia are presentations of restricted views of biomedical models and pure pharmacotherapeutic approaches. The views are of pessimism, while a sociocultural and person-centered approach has high level of optimism in studying the barriers and threats in the recovery of comorbid schizophrenia.
5. Proper therapeutic guidelines, psychosocial interventions, and personal recovery measures may show better outcomes.

Methodology

The databases used to search for relevant articles were Google Scholar, ScienceDirect, PubMed Central, Medline, and ResearchGate. In the first step, the various combinations of the keywords "comorbidity," "schizophrenia," "recovery," "recovery-oriented model," "recovery in schizophrenia," "quality of life," and comorbidities of

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Table 20.1 Literature review parameters

Database searched	Google scholar, ScienceDirect,
	PubMed Central, UpToDate,
	Medline, and ResearchGate
Primary parameters	Peer-reviewed published research article, English language, full-text articles, and published between 2006 and 2017
Excluded articles	Articles which did not meet the aim and relevance of the topic

schizophrenia (Table 20.1) were searched. Publications matching the search terms were selected. Primary parameters for the search were English language, full-text articles, and published between 2006 and 2017.

The initial search for articles retrieved 20,200 publications, and 20,111 articles were excluded based on title, relevance, and language. Based on the literature review aims, 89 full-text articles were selected. Table 20.1 describes the article search reduction process.

Literature was selected for this review if it was based on a study of empirical data, concerning comorbidity, recovery, or related concepts, or if it reported on theoretical concepts related to comorbidity of schizophrenia and its recovery. Furthermore, literature was evaluated on the effects of co-occurring diseases on the patient, the family, close friends, and society. Relevant references identified from citations and encountered during drafting, review, and editing of the article were also included. Themes relevant to the topic were distilled from the retrieved articles, and additional relevant articles were included in this review.

Comorbidity: Concept and Burden

Feinstein coined the term "comorbidity" for medical diagnoses 50 years back, and since then, there has been a plethora of knowledge through various studies and research in many directions, but all definitions assume the co-occurrence of medical condition. There has been a wider understanding of the implication of comorbidity in recent times that has motivated researchers and clinicians to search for effective strategies or guidelines to evaluate the impact of comorbidity. Should comorbidity in schizophrenia be considered as a concurrent comorbidity or complicating comorbidity is debatable.

According to Oreški, Jakovljević et al. [6], the simultaneous presence of multiple pathological conditions in the form of comorbidity and multimorbidity is more a rule than an exception in all populations of psychiatric patients, particularly in those with schizophrenia or bipolar disorder. Studies have shown an increased prevalence of anxiety, depressive, and substance use disorders greater than that found in the general population [6]. It is seen in such studies that nosologists have great difficulty classifying complex sets of symptoms in comorbid conditions [7, 8]. They generally adopt an implicit or explicit hierarchy system where schizophrenia dominates depression and anxiety. In case no supremacy can be determined, alternate labels such as "schizoaffective disorder" or even "schizo-obsessive subtype of schizophrenia" are used. Studies have found that 47% of patients also have a lifetime diagnosis of comorbid substance abuse [7]. Anxiety and depressive symptoms are also very common throughout the course of illness, with an estimated prevalence of 50% for depression, 15% for panic disorder, 29% for post-traumatic stress disorder (PTSD), and 23% for obsessive–compulsive disorder (OCD) [7].

Schizophrenia and Depression

Depression is one of the major psychiatric disorders that usually co-occurs with schizophrenia. A study by Buckley et al. found that an estimated 23–57% of adults with schizophrenia have comorbid depression [7]. Clinically meaningful subsyndromal depressive symptoms have also been reported to be more prevalent than full depressive episodes in some studies [9]. Depressive comorbidity is associated with substantial suffering, decrease in functional status, poor outcome, and suicidal idea/behavior. The probable risk factors for depression co-occurring with schizophrenia are "family history of

depression, high levels of expectations and family expressed emotions, stigma (personal stigma and societal stigma), higher intelligence and insight in schizophrenia, recurrent relapses and economic burden or economic drift, lack of psychosocial support and self esteem" [10]. Since onset of schizophrenia is in late teens, loss of hope and despair takes over. Aimlessness and boredom are also present, also known as existential neurosis (a term given by Richard Warner) which is a state of mind that self-imposes apathy on sufferers. Demoralization causes depression. These factors are also contributory as barriers of recovery, and alleviation of these factors has been demonstrated to better the recovery pattern.

Conley et al. found that depressive symptoms were associated with considerable long-term burden in the treatment of schizophrenia, and compared to those without depressive symptoms at enrollment, participants with depressive symptoms had poorer long-term functional outcomes in multiple domains [11]. The depressed were more likely to use relapse-related mental health service, to be of greater danger to self and others (violent, arrested, victimized, suicidal), to have more substance-related problems, to evidence poorer social and family relationships, and to have a poorer quality of life, lower motivational level, poorer level of functioning, poorer mental and physical health, lower level of medication adherence, and less general life satisfaction [11]. The findings also extend prior research done by others by demonstrating that the burden of depressive symptoms affects the criminal justice system in addition to the mental health system, and those with depressive symptoms had more frequent contacts with law enforcement agencies compared to those without concurrent depressive symptoms [11].

According to Felmet et al., there is little research on the treatment of depressive symptoms in patients with schizophrenia, especially in the elderly population. Furthermore, treatment guidelines for schizoaffective disorder, in general, are not well established [12].

It was earlier thought that people who had schizophrenia with comorbid depression had a better outcome. This is now known to be incorrect, as depression increases the risk of suicide, there are more relapses of psychotic symptoms, and there are more hospitalizations. Also, the presence of depression may motivate people to misuse drugs or alcohol, which are predictors of dangerous behavior such as suicide and violence [12].

It has been speculated by earlier scholars that persons who have depression with schizophrenia have greater insight, which might help in the recovery process, as they are better equipped to take informed decisions in their treatment, which reflects the Substance Abuse and Mental Health Services Administration (SAMSHA) principles of self-direction and empowerment. While insight and intelligence are aids in the recovery process of comorbid depression, the lack of psychosocial support and self-esteem support are deterrents in the pathway to recovery. The SAMSHA principles of hope, peer support, and strength-based recovery are compromised [13].

Psychosocial interventions along with medications can benefit by improving the social skills and reducing depressive symptoms, thereby adopting a holistic approach that encompasses different aspects of a person's life like education, employment, social standing, and community involvement. Lithium is found to be the most effective pharmacological intervention. A double-blind trial of imipramine by Siris et al. shows significant improvement and recovery from baseline function and also reduction of relapse rate [14].

Schizophrenia and Anxiety

Anxiety disorders frequently co-occur with schizophrenia. There is a limited body of work that supports the credibility of the hypothesis that anxiety disorders are part of the illness of schizophrenia, with the strongest evidence being for OCD [7]. A meta-analysis done by Achim et al. revealed high prevalence rates of all types of anxiety disorder in patients with schizophrenia spectrum (including schizophrenia, schizoaffective, schizophreniform, and delusional disorders and psychosis not otherwise specified) [15–17].

Some researchers have found that the presence of these conditions compounds the outcomes and higher levels of anxiety were associated with greater hallucinations, withdrawal, depression, hopelessness, better insight, and poorer function [18]. Recovery in comorbid anxiety is hampered by these, and increased peer support, individualized and person-centered approach, and instilling hope shape the recovery pathway.

Comorbid anxiety may have implications for treatment choice. Generally, anxiety is considered to be secondary to the psychotic condition, and it is expected to improve simultaneously with an improvement in the schizophrenic symptoms. There is some evidence that antipsychotic medication such as quetiapine has some degree of efficacy in reducing anxiety in schizophrenic patients [19].

In a study, 25% people of first-episode psychosis (FEP) were diagnosed with ICD-10 diagnosis of social anxiety disorder; there was also a further 11.6% of people who reported clear difficulties in social interaction and/or signs of avoidance which were not sufficient enough to reach formal diagnostic criteria and accompanied by high levels of depression [16]. Despite its high prevalence and severity, social anxiety remains under-recognized and undertreated in patients of schizophrenia [20].

Schizophrenia and OCD

Studies found that obsessive–compulsive symptoms are often recognized in a prodromal stage in patients with schizophrenia, and it is often difficult to cure with standard treatment. There has been a long controversy whether obsessive–compulsive schizophrenia is a distinct subtype or not. Comorbidity with obsessive–compulsive symptoms is often misdiagnosed or even neglected by psychiatrists. Epidemiologic reviews of schizophrenia revealed that the probability for comorbidity with obsessive–compulsive disorder is 3.5–15%. Another study suggests that obsessive–compulsive comorbidity leads to a poorer clinical course, lower levels of functioning, and longer periods of hospitalization compared with schizophrenics who are not obsessive–compulsive [9].

Schizophrenia and PTSD

Patients with schizophrenia may be at an increased risk for exposure to trauma which may be due to illness-related features, environmental influences, and/or comorbid substance use. Many factors complicate the diagnosis and investigation of co-occurring post-traumatic stress disorder (PTSD). Studies have shown that the presence of PTSD is associated with more severe psychopathology, higher rates of suicidal behaviors, and increased hospitalizations in patients with schizophrenia. Also, psychotic symptoms and experiences like involuntary hospitalizations, forced medications, and restraint may themselves be a traumatic event contributing to PTSD [21].

Schizophrenia and Substance Abuse

Abuse of alcohol and/or illicit drugs by persons with schizophrenia is a very common occurrence. Studies have found that nearly half of the people suffering from schizophrenia also present with a lifetime history of substance use disorders, which is much higher than the one seen among unaffected individuals [22]. Numerous studies indicate an increase of comorbidity of disorders caused by harmful use or abuse of alcohol and other psychoactive substances in the population of schizophrenic patients [23–25]. According to a study in CMHC outpatients, 35% of schizophrenics are currently diagnosed with alcohol abuse. Other abused substances were cocaine (20%), heroin (3%), and marijuana (15%). Nicotine use was the most common in this study, with a range of 70–90% in patients with schizophrenia [26].

In general, people with psychosis and substance use disorders are more likely to be male, have a family history of substance abuse, and be younger than their non-substance-abusing counterparts, with the possible exception of alcohol abusers [22].

Substance abuse is associated with relapse of psychosis, multiple hospitalizations, legal problems/violence, social isolation/homelessness,

noncompliance with medication, HIV risk, and family problems. When planning treatment strategies for substance abuse in schizophrenia, many limitations are encountered including therapeutic alliance, low motivation, cognitive limitations, low self-efficacy, and maladaptive interpersonal skills. A study showed that low motivation was found in abusers of alcohol (53%), cocaine (66%), marijuana (71%), heroin (87%), and nicotine (91%) in 224 patients with schizophrenia [25–27].

Several studies reported that there was a significant decrease in reported daily cigarette use during clozapine treatment compared with the level of use when patients had been treated with typical neuroleptics. Specific psychosocial approaches, including step-by-step behavioral therapy, are effective for the treatment of stimulant abusers [27].

There is a pressing need to evaluate further and find the best approach for treating schizophrenia and comorbid substance abuse, but currently, the widely accepted treatment standard is an integrated approach combining psychosocial interventions and pharmacotherapy, which yields the best possible outcomes [26, 28].

Schizophrenia and Personality Disorders

McMillan and colleagues found that along with mood disorders, anxiety disorders, and substance use disorders, the personality disorders have a high likelihood of co-occurring with schizophrenia. They analyzed the Axis II personality disorders and found extremely high rates of comorbidity among people diagnosed with schizophrenia. Avoidant and paranoid personality disorders were the most common Axis II disorders found in their community sample. They also concluded that Axis II personality disorders like paranoid, schizoid, antisocial, histrionic, avoidant, dependent, and obsessive–compulsive have received relatively little attention among patients with schizophrenia when compared to the other DSM Axis I disorders [27].

Schizophrenia and Physical Conditions

In a study done by Chadda et al., 70% of the participants were detected to have a comorbid physical condition. The common conditions included hypertension (21%), diabetes mellitus (15%), anemia (12%), tuberculosis (7%), obesity (6%), and menstrual disturbances (5%) [29]. Less frequent physical illnesses included thyroid disorder (4%), epilepsy (3%), cerebrovascular accident (2%), coronary artery disease (CAD) (2%), deafness (2%), liver disease (2%), other gastrointestinal illnesses (2%), and dementia (1%). Chadda and colleagues also concluded that increasing age, being female, being married, longer duration of illness, and longer duration of treatment were associated with higher risk of having a comorbid physical illness [29]. In a similar study conducted in Spain, the presence of physical comorbidity for individual illnesses such as hypertension, diabetes mellitus, anemia, obesity, and CAD produced identical findings [30]. Jacob et al. have also supported the findings of other authors that people with schizophrenia are at greater risk of developing obesity, type 2 diabetes, hypertension, and dyslipidemia as compared to the general population, which results in an increased incidence of cardiovascular disease, leading to greater morbidity and mortality in this group of patients [31].

Literature has reported that prolonged exposure to antipsychotics, especially the second-generation antipsychotics, is a known risk factor for the common physical comorbidities [32]. In another study done by Crump et al., it was found that patients with schizophrenia showed premature mortality, and the major causes were ischemic heart disease and cancer [33]. These conditions appeared to be underdiagnosed, and on an average, men with schizophrenia died 15 years earlier, and women died 12 years earlier as compared to the rest of the population [33].

This epidemiological discussion recognizes psychiatric comorbidity as an important clinical problem in the diagnosis, treatment, and prevention of mental illness [21]. Studies have identified that there is a need to appropriately identify and

manage these comorbidities as risk factors to improve the long-term outcome and thereby help in recovery of these patients [31].

This biomedical discussion of comorbidities shows high rates of incidence and prevalence associated with schizophrenia leading to severe psychopathology, poor long-term outcome, heightened risk of relapse and hospitalizations, poorly understood treatment implications, and high rates of polypharmacy because of clinical heterogeneity [21]. This is in concordance with our first hypothesis, proving that comorbidity in schizophrenia throws a bigger challenge in understanding the risk factors, burden, and barriers in management of schizophrenia.

The pessimism of the biomedical model is warded off by contrasting experiences of the clinician and the clients, wherein the picture is optimistic in the form of remission and reintegration, pointing to a need to study the sociocultural variables and nonpharmacological interventions which contribute to this recovery pathway [34, 35].

Recovery in Comorbidity

The term "recovery" has become prominent in mental health systems internationally [5, 36]. Yet across different countries and settings, the term is used inconsistently and with differing implications for policy and practice. This reflects an important debate about the core purpose of mental health service [5]. Current concepts of recovery are primarily based on Western European and North American models, and there is a need to broaden its evidence [37]. The incorporation of 'recovery ideas' into non-English-speaking countries is ongoing and needs to be a two-way process, where research from culturally more diverse countries would help to highlight both social and political inferences about the nature of recovery [38]. The recovery model is a social movement that is influencing development of mental health service around the world. 'Recovery services' or 'recovery interventions' thus would refer to (1) the subjective experience of optimism about outcome from psychosis, (2) to a belief in the value of the empowerment of people with mental illness, (3) to a focus on services in which decisions about treatment are taken collaboratively with the user and (4) which aim to find productive roles for people with mental illness [39].

Le Boutillier et al. have studied the evidences drawn from international guidelines which propose that mental health systems can support recovery in relation to four domains of practice: (1) promoting citizenship, (2) organizational commitment, (3) supporting personally defined recovery, and (4) working relationships [40].

Considering community-based services, Robert Liberman proposed that sustained recovery and integration of patients into their communities will depend upon services that are comprehensive, continuous, coordinated, collaborative, consumer-oriented, consistent with the phase of the disorder, competency-based with empirically validated techniques, connected with the patient's skills and deficits, and compassionate and cooperative toward the patients [41].

In a review of mental health recovery done by Jacob et al., similarities were found in the views of consumers, caregivers, and service providers. Three dominant themes were elucidated from the meaning of mental health recovery:

- Firstly, a future-oriented view on mental health recovery where consumers viewed mental health recovery as a transformation of self from an illness identity to an identity marked by meaning and well-being.
- Secondly, a cure-oriented view on mental health recovery that emphasizes cure or absence of symptoms and an achievement of the pre-illness state.
- Thirdly, some consumers also reported that mental health recovery was impossible.
- These differences in the views among consumers suggest both pessimistic and optimistic attitudes toward mental health recovery [42].

Recovery from psychosis can be considered either as an outcome or as a process. Clinical recovery, which can also be known as an outcome, involves a binary concept involving an absence or reduction of symptoms and also improvement in social functioning. This outcome-based recovery

model constricted by the concept of remission of symptoms or improvement in functioning when applied to schizophrenia with comorbidity will further aggravate the negative picture of recovery. On the other hand, personal recovery is a process that individuals go through in order to live a satisfying life [43], and hence, the principles and guidelines provided by SAMSHA (Substance Abuse and Mental Health Services Administration) of self-direction, individualized and person-centered, empowerment, holistic, nonlinear, strength-based, peer support, respect, responsibility, and hope—and NIMH (National Institute of Mental Health) of recognition, raising awareness, and respect—reflect the consensus statement that says recovery is a process of healing and transformation. This goes far beyond the restricted negative views of biomedical recovery pathways, and recovery in comorbidity will be better when these principles are followed [13, 44].

Though various studies have been conducted to establish the management and treatment strategies of comorbid conditions in schizophrenia, limited research has been done on the recovery-oriented model, and very limited literature is available on the recovery pathways in comorbid conditions. Further studies are required that support the fact that a recovery-oriented model can be applied for comorbid schizophrenia as well. Currently, this paucity does not lend any support to our second hypothesis. So recovery in comorbid schizophrenia can thus be regarded as being promoted or retarded through the dynamic interplay of many forces that are complex, synergistic, and linked [45].

Measurement of Recovery

Diverse assessment instruments have been created to appraise the process of recovery from psychosis [46–48]. These include the Recovery Assessment Scale (RAS), the client version of the Illness Management and Recovery (IMR) scales, the Integration/Sealing-Over Scale (ISOS), the Recovery Styles Questionnaire, and the Mental Health Recovery Measure (MHRM). A review of recovery measures by Burgess et al. produced 33 instruments (22 were designed to measure individuals' recovery and 11 were designed to assess the recovery orientation of services) which are applied in the context of "personal recovery" and evaluation of available modalities of treatment and services. These tools are yet to be applied for comorbid conditions in schizophrenia [49].

As a means of identifying a person's current stage of recovery, the Stages of Recovery Instrument (STORI) was developed by the University of Wollongong, Australia, as a method to measure recovery from serious mental illness. The five stages of recovery targeted in this assessment are (1) moratorium, (2) awareness, (3) preparation, (4) rebuilding, and (5) growth [50].

In another review of personal recovery measures by Shanks et al., a total of 13 measures of recovery were identified. The QPR (Questionnaire about Personal Recovery) had the strongest match with recovery, the RAS was the most widely published, and the STORI, the MARS (Medication Adherence Rating Scale), the QPR, and the RAS demonstrated the widest range of psychometric properties [51].

The CHIME framework for personal recovery was developed after a systematic review and narrative synthesis of recovery, and the acronym CHIME derives its name from the recovery processes, viz., connectedness, hope and optimism, identity, meaning and purpose, and empowerment. The framework consists of three categories of recovery: (1) characteristics of the recovery journey, (2) recovery processes, and (3) recovery stages [52]. These parameters stand high in their applicability on recovery of comorbid conditions, even though there are no studies published yet. Our third hypothesis proved that recovery-measuring tools in severe mental illnesses using these parameters can be applied for measuring recovery of comorbid schizophrenia.

Barriers/Challenges in Recovery

Studies conducted on barriers in recovery can be roughly classified in context focussed on stigma, dual diagnosis, electro-convulsive therapy, polypharmacy, insight, and sociocultural variables.

Stigma

A major barrier to recovery in psychiatric disorders is stigma, which has been studied extensively. It is necessary to understand the various facets of stigma in psychiatric disorders, as it is an important determinant of the help seeking, treatment outcome, and quality of life of persons with psychiatric disorders [53]. Balhara et al. have identified three levels of stigma in literature:

1. Public–negative attitudes/beliefs about persons with psychiatric illness that turns individuals against them and leads them to avoid, fear, or discriminate against those with psychiatric illness
2. Structural–institutional policies and practices
3. Internalized–negative feelings about oneself, maladaptive behaviors, and stereotype endorsement [53–56]

Stigma is more evident in persons suffering from schizophrenia with comorbidities. Patients with dual diagnosis are known to suffer from various kinds of stigma, which leads to treatment noncompliance, reduced self-esteem, social exclusion, discrimination, and relapse [57]. Not only does stigma cause reduced autonomy and self-efficacy, but it is also associated with less treatment seeking and worse treatment retention and adherence [58, 59].

Stigmatizing beliefs related to criminality have also been consistently reported in association with psychiatric illnesses such as schizophrenia, depression, and ADHD [56].

The SAMSHA principles of recovery like respect, peer support, empowerment, and hope will help in reducing the stigma associated with schizophrenia and its comorbid conditions. Societal acceptance and appreciation of people suffering from comorbid schizophrenia are important in achieving recovery. There is a need to protect the rights and also eliminate discrimination and stigma to instill self-acceptance and self-belief, which are vital parameters in the path of recovery. Respect and empowerment of persons suffering from comorbid schizophrenia will ensure inclusion and full participation in all aspects of their lives.

Dual Diagnosis

There are barriers in the treatment and recovery of patients with dual diagnosis. Firstly, different treatment systems address drug use disorders and other mental illnesses separately, and neither system may have sufficiently broad expertise to address the full range of problems presented by patients. There are also differences in opinions regarding the allegiance of patients toward mental disorder or toward addiction/substance abuse. So a bias remains in some substance abuse treatment centers against using any other medications, including those necessary to treat serious mental disorders such as depression. Another major barrier is that many of those needing treatment are in the criminal justice system.

Substance abuse is found usually among people belonging to the low socioeconomic strata, who have poor access to treatment and difficulty obtaining mental health services. When left untreated, it can contribute to a vicious cycle of lack of treatment and relapse, making it difficult to obtain gainful employment and have a good family and social life. Long-term medication is typically recommended, and monitoring is needed, as comorbidity reduces the medication compliance.

The fifth guiding principle for the delivery of recovery-oriented mental health services of NIMH emphasizes that recovery from mental illness is most effective when a holistic approach is considered; this includes psychological, emotional, spiritual, physical, and social needs. One of the fundamental components of SAMSHA corroborates the same principle that recovery is a holistic process and embraces all aspects of life, including housing, employment, education, mental healthcare treatment, addiction treatment, spirituality, creativity, community participation, and family support. Empowering of the persons for treatment choice may have better outcomes for the dually diagnosed. A holistic approach can ensure treatment compliance and assure improved outcomes [13, 44].

Electroconvulsive Therapy (ECT)

ECT has been used intensively in many parts of the world from the past 20 years. ECT proves advantageous not only for patients with schizophrenia and comorbid depression but also for positive symptoms and Brief Psychiatric Rating Scale indices of hostility, anxiety, and activation. ECT also shows effects in reducing agitation and aggression in general [60].

Polypharmacy

Studies show that initial line of treatment of comorbid schizophrenia comprises of antipsychotic medications (56%), and the other classes of drugs as adjuvants or add-ons in the treatment of schizophrenia include antidepressants (20%), mood stabilizers (15%), anxiolytics (7%), and drugs to treat extrapyramidal symptoms (6%) [61].

In comorbid schizophrenia, polypharmacy is used generally to address mood disorders, anxiety, cognitive disturbances, and obsessive–compulsive symptoms, but there is limited evidence about how to approach these comorbidities [62, 63]. There are no consistent global guidelines regarding polypharmacy or its effectiveness and safety [64]. There are no additional benefits of polypharmacy as compared to monotherapy [64]. Antipsychotic combination treatment has been associated with higher rates of extrapyramidal symptoms as well as increased use of anticholinergic agents [65–67] compared to monotherapy. Use of anticholinergic agents further compromises cognitive, visuospatial, and cholinergic functions, leading to decreased quality of life, somatic discomfort, and compromised functioning. In addition, sedation [68] and hyperprolactinemia have been observed in patients treated with antipsychotic polytherapy. This creates impedance in rehabilitative, reintegrative processes and building of self-esteem. The relationship between antipsychotic polytherapy and metabolic syndrome has not been clearly examined, but it has been very well established to show higher weight gain, hyperglycemia, dyslipidemia, and increased cardiovascular risk [26, 28, 46–48, 69]. Tiihonen et al. have reported a study to investigate the use of benzodiazepines, antidepressants, or multiple concomitant antipsychotics in comorbid conditions to be associated with decreased suicidal deaths but an increased mortality and significant morbidity including increased risk of cardiovascular, cerebrovascular, and osteoporotic conditions [71–73].

This shows that polypharmacy has been reported by various authors to have immediate and long-term impedance in perception of well-being, self-esteem, socio-occupational functioning, and higher risk of metabolic syndrome. This implies poor measurement of recovery, proving our fourth hypothesis.

Sociocultural Variables

A host of sociocultural factors have been cited as contributing to variation in the course of schizophrenia in different settings like family support and styles of interaction, industrialization, and urbanization. There is little evidence available from low-income countries that clearly demonstrates the beneficial influence of these variables [34].

Studies show that socio-environmental factors in schizophrenia are more modifiable than genetic factors and have a greater potential for impacting public health through prevention efforts than any known genetic variant [74].

On one hand, the biomedical model proposes sociocultural variables as a form of barrier in recovery and contemplates poor outcomes through the poor support of family, employability, and faith healing practices. Here, it can be interpreted that the biomedical model may promote pessimism for comorbid schizophrenia. On the other hand, social scientist and person-centered studies have acknowledged sociocultural factors given by SAMSHA and NIMH as modifiable variables in schizophrenia and hence provide a more optimistic view for our mission recovery.

Faith Healing

The limited existing data shows that religion has an influence on the expression of psychopathology, treatment-seeking behavior, and treatment outcome [75].

Studies suggest that up to 80% of patients use religious coping as a means of dealing with their illness. Patients with schizophrenia who have higher religious beliefs experience better psychological and existential well-being. Studies showed that many patients seek the help of faith healers to get rid of their symptoms, and it has also been shown that indigenous healing methods are considered complementary to the medical management of mental illness [76, 77].

Studies have emphasized holistic and person-centered approaches for the management of complex biopsychosocial disease like schizophrenia. Findings suggest that religiosity of mental health professionals can similarly influence patients who are managing a serious mental illness. But clinicians are rarely aware of the importance of religiosity, spirituality, self of the patient, and cultural backgrounds of the patients, which has always been emphasized for integration into patient care for better recovery [44]. Not only can family beliefs influence patients with a psychotic condition, professionals' lack of religious belief or inherent religious bias may also exert an influence on patients [60].

Authors have argued regarding factors influencing delayed therapeutic interventions caused by cultural taboos and stigmas as major psychosocial variables in schizophrenia, but there are some robust studies on burden bearing, cultural beliefs, and religiosity, reporting that these factors help to prevent recurrent hospitalizations [78].

In India, Hindus believe that their suffering from mental illness is also due to Karma of the past [76]. This law of Karma can be inculcated in psychosocial therapies to develop optimism and positive beliefs about suffering and burden of disease. These methods would enhance factors mentioned by SAMSHA (hope, person-driven, holistic) and NIMH (respect, recognition). It was noted that strength of religious belief plays an important role in helping family members to cope with the stress of caring for a mentally ill relative. Other studies, although, have not evaluated use of religious coping in dealing with mental illness, but some of these suggest that level of religiosity has inverse relationship with hopelessness and suicidal intent in patients of depression [76].

Some authors suggest that religious delusions can influence the health belief models and consequently lead to poor treatment compliance [75]. In some patients, higher religiosity has been linked to higher risk of suicide attempt [75]. Despite the close relationship of religion with various aspects of schizophrenia, this area has been mostly ignored in mental health assessment, diagnoses, and treatment [75].

Expressed Emotion (EE)

Another sociocultural variable, expressed emotion (EE), is an indicator of attitudes and behavior that is likely to induce emotional distress in patients like negative, controlling, or highly emotive communication. No literature is available that examines the predictive influence of expressed emotions in a comorbid sample. Studies have shown that patients from high EE environments were more likely to have a schizoaffective or mood disorder (54%) than schizophrenia (45%) [79].

Studies have concluded that employment is of prime importance to the concept of recovery in severe mental illness, but common comorbid conditions pose significant obstacles to persons seeking employment and benefiting from vocational rehabilitation [70].

The above discussion on barriers in recovery and sociocultural variable of schizophrenia with comorbidity emphasizes a definite need to consider proper therapeutic guidelines (polypharmacy, dual diagnosis), psychosocial interventions (stigmatization, faith healing practices, religiosity, expressed emotions), and person-centeredness (employability, empowerment, and sociocultural reintegration).

Psychosocial Recommendations in Support of Recovery

The schizophrenia Patient Outcomes Research Team (PORT) project has played an important role in the development and dissemination of evidence-based practices for schizophrenia and has produced comprehensive reviews of treatment recommendations for schizophrenia since

1998. PORT has produced treatment recommendations and other clinical guidelines to be disseminated to both clinicians and consumers and may prove very helpful for comorbid conditions also. The update process has resulted in recommendations for 16 psychopharmacologic and eight psychosocial interventions. The psychosocial intervention recommendations are being studied for comorbid conditions. It can be interpreted from various studies focussed on assertive community treatment, supported employment, skills training, cognitive behavioral therapy, token economy, family-based services, interventions for alcohol and substance abuse, and interventions for weight management can prove to be effective in comorbid conditions [35]. This discussion emphasized that proper therapeutic guidelines, psychosocial interventions, and personal recovery measures may show better outcomes which is our fifth hypothesis.

Conclusion

With the paucity of research on recovery parameters in comorbid schizophrenia, it was difficult to collect solid evidences or conclusive findings. However, applying interpretative means and with available conclusive evidences, the impact of comorbidities in schizophrenia has been studied. There is always a debate of the context of recovery measurement that change with the definitions considered for "recovery," comorbidity, and objective and subjective outcomes in schizophrenia. The incidences and prevalence of psychiatric and physical comorbidity are reported high by most of the studies, and hence, the recovery parameters are highly compromised. Barriers in recovery are accentuated in the presence of comorbidity, thus creating a larger negative impact of stigma, polypharmacy, social reintegration, and diagnostic dilemma. Various assessment instruments have been developed and prescribed to appraise the process of recovery but are hardly applied discretely for any study on recovery in comorbidity. The review concludes that the presence or absence of patient's normality is almost always viewed as requiring a reasonable degree of functional independence, positive social relationship, and the ability to work. This can only be achieved by an integrated, comprehensive approach to address the psychopathology, sociocultural functioning, and the "person" in schizophrenia.

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Part V

Intervention for Recovery

Peer Supports in Recovery

21

Timothy Schmutte, Kimberly Guy, Larry Davidson, and Chyrell D. Bellamy

Introduction

"Peer support" is a broad term that refers to the kind of support a person who has overcome, or learned how to live effectively with, a health-care condition and/or traumatic life event provides to another person who is experiencing the same or similar health-care condition or life event. The term "peer" refers to both people sharing such a common set of life experiences. Peer support is by no means limited to supports for persons with schizophrenia or other serious mental illnesses, as it has a long history in relation to numerous, diverse life experiences, ranging from alcoholism and bereavement to cancer, coping with children with special needs, divorce, paraplegia, and retirement [1, 2]. For a long time, however, persons with serious mental illnesses were considered to be too disabled by their condition to take care of themselves, much less to offer such support to other people. As a result, peer support among persons with schizophrenia and other serious mental illnesses was not introduced into contemporary mental health practice until the early 1990s and has only recently begun to accumulate an evidence base as to its effectiveness.

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We are intentional in pointing out that this is only within "contemporary practice," however, because this kind of peer support actually has a much longer history within the field of psychiatry than is ordinarily thought. Prior to Kraepelin's insistence that "dementia praecox" was an irreversible and progressive illness that resulted in premature deterioration and death, it appears not to have been uncommon for persons experiencing psychotic disorders to provide support, assistance, and perhaps mentoring to others similarly afflicted. In fact, the first recorded instance of this kind of peer support was implemented and documented by Jean-Baptiste Pussin, the governor of the Bicetre Hospital in Paris, where Philippe Pinel came to serve as medical director in 1793 [3, 4].

Having himself been a patient at the Bicetre (for a physical ailment) who worked his way up to becoming governor, Pussin was positively disposed to his fellow ex-patients and felt that those who had been hospitalized for mental illness (and had recovered) in particular made the most humane and effective staff for his psychiatric units. This was especially important, as he was already (prior to Pinel's arrival) trying to transform what had been inhumane, if not barbaric, treatment of the "insane" into more compassionate and effective care that would enable people to be discharged to take back up their lives outside the asylum. In his letter to Pinel describing the practices he had found most effective prior to

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Pinel's arrival at the Bicetre, Pussin wrote: "As much as possible, all servants are chosen from the category of mental patients… They are at any rate better suited to this demanding work because they are usually more gentle, honest, and humane" [3].

In the twentieth century, further examples of peer support in psychiatry can be found in Harry Stack Sullivan's practice of hiring recovered patients to staff his inpatient unit for persons with psychosis at Sheppard and Enoch Pratt Hospital outside of Baltimore in the 1920s and in the crucial, if unpaid, role that people who had achieved some degree of recovery played in the therapeutic community model adopted in many inpatient settings beginning in the 1950s. This model was built on the central roles that mutual support and peer role modeling, along with confrontation, conflict, and collaborative problem-solving, played in promoting the learning and acquisition of prosocial behaviors, the restoration of adaptive ego functioning, and the cultivation of healing relationships [1].

While the language and concepts that are used in describing the potential benefits of peer support for persons with psychosis have changed significantly since the 1950s, it may be useful to recognize that this is not an entirely new or radical development to be introduced into mental health practice. What is new, perhaps, is that peer support in its current form was developed first, and continues to be developed further, by persons in recovery themselves and is only secondarily being introduced into conventional mental health settings. This process raises considerable issues about the integrity, fidelity, and independence of peer support as it becomes a more widespread practice, moving from its initial position as a mutual assistance alternative to formal mental health services to becoming a mainstay of mainstream practice. We will consider these issues below, once we have defined the nature of peer support in some detail. Following this definitional work and consideration of the contextual factors that promote or impede the power of peer support, we will then turn to the research evidence that has been collected to date related to its effectiveness. We will close with a brief discussion of future directions for both practice and research.

What Is Peer Support?

As noted above, the contemporary form of peer support, which involved the hiring of people who have experienced mental illness and "recovered to some degree" to provide support to others in their own recovery, began in the early 1990s. At the time, this development was somewhat of a natural outgrowth of the mutual support groups and other peer-run alternatives that had been proliferating during the 1980s, stimulated by the Mental Health Consumer/Survivor Movement [5]. As sympathetic mental health practitioners became aware of these community-based groups and organizations, and witnessed their restorative power firsthand, there were initial efforts to bring some of the benefits of this approach into the mental health system itself. This move was not without controversy, as the Mental Health Consumer/Survivor Movement began as a protest against conventional mental health care and proposed to develop alternatives to it. This tension remains to this day, as arguments continue about whether peers who work inside of mental health systems can preserve their integrity and reformist vision while being paid by the same system they had been, or are, protesting against; more specifically, can mental health systems honor the role of peer support, its values, and ethics rather than hiring people as peer supporters but assigning them to provide case management or other traditional services? At the same time, volunteer positions were soon replaced precisely by such paid positions, and by the early 1990s, persons in recovery were beginning to play a variety of provider roles, from case management assistants and residential staff to new roles like that of recovery educator, under the auspices of conventional mental health programs [6]. The number of people in recovery (PIR) who have been hired to provide peer support, both inside and outside of conventional mental health settings, numbers in the tens of thousands. The Veterans Administration in the USA alone has already hired over 1200 PIRs in peer support positions. Over 35 states in the USA use Medicaid waivers to fund peer-delivered services.

An international network of peer support has formed and currently has a listserv of over 3000 members, which is roughly the same number of peers who have given input into the development of the first set of practice guidelines and provider competencies for this rapidly growing profession. As peer support has become a global phenomenon, the most recent development has been the publication of an international charter covering the essential values and practices for this field [7]. In terms of precisely what this new profession involves, according to this charter: "Peer supporters are defined as people who have experienced mental ill health and are either in or have achieved recovery. In their role as peer supporters, they use these personal experiences, along with relevant training and supervision, to facilitate, guide, and mentor another person's recovery journey by instilling hope, modeling recovery, and supporting people in their own efforts to reclaim meaningful and gratifying lives in the communities of their choice" [7].

This is a dense definition that bears unpacking. First of all, peer supporters utilize their own life experiences of illness and recovery—along with those of mental health service use—as the foundation for their work with the people they support. They receive additional training and supervision (and are typically certified to practice), but even this training and support emphasizes the useful and effective ways in which they can use their own "lived expertise" to benefit their clients. On this basis, they offer hope and provide a tangible role model of the possibility and of the face of recovery, serving as a guide or mentor in assisting people figure out how to go about building the kind of life they would like to lead. In addition to coaching and sharing self-care skills, this also entails sharing the "expertise" they developed in living through adversity, in dealing with stigma and discrimination, and in negotiating the use of conventional mental health services.

In addition to this definition, the international charter identified four key principles in operationalizing peer support in practice. These are:

1. Peer support is based on a human/civil rights perspective, with a primary focus on empowering people as central agents of their own recovery and enabling them to have a sense of belonging to their community.
2. Peer support does not serve a social control function and strives to preserve and enhance the autonomy and decision-making capacity of the people being supported. This remains true even in times of crisis, with the peer supporters acting as an advocate for the person.
3. The credibility and utility of the peer support role derives primarily from the person's own life experiences, with training and supervision used to augment and expand on the foundation provided by these experiences, not to override them.
4. Peer support relationships are by definition reciprocal in nature. For this form of support to be effective, peer supporters must relate to the people they support as "peers," that is, as whole human beings who share with them a common sense of humanity.

Given that client–provider relationships in mental health care have long been held to be one-directional in nature—as are health-care relationships in general—the emphasis on mutuality challenges conventional notions of "boundaries" and remains a focus of lively debate in the field.

Contextual Factors that Promote or Impede Peer Support

This challenge to conventional notions of boundaries in provider–client relationships is only one of many that have arisen in the process of deploying peer supports in mental health settings. To identify such issues, and other contextual factors that promote or impede peer support, we augmented our own practical experiences with a review of the qualitative research that has been conducted to date on these, and related, topics. First, we concentrated on two recent review articles that synthesize the qualitative literature on peer support. In 2016, Vandewalle and colleagues [8] reviewed 18 studies focused on perceived barriers to implementation. Most of the studies were conducted in the USA (n = 8) and involved peer

workers in mental health settings, with some conducted in peer-led organizations. Ten of the studies explored the views of multiple stakeholders (e.g., peer providers, supervisors, service users, and directors). Barriers were categorized according to multiple levels including (1) characteristics of peer workers and their roles, (2) individual professional, (3) service user, (4) social context, (5) organizational context, and (6) economic/political context. The second review article, from 2012, was Walker and Bryant's [9] review of 27 qualitative studies addressing a range of experiences of peer support from the perspectives of service recipients, peer support workers, and professional colleagues. Eighteen of the studies were conducted in the USA and 12 included at least 2 types of participants (i.e., peer providers, non-peer staff, and/or service recipients). Four articles were included in both review articles [10–13].

We then searched for additional qualitative studies that were not included in the reviews above. One study focused on young adult peer providers and their supervisors to examine facilitators of success in community mental health settings in the USA [14]. A second US study interviewed service users who had received substantial individual peer support [15]. A third study interviewed psychiatrists in the UK about their perceptions of peer support workers [16], and a fourth, also conducted in the UK, was with individuals on an inpatient psychiatric unit about their perceptions of peer support staff [17]. A fifth study examined peer support staff and non-peer support staff perceptions of the organizational barriers and facilitators of implementing peer support in an Australian community mental health center [18].

One of the most recurring themes that emerged from our review of the qualitative literature revolves around unclear definitions for, and lack of clarity of, the peer support role [8, 9, 14, 18]. Vaguely defined roles, as well as lack of recognized certification and sufficient training and supervision, also seem to play a role in peer support workers feeling as though their position lacks credibility in eyes of other stakeholders [8, 9]. Patronizing and stigmatizing behavior from coworkers is a pressing concern, such as peer staff being treated more like a "patient" than a colleague and being assigned "nonessential" or "menial" tasks [8, 9, 14, 16]. Peer support staff often struggle, at least in the beginning, to justify their role, and many continue to feel as though their role is misunderstood, belittled, or ignored [8, 9, 14]. At least in some settings, this dynamic between peer support and non-peer support staff recedes with time. Factors that contribute to better acceptance include proactive planning and concurrent culture change initiatives that highlight the value of peer support, peer staff realizing that other team members' roles can also be somewhat generalist and/or unclear, and persisting through negative team dynamics [8, 9].

Such a lack of clarity in the peer role, as well as in workplace policies, also appears to relate to other struggles. One example is with self-disclosure relating to their lived experiences of mental illness, which at times can be a unique contribution from peer supporters in their work with clients [8, 9, 16]. Also, peer support staff may use self-disclosure to advocate for clients' needs and/or to educate non-peer support staff about alternative perspectives [9, 15, 16]. At the same time, self-disclosure can be perceived as "unprofessional" by non-peer support staff and present challenges for peer supporters in establishing a different set of boundaries with service users [8, 16]. For some peer providers, role ambiguity can be associated with a conflicted sense of identity by being both service provider and service user [9]. Other challenges expressed by peer workers that can contribute to interpersonal challenges with clients and coworkers include residual symptoms that can contribute to coping difficulties and burnout. The importance of role clarity is underscored by its robust prediction of job satisfaction and by its possibly being conducive to transitioning from service user to peer service provider [8, 9]. Similarly, lack of clear roles and organizational supports and resources are seen as a major barrier to implementing peer support [8]. Concerns about low pay are one of the most frequently cited themes about the experience of working as a peer supporter [8].

As seen in the above list, the most formidable obstacles to the successful deployment of peer

support in mental health organizations are not the conditions from which the peer staff are recovering (i.e., mental illness), but rather are the cultures of the organizations and problematic attitudes and behaviors of (some) non-peer support staff. Underlying this form of discrimination is the deeply held belief that once a person has a serious mental illness, then he or she is no longer a "normal" person; he or she will have it the remainder of his or her life and will be compromised in his or her ability to function permanently as a result. The very presence of peer support staff in mental health settings challenges this long-standing, entrenched belief. And it was, in part, for this reason (i.e., to challenge and disprove such beliefs) that peer support staff were initially introduced [19].

Effects of Peer Support

Working as a peer supporter is frequently seen as helping the person's own personal recovery with increases in self-confidence, self-esteem, and social networks being among the most frequently described effects of working as a peer support worker [8, 9, 15–18]. Among non-peer staff, greater understanding of, and empathy for, people in recovery resulted from working with peer providers [8, 9, 15–18]. On the other hand, a not uncommon concern among some non-peer support staff was that their position would be supplanted by the "cheap labor" provided by peer support staff [8, 9]. As noted above, from an organizational perspective, the most common theme is that the inclusion of peer support staff helps to destigmatize mental illness [8, 9].

As for clients, the most common theme was viewing peer support workers as role models [8, 9, 15, 17]. Other frequent outcomes for service recipients are feeling more hopeful and motivated as a result of working with peer support workers. This can be in the form of receiving tangible or practical support, social connection, and emotional support [9, 15]. Peer supports are often experienced as inspirational role models who help "normalize" one's disability and foster greater openness about personal struggles. Service users tend to establish rapport more easily with peer staff; however it is interesting to note that in Vandewalle's review [8], the most commonly cited barrier at the level of service users was their perceived lack of interest in receiving support from peer workers. As this was a fairly isolated issue, we can imagine that it reflects on some sites being early on in their implementation process, prior to clients learning about the value of peer support, perhaps also reflecting their own stigmatizing attitudes toward their people in recovery providing supports. But this could also be indicative of clients feeling as if they are being offered "lesser" services rather than service provision by licensed clinicians.

In terms of quantitative research, paid peer staff have progressively shown that there are many benefits to their employment beyond the transformative effects they can have on organizational culture. Early studies focused on the feasibility of training and hiring persons in recovery with histories of serious mental illnesses to provide mental health services. In most of these studies, however, the people in recovery were hired to provide conventional mental health services, such as functioning as case management assistants or residential support staff. In these roles, they were found to function equally as well as non-disclosed staff in the same roles, with no differences found in outcomes or other variables [20].

Over the years, peer support services have proliferated as recovery-oriented care has been increasingly adopted in mental health settings. More recently, focus has broadened from mental health to improving the quality of care and self-management of physical health to address the disproportionate prevalence of medical morbidity and premature mortality [21]. Peer specialists may be particularly well-suited to function as health navigators or wellness coaches. As peer services have evolved, a body of knowledge has formed consisting of observational studies and randomized controlled trials (RCTs) devoted to peer-provided services for mental and physical health outcomes.

Although the results of these individual studies are largely positive, as we will discuss shortly, recent meta-analyses provide a more nuanced

picture of the state of the art of research on the effectiveness of peer support [22]. Moreover, replication studies with larger samples and greater methodological rigor are needed to determine in what settings peer staff enhance outcomes and to disentangle the unique strengths and contributions of peer staff, if any, from the overall impact of treatment services provided by non-peer providers. For this review, first, we searched for meta-analyses and systematic reviews of peer support for mental and physical health outcomes in adults with serious mental illnesses. Then, we found published studies that were not included in the review articles.

For mental health outcomes, we found three meta-analyses [23–25], two systematic reviews [26, 27], and one individual study [28]. With respect to standard clinical outcomes, such as hospitalization rates, severity of symptoms, and employment, peer-led services and peer providers are, as a whole, associated with equally positive outcomes as traditional services provided by non-peer staff. Although the specific programmatic and participant characteristics have yet to be elucidated and corroborated by additional research, there is promising evidence that peer services are associated with greater reductions in cost of services associated with inpatient hospitalization and crisis emergency visits compared to usual care conditions. On the other hand, the evidence is stronger for recovery-related outcomes, such as service users' hopefulness, empowerment, and quality of life. In short, the evidence for peer support services is promising but confounded by heterogeneity in setting (e.g., respite vs. outpatient vs. community-based case management), category of outcome measures, and quality of methodological rigor (e.g., blinding of raters, randomization procedures).

The research base for peer-based health interventions is considerably new, and therefore smaller, compared to mental health services. To date, only one systematic review of 18 studies [29] and three additional studies [30–32] could be located. As with the reviews for mental health outcomes, the strength of the evidence for health interventions provided or co-facilitated by peer specialists is mixed, due to methodological limitations and heterogeneity in scope and outcome. Beneficial effects are most consistently found for improving self-management (e.g., self-efficacy, health locus of control, goal-setting, and action planning), healthy dietary changes, and communicating with medical providers. In other health-related domains, the results are mixed or limited (i.e., physical activity, smoking cessation, medication adherence, cardiometabolic outcomes, use of services, and quality of life). A recent RCT [30] involving 151 adults with serious mental illness found those who were assigned a peer health navigator demonstrated significant improvements in their use of primary care, relationship with their physician, detection of chronic health conditions, and confidence in their self-care abilities. Moreover, those with a peer navigator displayed a decreased preference for emergency/urgent care or avoiding health services as well as reductions in pain. To summarize, the most promising approaches for peer-based health inventions to date are self-management approaches and peer health navigators.

Conclusion

In its current form, peer support has rapidly proliferated and branched out into new areas across the globe in the last decade. Initially introduced as a way to destigmatize mental illness, engage people who were disaffiliated with the mental health system, and help clients establish meaningful and purposeful lives in the community, peer support has increasingly focused on activating people for, and supporting them in, their own self-care both for mental health and for medical issues. Moving in this direction, especially without being explicit and clear about the role of peer staff, risks heightening the tension that already exists between peers supporting the needs and autonomy of their clients and peers serving the needs of the health-care system, which is not always viewed as giving priority to the best interests of the client. As long as peer supporters can be confident and comfortable that they can advocate for their clients within the parameters of their paid role, such tensions need not arise.

To the degree to which some health-care systems are viewed as untrustworthy, impersonal, and nonresponsive, though, approaches to organizational cultural change are needed to transform the settings and systems in which they work. In this respect, future practice and research may need to take into account more the contextual factors that impede or promote peer support, as well as the contextual effects implementation of peer support generates outside of the scope of individual level outcomes.

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Early Intervention in Psychosis

22

Swaran Preet Singh and Benjamin I. Perry

Introduction

Three-quarters of adult mental disorders first appear between early adolescence and young adulthood [1], initially presenting in milder, subthreshold or polymorphous forms [2]. The onset of many mental disorders thus occurs at a time of multiple, complex and dynamic developmental transitions in the lives of young people. It is vital therefore that services minimise the risk of delays in treatment or poor treatment of emerging serious mental disorders [3].

Psychotic disorders such as schizophrenia are common, with 23.6 million prevalent cases worldwide in 2013 [4]. One in two people living with schizophrenia worldwide does not receive care for the condition [5]. The recovery rates (one in seven) [6] and associated disability (11th cause of disability worldwide in 2013) [4] following a first episode of psychosis (FEP) have not improved over the past 70 years under routine clinical care [7]. Although psychopharmacological treatments are effective against positive symptoms of psychosis, symptomatic recovery does not equate with functional improvements [8].

The annual national costs for the schizophrenia population ranged from US $94 million to US $102 billion worldwide, up to 1.65% of the gross domestic product [9]. Furthermore, risk of all-cause mortality for psychotic disorders is twice (risk ratio 2.54) that of the general population [10]. There is thus an urgent clinical and societal need for improving outcomes of psychosis, particularly in our younger patients, hence the rise in importance of early intervention (EI) services.

Traditional primary healthcare services have catered largely to physical illness and consequently have been designed for those who bear the majority of physical health burden in a population, namely, the very young and very old. Furthermore, the culture of care has been largely insensitive to the specific needs and priorities of young people, who consequently fail to engage [11].

Furthermore, young people's complex, arguably less well-understood and evolving symptom profiles often do not meet the narrow criteria required for acceptance into an adult service, despite the significant distress and impairment already manifest.

In the past few years, the evidence confirming the superiority of specialised early intervention services over generic care in managing the critical early phase of psychosis has grown steadily, with two large RCTs in the UK (LEO trial) [12] and Denmark (OPUS trial) [13] and several effectiveness studies of "routine" early

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intervention for psychosis (EIP) services. Under specialised early intervention services, individuals experience better clinical, social and vocational outcomes, have reduced in-patient stays and are better engaged [14]. Table 22.1 outlines some of the important trials to date comparing EIP specific to standard care.

Table 22.1 Trials involving EI services

Name	Location	Sample	Interventions	Outcome	Key findings
LEO trial (Craig et al.) [12]	UK	*n* = 144 first- or second-episode patients	Assertive outreach with evidence-based biopsychosocial interventions **vs** standard care	Rates of relapse and readmission to hospital over 18 months	Limited evidence shows that a team delivering specialised care for patients with early psychosis is superior to standard care for maintaining contact with professionals and for reducing readmissions to hospital
OPUS trial (Bertelsen et al.) [13]	Denmark	*n* = 547 FEP	2 years of an intensive early-intervention programme (assertive community treatment, family therapy, social skills training) **vs** standard care	Psychotic and negative symptoms, use of services and social functioning over 5 years	The EIP programme improved clinical outcomes after 2 years, but effects were not sustainable at 5 years; however, those in EIP group had lower use of supported housing and reduced hospital visits at 5 years
TIPS study (Johannessen et al.) [15]	Norway, Denmark	*n* = 161 FEP patients	3 months of specific early-intervention services **vs** standard care	Demographics, functioning, recovery, symptoms, early detection	Intervention group consisted of significantly more males with a longer DUP, less dramatic symptom picture and better functioning; however, they faced a slower recovery and significantly higher symptom scores at 3 months
Danish National Schizophrenia Project (Rosenbaum et al.) [16]	Denmark	*n* = 562 FEP patients	1 year of integrated, assertive, psychosocial and educational treatment programme **vs** Standard care + supportive psychodynamic psychotherapy **vs** standard care	General assessment of functioning (GAF) scores at 1 year	Significant improvement in all groups, but no significant difference between groups
Swedish parachute project (Cullberg et al.) [17]	Sweden	*n* = 253 FEP patients	"Need adapted treatment" **vs** standard care **vs** historical controls	GAF scores, hospitalisation, medication use	GAF scores were higher in intervention group. Hospitalisation was lower as was prescription of neuroleptic medication

Table 22.1 (continued)

Name	Location	Sample	Interventions	Outcome	Key findings
Grawe et al. [18]	Norway	$n = 50$ schizophrenia <2 years	2 years of early intervention specific care **vs** standard care	Psychopathology, functioning, hospitalisation and suicidal behaviours	Integrated care proved superior in reducing negative symptoms, minor psychotic episodes and stabilising positive symptoms, but did not reduce hospital admissions or relapses
COAST trial (Kuipers et al.) [19]	UK	$n = 50$ with psychosis <5 years	9 months of early intervention specific care **vs** standard care	Hospitalisation, quality of life	Both groups improved with treatment, but no significant difference between intervention and control group
EASY trial (Chen et al.) [20]	Hong Kong	$n = 1400$ FEP patients	3 years of early intervention specific care **vs** standard care	Functional outcome, symptom levels, relapse, recovery, suicidal behaviour	Early intervention compared favourably, particularly with respect to functional outcome and reduction in hospitalisations, suicides and disengagements, but there was no difference in relapse rate

Some of the controversy surrounding EIP is generated by the confusion over the different ways in which the term "early intervention" is used [21]. EIP can mean improving outcomes in established cases of psychosis by facilitating and consolidating recovery (EI services), detecting hidden morbidity in the community or within mental healthcare by identifying untreated cases (early detection for reducing duration of untreated psychosis (DUP)) or preventing the emergence of psychosis in prepsychotic and prodromal states [14]. These are different aims, requiring different service strategies, and have differing weights of evidence supporting their use.

History of Early Intervention Services

Apart from the transient and illusory optimism generated by the mental hygiene movement in the 1920s, early intervention in psychotic disorders was not a clinical priority for clinicians and researchers. The initial optimism following the discovery of antipsychotic medication was replaced by relative therapeutic pessimism as it became clear that functional outcomes did not marry with clinical recovery. Furthermore, investment into community care following closure of large institutions did not lead to an improvement in outcomes in FEP [22]. However, since the early 1990s, research into early intervention services has gained ground and widespread national and international efforts for reform in services and treatment approaches, even setting the scene for more serious efforts in early intervention in other mental disorders [23–25].

Early studies in EIP [26] and Wyatt's seminal papers [27] confirmed the prognostic influence of DUP on outcome. In the 1990s, three emerging and interwoven strands of evidence supported the case for specialised EIP services. First, the existence of an early window of opportunity, "the critical period", was postulated on the basis of strong evidence that early trajectory and disability were strongly predictive of long-term course and outcome [12] and the greatest impact on the illness might occur during this period of neuronal and psychosocial plasticity [28]. Second, the

association between longer periods of untreated psychosis and poorer outcomes became firmly established [29]. Third, it became clear that even well-resourced community services were not meeting the needs of young people in their FEP and had not improved their outcomes [15, 30]. Politically, an important lever for change was pressure from service users and their carers determined to tackle the "scandal of delays in care" for young people with FEP [31].

Building on important research on FEP [32, 33], front-line EIP clinical services were established, first in Melbourne, Australia [26], and soon after in many key locations in the UK, Europe, North America and Asia. There are now hundreds of EIP programs worldwide, of varying intensity and duration, which focus on the special needs of young people and their families. International clinical practice guidelines and a consensus statement have been published, and clinical practice guidelines for the treatment of schizophrenia, including the DSM-V for the first time, now typically have a section on early psychosis (NICE guidelines). The International Early Psychosis Association (www.iepa.org.au), an international organisation which seeks to improve knowledge, clinical care and service reform in EIP, has been in existence for over 10 years, led by a highly collegial leadership group of clinicians and researchers. The typical functions of a modern EIP service are displayed in Table 22.2.

Table 22.2 Typical functions of a modern EIP service

Early detection
• Community education programmes
• Anti-stigma campaigns
• Training programmes for general practitioners and other key agencies such as educational authorities, youth services, young offender programmes, etc.
• Disseminating information about pathways into care
Facilitating recovery with phase-appropriate interventions
Acute phase
• Multidisciplinary assessment of mental state, risk, support and needs
• Diagnosis to establish broad psychosis rather than narrow schizophrenia
• Initiating treatment in community and low-stigma settings but treat as in-patient if needed
• Use of low-dose atypical antipsychotics
• Therapeutic engagement
• Allocation of care coordinator
Recovery phase
• Ensuring medication adherence
• Individual therapy, including cognitive–behavioural therapy (CBT)
• User contribution to needs assessment and care plan
• Psychoeducation for carers
• Behavioural family intervention, where needed
• Assessment and management of comorbidity, especially depression and substance misuse
• Monitoring of mood for early identification of hopelessness, pessimism or suicidal ideation
• Engaging carers as therapeutic allies
• Vocational assessment
• Regular and documented multidisciplinary review of care plan along with user and carers
Consolidating recovery and discharge planning
• Relapse prevention strategies
• Early warning signs drill
• Recovery groups
• Vocational rehabilitation
• Enhancing independence by addressing social outcome, leisure activities and housing

Duration of Untreated Psychosis

DUP is commonly defined as the time interval between onset of definite positive psychotic symptoms and first appropriate treatment, which can include antipsychotic medication or engagement in an EIP service. However, the definition of DUP can vary significantly in the literature, with many studies favouring "time to pharmacological treatment" [34], though this definition can also vary between studies because of lack of consensus on dosage, compliance, response and recovery. Whilst recovery rates did increase in the mid-twentieth century, antipsychotics have not made a significant difference to the proportion of patients in remission in long-term follow-up studies [35].

Nevertheless, DUP has garnered increasing amounts of interest in research and development of EIP services for several reasons. Firstly, there is a hypothesis that untreated or repeated episodes of psychosis are "neurotoxic" and may

induce irreversible brain damage [36]. This may have biological plausibility; however, results should be interpreted with caution since patients recruited to these studies had varied but significant exposure to antipsychotic medication; thus, the brain changes cannot be discerned from the changes that may occur following chronic antipsychotic use. Nonetheless, the hypothesis states that the longer the time between the emergence of psychosis and the initiation of treatment, the poorer the outcome. A systematic review including 26 studies on FEP [37] found that although a longer DUP was not associated with worse symptoms or functioning at first presentation, at 6 and 12 months following treatment, longer DUP was associated with not only more severe overall symptomatology and worse overall functioning but also a reduced remission rate at 6, 12 and 24 months. A meta-analysis in 2005 [38] found FEP with longer DUP to be associated with more negative symptoms and lower levels of functional recovery. Shorter DUP was thus not only associated with greater "treatment responsiveness" but also with greater reduction in negative symptoms. It is, however, still contentious whether a long DUP causes a poor outcome or whether reverse causality is at play, where a long DUP is caused by illness-related factors such as an insidious onset with nonspecific prominently negative symptoms, which can delay accurate diagnosis, or poor premorbid functioning, which may delay help-seeking behaviour.

So far, no demonstrable relationship has been confirmed between effect size of DUP on outcome and the cut-off point chosen to define long or short DUP. One study [39] suggested that a DUP must be shorter than 6 months for treatment to enhance outcome; however, another more recent study [40] shortened this cut-off for treatment effectiveness to just 3 months. However, the "critical period" hypothesis has been an important focus point for EIP research and service planning. Max Birchwood first coined the term, describing the first 3 years of schizophrenia [41], which he considered as being the time of maximum deterioration in social, occupational and cognitive functioning, and during which repeated relapses are common. It is argued that during this time, a "revolving door" pattern of admissions may be established, long-term treatment-resistant symptoms may emerge, and major personal, social and occupational disabilities can accumulate. Some argue that the level of disability attained in the first two years of the illness may set a "ceiling" for recovery in the long-term, thus making a compelling case for effective interventions in that period [42]. In the UK today, an ambitious "two-week target"' has been set to engage those suffering FEP in EIP services.

The relationship between DUP and functional outcome is not linear. Deterioration in schizophrenia is unlike that seen in other neurological conditions such as Huntington's chorea or Alzheimer's disease in that it seems to reach a plateau [43]. In an important and valuable study of untreated patients from Chennai, India [44], a DUP of less than 5 years predicted good clinical but not occupational outcome (though this may be partly due to local cultural or socioeconomic factors), yet in that study, treatment response was seen even with a DUP of up to 15 years. McGlashan [43] has postulated a "window of deterioration" in the late prodromal phase when maximum neurocognitive decline occurs. Studies of long DUP are becoming more difficult as services improve around the world and may indeed only be feasible in resource-poor settings, where research capacity may also be limited.

Long DUP is clearly associated with poor outcome, and EIP services focus great efforts on reducing this, with the aim of improving short- and medium-term outcomes [42]. Given that we are unable to alter other significant risk factors such as age of onset, family history, previous traumatic abuse and gender, DUP is the one malleable variable which should and perhaps can be reduced [45]. However, two caveats remain: first, to make studies adhere to a consensus on definition, and, second, DUP is not a valid measure for establishing the effectiveness of valued EIP services that aim solely to provide evidence-based care in an assertive manner without an early detection arm. One might argue that their effectiveness and rationale should be judged on criteria more akin to whether they meet clinical

need early, comprehensively and with the best available combination of psychosocial and biomedical interventions, rather than solely on the reduction of DUP.

Treatment

Some have argued that specialist EIP teams are "no different from those that would be considered best practice by multidisciplinary psychiatry teams" [46]. Evidence does not support this assertion, with generic mental health teams themselves identifying lack of skills and expertise in managing first-episode cases [22]. Young people who make a transition into psychosis even whilst under the care of generic teams still have long delays in receiving effective care [47]. Provision of good multidisciplinary care may well be contingent on specialisation, and a specialist team is a prerequisite for the delivery of highly skilled evidence-based care. As an outline, the care provided in EIP services can broadly be divided into pharmacological and psychosocial.

Pharmacological

Pharmacological treatment in patients with FEP has a markedly positive effect on the likelihood of remission [48] and risk [49] or rate [50] of relapse. Although the effect is associated with both oral and long-acting injectable (LAI) antipsychotics, one study reported a rate of remission sustained for ≥6 months with LAIs that compared favourably relative to that reported in FEP treated with oral antipsychotics [51].

A randomised, double-blind study that evaluated the onset and duration of remission in 160 treatment-naïve patients with FEP after 1 year of treatment with clozapine or chlorpromazine [48] with "time to remission" as the primary outcome found a high degree of treatment responsiveness for both drugs at study end point, with no differences in the rates of achieving remission before discontinuing or completing the 52-week study; however, time to remission was quicker with clozapine.

Another study measured the time course of relapse of 555 patients with FEP who were randomised to receive treatment with haloperidol or risperidone over 4 years [52]. In this cohort, the median time to relapse was 205 days in patients treated with haloperidol and 466 days in patients treated with risperidone; the overall relapse rates were 55% and 42%, respectively, in 400 of the patients who initially achieved clinical improvement.

Furthermore, durable cognitive benefits from atypical antipsychotics have been observed in patients with FEP following treatment ranging from 6 months to 2 years. A meta-analysis [53] found four of the seven studies examining cognitive functioning included comparisons of first-generation antipsychotics (FGAs) with second-generation antipsychotics (SGAs), and all but one of the studies reported comparable and significant improvements in cognitive assessments between the FGA and SGA treatment groups. The one study that found between-group differences in cognitive functioning with SGAs versus FGAs was conducted in patients with FEP, where significant improvements from baseline at 54 weeks on a composite score of cognitive functioning were observed with olanzapine and risperidone but not with haloperidol.

Non-psychotropic medications have also been trialed as preventative measures for psychosis. A double-blind randomised controlled trial [54] was completed on 81 participants at high risk for development of psychosis, comparing polyunsaturated fatty acids with placebo, with the main outcome measure as conversion to psychosis. The trial found significantly reduced rates of conversion in the polyunsaturated fatty acid group compared with placebo, reduced positive symptoms and improved functioning. The incidence of adverse effects did not differ between groups.

Psychosocial

Cognitive and cognitive–behavioural strategies, most commonly cognitive–behavioural therapy (CBT), are perhaps the most widely studied psychosocial interventions in FEP. CBT has estab-

lished efficacy for common comorbidities such as anxiety and depression, whose symptoms are reported to be most distressing [55]. CBT, therefore, has potential benefits for addressing symptoms and functioning both specific and nonspecific to psychosis. Furthermore, common adjunctive treatments include case management, assertive community treatment and crisis management or intervention. These include intensive multidisciplinary team-based approaches and assertive efforts to enhance engagement, provide in vivo treatment and maximise independent living skills, treatment compliance and patient satisfaction [56].

Family therapies are another logical treatment choice for those at risk of psychosis due to their robust efficacy regarding relapse prevention with established psychotic disorders. Family therapies are particularly relevant for the early psychosis group, as the onset of illness often occurs at a time when many young people are still living at home [57, 58]. There is evidence to suggest that family support can be linked to significantly fewer rates of relapse and rehospitalisation [47] and reduced mortality and treatment engagement [59], though studies on family therapy alone showed diminished and insignificant findings over time. Family therapies aim to work on "high expressed emotion", a term denoting emotional over-involvement, alongside critical comments and hostility within the family unit.

Not surprisingly, given the range of ages, functional difficulties and contextual factors relevant to treating those at risk of psychosis, there have been numerous efforts to integrate treatment, similar to what may be prescribed by modern EIP services. The earliest model was developed by EPPIC in Australia. This model integrated CBT, low-dose antipsychotics, needs-based case management and pharmacological treatment of comorbid disorders [60]. Other examples include the OPUS programme in Denmark [61] (assertive community treatment, social skills treatment and multifamily group psychoeducation). A widely disseminated American model of integrated treatment tested in a quasi-experimental trial is FACT (multifamily group psychoeducation, modified assertive community treatment, supported employment and education and pharmacological treatment by protocol) [62]. All have shown positive significant short- and medium-term outcomes, and several have been shown to be cost-effective in comparison to standard care alone.

Treatments Under Investigation

Preliminary trials have examined pharmacological agents including amisulpride and aripiprazole, other types of psychotropic medication including antidepressants and lithium as well as other non-psychotropic medications such as glycine, aspirin and D-serine [63–67]. Innovative psychosocial interventions being developed and tested include mobile technologies, social networking, exercise-based cognitive remediation and multiuser biofeedback video games [67]. Additional targets of these new interventions include inflammation, healthy brain development, engagement and motivation, generalisation and durability of effects and enhanced effects for younger cohorts. Given their strong evidence base for addressing functional difficulties associated with established psychosis, adaptations of supported employment and education, social skill-building and cognitive remediation are also of interest.

Finally, there is genuine uncertainty about how long intensive EIP services should be provided and whether all cases should receive the same fixed period input. Longer-term cohort studies have shown that, following the transition from EIP services to standard mental health services, clinical gains are lost in the long term, with no reduction in long-term remission rates or improvement in social, occupational or personal functioning. Current evidence suggests that interventions are therefore effective only as long as they are actively implemented. Some argue [41] that the length of EIP service provision should be much longer than is currently provided, and others have hypothesised that the heterogeneous trajectories of early psychosis require differentiation, with EIP service provision being tailor made for longer periods for those with poorer early outcomes.

Psychosis Risk and Prevention

Primary prevention in mental health aims to reduce the incidence of symptoms and ultimately of mental disorders. The three categories of primary prevention identified by the World Health Organization (WHO) are as follows: universal prevention, targeting the general public or a whole population group that has not been identified on the basis of individual risk; selective prevention, targeting individuals or subgroups of the population whose risk of developing a mental disorder is significantly higher than the rest of the population; and indicated prevention, targeting high-risk individuals who are identified as having minimal but detectable signs or symptoms foreshadowing mental disorders.

Primary prevention of schizophrenia is an attractive but nebulous concept. When a debilitating and often progressive disorder frustrates efforts at effective treatment, prevention may offer the only realistic hope of avoiding its consequences. The first generation of prevention studies for psychosis focused on patients, usually adolescents, who were beginning to experience prodromal symptoms [68]. As the field has evolved, however, the focus has shifted to not only interventions earlier in life but into high-risk groups and even the population as a whole.

Universal primary prevention for EIP must take the form of a safe population-wide intervention that promotes normal development. Research in this area is still in its infancy, because no established pathophysiological mechanisms to be targeted have been validated [69]. Furthermore, universal primary prevention may be hampered by difficulty in assessing the effectiveness of any intervention, due to numerous reasons such as the rich variation in incidence of the disorder, low absolute incidence and long latency between exposure of the intervention and potential manifestation of the disorder. These are limitations not only significant in psychiatric research but in the majority of medical sciences; thus, surrogate end points may be used, though these are yet to be validated in psychosis research.

Despite these difficulties, there are several potential population-wide interventions that could have a positive effect on the future incidence of psychosis. Improving social cohesion and opportunities—especially for migrant minority groups—increasing government spending on mainstream education, improving education on illicit substances (particularly high-THC forms of cannabis) and improving early support for young persons subject to traumatic abuse are all means to address the risk factors for psychosis. However, the currently known risk factors **(**Fig. 22.1**),** either alone or taken together, may not be sufficient for prediction and prevention without knowledge of the complete predispositional basis and the gene–gene and gene–environment interactions, which are probably numerous [71].

Select studies have also attempted to trial more specific universal prevention interventions. A randomised placebo-controlled clinical trial of dietary phosphatidylcholine supplementation was conducted in a small sample of healthy pregnant women [72], starting in the second trimester and continuing through the third postnatal month. The intervention aimed at correcting delays in cerebral inhibition that may develop perinatally, as evidenced using electrophysiological biomarkers. The intervention was free of significant side effects and showed proof of concept efficacy. Although larger studies need to be conducted to validate these initial findings, future research in this field is warranted over the next decade.

Selective prevention has also garnered increasing interest, targeting young persons, often from families with histories of schizophrenia that put their offspring at increased risk. In the last decade, six meta-analyses have been conducted investigating individuals seen as “at risk”. This is defined variably in the literature, from “familial high risk” for those with a positive family history to “ultra-high risk” or “clinical high risk”, which may depend more on early signs and symptoms, and will be discussed under “indicated prevention”. A recent meta-analysis of studies examining selective prevention methods for psychosis by van der Gaag et al. [73] included five randomised control studies of a mixture of psychological therapies and psychotropic medication, finding an overall risk reduction for conversion to psychosis at 12 months of 54%, dropping to 37% at 48 months. However, current evidence from genome-wide association studies suggest

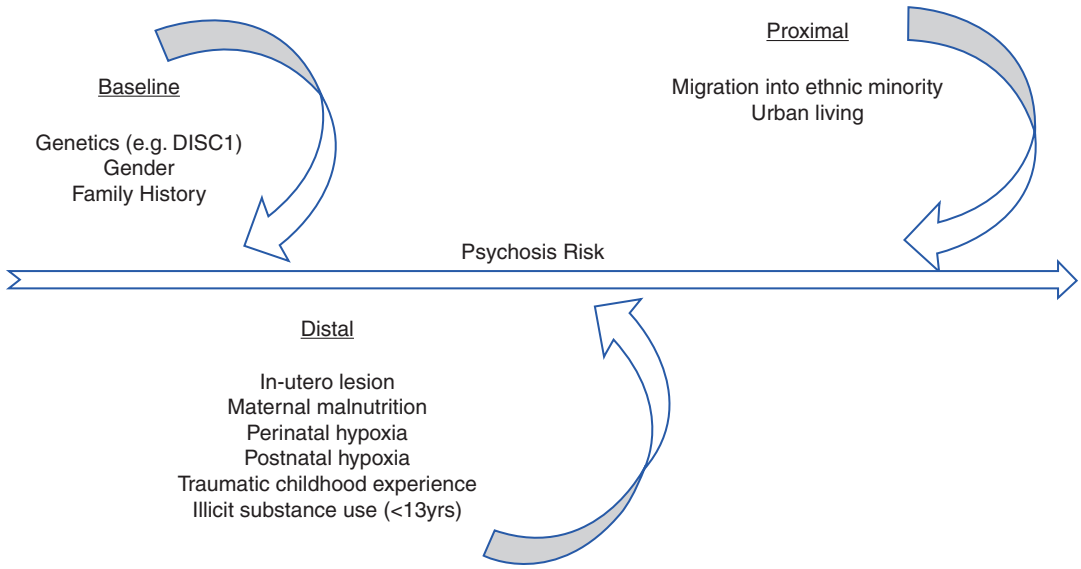

Fig. 22.1 Psychosis risk. Adapted from Hecker [70]

that schizophrenia (as other psychotic disorders) does not result from a single gene or genetic abnormality, but rather the complex interaction of hundreds of specific genes [74]. Though still in nascent stages, the implication of this work is that individuals could be given a risk score, based on their specific genes. Until this work is complete, family history is still the best proxy for genetic risk.

Aside from genetically mediated risk, research has also attempted to define other high-risk groups that may benefit from selective prevention. Research methods range from molecular genetics via proteome research to cell biology, neurophysiology, brain structural and functional imaging and neuropsychology. With all these methods, several indicators for an increased risk of schizophrenia have been identified. However, the currently recognised neurobiological risk factors are not sufficiently predictive to allow the development and application of "selective" prevention measures targeting asymptomatic persons at risk. For neuropsychological risk factors, this became evident in the large-scale attempt of the North American Prodrome Longitudinal Study (NAPLS) group to improve their multivariate model by integrating the examined neurocognitive variables [75].

Much work has also been conducted on indicated prevention, by identifying clinical "prodromal" phenotypes that may indicate a high risk for psychosis, before the onset of any clinical psychotic symptoms. However, many symptoms typically referred to as the prodrome in psychosis, such as withdrawal, anhedonia, attention dysfunctions or social difficulties, are not specific to emerging psychotic disorders. They may reflect any of several causal mechanisms or contributing factors and, at the same time, be predictive of outcomes other than psychosis. In the absence of definitive markers of impending illness, prevention and early intervention of psychosis are based on an assessment of probabilities. These probabilities are typically based on risk factors and risk indicators, of which indicated prevention attempts to capture the latter. "Attenuated psychosis syndrome" now features in Section 3 of the DSM-V—under "conditions for further research". Another approach has focused on "basic symptoms" or subtle alterations in mental experiences that are thought to emerge earlier than prodromal syndromes [71].

An important study [71] on the early course of FEP has shown that the earliest and most common symptoms, which generally dominate during the prodrome, are nonspecific and cannot

be distinguished from the impairment in mood, drive, contact and concentration in depressive episodes. However, the definition and use of high-risk criteria and transition differ—sometimes considerably—between studies regarding requirements on onset, frequency and functional impairment and consideration of axis-I diagnoses and substance use. Data from the PACE (Personal Assessment and Crisis Evaluation) clinic in North-Western Melbourne, which uses a different operational definition of risk, suggest that 95% of the subjects that eventually develop schizophrenia are not detected by the current strategies [76, 77]. The number of false positives is also high. Forty-five to 85% of the subjects identified as "at risk" (depending on the definition used in each study) will never develop schizophrenia, even in the absence of any specific preventive strategy [78]. Finally, the efficacy of different measures proposed to prevent the onset of overt psychosis in subjects at risk has not been conclusively established [79].

Early Intervention: Extending the Paradigm to Youth Mental Health

UK

England was the first country to develop universal early intervention services [80] and still has perhaps the best EIP coverage of any other nation. The importance of these services has been reinforced by several influential reports over recent years. Findings from the Transitions of Care from Child and Adolescent Mental Health Services to Adult Mental Health Services (TRACK) study [81], which found wide variation in the care provision for patients transitioning from child and adolescent mental health services (CAMHS) to adult services, have sharply focused the attention of policymakers and service providers on the need for improving transition. As a result, several policy documents have been launched; New Horizons, a Department of Health (DoH) policy document [82], outlined a new access and waiting time standard for EIP services for adults, children and young people with FEP. Shortly afterwards, a cross-party review entitled "No Health without Mental Health" [83] was published, aiming to achieve parity in funding, access and care between physical and mental health; and the Social Care Institute for Excellence [84] published a report on the transition between CAMHS and adult services. Finally, Dame Sally Davies' 2013 report [85] "Our Children Deserve Better", for the Department of Health, noted regarding youth mental health "key themes emerge around the importance of data, service provision, and prevention".

In the UK, all major political parties have included youth mental health as a major strategic priority in their health plans. In September 2014, the UK Department of Health set up a Children's and Young People's Mental Health and Wellbeing Taskforce [86] to improve children and young people's access to mental healthcare and to redesign the organisation and commissioning of such services. However, despite much media attention and government promises, substantial investment in services is still awaited [87].

A local initiative in Birmingham to develop a dedicated youth mental health service showed positive results including a low attrition rate, rapid responses and delivering high-quality assessments [88]. As a result, a new 0–25 service has been commissioned, offering a range of new services and facilities, based upon the principles of prevention, choice and personalised care.

Australia

In 2006, the Australian government established the National Youth Mental Health Foundation, which was tasked with devising and building a national youth mental health service stream designed to provide highly accessible, youth-friendly centres that promote and support early intervention for mental and substance use disorders, including psychosis, for young people.

A study sampling 22,000 young people accessing the service nationally found that the service is performing well in addressing the issues of access and engagement [89]. However,

the project is still a work in progress. Important gaps remain, notably the fact that more than half of Australia is not yet covered, as the current level of funding, together with Australia's geographic constraints, does not yet allow full national coverage. Furthermore, access rates for young men, some ethnic populations and young adults, whilst improved, are low, and the programme may not yet adequately cover those with more complex and serious stages of mental illness.

Republic of Ireland (Ireland)

Ireland has a population of just over 4.5 million, with 19% between the ages of 10 and 24 years [90]. Unlike other jurisdictions such as Australia, the UK and Canada, the origins of Ireland's youth mental health movement can be traced back to high levels of public concern about seemingly endemic rates of youth suicide (fourth highest in Europe for 15–25 years old) [91] and mental distress among Irish youth. Ireland is therefore an interesting example of how the convergence of a range of factors at a point in time became a catalyst for change, for innovation and for the development of youth mental health services.

In 2008, a national Special Interest Group in Youth Mental Health was established that quickly became a forum for professionals across sectors and disciplines, and from both Ireland and beyond, to share knowledge and to promote the need for developments in the field of youth mental health in Ireland, including for psychosis. The group established an annual Youth Mental Health Research Conference and hosted the Killarney Summit in 2010, at which a consensus was reached among leaders from across the globe to create a Declaration on Youth Mental Health.

Canada

In Canada, addressing the larger problem of youth mental health at a national level has taken longer relative to the nations already discussed, despite earlier attempts at improving aspects of youth mental health services in some jurisdictions [92]. The national transformation of youth mental health services has moved forwards more recently with the development of the Transformational Research in Adolescent Mental health (TRAM) initiative [93], funded jointly by the Canadian Institutes of Health Research (CIHR) and the Graham Boeckh Foundation, the latter being dedicated to improvement of care and outcome in mental health. Launched in October 2012 as a competitive process, the explicit purpose was to establish a national network project that would demonstrate transformation of youth (11–25 years) mental health services and provide evidence of its effectiveness over a period of five years. Limiting its scope to youth with established or emerging mental health problems and precluding primary prevention activities, the intention was to bridge the science–practice divide by applying existing evidence to transform the delivery of mental healthcare and to produce better outcomes.

USA

The USA's National Institute for Mental Health (NIMH) has supported empirical research into early psychotic illness. Results from the Recovery After an Initial Schizophrenia Episode (RAISE) project [94] highlight the value of early intervention for reducing the duration of untreated illness, speeding patients' and family members' access to appropriate care and restoring normal school and work trajectories among individuals who receive evidence-based treatment. In 2015, the Early Psychosis Intervention Network (EPINET) was set up to improve early psychosis care in the USA.

NIMH estimates that approximately 60 clinics in the USA currently offer evidence-based early detection, indicated prevention and treatment services to individuals in the earliest stages of psychotic illness. By 2017, this number will have increased to over 100 clinics, as a result of new federal funding for early SMI treatment programs [95].

Low- and Middle-Income (LAMI) Nations

It is indeed noticeable that the majority of research on EIP has thus far been conducted in developed nations. A systematic review on DUP in LAMI countries returned data from only 18 of more than 150 LAMI and only 3 of more than 50 African countries [96]. The relatively low priority and therefore funding afforded to mental health in LAMI countries [97–99] and the widely accepted but controversial notion that schizophrenia carries a better prognosis in developing countries might have hindered the development of services for psychosis. The review found a significantly higher mean DUP in studies from LAMI nations (125 weeks) than in high-income nations (63 weeks). Using the data on gross domestic product (GDP), the review demonstrated that, within the studies from LAMI nations, mean DUP fell by 6 weeks for every $1000 of GDP purchasing power parity.

The development of EIP services in LAMI nations faces formidable obstacles. However, the seriously mentally ill in LAMI regions are among the most disadvantaged people on earth. Making treatment available is a moral necessity, and providing early treatment is likely to be cost-effective.

Conclusions

Knowing now the emerging epidemiology of youth mental health problems, were we to start again, we would simply not have a child and adolescent/adult mental health service split at point of maximum risk of emerging mental illness [2]. The long shadow cast by childhood physical and mental health problems on adult life [100] and the impact of untreated or poorly treated disorders of children and young people extend far beyond just service use. However, the last 20 years have forged a significant path towards improving short-term outcomes for young people suffering FEP. EIP services are now commonplace across the developed world, though much more needs to be done to improve services in LAMI nations. Research and progression in the next decade and beyond will be vital to ensure the short-term improvements can be extended, not only to convince policymakers to extend services but to ensure our patients are afforded every conceivable chance towards recovery and a normal life.

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Yoga and Outcome of Schizophrenia

23

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Introduction

Schizophrenia is a chronic debilitating psychiatric disorder characterized by positive, negative, and cognitive symptoms. Heterogeneity in the course and outcome of schizophrenia has been recognized for more than a century, and study of course and outcome of schizophrenia is still an active area of research. While the term "course" refers to the pattern of progression of illness over a period, the term "outcome" is used to describe the status of an individual at a single point in time or at the end. Considering that schizophrenia is a chronic condition, the majority of the studies have examined outcome at the end of a few years. Earlier studies focused predominantly on clinical symptoms and their improvement for outcome. However, it has been increasingly recognized that other domains are equally important for functional outcome. Hence, studies have focused not only on improvement in clinical symptoms and signs but also on other outcome measures such as social functioning, employment status, family burden, quality of life, etc. Several studies have consistently demonstrated that negative and cognitive symptoms play critical roles in determining outcome, and some authors have suggested their primacy over positive symptoms as predictors of poor outcome [1].

Several lines of research have also demonstrated that the efficacy of available antipsychotics, both first-generation and second-generation, in the treatment of negative and cognitive symptoms is modest at best and the degree of improvement is not clinically meaningful. Hence, other treatment modalities have been examined as complementary to antipsychotics to improve the functional outcome of schizophrenia. Amongst the physical mind-body therapies, yoga is promising. Yoga, as the name suggests, connects the mind and the body to achieve equilibrium. This is brought about by practicing "asanas" (physical postures), "pranayama" (breathing exercises), spiritual and ethical lifestyle, as well as meditation. Yoga has gained a prominent role as a complimentary treatment in medical conditions. Though the interest of yoga as a treatment for psychiatric disorders is recent, several studies in the past decade have indicated the feasibility, efficacy, and safety of yoga in treatment of schizophrenia. In this chapter, we will selectively review the application of yoga for treatment of schizophrenia and its effect on outcome of schizophrenia.

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Yoga as Treatment

Yoga as treatment for schizophrenia is examined in three major areas based on the following rationale. First, despite advances in the pharmacological treatment of schizophrenia, a considerable proportion of patients are resistant to available medications and continue to be symptomatic. Second, side effects of treatment are a reason of distress, as antipsychotics are associated with metabolic, neurological, and endocrine side effects. Yoga is beneficial in correcting metabolic, neurological, and endocrine abnormalities in nonpsychiatric conditions. Third, the efficacy of available medication on negative and cognitive symptoms of schizophrenia is limited.

Both open-label trials and randomized controlled trials have been conducted to examine the efficacy of yoga as treatment in schizophrenia. These studies examined the effect of yoga in comparison to treatment as usual or in comparison with physical exercise. All studies included asanas (yoga postures), breath control, and meditation/relaxation. Importantly, all studies suggested feasibility of yoga practice by patients with schizophrenia without any serious adverse events. In one of the first studies, outpatients were randomized to receive yoga or physical exercise for 12 sessions from an instructor and were advised to continue at home. At the end of 4 months, there was a significant benefit in negative symptoms, with minor change in positive symptoms, possibly because they were already treated and had minimal score for improvement [2]. In a similar randomized controlled study, but with an additional group of "wait-listed" subjects, these results were replicated with significant improvement in negative symptoms [3]. Later, patients in the wait-list group after 1 month of yoga therapy had improvement in negative symptoms, providing further evidence to the efficacy of yoga in the treatment of negative symptoms. These two studies examined stabilized outpatients with minimal positive symptoms. The effect of short-term yoga module was examined in inpatients with acute (first episode) psychosis, including schizophrenia. Like earlier studies, patients were randomized to receive yoga or physical exercise. At the end of 2 weeks, both groups had comparable reductions in symptom scores [4]. By 6 weeks, the yoga group had lower severity scores on clinical global impression.

Studies from other countries also have suggested the beneficial effect of yoga in the treatment of schizophrenia. Significant improvement in quality of life has been reported by two studies following add-on yoga compared to treatment as usual with antipsychotics [5, 6]. A considerable heterogeneity was present in the patients as regards symptom severity and stage of the illness, hence making comparison between studies difficult. Put together, studies consistently reported improvement in quality of life, negative symptoms, cognitive symptoms, and social functioning with yoga treatment. The effect on positive symptoms and negative symptoms was varied, possibly due to differences in study methodology and study population. A meta-analysis by Cramer and colleagues examined the pooled differences between yoga therapy and treatment as usual or physical exercise using five randomized controlled trials. The meta-analysis suggested moderate effect of yoga on quality of life compared to treatment as usual [7].

Schizophrenia patients demonstrate deficits in several domains of cognition, including working memory, attention, processing speed, and social cognition. Cognitive deficits appear before the onset of other clinical symptoms of schizophrenia and respond poorly to antipsychotics. Several studies have demonstrated that cognitive deficits are important predictors of functional outcome and may play a greater role than clinical symptoms. Yoga therapy, targeting cognition in schizophrenia, involves postures (asanas) and suryanamaskara, breathing exercises (pranayama), nasal cleansing (jal neti), Sithilikarana Vyayama, and relaxation techniques. The results from these studies demonstrated a significant improvement in various domains of cognitive functioning, including attention, memory, and working memory, with a moderate effect size [8, 9]. The study by Bhatia and colleagues even demonstrated maintenance of improvement during follow-up (6 months), indicating sustained improvement.

Deficits in social cognition are increasingly being recognized as an important predictor of functional outcome of schizophrenia. Two studies have examined the effect of yoga on emotion recognition in schizophrenia. Patients on stable antipsychotics, when given yoga therapy, showed a significant improvement in emotion recognition tasks and socio-occupational functioning, which persisted up to 4 months follow-up [10, 11].

A pilot study examined the role of yoga and exercise in combating stress and anxiety in schizophrenia [12]. A single 30-minute yoga session, consisting of warming up exercises, abdominal breathing exercise, asanas, and relaxation exercise, was administered. Results indicated significant improvement in state anxiety and psychological stress. Patients also reported increased subjective well-being compared to the control group.

Postural instability and consequent falls and fractures are a major concern in elderly patients with schizophrenia. One study has examined the impact of yoga on postural stability in schizophrenia patients in a single-blinded RCT and reported significant beneficial effect of yoga on postural stability in schizophrenia patients which lasted for nearly 8 weeks even after stopping the yoga sessions, suggesting sustained benefits [13]. Considering the chronic nature of schizophrenia, the burden on caregivers is significant. Efficacy of yoga therapy in caregivers of outpatients with psychosis was examined in a randomized, wait-list controlled study. Caregivers reported significant decrease in burden and improvement in quality of life in the absence of significant change in anxiety or depression [14].

Potential Biological Mechanisms

The mechanisms through which yoga brings changes are yet to be understood. Different mechanisms have been proposed:

(a) In a study examining the effect of yoga on social cognition in schizophrenia, there was increase in oxytocin level in patients receiving yoga but not in the wait-list group. There was also significant improvement in facial emotion recognition after yoga therapy. Considering the critical role of oxytocin in the human social behavior and reproductive functions, it is possible that one of the consequences of regular yoga practice is elevated oxytocin that may mediate prosocial behavior [11].

(b) Neuroplasticity mediated by brain-derived neurotrophic factor (BDNF) is another possibility. A previous study has shown elevation of BDNF after regular yoga treatment in patients with depression but not in those with irregular practice. It is possible that BDNF elevation could be one of the mechanisms for improvement in schizophrenia as well.

(c) Several studies have reported decrease in cortisol levels after yoga practice. In the same way, decrease in tumor necrosis factor-alpha levels has also been reported. These immune markers are altered by stress with deleterious effect on the hippocampus and other structures. Interestingly, another study examining the effects of yoga in elderly individuals showed 6-month yoga practice to increase hippocampal size [15]. Considering the crucial role of hippocampus in schizophrenia, it is possible that yoga may mediate the effects through changes in hippocampus.

(d) As yoga and meditation techniques are shown to strengthen the medial prefrontal networks involved in mentalization, changes in mirror neuron systems leading to better social connectedness have also been proposed [16]. Put together, both bottom-up and top-down changes following yoga have been proposed as a heuristic model for mechanism of action of yoga [17].

Limitations of Yoga Research and Challenges

While these initial studies suggest the efficacy of yoga in treating the negative and cognitive symptoms of schizophrenia and improving quality of life, postural stability, and functional outcome, application of yoga therapy in schizophrenia is

still in its preliminary stages. Despite the initial results and widely practiced by the general population, yoga is not commonly used by psychiatrists as treatment for schizophrenia. Few limitations of the existing literature need to be considered. First, the sample size in the available trials is small, and there has not been a multicentric randomized trial with a substantial number of subjects to examine the efficacy of yoga in schizophrenia. Second, absence of blinding the subjects is another important challenge. As in other body-mind treatments or psychotherapy, blinding the subjects for treatment received is not possible in yoga trials. In the absence of objective markers for improvement or potential mechanism, it is hard to factor out the expectation bias in these trials. Using blinded raters for assessment is a crucial step to be followed in future trials to prevent the rater bias. Third, considering the absence of negative studies, one needs to be cautious whether a reporting bias is present. It is essential to report negative trials if any.

Conclusions and Future Directions

Yoga, added on to ongoing treatment, is a promising, effective, and safe strategy in schizophrenia treatment. The studies examining the efficacy of yoga in treatment outcome in schizophrenia have mainly used "asana," "pranayama," and "relaxation techniques," which are relatively simple and easy to follow. The results of these studies in schizophrenia demonstrate improvement in negative symptoms, cognitive symptoms including social cognition, and postural stability, as well as improvement in socio-occupational functioning and quality of life. Although the current reports are promising, there is a need for more evidence in a larger sample with a standardized and uniform methodology, preferably using a multicentric design. In addition, the potential mechanisms underlying the improvement of symptoms in schizophrenia need to be elucidated. Studies elucidating the neurobiological correlates of yoga in schizophrenia may employ a wider range of techniques like MRI, functional near-infrared spectroscopy (fNIRS), measuring neuroplasticity markers like BDNF, etc. With better scientific evidence, yoga therapy can find wider acceptance and could help to improve the outcome of patients suffering from schizophrenia.

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Psycho-Education in Schizophrenia

24

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Introduction

Schizophrenia is a chronic psychiatric disorder in which a person's perception, thoughts, emotional responsiveness, and behaviour are significantly altered. The symptoms in schizophrenia are usually divided into "positive symptoms", which include hallucinations and delusions, and "negative symptoms", such as emotional apathy, lack of drive, poverty of speech, social withdrawal, and self-neglect. The symptoms vary from person to person, and each person has a unique set of symptoms and experiences [1].

Schizophrenia usually begins in adolescence with a prodromal period characterised by some deterioration in personal functioning. These may include a transient episode of psychotic symptoms, memory and concentration problems, unusual behaviour and ideas, disturbed communication and affect, and social withdrawal, apathy, and reduced interest in daily activities. This prodromal period is followed by an overt episode marked by hallucinations, delusions, and behavioural disturbances.

Classically the course of schizophrenia is of exacerbations and remissions, with subsequent psychotic episodes in which the patient is unable to achieve complete remission. During cycles of exacerbations and relative remission, patients often deteriorate and reach a plateau stage with persistent symptoms and functional disability and occasional symptom exacerbations [1].

Although this is the common pattern, the course of schizophrenia varies considerably. Some people may have positive symptoms very briefly; others may experience them for many years. Others have no prodromal period, the disorder beginning suddenly with an acute episode.

The chronic and deteriorating course of the illness may have a major impact on daily routine, quality of life, and functionality of the patient. Thus, patients need systematic and long-term support in order to be able to cope with everyday life.

The optimal treatment of schizophrenia patients requires both medical and psychosocial treatments and has to be planned keeping in mind the individual needs of the patients and their families. The combined approach is more effective in targeting all areas of the patient's illness and

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functionality rather than a single therapy-based approach. In the combined approach, psycho-education invariably comes into the picture as an adjunctive psychotherapy [2].

Benefits of Psycho-Education

Psycho-education has emerged as an effective treatment which can improve the level of understanding of people about schizophrenia, and thus ensuring active participation of both the patients and their caregivers in the treatment.

According to the guidelines of the American Psychiatric Association (APA) [3] and the DGPPN (German Society for Psychiatry, Psychotherapy and Neurology), psycho-educational interventions belong to a standard therapy programme in acute and post-acute phases of patients with schizophrenia [4]. In the Cochrane analysis, it was found that psycho-education was accompanied by a higher level of compliance, lower rate of relapse, and improved psychopathological status [5].

There is evidence supporting the fact that psycho-education of the patients with schizophrenia improves understanding of the illness, betters the quality of life, improves compliance with medications, and can reduce relapse rates [6]. Psycho-education is also an effective intervention in order to reduce rehospitalisation, the cost into the illness, and substantial human suffering in schizophrenia [6].

In a literature review, it was observed that patients suffering from schizophrenia who were part of an educational intervention gained benefits that included "improved compliance with the medication regimen, lower relapse rate, longer participation in aftercare programmes, improved social functioning and quality of life, decreased negative symptoms, improved insight into illness, improved skills acquisition, improved attitudes toward medication intake, and a better understanding of mental illness" [7].

In another randomised controlled study by the same authors, patients with schizophrenia were delivered an educational programme intervention. The educational intervention included topics on diagnosis, prevalence, course, causes, prognosis, medication management, non-medical treatments, stress factors, community resources, substance abuse, and legal issues related to schizophrenia. It was found that there was a significant improvement in knowledge about schizophrenia and illness insight and a significant decrease in negative cognitions about medication intake [7].

There is also a growing evidence for community-based interventions for patients with schizophrenia where family members would be actively involved in the care and rehabilitation of these patients [8].

Over the course of treatment guidelines in schizophrenia, evidence has emerged for the need for education, guidance, and support for the family members regarding the illness [9]. And a variety of interventions referred to as "family psycho-education" programmes have been developed and practised all over the world in schizophrenia rehabilitation programmes [10].

It has been observed that integrating family members of patients with schizophrenia into psycho-educational groups or family interventions reduces re-hospitalisation rates within 2 years by 20% [11], and it also helps in reduction of costs to the health system and expenditure on the illness, and thereby substantial suffering of people with schizophrenia and their families could be avoided.

In a study conducted over a period of 2 years involving 106 patients and their families, family psycho-education showed to have reduced relapse rates when it was combined with standard treatments for schizophrenia. The patients whose families received psycho-education had lower expressed emotion scores and did better at a society level and employment level at the end of 2 years [12]. Thus family psycho-education is effective in reducing patient relapse and enhancing the outcomes of rehabilitation process for patients with schizophrenia [13].

Family psycho-education is a strongly supported evidence-based practice in the treatment of schizophrenia [14–16]. Psycho-education for the families of patients with schizophrenia can reduce the relapse rates [12, 17], positively

influence the course of the illness [18], and help the families and patients to better cope with the illness [6].

Definition of Psycho-Education

The term "psycho-education" was first used to describe a behavioural therapeutic concept consisting of four elements: (1) briefing the patients about their illness, (2) problem-solving training, (3) communication training, (4) and self-assertiveness training, in which relatives were also included [19].

Bäuml et al. [20] defined psycho-education as *systematic*, *structured*, *didactic information on the illness and its treatment*, *and includes integrating emotional aspects in order to enable patients—as well as family member—to cope with the illness*.

Psycho-education is also defined as the "process of teaching clients with mental illness and their family members about the nature of the illness, including its aetiology, progression, consequences, prognosis, treatment and alternatives" [21].

Mechanisms

There can be various reasons for the success of a psycho-educational intervention. It was found that the psycho-educational interventions enhance the participants' sense of dignity and self-esteem, which in turn is due to the importance to self-management skills improving the self-care and increased trust on his or her own skills [22].

Psycho-education is effective because it increases an individual's resilience to stresses, coping skills, manageability, ability to comprehend life, and the level of their individual life meaning [23, 24].

Another mechanism described for the success of psycho-education is based on a tripod model comprising regularisation in lifestyle and sticking to healthy habits, early detection of warning signs, and treatment compliance [25].

One widely accepted concept is the creation of a positive cycle involving treatment and rehabilitation. Adhering to the treatment regime allows an individual to take part in psycho-educational programmes, which may in turn improve their insight into the mental illness and its treatment, thereby further facilitating the treatment regime adherence [24].

Models of Psycho-Education

Family Psycho-Education

The family psycho-education model focuses on developing a connection with the family, educating about the illness, and support and crisis management in the rehabilitation process [26]. In a 2-year study involving 106 patients, family psycho-education has proven to reduce relapse rates when it was combined with standard treatments. The patients and families who received psycho-education had lower expressed emotion scores, performed better at the employment level, and did better at a society level at the end of 2 years [12]. Thus family psycho-education is effective in reducing patient relapse and enhancing the outcomes of vocational rehabilitation for patients with schizophrenia [13].

According to the *Schizophrenia Patient Outcomes Research Team* (*SPORT*) *Updated Treatment Recommendations for 2009*, patients with schizophrenia who have ongoing contact with their families should receive a family intervention that lasts at least 6–9 months [27]. Interventions lasting 6–9 months significantly reduce relapse and re-hospitalisation. The family members also have lower levels of burden and distress and have improved family relationships.

Key components of family interventions include education into the illness, crisis management, emotional support, and training in coping skills towards illness symptoms and related problems. The selection of a family intervention should be after a collective decision amongst the patient, family, and treating doctor.

For those whom a longer intervention is not feasible or acceptable, a family intervention that

is shorter than 6 months, but is at least four sessions in length, should be offered to patients who are in contact with their families. Components of the brief intervention include focus on education, training, and support. Patients have various benefits that include reduction in the symptomatology, better compliance to medications, improved functional and occupational status, and increased satisfaction with the treatment. Positive family outcomes include reduced family burden and increased satisfaction with family relationships [27].

This psycho-educational model also includes home visits to hold family meetings, providing thorough daylong workshops for families, and conducting seminars for coping strategies for the family and significant others involved in the life of a person dealing with schizophrenia. The purpose of these meetings is to help the family understand schizophrenia as a biologically driven entity and to refrain from blaming or criticizing the affected person. It also promotes special care towards the family member who is most often involved in overseeing the daily life of the schizophrenia patient to avoid caregiver burnout [28].

Behavioural Family Management Model

This is a family-based approach that involves illness education, structured training in problem-solving, and importance of effective communication within the family [29].

In this model, maximum importance is given to the family, and family is viewed as the most important resource for community rehabilitation of schizophrenic patients. As per this model, healthy functioning can be achieved by teaching positive coping mechanisms. Positive coping mechanisms can act as a buffer against the negative effects of environmental stresses and also can help family members plan and devise various tasks necessary for rehabilitation and care of the patient. The behavioural family management model also seeks to better the coping skills of family members through implementing efficient family problem-solving skills [2].

In behavioural family management, the active phase of intervention typically lasts 1–2 years, and sessions are conducted within the home to increase accessibility, treatment adherence, and generalisation of skills [30].

In one of the studies using this model, 36 patients and their families were assigned to behavioural family management or a supportive individual therapy condition. After 9 months, 6% of behavioural family management patients had relapsed compared with 44% who were treated individually [31]. The behavioural family management group also showed lower relapse rates and lower hospitalisation days in a 2-year follow-up [31]. In a number of research studies, behavioural family management has been found to impact important patient outcomes (reduced relapse rates, improved symptoms) and improve family member knowledge and well-being [32, 33].

Psycho-Educational Multifamily Groups

This model of psycho-education was developed by William McFarlane. The aim of this model is to engage families in the rehabilitation and aftercare programmes of schizophrenia. The model acknowledges the chronic nature of schizophrenia and aids in the rehabilitation process by creating a long-term working partnership with the families. This model strives to help the patient and family in accepting and understanding the disease, as well as developing social support systems for the reduction of confusion, anxiety, and weariness in the patient's family, while they learn adaptive strategies [17].

The core of the model is the multifamily group that the patient and family members join and attend, with group sessions that focus on enhancing problem-solving and coping skills. The group is structured to provide a support network for the patients and family members [34]. Controlled research studies have indicated that the programme significantly reduces relapse rates and improves the functioning of patients with schizophrenia [35, 36].

The sessions could comprise as few as two families or as many as ten. The advantages of multifamily groups are that it enhances the support elements for families, removes the shame in having a family member who has schizophrenia, aids in cross-family learning by allowing a family to see and learn from other families in the group, is a platform for broader exchange of knowledge and coping strategies, and counters the isolation that the family suffers for having to care for a schizophrenic patient [37].

In a study where this model was used in an outpatient group, 63 outpatients with schizophrenia were randomised to receive either standard care or multiple family group psycho-education at a large community mental health centre. Amongst the 42 patients who completed 1 year of the study, the multiple-family group treatment was found to significantly reduce levels of negative symptoms, compared with standard care [38].

Peer-to-Peer Psycho-Education Approach

The rationale of this approach is that people who had the problem earlier could empathise the problem of people who have recently developed that problem in much better manner than those people who never had it. In peer-to-peer psycho-education programme, schizophrenic patients are given the access to mix with the patients who were diagnosed to have schizophrenia but have recovered significantly. These people can motivate the patients to a considerable extent and provide them a new ray of hope [39].

It is stated that individuals can gain information about their illness by interacting with and listening to their peers. The mechanism for the benefits obtained in such a programme is due to non-specific treatment effects rather than any specific applied learning theories. These non-specific treatment effects include participant expectations, motivation to participate, the level of interpersonal assistance from study peers, participant promotion to express and validate their stress and questions, the presence of positive peer role models, being part of a cohesive group, and being able to realise that they were not alone in their experience of the illness [17]. In one of the studies, Rummel et al. [40] proposed a five-step psycho-education programme in which they trained individuals with schizophrenia or schizoaffective disorder to deliver psycho-education to their peers. They found the results of such an education programme comparable to professionally lead psycho-education. They attributed the effectiveness of their delivery of psycho-education to the same advantages of that of peer-to-peer interactions mentioned above; they particularly emphasised the peer instructor's trustworthiness with their peers and their function as a role model [40].

The Skill Training Model

Social dysfunction is a defining characteristic of schizophrenia. People with this illness have difficulty in attaining social roles and have difficulty fulfilling their own needs when social interaction is needed. Social dysfunction plays an important role in the course and outcome of the illness. Social skill deficits are very common with schizophrenia and tend to be relatively stable over time. These deficits are also difficult to manage with pharmacotherapy, which is not surprising because social dysfunction results from failure to learn important skills in childhood and early adulthood, social isolation and withdrawal, and environmental stressors, rather than from distinct changes in neurotransmitter systems [41].

The model also hypothesises that skill deficits can be corrected with a structured behavioural intervention called social skills training (SST). It is based on social learning principles and highlights the role of behavioural rehearsal in skill development.

The primary method of SST is through role play. The trainer first instructs on how to perform a skill and then models it to demonstrate how it is performed. After identifying a social situation in which the skill might be used, the patient engages in a role play with the trainer. This is followed by feedback, positive reinforcement, and suggestions to better the response. This sequence

is repeated until the patient can perform the response adequately. Social skills training is conducted in small groups (six to eight patients), in which case patients can perform role playing amongst themselves under the guidance of the trainer and provide feedback and reinforcement to one another. The content of training programmes is individualised and organised into a curricula, for example, how to use a telephone to make an appointment, medication management skills, or job interview skills. The duration of the training can be as few as four to eight sessions and sometimes up to 6 months to 2 years for a comprehensive programme including conversation skills, how to make friends, requesting help, and managing problems in group living situations. Typically the training sessions are held three to five times a week. To aid in the training, sizeable use of audio-visual aids and instructions in handouts and flip charts or on whiteboards are widely advocated. The material is given in small sections, and there are frequent practice sessions before engaging in actual role play [41].

The *Schizophrenia Patient Outcomes Research Team* (*SPORT*) *Updated Treatment Recommendations 2009* recommends social skills training to all individuals with schizophrenia who have deficits in the skills needed for everyday activities in order to help them in social interactions, independent living, and other outcomes relevant to community functioning [27].

Mindfulness-Based Intervention Model

Described as one of the newer methods to help schizophrenia patients, mindfulness-based interventions are gaining significant interest as an intervention for patients who have low adherence to treatment or are only partially responsive to standard treatment and/or psychosocial interventions [42]. Intervention using mindfulness principles helps the patient to develop cognitive changes and higher acceptance about the illness and to focus on the present and, most importantly, offers relief from symptom-related distress and anxiety [43].

In a recent controlled trial, the effectiveness of five-session mindfulness followed by home practices for 11 schizophrenia sufferers was tested, and improvement was noted on subjective well-being (mindfulness), severity of psychotic symptoms, and life functioning immediately after intervention [44].

Recent controlled trials also suggest that the standardised mindfulness-based stress reduction (MBSR) programmes improve patient self-care, symptom management, and insight into the illness and help overcome the distressing thoughts in depressive and anxious conditions [45, 46].

It is stated that the positive effects of mindfulness programmes could be viewed in terms of reduced ruminative thinking and improvements in awareness about and clarity in describing psychiatric symptoms, which in turn might lead to reduction in the negative thoughts and depressive or anxiety reactions [47]. With the growing evidence about mindfulness-based interventions in schizophrenia, future research on the subject has to be focused on integrating mindfulness-based intervention with the other psycho-educational programmes in practice to further strengthen the evidence on mindfulness and its inclusion as a routine practice in management of schizophrenia.

Use of Films for Psycho-Education in Schizophrenia

Audio-visual techniques have long been used as a successful aid to psycho-education in schizophrenia. The use of films in educating patients about schizophrenia can serve as a cost-effective and time-efficient approach. In a recent study, six films of about 17 minutes each in length were used as a psycho-educative programme which was found to be well received by the patients. The findings included positive effects on knowledge about the illness, compliance to treatment, insight into the illness, and quality of life after the use of films. Psycho-education with the use of such films could be a valuable tool, especially in hospitals with a limited staff. The treatment could begin at the hospital setting and can be continued to the home-based setup with review-

ing the films time and again. It would serve as a good medium to educate the family members also, even when they are not enrolled in a specific intervention programme. This method also adds a versatility dimension to the already existing psycho-education models, especially with scarcity of resources. However, the findings of the above-mentioned study need to be confirmed by future research and tested against a suitable control group, as future research is needed to focus on the effectiveness of such a programme comparable to other methods, such as standard group psycho-education led by an expert or a peer [48].

Team Approach in Schizophrenia

The model of team approach is very important in achieving an adequate outcome in schizophrenia treatment. Due to the busy practice, most clinicians would face the difficulty in striking a balance between several aspects of treatment for schizophrenia such as initial rapport establishment, investigations, providing psycho-education, rationalising the pharmacotherapy to suit individual needs, and also arranging follow-ups. Various team approaches already in practice are collaborations with professional colleagues like clinical psychologists and psychiatry social work professionals. A newer model of a team approach that can help in countering the above-mentioned issues is using assistance from the pharmacist. Clinical pharmacists have training and expertise in various medicine-related matters and can assist in the treatment of an illness like schizophrenia where comorbid medical conditions are common and the use of polypharmacy is unavoidable. The patients of schizophrenia face significant difficulty with the use of medications, due to the cognitive impairment of schizophrenia and poor insight into the illness. Pharmacists with appropriate training can assist clinicians in safe and effective practice in the management of schizophrenia. An example of one such collaboration is between the departments of clinical pharmacy and psychiatry where a special counter has been set up in the psychiatry outpatient department at JSS Hospital, Mysore, India. The objectives of this collaborative initiative, "JSS MINDS" (Medication Information for Neuropsychiatric Disorders and Sensitization), are to provide information and education to patients on the safe use of medication, improve adherence, and also provide telephonic reminders on follow-up visits through a dedicated phone number. Since the start of the programme, 700 patients have received the service, and 75% of them sustained follow-up and scheduled their next visit, confirming their satisfaction and benefits such as good compliance and better treatment outcomes [49].

Undergraduate Training Model as a Psycho-Education Tool

Mental health in Southeast Asian countries has a lacuna due to the lack of awareness amongst the public about psychiatric illness and also inefficient training in psychiatry for medical undergraduates [50].

A significant number of undergraduates in health care of a country are inadequately trained to diagnose, educate, and manage various psychiatric illnesses. Training of undergraduates in the field of psychiatry can enhance the manpower in countries that already lack trained professionals dealing with psychiatric illnesses. At various levels, the services of the undergraduates who have been trained in diagnosing and managing the illness can be utilised in psycho-education of schizophrenia patients and their families. Training of such undergraduates has to be done with the collaboration of various bodies including the psychiatry society of the country, the medical council, various health-care universities, and the psychiatry departments of various colleges and hospitals. This can only be achieved with the help of each faculty and the department as a team, where they have to use their knowledge and passion in delivering psychiatric training to these students, which can then be further utilised in psycho-education of patients.

There can be various ways to improve such training and incorporate this model at each level in the management of schizophrenia. This can

be achieved in ways like changing the curriculum for undergraduates, incorporating compulsory training in psychiatry, creating various programmes like CMEs at undergraduate level focused on training in psychiatry, using innovative methods like awards to promote psychiatry training, launching exclusive journals for undergraduates, etc.

This focused training for undergraduates is going to go a long way in helping already overburdened mental health professionals and can be a valuable tool in psycho-education of various psychiatric illness, especially schizophrenia [50].

Psycho-Education Using Digital and Advanced Technology

Technology today is an integral part of our day-to-day life. Technology makes the world a new and better place. The advancement in technology and its use in various medical specialities have been well observed over the years. Psychiatry is a speciality of medicine where the use of digital and advanced technology in the management of patients is still finding its roots. Due to the lack of awareness about psychiatric illness, there is a delay in early identification and intervention, leading to significant mortality and morbidity. This leads us to focus our attention as to how the awareness about the illness can be improved using the technology-based resources available, especially in areas with fewer tertiary care centres and lack of psychiatry care facilities. In a retrospective study done at JSS Hospital in Mysore, India, Google maps were used to locate the patients who were admitted under the psychiatry department, and the results were assessed. The patient addresses were marked on Google maps to the exact location shown by the Google maps search. The results showed certain areas with high density of patients who had visited the psychiatry department for consultation. These high-density areas suggest the need and the high potential for spreading psycho-education in these areas. Following this, various community-based psycho-education programmes were conducted in these areas, including distributing public awareness newsletters and conducting street plays, etc. It is interesting to point out how a simple Web-based technology which is used by us in day-to-day life was used to locate the patients and psycho-educate them. This newer, simple, and accessible model of psycho-education can have a wide range of implications from prevention, early diagnosis, and early intervention and also follow-up and adherence to treatment in schizophrenia and should be considered for use along with other well-established psycho-education programmes [51].

Conclusion

Psycho-education is a bio-psychosocial programme that helps schizophrenia patients and their families initially by helping the traumatised family to stabilise and providing the initial knowledge about the illness. Psycho-education aims at working with the family as a team in the management of schizophrenia. The emphasis of psycho-education is to improve the quality of life of the patient as well as the caretakers, along with various means to keep the symptoms in check. This is achieved by various methods like crisis management, emotional support, training in coping skills orientation toward illness symptoms and related problems, improving treatment adherence, improving functional and occupational status, social skills training, problem-solving skills, etc.

There is sufficient literature that has shown the efficacy and effectiveness of various psycho-educational programmes. Each programme has its own unique benefits, and it is important that psycho-education be individualised or tailor-made for each patient and their families considering the stage of the illness, severity of symptoms, social and demographic factors, and cultural beliefs so the programme suits them and they receive maximum benefits from it.

Psycho-education is by no means a replacement to pharmacotherapy, cognitive behavioural therapy, or other forms of psychotherapy in general. On the contrary, psycho-education should be considered as a tool to enhance the effectiveness

of other forms of therapies such that the patients and their families are in a position to understand the illness, recognise the problem areas, and choose the form of treatment optimal for the management of schizophrenia.

Emphasis has to be given to optimise the use of various psycho-educational programmes and the use of technology to reach out to patients and routinely include them in the management of all patients diagnosed to have schizophrenia. Future directions include promotion of newer and innovative methods in psycho-education and utilisation of all the available resources to better the psycho-education in management of schizophrenia.

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Part VI

Clinical Practice

25 Transitioning from Hospital-Based Care to Community-Based Models of Care

Jatinder Takhar and Esther Vander Hyden

Introduction

Historically, models of collaboration have been based on certain fundamental principles such as common purpose, open communication, paradigm, location of service, business management, and relationships. While relationships remain central to the concept of the model, sharing of care among the different disciplines is the core element that promotes optimum treatments to improve care and satisfaction with the service.

This chapter will introduce readers to the shared-care concept, with some background and description of different models of shared care that exist nationally, internationally, and locally for people with serious mental illness (SMI). The authors will use examples of successful implementation of these renowned models within the context of patient-centeredness. The authors will further describe the process of care/referral, roles of each player within the context of this model, services within these models, and case examples within the model, strengths, challenges, and the future. Although the discussion will focus largely on relevant experience in Ontario, experience from other jurisdictions will be noted.

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Background: Collaborative Care of Patients with Psychiatric Disorders

Dating back to the 1970s, there has been recognition of the need for a closer working relationship between psychiatrists and primary care physicians in the management of patients with psychiatric disorders within collaborative care models. The reasons for this are varied and numerous; but central among them is the issue of health service resources, including their costs and the number of psychiatrists available to provide them. Another reason is that, traditionally, up to 80% of patients with psychiatric disorders have their conditions diagnosed and managed by primary care physicians [1]. Consequently, a variety of collaborative care systems—in which psychiatrists not only provide consultation services but also directly interact with primary physicians in a variety of contexts—have been set up in countries worldwide, including the United States [2], the United Kingdom [3, 4], Germany [5], Portugal [6], Israel [7], and Australia [8–11].

Family practice service delivery models have definite strengths for managing individuals with serious mental illness (SMI) including accessibility, lack of associated stigma, possibility

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for long-term continuity of care, sensitivity to community and family issues, and the ability to provide integrated management of multiple problems. Unfortunately, they frequently consider themselves under-prepared to treat the more severe mental health problems [12]. Furthermore, they also feel inadequately supported by the health-care system in this role, with problems involving communication and other issues being consistently reported in the relationships between family physicians and psychiatrists (for more on this, go to http://www.cpa-apc/prg/Professiona/shared_care.pdf). Thus it becomes difficult to establish and maintain continuity of care, collaborative planning, and a holistic approach. The resulting undertreatment of mental illness has a significant impact on the individuals' functional abilities and health-care costs [13, 14].

The concept of shared mental health care, in which primary care physicians, psychiatrists, and allied mental health providers form part of a single mental health-care delivery system, was developed as a result of several issues. These are as follows: (a) the dissatisfaction experienced by patients, family members, family physicians, and mental health service deliverers; (b) problems with accessibility to psychiatric expertise; and (c) political and economic efforts to reform the ways in which care is delivered [15–17].

The focal point in most collaborative care models is the patient. The care is truly patient-centered as it considers the patient's personal preferences, needs and values, family situations, and lifestyles. The model makes the patients and their families an integral part of the decision-making process [18].

An internationally recognized shared mental health-care model for SMI, the Consultation-Liaison in Primary-care Psychiatry (CLIPP) program, has been successfully implemented in Australia [8, 19, 20]. The CLIPP program involves collaboration in consultation, liaison, and continuing shared care and sets procedures to meet the needs of general practitioners, area mental health services (AMHS), and, thereby, those of patients and carers [21, 22].

In 1998, Meadows established a collaborative care program that included a component directed specifically at SMI individuals. This model provided consultation to patients referred by family physicians, but in addition also identified individuals with SMI who were being cared for in a traditional outpatient setting and who were stable for transfer to shared care. In this model, specially trained psychiatric nurses reviewed each patient's file, prepared a detailed summary and a treatment plan, and then arranged for a bridging meeting for the individual with SMI, the family physician, and the psychiatrist who would provide ongoing backup. SMIs were reviewed every 6–12 months by the psychiatrist, with the family physician monitoring their status in between. The advantages of this model are that it addresses concerns that shared care tends to focus on the less severely ill [23], it works actively to promote flow through the larger mental health system, and it is better integrated into that system.

Working Model

The first step involves transferring selected individuals with SMI from tertiary care mental health services into family practitioner-based collaborative care. A designated nurse associated with community mental health services actively identifies cases suitable for transfer and then engages with case managers and the psychiatrist to support prospective individuals with SMI for transfer. These individuals have some insight, are clinically stable, and have social supports. The model allows for onsite communication between primary care, psychiatry, and the individual with SMI in a least restrictive means with low stigma experience.

This above model requires completion of a referral form, demographic data instrument, and the Threshold Assessment Grid (TAG) [24] and assigns a baseline Global Assessment of Functioning (GAF) score [25] for each patient. The TAG is an instrument that is used to assess the severity of mental health problems in an individual along seven domains under three categories of risk, safety, and needs/disabilities. The nurse is responsible for identifying patients who are suitable for the clinical collaborative care program.

Once a referral is determined to be appropriate, the preparation for transition and subsequent discharge into primary care practice begins.

The collaborative care clinical services include both direct consultation and indirect services through the following venues:

1. *Direct consultation* involves providing a transfer summary and a relapse signature plan [8] to simplify long-term management of individuals with SMI. The patient is officially transferred to the family physician at a face-to-face transition meeting. The meeting is conducted at the primary care practice site with the psychiatrist, mental health nurse, and patient, with some of the family members in attendance. The mental health nurse is responsible for inviting family members. The family members provide support to the patient and assist with the collection of collateral information that may help with relapse prevention and adherence to treatment. The relapse signature plan provides an early-intervention strategy for the patients at high risk for relapse. The emphasis is on the total wellness of the patient, prevention of hospitalization, and maintaining community integration.

A nurse with specialized mental health training visits the family physician at intervals of 1–3 months, and the psychiatrist visits at intervals of 3–6 months. The contacts are increased or decreased in frequency depending on the patient's need. During the visits, the patient's progress is reviewed and documented by the collaborative team, and future management planning is done in a shared and collaborative manner; for example, the patient's symptoms, relapse signature list, and medications are reviewed. In between the visits, the family physician monitors the patient's overall health status and consults the psychiatry services when issues related to medication adjustments, emergence of symptoms, or additional support services are required. If access to other services is required, the nurse acts as the facilitator and assists the family physician and the patient in a timely manner.

2. *Indirect services* include telephone consultations with the psychiatrist and the mental health nurse, facilitation of access to community services, telephone support to the patient as required, and a review of the patient's documentation at the family physician's office. The concept of the model is based on patient-centeredness, community reintegration, and accessible support services [8, 26].

Collaborative Care Systems in Canada

There have been efforts to create similar collaborative care systems within Canada, dating back at least to 1982 [27]. The inception and advancement of these collaborative care efforts were pioneered by Dr. Nick Kates, who is now "Promoting Collaborative Care in Canada: The Canadian Collaborative Mental Health Initiative" (CCMHI) with his team [28]. This was funded through Health Canada's Primary Health Care Transitional Fund and comprises 12 national organizations. The CCMHI demonstrated the commitment to address collaborative mental health care nationally in Canada. They identified and described approximately 91 collaborative mental health-care initiatives through a needs analysis and created a toolkit for implementation of these programs across the country, for example, Pacific, Western, Central, Eastern, and Northern (Fig. 25.1) [29].

In Ontario, Canada, patients receiving intensive mental health services are frequently transferred back to their family physician because of the province's mental health-care reform. The goal of the reform is to develop comprehensive continuum of service supporting a seamless transition between hospital- and community-based care delivery. In addition to more efficient use of resources, better coordination of services, easy access, and community tenure [30, 31], it's been found that family physicians can be an important part of shared mental health-care models if systemic barriers such as poor communication, insufficient access to psychiatrists, and lack of continuity in mental health care are removed and collaborative practice is encouraged.

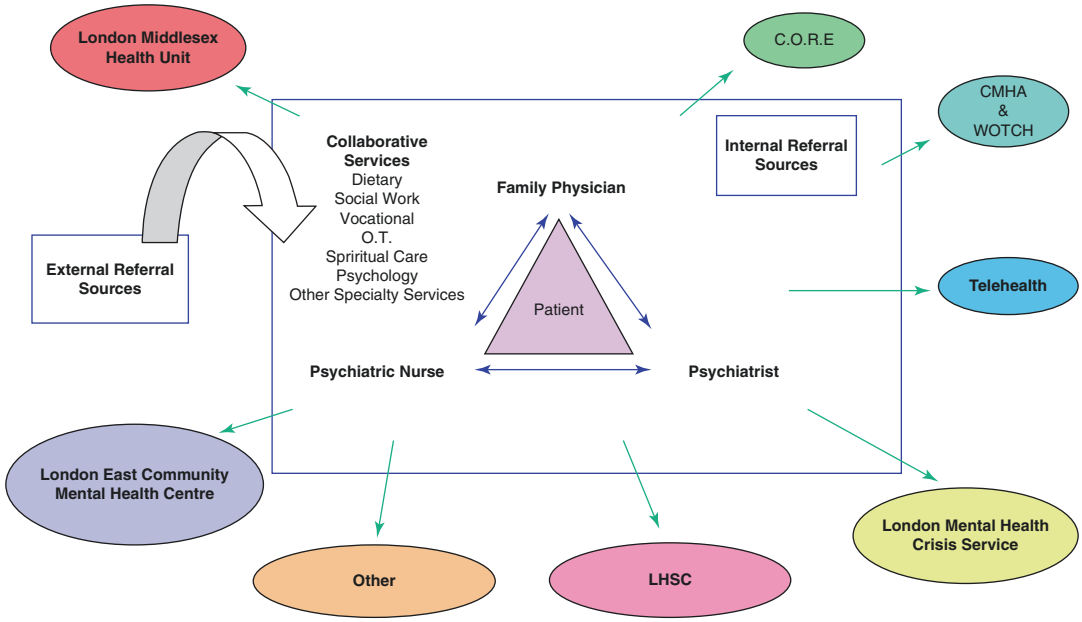

Fig. 25.1 Transition into primary care psychiatry model

The Canadian Psychiatric Association and the College of Family Physicians of Canada have identified shared mental health care as a solution to support both family physicians and psychiatrists, leading to better outcomes for patients.

Few formal definitions exist for this type of service, but the broadest characterization by Health Canada is "collaborative care requires a broad network of collaborative interactions among a variety of health service providers, patients, their families and caregivers, and the community, with patients being focal points and full-fledged partners of the overall effort" [32].

Despite both long-standing and recent interest in collaborative care, there is paucity in the literature on implementing patient-centered care within these models from the patient's perspective [27].

National and International Collaborative Care Models

Most national and international collaborative care models involve a team-based approach. The few models that exist for the SMI group of patients [26, 33–35] involve a team consisting of a mental health nurse with expertise in psychiatry and a psychiatrist, following each person during the transition. Services in the community (e.g., crisis intervention, psychoeducation, short-term psychotherapy, brokerage case management through the Canadian Mental Health Association, vocational and occupational rehabilitation services) may also be utilized based on the needs of the patient.

The role of the family physician in caring for the SMI group is an important one, but it remains ill-defined. The following is an example of a local model that has been implemented out of a tertiary care facility.

The TIPP Model

The Transition into Primary-care Psychiatry (TIPP) program is a working example of Ontario mental health care reform, which was developed to enhance the collaborative relationship between family practitioners and psychiatrists (see Fig. 25.1).

Its primary goal has been to streamline patients' access to mental health care by encour-

aging shared care models for patients with multiple service needs [33]. A modified version of Australia's Consultation-Liaison in Primary-care Psychiatry (CLIPP) model [26] TIPP is a "stepping down" service that facilitates the transition from tertiary or ambulatory care to care provided by a primary care physician for patients recovering from episodic or other types of mental health illness [33]. Patients can be enrolled in TIPP services if they have stable but persistent and/or SMI and have maintained a period of wellness, as demonstrated by no requirement for significant medication adjustment or hospital-based care over the preceding year.

The TIPP team consists of the patient, the family physician, the psychiatrist, the nurse with mental health experience, and other community services available if needed. Ideally, service initiates with a face-to-face meeting of the entire team; the nurse and psychiatrist typically visit the family physician every 1–3 months and every 3–6 months, respectively, to discuss the patient's progress and to plan future management strategies. This frequency can be increased or decreased depending upon the patient's level of well-being. Between meetings, the family physician monitors and evaluates the patient's quality of life, symptoms, function, illness severity, and perceived need of care, in addition to the team's level of satisfaction with service delivery [33].

Approaches Within the Context of TIPP for Patients

The authors provide some real case-based examples of how this model strives toward a patient-centered focus:

Managing the Patient with the Least Restrictive Means

Case 1 (MF) is a 62-year-old woman who has been married three times in the past.

The marital difficulties resulted from the emotional abuse that MF was subjected to during her marriages. She has three children ages 48, 46, and 43. The relationship with her daughter is very close, while with her sons, it is dynamically turbulent. She is supported by the Canada Pension Plan (CPP), inheritance, and alimony; lives independently in the community; and is socially well engaged with the church and community agencies. She possesses excellent social skills.

Her diagnosis has been bipolar mood disorder over the years. There is a significant family history of psychiatric illness. She has had multiple admissions for this disorder in the past, but no suicidal attempts. The admissions have mostly been voluntary, and she was successfully treated and maintained in the community for a number of years.

The medical history revealed a series of transient ischemic attacks (TIAs) in the past, hypothyroid state, hypertension, and high lipid levels, for which she received optimum care with medications.

Upon being accepted into TIPP, her mental health care was assumed by her family doctor, with backup psychiatric services from the TIPP team. Her interepisodic functioning remained good, enabling her to work in several different volunteer positions. Her adherence to medications had been relatively good over the years.

In the fourth year of treatment, she became increasingly involved in church activities and the relationship of her family to this religious organization. She began to deteriorate slowly after this engagement with the church, as she "found God," became very religious, began to preach to others on the benefits of Christianity, and became suspicious of other religious denominations. Her symptoms included delusions of persecution, overvalued ideas of obtaining justice, and advocating on behalf of others with mental illness. She firmly believed that she was wrongly diagnosed and treated in the past. She thought it was just "a little stress." She made the choice to go off all the medications for a period of 8 months.

Several attempts were made to get her to comply with medications, such as change in pharmacy to reduce the paranoia, blister-packing the medications, having her consume the medication at another site with TIPP nurse present, or daily dispensing of the medications with the pharmacist. All of these attempts were unsuccessful, even with family engagement. Over time her mental status deteriorated to the point

of her having clear delusions about people tampering with the medications/food, and a thought disorder was evident. She became very demanding, belligerent, and intrusive. These symptoms impacted her excellent social graces and interpersonal style. Her mood became labile and irritable, while her speech increased in volume and tone. She became impolite toward the care team.

In our attempts to remain objective and person-centered, we complied with her wishes, and we attempted to obtain a second opinion from a senior psychiatrist. However, the patient gradually disengaged from the TIPP team and her family doctor. In order to intervene in the least intrusive means, we declared her incompetent as an outpatient with support from the substitute decision-maker. When this intervention failed, the team decided to admit her into hospital as an involuntary patient.

Once again to assist her in retaining dignity in the community and maintaining privacy, the TIPP nurse, along with Thames Valley Ambulance, worked collaboratively to ensure safety in transport to the emergency department as opposed to calling the police as the primary intervention. The TIPP nurse provided support and education regarding the process and remained with her in the emergency room until the next team was able to assume care. During this time, regular communication and updates were provided to the family doctor and her family.

Transition from Adolescent Services to Primary-Care Psychiatry

Case 2 (DT) is a 21-year-old single male who was referred to TIPP at age 18 years and is now living in the community with his mother. Past history dates back to age 12 years. The first symptoms noted were problems with behavior, academic delays, poor school attendance, short attention span, significant distractibility, and inability to complete assigned school work. An early elementary examination showed results consistent with attention-deficit hyperactivity disorder (ADHD), poor fine motor skills, and some language difficulties, and he was treated with stimulants. A few years later, symptoms of obsessive compulsive disorder emerged along with insomnia and paranoid and aggressive behaviors. Subsequently, a diagnosis of early-onset schizophrenia was made and treatment with antipsychotic agents initiated. He was unable to complete any schooling, but did some vocational training and worked part time in sheltered employment. On his first visit, he was noted to have difficulties with attention, memory, and information processing, consistent with an intellectual disability.

Over the years, the course of his illness was complicated by depressive episodes, suicidality, impulse control behaviors, and substance addiction. Care in the past included multiple antidepressants, antipsychotics, and benzodiazepines, but no mood-stabilizing agents. The diagnostic category was revised to schizoaffective disorder (mixed type) during adulthood. The addition of a mood-stabilizing agent assisted in gaining stability in his overall state (i.e., impulsivity, suicidality, mood instability) and adherence to follow-up appointments.

There was significant family history of psychiatric illnesses; his biological father suffered from depression and had attempted suicide. The mother as well has depression/substance abuse, while maternal uncle has schizophrenia.

The social/developmental context in which this young man was raised and lived in was chaotic. The family dynamics were complex. Further complicating the situation was his level of intellectual functioning, which had not been formally assessed. His development was delayed in terms of motor skills and academic performance, and his social adaptation was limited.

Care for this patient was approached with an emphasis on integration and adaptation to his needs. A formal comprehensive psychological assessment was facilitated to develop a plan for community integration, housing, social adaptation, and possible employment opportunities. Medication adjustments were made in consultation with his family doctor, mother of patient, and the patient, along with the TIPP nurse and psychiatrist so that a simplified balance of optimum care with greater concordance and minimal side effects could be instituted.

His goal of obtaining employment provided the opportunity to constructively address issues of hygiene, attire, attitude, and behavior. Graduation from vocational training promoted increased social exposure and prepared him for balancing the demands of working and his formerly neglected activities of daily living. He began to take pride in himself and his accomplishments. He remains dedicated to his volunteer position at an amusement park for the summer, with intent to work toward meeting a girlfriend and eventual paid employment. The latter took approximately 2 years to achieve, with provision of continuity of care, emphasizing the relationship with family, the patient, empowerment in decision-making process, and using more concrete visually constructed psychoeducational methods.

Evaluation in TIPP

The decision to transition patients from a tertiary mental health care team into primary practice should be made when the need for direct service provision or ongoing monitoring is no longer present or the need for case management is no longer required [36].

The collaborative care models may improve outcomes through earlier contact with services, may provide GPs with greater knowledge and comfort managing psychiatric disorders, and appear to enhance satisfaction with mental health services overall [11, 37]. Most studies show that a majority of GPs would support a policy of shared care of psychiatric patients who are stable [38, 39].

The Transition into Primary-care Psychiatry (TIPP) model based out of a tertiary care mental health hospital ensures patients receive coordinated services based on the underlying principles of client-centered care.

There is paucity of literature in the area of what factors make these models successful; in order to understand this better, we conducted a literature review to delineate factors that bode a successful transition to primary care from secondary care service. Based on this search, a tool was developed consisting of ten factors frequently thought to play a role in most studies reviewed.

This tool was used to conduct chart audits on 59 patients who had been transitioned, in anticipation that useful predictors for successful discharge or potential barriers to discharge could be identified (Fig. 25.2).

We looked at a 5-year period, where 59 patients were transitioned from the TIPP program to the community family doctors. The results showed that 49 (83%) were successfully discharged to primary care, while the remaining 10 (17%) patients required a return to tertiary ambulatory care services and were considered an unsuccessful discharge. Twenty-six patients required readmission to hospital for their mental health. The patient characteristics are given below:

- Sex: 27 (46%) males, 32 (54%) females
- Age: mean 55.8 years old (SD 12 years)
- Primary psychopathology: 31 primary psychotic disorder; 13 bipolar disorder; 8 depression; 4 anxiety disorders, including PTSD; 1 intellectual disability; 2 personality disorders
- GAF: mean 60.8 (S.D. 11)
- TAG: mean 3.7 (S.D. 2.9)
- Insight: good 24 (40%), fair 12 (20%), poor 7 (12%)
- Motivation: good 26 (43%), fair 7 (12%), poor 8 (13%)
- Compliance: good 35 (58%), fair 5 (8%), poor 12 (20%)
- Medical comorbidities: diabetes mellitus, hypothyroidism, dyslipidemia, asthma, COPD, GERD, seizure disorder, glaucoma (Fig. 25.3)

We found that characteristics of patients successfully transitioned from TIPP into primary practice revealed a positive association with higher GAF scores, good insight, good motivation, good compliance, and social supports.

Good medication compliance has similarly been found to be one of the most important criteria for effectively transitioning patients in other studies [39, 40]. The presence of substance abuse, medical comorbidities, and community supports

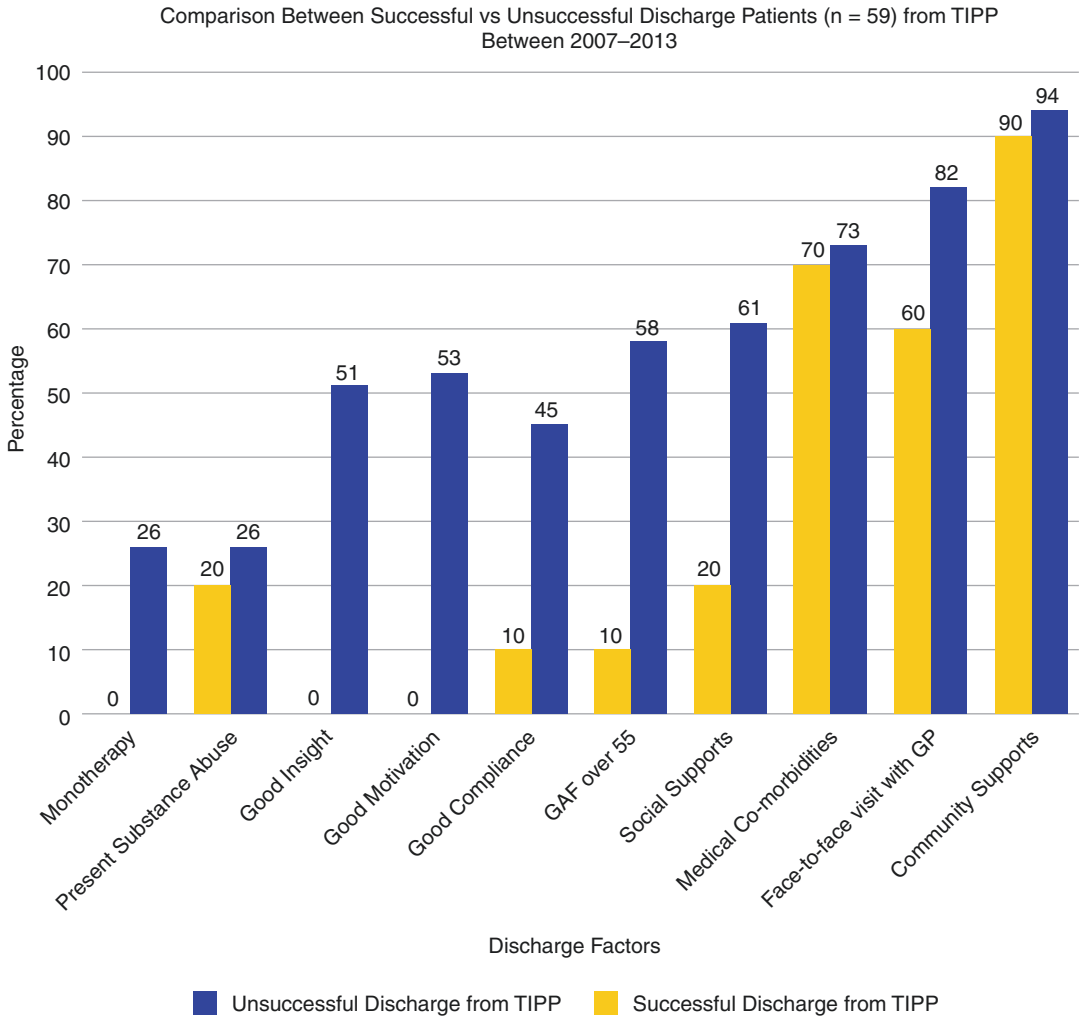

Fig. 25.2 Comparison between successful and unsuccessful discharge patients ($n = 59$)

did not appear to differ among the two groups. Contrary to our study findings, involvement with other community resources was found to be one of the most useful factors predicting successful discharge in one study [41].

Due to a low number of patients ($n = 10$) involved in community mental health organizations (WOTCH, CMHA), community supports were expanded to include financial supports (CPP, ODSP, WSIB), as well, which may have minimized the effect.

There were a high number of readmissions to hospital, suggesting the need for some specialist support in the post-discharge period.

A study by Backen et al., however, noted decreased frequency of specialist contact over a follow-up period of 3 years, which may reflect an initial adjustment to living in the community without case management [36].

This highlights the importance of relapse prevention signatures and management plans at transfer point.

A systematic and planned approach to discharge has shown an increase in successful transition to primary care practice [36]. We recognize there was some limitation to this study: the small sample size, uncontrolled retrospective design, and perspective of the patients or

Factors in Successful Discharge of Clients from TIPP 2013

Patient initials:	Gender:	Stable:	Face to Face with GP at transfer visit:	Supports:
Diagnosis				
GAF				
TAG				
Insight				
Motivation				
Compliance				
Medical Co-morbidities				
Medications: Polytherapy Monotherapy				
Substance abuse: Past Current				
Other				

Fig. 25.3 Factors in successful discharge of clients from TIPP over a 5-year period

primary care practitioners were not taken into consideration.

Looking forward, we aim to expand the study population in order to obtain a clearer indication of which factors are most important in deciding who is appropriate for discharge. The latter could be a part of the LOCUS (Level of Care Utilization System) being implemented in the hospital in assessing outpatients to determine level of care placement decisions to inform what level of service is required to meet the need in the community [42].

Conclusion: Strengths, Challenges, and the Future

The greatest benefit of the collaborative care approach between primary care and specialists is building the capacity of the family physician and the primary health-care sector. The model itself can provide continuity of care, a comprehensive approach to complex mental health problems within a team-based setting.

The major challenge when models are based out of tertiary care is disengagement between the patient and clinical staff can be difficult—a potential barrier to optimal patient independence. Development of training and expertise specific to the unique challenges of this transition is needed. Current funding models in primary care are "fee for service," and this can curtail effective communication between primary and secondary care.

The future involves the need for best-practice models to help practitioners incorporate collaborative care principles into daily practice. More research is required into the evidence for the effectiveness of such models. The overall system needs to adopt incentives and payment schedules that support collaborative care models, which may include engaging the community-based psychiatrists and working with community agencies for sessional fees. It is essential to incorporate collaborative care methodologies in the training of health practitioners, medical students, and residents for expansion and sustainability of this model. In the future, supporting such quality care initiatives will become more important.

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26 Cognitive Behavioural Therapy and Its Role in the Outcome and Recovery from Schizophrenia

Pragya Lodha and Avinash De Sousa

Introduction

Cognitive therapy has been evolving for the last 40 years [1]. From successful treatment for depression and (lesser so) for anxiety disorders, and effective outcomes for bipolar disorder, PTSD, eating disorder and some symptoms of the OCD spectrum disorders, cognitive therapies have also shown results for psychosis in the last 20 years [2]. Cognitive behavioural therapy (CBT) for schizophrenia isn't deliberated to study effectiveness of the therapy on a particular type of schizophrenia, but research has shown improvement in residual symptoms (negative and positive symptoms) of the illness.

Even with best practices in place, there are limitations to the effectiveness of treatments that include medications for this disorder [3]. Relapse rates are high and those with the illness often remain symptomatic, with functional and socio-occupational impairment. Evidence still suggests that individuals with schizophrenia do best with a combination of pharmacological and psychosocial intervention [4]. Treatment planning for persons with schizophrenia has three goals [5]: (1) to reduce or eliminate symptoms, (2) to maximise quality of life and adaptive functioning and (3) to promote and maintain recovery from the debilitating effects of illness to the maximum extent possible. One psychosocial treatment that has received much attention is cognitive behavioural therapy (CBT). CBT has proven to be a successful therapeutic model of treatment for various psychiatric illnesses (major depressive disorders, post-traumatic stress disorder, obsessive-compulsive disorder) that have depression and/or anxiety as focal symptoms. As a treatment modality for psychosis, CBT has been acclaimed as effective by many researchers and experts. CBT involves management of psychosis, not just from the standpoint of a therapist, but has also demonstrable consideration for caregivers' well-being in symptom management and care. In the term of the therapeutic learning, the patient also learns to develop self-care practices through the CBT model.

History of CBT and Its Role in Schizophrenia

In treating people with schizophrenia, using CBT is not an entirely new approach. Beck, in 1952, described successfully treating a delusional belief held by a patient with schizophrenia using CBT [6]. Despite having been encouraged by the work of Beck and Shapiro and Ravenette in the 1950s [7], specific symptom interventions for

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schizophrenia did not appear until much later in the later 1900s. Initial systematic efforts to use CBT for the treatment of schizophrenia focused on the treatment of acute symptoms experienced by inpatients [8]. CBT is a psychotherapeutic model (referred to as a psychosocial model as well) directed toward problem-solving and introducing teaching skills to modify dysfunctional thinking and behaviour in a structured, time-sensitive and here-and-now manner. CBT for schizophrenia is also called CBT for psychosis or CBT-p.

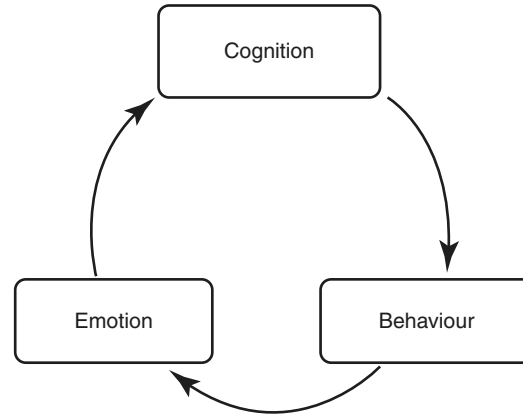

Fig. 26.1 A simplistic representation of the CBT model that was originally presented by A. T. Beck in 1952

CBT-p: A Treatment Modality for Schizophrenia

Treatment modalities for mental illnesses have seen a renewed interest in psychosocial interventions (including psychotherapy) in the treatment of schizophrenia [9]. Adapting cognitive behavioural therapy (CBT) techniques for more severe mental disorders [3] has been one of the more discussed and tried interventions that were previously used in the treatment of mood and anxiety disorders. CBT-p is numerously tried and tested on persons with schizophrenia with varied results obtained [10] depending on the duration of CBT, the level of training and skillset of the therapist conducting the trials, the severity of symptom presentation and phase of illness during which CBT was done with patients. There isn't much evidence to support the implementation of CBT in relation to prodromes, first-episode schizophrenia, acute relapse, forensic patients with psychosis or those with comorbidity such as substance misuse, personality disorder, or learning disability nor for psychosis in adolescence and old age [11]. Positive effects of CBT implementation have been recorded predominantly for residual symptoms of schizophrenia solely.

The core symptoms of schizophrenia, especially negative symptoms, in many people have proven to be resistant to treatment with medication alone and have been targeted for treatment with CBT [12]. CBT has shown improvement in interpersonal relationships and success at work in people with schizophrenia [1]. CBT has also shown effective results in persons with schizophrenia with comorbid mood and anxiety disorders [3]. Moreover, CBT has also been an intervention of interest along with psychoeducation in times of failed rehabilitative treatment programmes and non-compliance of psychopharmacological treatment in patients with schizophrenia [13]. In these instances, CBT (CBT-p) has been implemented and findings have suggested enhanced insight and facilitated coping and adherence to medication. Studies like those conducted by Kemp et al. [14] have shown the effectiveness and durability of CBT in improving compliance to medication, which failed with sole psychopharmacological intervention [15] (Fig. 26.1).

Since the later 1990s, there has been considerable advocacy of cognitive behavioural therapies as treatment modality for schizophrenia—having cited verifiable effects of CBT-p. There are several cognitive therapies that come under the umbrella of CBT that have been studied for interventional purposes for trials in persons with schizophrenia.

Recovery-Oriented CBT: Schizophrenia Treatment Outcomes

The enthusiasm for use of these cognitive therapies precluded dispassionate evaluation of the effectiveness of this treatment. Based on

the cognitive model, recovery-oriented cognitive therapy (abbreviated as CBT-R) is one of the adjuncts to the milieu of CBT [16]. CBT-R involves meeting people where they are (assessing the here and now), accessing their adaptive mode, developing aspirations and steps toward successfully achieving them, strengthening positive beliefs, weakening negative beliefs and developing resiliency in regard to stress and challenges [17]. It is an empirically supported procedure for successfully operationalising and realising recovery for individuals with serious mental illnesses, likewise to the cognitive behavioural model [16, 17].

Recovery-oriented cognitive therapy can lead to lasting improvement among individuals with schizophrenia, even among those with the most chronic illness, according to a study published online [18]. CBT-R is a collaborative treatment approach that prioritises attainment of personally set goals, removal of roadblocks and engagement of individuals in their own psychiatric rehabilitation [16–18]. CBT-R can be implemented in multiple settings—individual, group, or team approach—with barely any effect on treatment outcomes. CBT-R is person-centred, with all interventions based on the individual's cognitive case formulation, tailored for patients who have difficulties with attention, memory and executive functioning and/or who have low motivation [16].

The prevailing belief in the field has been that the observed social withdrawal and inactivity in persons with schizophrenia are based on impaired brain functioning, specifically attention, memory and executive function [19]. After conducting several interviews with individuals experiencing negative symptoms, Beck and Grant concluded that these individuals appeared to have a system of negative beliefs which accounted for their low functioning. They speculated that defeatist and asocial beliefs reduced access to the motivation required to initiate and sustain activity.

A series of studies found (as predicted) that negative attitudes had a direct impact on the negative symptoms, while the impairments in attention, memory and executive functioning impacted only indirectly [20]. It stood to reason that if the disabling attitudes could be modified, then the disabling behaviours could be relieved.

Another study discovered that therapy promoted recovery by targeting these beliefs and included forming an emotional and energising engagement with the individual [21]. Therapy also involved several other aspects such as eliciting their unique meaningful aspirations, breaking down and planning action toward the goals, drawing conclusions regarding the meaning of each success experience and identifying and mastering the obstacles to reaching these goals.

In a randomised controlled trial, individuals with elevated negative symptoms were recruited. Results of the trial demonstrated that recovery-oriented cognitive therapy improved global functioning, reduced amotivation (the inability to see value in an activity), and reduced positive symptoms relative to standard care (medications, targeted case management, etc.) in persons with schizophrenia. Grant and Beck concluded that therapy produced a cycle of recovery in which there was a positive correlation between what individuals were doing and their level of motivation and a negative correlation with the amount of time they had to dwell on hallucinations and delusions [20, 21]. Thus, there was more time to engage in meaningful activities, greater motivation and reduced positive symptoms (hallucinations and delusions).

Findings of CBT (CBT-p) in Schizophrenia Treatment Outcomes

For schizophrenia, cognitive behavioural therapy has shown the most promising outcome in conjunction with medication and with a precondition of considerable insight in the person. As opposed to the failure of psychodynamic psychotherapy and family therapy, cognitive behavioural therapy (including the adjunct cognitive therapies) involves an active participation of the caregivers and the patients to actively control for the psychotic symptoms observed in schizophrenia. Tarrier et al. have shown improvements in both negative and positive symptoms

of schizophrenia, using cognitive behavioural therapy [22]. The therapy primarily facilitates engagement and the establishment of collaborative empiricism, with reality testing based on guided discovery rather than confrontation [23]. Insight is a prerequisite for CBT-oriented outcomes in patients of any disorder. Accordingly, then, people with schizophrenia are (must be) stabilised with medication before they participate in cognitive behavioural therapeutic intervention. It is only when the person stabilises that he or she can learn to manage their symptoms. Hallucinations, delusions, negative symptoms and depression—all of these symptoms have shown to be responsive to CBT. A CBT therapist can help the person identify triggers of their symptoms and how to reduce these triggers or prepare themselves to care for self in the presence of triggers [6, 11–13]. A therapist can review social skills and other problem-solving techniques in session, which the person can practice to manage other situations that may come forth outside the therapy setting and in the future. Thus, CBT can help people with schizophrenia handle their responsibilities and life stresses better. Techniques range from more superficial peripheral questioning of delusional content to deeper work on underlying dysfunctional beliefs about the self (e.g. "I am evil, deficient, damaged" or "I am special, unique, different"). Homework exercises allow patients, often with the help of carers, to begin to make sense of their distressing experiences and to see the effects of working on avoidance, rational responding, or changing coping strategies [16, 17]. Cognitive behavioural therapy is therefore an individualised intervention based on a case formulation which helps the patient to answer the question, "Why have I changed so much?", and to begin to see the point in taking medication and attending social treatment options [23].

One consideration that must be kept in mind while evaluating the effectiveness of outcome of CBT in persons with schizophrenia is the training and skillset of the professional carrying out the intervention with patients. The debate involves discussing the efficacious outcomes of this psychosocial intervention with regard to the trained CBT professionals, who are demonstrated to show better outcomes with CBT used as intervention as compared to psychiatrists, psychiatric nurses and other mental health professionals, all who are less trained to use CBT as treatment modality with persons with schizophrenia [3, 11, 12, 16].

Some considerations for the therapeutic process involving CBT for patients with schizophrenia [3]:

- Anticipating problems with engagement because of mistrust or auditory hallucinations which can typically prevent misunderstandings.
- Immediate concerns (e.g. suicidal thoughts, difficulties in getting to therapy sessions) should be dealt with before an assessment.
- Challenging delusions in the early stages of therapy is not productive; listening and trying to understand the patient's perspective proves more beneficial.
- Occasionally focusing on positive aspects and achievements of the patient can be extremely helpful.

Patients with psychosis often present with low self-esteem, difficulties with trust and fears about others viewing them as "crazy"; unconditional positive regard shown by the clinician can help circumvent these negative self-views that can hinder rapport and therapy engagement.

The clinician should bear in mind the psychological ideas and models and may inquire about the following when in a therapy setting with patients suffering from schizophrenia: [24].

- What is the patient's emotional state?
- What evidence makes the patient believe that the delusional thoughts are accurate?
- What are the kinds of experiences for the patient?
- How does the delusional belief build on the patient's ideas about the self and others?
- What are his beliefs about the hallucinations?
- How do the delusional thoughts or interpretations of hallucinatory experience make sense given the patient's previous life events?
- Are there negative images?

- What is the reasoning style concerning these experiences?
- Are there behaviours (e.g. avoidance) that contribute to the persistence of the thoughts?
- What is the patient doing during the week?

CBT has shown improvement in the levels of insight of patients with schizophrenia [25], which has not just brought relief to the patient but also to the caregivers. Interview studies have documented the course of change in expressions of frustration and guilt to that of being more hopeful in carers of persons with schizophrenia. Additionally, the reduction in relapse of rehospitalisation has also been shown to be a positive outcome as a result CBT being used with persons with schizophrenia [26]. For over the last two decades, CBT has been welcomed by patients and caregivers as intervention for managing the symptoms of schizophrenia. Therapists have shown increasing interest to test trials and develop on the potential of the same further.

CBT has been well tested in relation to the treatment of residual symptoms of schizophrenia and is of proven efficacy and cost-effectiveness [27]. Apart from the several other psychological treatments that have worked with persons with schizophrenia, CBT is the only one that has given results of betterment with proven durability in the shortest span of time [28]. One study has also proven the benefits of CBT being translated into community settings of care. The same was confirmed with a randomised controlled trial over a 10-day period and continued supervision [13]. CBT was effectively used for insight improvement and reduction in overall symptoms of schizophrenia and depression. Turkington in another study showed the effectiveness of brief CBT in reduction of symptomatic complaints in persons with schizophrenia. This was successfully translated in community settings of care (with trained community psychiatric nurses) to achieve symptomatic reduction without increase in suicidality. In the group exposed to CBT, insight development was marked to be clinically significant. As cautionary note, it must be considered that for certain types of psychotic symptoms (e.g. command hallucinations linked to trauma or systematised or grandiose delusions), distressing affects can emerge as the psychotic symptom is worked with [11–13].

CBT-p is a verbal therapy to ease distress by reducing positive symptoms [29]. It does this by mobilising the client's capacity to reflect on and to question delusional or self-evaluative beliefs through a "collaborative empirical" enterprise. The therapist joins forces with the client to question beliefs that limit the achievement of personal life goals. The journey through therapy (usually 20 or so sessions over 6–9 months) allows for the collaborative development of an understanding of distressing psychotic experiences [11, 12]. The clients are then guided to re-evaluate their appraisals of experiences and identify new ways of responding to them. Toward the end of therapy, further collaborative work on maintaining factors is carried out to support the individual to prevent relapse. Usually this involves issues such as reasoning style, self-concept, social isolation, appraisals of psychosis and emotional processes. Models are provided for therapy development [30], and all therapists are expected to cultivate a shared formulation of the relationship between the experiences, the thoughts and the problematic behaviour [31].

When compared with other psychological intervention, meta-analyses have demonstrated far more effectiveness of CBT-p over other modalities, depending on specific factors in interventions and specific targets. CBT-p has been proven more successful over other psychological treatments such as social skills, cognitive remediation, befriending, psychoeducation and supportive counselling. Thus, there are differences in efficacy of psychological treatments for psychosis which can guide treatment choice and which depend on what individual patients select as their main goal.

The effectiveness of CBT-p therapy has been replicated and confirmed by several meta-analyses that have been carried out using randomised controlled trials. Most studies (single-blind, individual assessors being blind to the treatment allocation which was also the most significant predictor of the bias) showed effective outcomes on positive symptoms of hallucinations

and delusions [30–32]. CBT-p has expanded to include targets such as negative symptoms, social outcomes and compliance with command hallucinations, among many others.

Research Findings Related to CBT in Schizophrenia Outcomes

Several randomised control trials have been carried out in the previous two decades that have shown the effectiveness of brief as well as long-term CBT for various associated conditions. Ranging from distressing psychotic symptoms and positive symptoms to reducing the risk for suicidality and significant low readmission rates—all have been demonstrated with CBT as intervention for schizophrenia. Though some studies such as those done by Drury and colleagues claim that brief duration of CBT is ineffective [8], others say that brief CBT has shown efficacious results [1]. Another aspect also discusses the effectiveness of long-term (20 sessions) CBT [30] as treatment modality. Other deliberations also include the "training and expertise" of the therapist to determine the effectiveness of CBT outcome for schizophrenia. It has been demonstrated that more skilled and trained therapists in CBT are required in order to achieve better outcome results for patients with schizophrenia. The literature generated from randomised, controlled trials on the efficacy and effectiveness of cognitive behaviour therapy for medication-resistant schizophrenia is larger than for any other individual psychotherapy of schizophrenia in recent history [12].

The results of the trials carried out by several researchers can be concluded in the following findings [8, 11–13, 30]:

- Randomised controlled trials (RCTs) have shown moderate effect sizes for positive and negative symptoms at the end of therapy, with sustained effects.
- Reduction in relapse rate of rehospitalisation.
- Effective in clinical as well as research settings.
- Improvement in levels of insight.
- Management of depression in persons with schizophrenia.
- Responsive in management of positive symptoms: hallucinations and delusions.
- Negative symptoms respond initially; improvement remains at medium-term follow-up.

Key Research Papers for CBT in Psychosis: Recent Research

After 15 years of the initial substantive trial, CBT has become the first form of psychotherapy to achieve widespread acceptance in schizophrenia.

Candida et al. found numerous systematic reviews support the immediate and long-term efficacy of CBT to reduce positive and negative symptoms in patients with schizophrenia [33]. Brain regions supporting high-level cognitive functions were found to be associated with CBT responsiveness. The review claimed evidence for increase in prefrontal dependence in the top-down modulation of social threat activation as a consequence of CBT implementation.

In a systematic review and meta-analysis of the effectiveness of CBT for schizophrenic symptoms that includes an examination of potential sources of bias, the data were pooled from randomised trials providing end-of-study data on overall, positive symptoms (33 studies) and negative (34 studies) symptoms. It was found that CBT has a therapeutic effect on schizophrenic symptoms in the "small" range. This was seen to reduce further when the sources of bias (particularly masking) were controlled for [32].

A meta-analytic review was conducted to study the effect of CBT on medication-resistant psychosis. The results of the study proposed that for patients who continued to exhibit symptoms of psychosis despite medication, CBT could confer beneficial effects above and beyond the effects of medication. Overall, beneficial effects of CBT for 552 patients were found at post-treatment for positive symptoms and for general symptoms and were maintained at follow-up for both positive and general symptoms [34].

A randomised trial to evaluate the efficacy of cognitive therapy for low-functioning patients with schizophrenia was carried out by Grant, Beck and others. Results showed that patients treated with CBT showed a clinically significant mean improvement in global functioning from baseline to 18 months that was greater than the improvement seen with standard treatment. The study concluded that cognitive therapy can be successful in promoting clinically meaningful improvements in functional outcome, motivation and positive symptoms in low-functioning patients with significant cognitive impairment [19, 20].

In the longitudinal study, baseline asocial beliefs of 23 outpatients diagnosed with schizophrenia or schizoaffective disorder predicted asocial behaviour 1 year later. Asocial beliefs predict poor social functioning in schizophrenia and may be modifiable by psychological interventions like CBT [19].

A growing body of evidence supports the use of CBT for the treatment of schizophrenia. A course of CBT, added to the antipsychotic regimen, is increasingly being considered to be an appropriate standard of care across several countries. Recent studies have proposed to combine CBT with other evidence-based approaches such as supported employment, family psychoeducation, motivational interviewing, social skills training and third-wave cognitive behaviour therapies including acceptance and commitment therapy and brief CBT among others, for long-term positive outcomes. Future progress will depend on the further development of psychological models of psychotic symptom onset and maintenance and on the development of more refined treatment manuals. CBT would appear to have the possibility of an enhanced effect when given with cognitively sparing antipsychotic medication or when combined with cognitive remediation [11, 12, 29]. It will be very interesting to note any functional imaging changes through a course of CBT when psychotic symptoms are improving.

Succinctly, CBT for people with schizophrenia has been used for primary symptoms of illness, the secondary social impairments and comorbid disorders and for enhancing the effectiveness of other treatments and services, such as medication and vocational support. A summary of various recent key studies in psychosis is given in Table 26.1.

Table 26.1 Key studies of CBT in schizophrenia outcome (2000–2018)

Author	No. of subjects	Study characteristics	Duration	No. of sessions	Outcome
Turkington and Kingdon (2000) [35]	64	Each patient 6 sessions over 2 months averaging 20–40 mins. Families were interviewed as available	2 months	24 group sessions	6-month follow-up period of CBT group tended to have a shorter period in hospital
Sensky et al. (2000) [36]	90	RCT to compare the efficacy of manualised CBT developed for schizophrenia vs befriending control	9 months	19 individual sessions	CBT is effective in treating negative and positive symptoms in schizophrenia resistant to standard antipsychotic drugs, with its efficacy sustained over 9 months of follow-up
Lewis et al. (2002) [37]	315	To test the effectiveness of added CBT accelerating remission from acute psychotic symptoms in early-onset schizophrenia	5 weeks	5 weeks CBT programme and routine care	CBT shows transient advantages over routine care alone or supportive counselling in speeding remission from acute symptoms in schizophrenia

(continued)

Table 26.1 (continued)

Author	No. of subjects	Study characteristics	Duration	No. of sessions	Outcome
McGorry et al. (2002) [38]	59	Needs-based intervention compared with specific preventive intervention comprising low-dose Risperidone therapy and CBT	6 and 12 months	Treatment provided for 6 months 10–12 sessions of CBT	More specific pharmacotherapy and psychotherapy reduces the risk of early transition to psychosis in young people at ultra-high risk, contributions not determined
Morrison et al. (2004) [39]	58	To evaluate the efficacy of cognitive therapy for the prevention of transition to psychosis	6 months	Therapy provided 6 months, and all patients monitored monthly for 12 months	Cognitive therapy appears to be an acceptable and efficacious intervention for people at high risk of developing psychosis
Addington et al. (2010) [40]	51	CBT versus supportive therapy in reducing the conversion rates and symptom improvement	6 months	Sample was assessed at 6, 12, and 18 months	Significant implications for early detection and intervention in pre-psychotic phase and for designing future treatments
Freeman et al. (2013) [41]	150	Effects of CBT for worry persecutory delusions in patients with psychosis	6 sessions	3 months	CBT might be a beneficial addition to the standard treatment of psychosis
Li et al. (2015) [42]	192	Compare efficacy of CBT and supportive therapy (ST) in schizophrenia	15 sessions of either CBT or ST	84 weeks	CBT significantly more effective than ST on overall, positive symptoms and social functioning of patients with schizophrenia
Naeem et al. (2015) [43]	116	Assess effectiveness of culturally adapted CBT for psychosis in low-middle-income countries	6 individual sessions	4 months	Culturally adapted CBT for psychosis is effective when provided in combination with other treatments as usual

Critical Clinical Issues on CBT Improving Outcomes in Schizophrenia

CBT for people with schizophrenia is used for the management of primary symptoms of illness, secondary social impairments and comorbid disorders and for enhancing the effectiveness of medication and vocational support [3]. Though a few recent reviews and studies have questioned the true effectiveness of CBT for schizophrenia and other severe mental disorders and comorbid conditions, it has been shown to be effective in several study trials [44]. There isn't much evidence to support the implementation of CBT in relation to prodrome, first-episode schizophrenia, acute relapse, forensic patients with psychosis or those with comorbidity (substance misuse, personality disorder, or learning disability) nor for psychosis in adolescence and old age [45]. Positive effects of CBT implementation have been recorded predominantly for residual symptoms (eccentric behaviour, emotional blunting, illogical thinking, or social withdrawal) of schizophrenia solely. The core symptoms in patients with schizophrenia have shown resistance with pure psychopharmacological treatment, which is why psychosocial interventions such as CBT have been incorporated in the treatment plan. CBT as therapy (in study trials) has shown significant improvement in targeted areas such as impairments in major

role function due to negative symptoms (some of which have proved especially obstinate to pharmacologic agents), to improve relationships with family and friends, success at work, with comorbid mood and anxiety disorders, and working upon past traumas [46, 47].

What Techniques of CBT Have Been Used to Improve Outcome in Schizophrenia?

Within the CBT spectrum, there are various techniques that are of greater suitability while measuring for outcomes in schizophrenia. Tarrier and Haddock [48] advocate for specific cognitive and behavioural techniques for:

- Attention switching
- Attention narrowing
- Increased activity levels
- Social engagement and disengagement
- Modification of self-statements
- Internal dialogue
- De-arousing techniques
- Increasing reality or source monitoring
- Belief and attribution modification

Beck and Rector [49] discuss the implication of typical CBT techniques: building trust and engagement; working collaboratively to understand the meaning of symptoms; understanding the patient's interpretation of past and present events, especially those that the patient feels are related to the development and persistence of current problems; normalising these experiences and educating the patient about the stress-vulnerability model; and socialising the patient to the cognitive model, including the relationship between thoughts, feelings and behaviours. The primary strategic techniques that therapists may consider are:

- Patient's perspective is crucial for developing therapeutic alliance.
- Developing alternative explanations of schizophrenia symptoms.
- Attempting to reduce the impact of positive and negative symptoms.
- Offer alternatives to address medication adherence.

Peripheral questioning is a technique that questions to understand the origin of the delusional beliefs. This technique is deployed by therapists to reduce positive symptoms in patients. It is also linked with graded reality testing to introduce doubt and postulate other explanations.

Behavioural self-monitoring, activity scheduling, mastery and pleasure ratings, graded task assignments and assertiveness training are several other techniques that can monitor negative symptoms such as amotivation, anergia, anhedonia and social motivation.

Birchwood [50] suggests that CBT might specifically focus upon the following:

- Reduction of distress, depression and problem behaviour associated with beliefs about psychotic symptomatology in schizophrenia
- Emotional and interpersonal difficulty in individuals at high risk of developing psychosis
- Relapse prodromes to prevent relapse in psychosis
- Comorbid depression and social anxiety, including the patient's appraisal of the diagnosis and its stigmatising consequences
- General stress reactivity and increasing resilience to life stress and preventing psychotic relapse
- Increasing self-esteem and social confidence in people with psychosis

The overall goal of CBT treatment (along with medication) is symptom reduction, improvement in functioning and remission of the disorder, so the patient becomes an active participant in a collaborative problem-solving process. Modern CBT refers to a family of interventions that combine a variety of cognitive, behavioural and emotion-focused techniques [51]. These strategies augment cognitive factors and physiological, emotional and behavioural components for the role that they play in the maintenance of the disorder.

Can CBT Improve Outcomes in Schizophrenia?

Tai and Turkington [1] summarise the results of the CBT studies:

- Randomised controlled trials (RCTs) have shown moderate effect sizes for positive and negative symptoms at the end of therapy and with sustained effects.
- CBT has been effective in clinical as well as research settings.
- Hallucinations and delusions respond to CBT.
- Negative symptoms respond initially, and improvement remains at medium-term follow-up.

On the other hand, they also acknowledge:

- CBT is not as effective when people do not view themselves as having a mental health problem, have delusional systems, or have extreme primary negative systems.
- CBT can be less effective when people have comorbid disorders, such as substance misuse, as it becomes difficult to engage and treat them.

Drury et al. [52] have outlined various factors that may predict improvement with CBT, and these factors have been identified in several studies. These factors encompass early work with acutely psychotic inpatients, female gender, shorter duration of illness and shorter duration of untreated illness predicting better outcomes. Tarrier and his group [53] also found shorter duration of illness and less severe symptoms predicted the greatest improvement with CBT-p.

Conclusively, results from clinical trials of CBT-p have shown effective implications on patients and family members of these patients, making CBT a compelling treatment to consider as an integral part of early psychosis intervention and management.

Is CBT a Stand-Alone Treatment in Schizophrenia or Does It Work Better When Combined with Pharmacotherapy?

The combination of pharmacotherapy and psychosocial intervention has been recommended for treatment of schizophrenia by practice guidelines for psychiatrists [54]. Patients in early stage of the illness (schizophrenia) receiving medications and psychosocial intervention have reported a lower rate of treatment discontinuation or change, lower risk of relapse and improved insight, quality of life and social functioning [55].

CBT for psychosis (CBT-p) is best implemented with reduced/controlled acute symptoms and when the patient can be successfully engaged in treatment. The goals of CBT intervention are to reduce stress on the patient, enhance the patient's ability to rehabilitate into the community, provide support to minimise relapse rate and facilitate continued reduction in symptoms and consolidation of remission.

What Other Psychosocial and Psychotherapeutic Treatments Can Be Used to Augment CBT?

Psychotherapy is a constantly evolving therapeutic area which may be individual, group and cognitive behavioural [56]. Controlled study trial evidence suggests no clear advantage of CBT over other therapies for people with schizophrenia [57].

There are several other psychotherapeutic interventions incorporated within the treatment modality for schizophrenia, either along with CBT or independently. Some of the considerable ones are enlisted below [58].

Psychoeducation Teaching patients and caregivers about the symptoms, treatment and course of mental illness and afford patients and family members the opportunity to ask questions about psychiatric disorders and treatment options.

Family Intervention Developing collaboration with the family; teaching patients and their families to cope with stressful situations and the illness; teaching patients and their families to detect signs of relapse and intervene in crises; and enhancing family communication.

Social Skills Training Modules on medication management and symptom self-management, dealing with stigma, social problem-solving and independent living skills.

Cognitive Remediation Developing cognitive rehabilitation programmes to increase memory capacity, attention and high-level problem-solving skills.

Assertive Community Training Involving psychiatrists as well as other mental health clinicians. This team approach allows for integration of medication management, rehabilitation and social services, along with encouragement to involve family support.

The Place of CBT in Treatment Algorithms for Schizophrenia

Pharmacotherapy is the mainstay of schizophrenia treatment; however, residual symptoms may persist. For that reason, nonpharmacological treatments, such psychotherapy, are also important [58]. Nonpharmacological treatments should be used as an addition to medications, not as a substitute for them [59]. In the nonpharmacological treatments, CBT and individual supportive therapy are the two major psychotherapeutic intervention modalities. CBT has been shown to be the most tested and relatively successful intervention in the management for schizophrenia. From symptom management to reduced hospitalisation and relapse rate and greater level of insight in patients, effectiveness of CBT has shown varied patterns within the context of duration of trials, intervention control, severity of symptoms and professional skillset involved.

Limitations of Implementing CBT with Psychosis

CBT-p as a trial intervention in several randomised control studies has shown results for both short-term and long-term therapy sessions. Where, on one hand, CBT has several positive outcomes in the treatment for persons with schizophrenia, there are limitations to the approach. There were several factors that potentially affected the effectiveness and outcome of CBT-p as a treatment modality. They include [1–3, 11, 12, 15]:

- There has not been one standardised model of CBT that has been developed or validated to be implemented as therapeutic treatment modality for patients with schizophrenia. Thus, variations in the intervention interfere with findings reported in the randomised control studies.
- Professionals implementing CBT to persons with schizophrenia were not skilled in delivering the therapy.
- The duration of therapy has varied from short term (six to seven sessions) to long term (20 sessions), which has affected the outcome of treatment effectiveness in persons with schizophrenia.
- It is a prerequisite that the person must have some level of insight in order for CBT to be started off as an intervention.
- Persons with schizophrenia with residual symptoms are shown to be most benefitted by CBT-p as opposed to those in the acute phase, prodromal phase, first episode, relapse, forensic patients with psychosis, or those with a comorbid disorder (substance abuse, personality disorder, or learning disability) neither for adolescents and geriatric population with psychosis (Table 26.2).

Table 26.2 Cognitive behavioural therapy for schizophrenia: summary

Goals	Replace maladaptive thoughts and beliefs Develop adaptive coping skills
Design of CBT	Combine cognitive restructuring with multiple behaviour methods Focus on perpetuating factors
Efficacy	Brief treatment outcomes for negative symptoms Improvement in insight levels Management of hallucinations and delusions Reduction in relapse of rehospitalisation
Limitations	No standardised model developed or validated Less trained professionals in CBT May or may not be effective in short-term (and long-term) therapy Prerequisite that person must have insight Effective only for residual symptoms

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27

Experience of Psychiatrists Regarding Recovery of the Mentally Ill in Rural India, with Case Reports

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Introduction: Overview of Mental Illness in India

Epidemiological studies report prevalence rates for psychiatric disorders from 9.5 to 370/1000 population in India. These varying prevalence rates of mental disorders are not only specific to Indian studies but are also seen globally. Available data from the Indian studies suggests that the prevalence of psychiatric disorder comes to about 20% [1]. It is estimated that in 2000, mental disorders accounted for 12.3% of disability-adjusted life years (DALY) and 31% of years lived with disability. Projections suggest that the health burden due to mental disorders will increase to 15% of DALY by 2020 [2]. The National Mental Health survey of India, 2015–2016, reported a prevalence rate of 10.6% for any mental disorders in India [3]. Mental health disorders account for nearly a sixth of all health-related disorders. Yet in India we have just 0.4 psychiatrists and 0.02 psychologists per 100,000 people, and 0.25 mental health beds per 10,000 population. If access to mental health care is to be improved, mental health care must be provided at the community and primary level [3]. India only has 23% of required psychiatrists, 25% of psychiatric nurses, and only 3% of clinical psychologists and psychiatric social workers [4].

In India, neuropsychiatric disorders contribute an estimated 11.6% to the global burden of diseases. According to data from WHO in 2011, there are 0.301 psychiatrists, 0.166 nurses, and 0.047 psychologists for every 100,000 patients in India. WHO data also suggest that in India the number of psychiatric beds per 10,000 patients in psychiatric hospitals is 1.490, and in general hospitals is 0.823. Of the total health budget, a mere 1–2% is spent on mental health [5]. The WHO figures reflect this underfunding "Most people are unaware that mental illness is like medical illness and can be treated in the same manner" [5].

The total facilities of psychiatric beds in general hospitals are 0.823/100,000 population. There are 43 mental hospitals in India. The total beds in mental hospitals come to 0.004/100,000 population [5].

In India, psychiatrists and health professionals working in the mental health sector are

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0.301/100,000 population, psychologists are 0.047/100,000 population, and social workers are 0.033/100,000 population.

Schizophrenia: Indian Scenario

Schizophrenia is a disease of the brain that manifests with multiple signs and symptoms involving thought, perception, emotion, cognition, and behaviour. It is a devastating illness causing enormous suffering not only to the individual but also family members [6]. The age-corrected prevalence rate of schizophrenia was 3.87/1000. Other studies in India have reported prevalence of 0.7/1000–14.2/1000. However, comparability amongst studies has been limited by variations in population size, geographical area, and diagnostic criteria [7]. Reddy and Chandrashekar conducted a meta-analysis of 13 psychiatric epidemiological studies consisting of 33,572 persons in 6550 families which yielded an estimate prevalence rate of 58.2 per thousand population. A prevalence of 2.7 for schizophrenia was found [8]. Ganguli reviewed major epidemiological studies in the last four decades and came out with a national prevalence rate of 2.5 per 1000. He also concluded that schizophrenia is the only disorder whose prevalence is consistent across cultures and over time [9]. The National Institute of Mental Health and Neuro Sciences (NIMHANS) study reported prevalence of schizophrenia and other psychoses as 0.64%. The chronic course and debilitating effects of schizophrenia combine to create a disease that has tremendous clinical, social, and economic consequences on society, resulting in it being a leading contributor to global and regional levels of disability and the overall disease burden [3].

Despite prior and current efforts in enhancing mental health-care delivery across the country, the study revealed that a huge treatment gap still exists for all types of mental health problems: ranging from 28% to 83% for mental disorders and 86% for alcohol-use disorders. Except for epilepsy, all the other mental disorders reported a treatment gap of more than 60%, with the highest treatment gap being for alcohol-use disorders. Most of those identified had not sought care or were not able to access appropriate care, despite wanting to seek treatment. Multiple factors ranging from lack of awareness to affordability of care, which varied between rural and urban areas, appear to critically influence these wide treatment gaps [3]. There are other factors that determine the appropriate care of a person suffering from schizophrenia. Some of the most significant barriers in treatment of schizophrenia apart from the above causes are superstition, treatment in the hands of faith healers, stigma, and discrimination.

Below we discuss two cases of schizophrenia that will further highlight the above factors.

Case 1

Mr. SRG, a 45-year-old divorced male, and resident of district Wardha, was brought by his younger brother and mother at 2 a.m. Shockingly, he had been chained by his hand to a tree outside their house in the village for the last 15 years. The duration of his illness was 20 years, and his predominant symptoms were withdrawn behaviour, fearfulness, abusiveness, aggressiveness, suspiciousness, sleep disturbance, and poor personal care. The patient had two suicidal attempts in the past—once by insecticide poisoning (18 years ago) and once by jumping into a well (17 years ago). He was admitted four times to a regional mental hospital in Nagpur, Maharashtra (once for 3 years and three times for 1 year each). He also underwent faith healing. He was violent towards the villagers and his family members. With the consent and possibly support of the villagers, he was tied by a chain to a tree. He had not showered or practiced basic personal hygiene for almost 15 years. He was dishevelled and had a shaggy beard and wild overgrown hair. He came to be known amongst the villagers as "Bedi wale Baba" (Chained Baba) for the last 13 years. Villagers would come and ask him questions during the village fare at a nearby temple. When he would slap the villager who was asking the question, they considered it an omen that their work would be done. There was family

history of mental illness in his grandfather. He had an 18-year-old daughter living with his divorced wife. On mental state examination on the day of hospitalization, the patient was a middle-aged male of average build sitting comfortably on a chair with hair and beard grown and soiled. The patient smelled very badly; his clothes were soiled and dirty. He had a metal chain around his left hand and had a scar mark around his right hand. His behaviour was withdrawn and he had reduced psychomotor activity. Rapport couldn't be established. He had a monotonous speech with a low volume and productivity. His thought stream was retarded and his affect was blunt. He demonstrated echolalia as well. On cognitive testing, the patient was alert and fully oriented. However, the patient did not cooperate for further mental state examination. He had no insight towards his illness. He was hospitalized at psychiatry inpatient unit of Mahatma Gandhi Institute of Medical Sciences, Sevagram, whilst chained [10].

Case 2

Mrs. RK, a 30-year-old married lady and resident of Assam, was brought by her mother and brother in August 2016. She was being brutally beaten on her back by sticks and with hot iron rods being stroked on her forehead. Her illness was present for the last 10 years. Being from a rural background and poor socioeconomic status, she was married at 19. Within a few months of her marriage, she got pregnant with her first child. A few weeks after she gave birth, she started having sleep disturbances. Gradually she started to remain withdrawn and irritable in trivial issues. She would be seen muttering to herself and would smile and giggle without any reason. She started neglecting her baby and would refuse to care for her. Subsequently she would became very suspicious and started crying and shouting. She was very aggressive and would assault her family members on occasions. At time she shouted that someone was doing black magic on her. Her in-law's family, including her husband, feared that she was being possessed by an evil spirit and took her to a faith healer who performed different types of rituals on her, including spanking her back with sticks and stroking her with iron rods. Her symptoms fluctuated throughout these 10 years. She was taken to multiple faith healers or *bej/ojha* (local name for a faith healer). She never received treatment from a doctor in these 10 years. At the time she was being deemed a witch (or a *diyan*), and villagers would blame her on occasion for bringing a bad omen to her community. Five months prior to when she was brought to the doctors, her hair was also tonsured. Although at times her own parents wanted to bring her to the doctor, her husband resisted and kept her locked inside a room. However, this time around, her younger brother, along with the help of a local NGO, brought her to a psychiatrist. On mental state examination on the day of admission, the patient was a young lady of average build sitting comfortably on a chair with hair dishevelled. The patient had poor grooming. She had scar marks on her forehead and back. Her behaviour was withdrawn, and she had reduced psychomotor activity. Rapport couldn't be established properly. She had a monotonous speech with a low rate and volume. Speech was irrelevant on occasion but coherent. There was derailment in the form of thought. Delusion of persecution and reference were found in the content of thought. Auditory hallucination was denied. There was a total impairment in judgement, abstraction, and insight.

Discussion

In both cases, we find that in rural India there is still a huge lack of understanding of mental illness. Superstition, discrimination of the mentally ill, and treatment by faith healers are still prevalent in this modern era. The commonest reason for not accessing treatment was lack of awareness of a biomedical disorder and the beneficial effects of psychiatric treatment. Logistic factors like distance, transport facilities, and financial problems were other important factors that prevented access to treatment. Multiple factors preventing each patient's access to treatment should

be considered whilst planning programmes that attempt to bring all patients with psychoses under treatment.

There are multiple factors which influence barriers to access for those with severe psychiatric illness:

- Social pressure for taking patients to faith and religious healers
- Poor knowledge about mental illness
- Firm beliefs in spiritual and religious help for mental illness
- Stigma about psychiatry and treatment
- Poor cooperation for treatment by patients
- Poor knowledge about availability of treatment
- Poverty
- Distance from the village to mental health facilities
- Patient's behaviour tolerated by the family members

Stigma and Discrimination

The stigma associated with mental illness contributes significantly to the burden of schizophrenia. Subjective accounts of persons affected by mental illness testify that its effects are often perceived as more burdensome and distressing than the primary condition itself [9]. The term stigma refers to "a social devaluation of a person".

Marriage

Marriage is an important social institution in Indian culture. Marriage is implicated to be a significant psychosocial variable in schizophrenia. Many family members believe that marriage is the solution and that marriage can help in alleviating the symptoms. In India, marriages are usually arranged by parents and are influenced by a number of factors such as astrological compatibility, caste regulation, geographic proximity, and expectations of dowry [11]. Female psychotic patients in India have multifold psychosocioeconomic problems than males because of male dominance in selecting a partner. Female patients undergo tremendous stress in getting married, and having a pre-existing mental illness further adds to the situation [12].

Almost all females face many of the following problems in getting married and sustaining married life: First, at the time of proposal, when a girl is shown to the male partner, it is a stress due to the uncertainty of the situation. Second, the question of dowry hampers and causes stress. Third, after marriage, she has to leave her parents' house where she has spent 18–20 years of her life. Fourth, she goes to a new house where she has to cope with new family members of different temperaments. Fifth, if she is on drugs for maintenance of improvement from psychoses, she has to face difficulties such as her in-laws, who may ask her the reason for taking drugs, and she may stop taking them because of impending risk of questioning, which may then lead to relapse. Sixth, she has to undergo her first sexual experience, which may be traumatic to her. Seventh comes pregnancy, which itself is a stress (wanted or unwanted). Eighth, she undergoes the stress of having a male or female baby, because male babies are socially much more accepted and preferred over female babies. And finally, childbirth adds more stress [13–15]. Because of the abovementioned stressors, female psychotic patients may have more episodes of exacerbation of symptoms or relapse of psychotic illness [12, 13].

Conclusions

In summary, the pertinent points from these two case reports are as follows: (1) There is strong family support in India for mentally ill patients. (2) The patient may discontinue medication on their own without a doctor's advice, as improvement by family members is judged by work, that is farming or occupation performance. They strongly believe in faith healing, and if it is stopped by a therapist, they drop out of treatment. In our experience, if we allow non-interfering customs like use of ashes, worship, or amulet (*tabiz*), there is significant improvement in the follow-up and drug compliance.

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28 Evidence-Based Outcome for the Interventions in Childhood-Onset Schizophrenia

Daria Smirnova and Konstantinos Fountoulakis

Introduction

Childhood-onset schizophrenia (COS) is a devastating mental disorder, belonging to the group of very-early-onset psychoses, manifesting before 12 years [1] or 13 years of age [2], irrespective of gender differences [3]. Although this psychotic disorder is often misdiagnosed, COS has an incidence of 0.04–0.05% [4], occurring in 1 per 10,000 children before the age of 12 [5]. This incidence is less than adult-onset schizophrenia, but COS is more severe and disabling [6, 7]. COS has a strong genetic component [2], such that parents of COS children have a high risk of diagnoses of mental illness such as psychotic disorders (15% versus 5% families without COS) [8]. The onset of COS is often preceded by soft neurological signs, complications during delivery and birth, slow habituation, and increased baseline autonomic nervous system activity [5]. In addition, COS is associated with various contextual factors, including high rates of family disruption, certain cognitive schemas in family communication, and high-expression emotions such as criticism, hostility, and over-involvement in the relationship among family members of these patients [9, 10]. COS is twice as frequent among children with early attention deficit, hyperactivity symptoms, uncontrollable and disruptive behavior, and premorbid speech, language, and motor impairments [4, 11], cognitive dysfunction and memory decline, intellectual and educational difficulties, and early school leaving [12, 13]. While clinical signs of autism spectrum disorders appear during the first 3 years of life, initial COS manifestations of prominent positive and negative symptoms are mostly observed at the age of 7 and predict for poor prognosis and increased treatment resistance [14–16].

COS has an ominous prognosis, being linked to *worse outcome and poor quality of remissions, a tendency toward chronic non-episode course, and lower functioning, with high risks of social disability*, compared to adolescent-onset psychosis [1, 17–19]. Eggers et al. [19] undertook a 42-year long-term follow-up of 44 COS patients with the average age of onset of 11.8 ± 2 years; they reported that patients with a more insidious had an absence of remission in 82% of cases and partial remission in only 18%, while those COS patients with acute onset had a more benign course, with absence of remission in 40%, partial remission in 27%, and complete remission in 33%, all according to the DAS global psychosocial adaptation score. Their second study sample,

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consisting only of acute-onset COS cases, showed no remission in 50%, and 5% with partial remission, and 25% with very good remission. Children with the age of onset before 12 years showed more premorbid abnormalities within the M-PAS global score, which was associated with greater social impairment later in the disease course [19]. Another 42-year follow-up study of COS patients found only 16% with good outcome and 24% with moderate outcome according to the Global Assessment Scale (GAS), high incidence of severe or moderate depressive symptoms according to BPRS depressive scores (62.5%), high mortality rate (39.5%), and retrospective diagnostic stability in 91% of COS cases [20]. Earlier age of onset positively consistently correlated with the severity of disorder course, so that the timeline clinical progression of COS depends on the age of onset and IQ score at the time of first appearance of symptoms [21]. In this regard, COS patients continue to have more and longer hospital admissions throughout their lives [22].

According to the study by Inoue et al. [23], 47% of COS patients were unable to work at follow-up, 16% had limited work ability, 21% were working at lower level than previously, and only 16% were working as before. A follow-up study of 18 COS patients with onset from 6 to 11.3 years reported minimal improvement by the Children's Global Assessment Scale in 44% of the cases, deterioration in 17%, moderate improvement in 28%, and good improvement in 28% [24]. A systematic review of 21 studies, including very-early- and early-onset schizophrenia, demonstrated poor outcome in 60.1%, moderate outcome in 24.5%, and good outcome in 15.4% by diagnoses, and, respectively, 58.7%, 27.0%, and 14.3% according to general functioning and 54.5%, 30.5%, and 15.0% in study-specific functioning, with dropout rates ranging from 18.8% to 49.1% [15]. Vernal et al. [25] reported no cases of good outcome in patients with early-onset schizophrenia treated with aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone and high discontinuation rates (40.8%) at 12 weeks of treatment because of patients' or family decision (18.0%), side effects registered by the practitioner (12.3%), or a lack of efficacy (11.5%).

MRI rescan studies have shown *progressive brain abnormalities* in COS patients, notably an ongoing loss of gray matter volume during childhood extending through early adulthood; loss was seen in frontal, temporal, and parietal cortical areas and in the total brain volume, with these effects seemingly being specific to COS rather than other psychoses [26–28]. Moreover, the extent of cortical thinning in COS patients is strongly related to their cognitive/executive dysfunction [29]. Among many regions, both cortical and subcortical, with volume loss in that study, hippocampal volume reduction and shape abnormalities were significantly associated with COS [30] in relation to worsening negative symptoms and declining global functioning [31]. Others have attributed these effects rather to medication side effects [32] or neurodevelopmental disease progression [33].

Consistent with data for schizophrenia of all types, COS is also characterized by greater dilation of the ventricles, especially the lateral ventricles, but also the fourth ventricle, to an extent that is not found, for example, in adolescent-onset schizophrenia [34–36]. White matter abnormalities and structural connectivity damage are also observed in COS, as they manifest during the vulnerable pre-pubertal period of brain development and brain maturation, characterized by active synaptic pruning and completion of myelination; these pathological changes in white matter presented significantly worse in COS cases accompanied by prominent language impairments [37]. In turn, language impairments and thought disorders in COS are linked to specific abnormal patterns of functional specialization for semantic and syntactic processing of language and are ultimately an important factor in social interaction difficulties later in life [38].

Early detection and early treatment interventions are of priority for COS patients [39–41]. Early detection, management, and integrated-care programs like EPPIC and ACCESS III are useful to improve the efficacy and quality of therapy in young patients with psychoses [39, 42]. In 2013 NICE detailed clinical guidelines for psychosis and schizophrenia in children and young people that should be used for first-episode

psychosis COS patients. One of the relevant recommendations by AACAP [43] states that patients at risk of developing psychosis must be monitored using screening questions for psychosis, and at different stages of physical and psychosocial development: "Youth with suspected schizophrenia should be carefully evaluated for other pertinent clinical conditions and/or associated problems, including suicidality, comorbid disorders, substance abuse, developmental disabilities, psychosocial stressors, and medical problems." As stated above, antipsychotic pharmacotherapy is the first-line treatment modality for COS [43–47]. As such, COS patients are the youngest recipients/consumers of antipsychotic treatments and are particularly at risk for severe side effects, while having higher discontinuation rates, primarily due to inefficacy rather than other reasons [13, 25, 47, 48]. Researchers consider that the antipsychotic medications are apt to perturb brain development in children, leading to gray matter loss [49, 50].

Among *atypical antipsychotics*, aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone are FDA-approved for the indications of schizophrenia in adolescents after the age of 13 [51, 52]. According to the list of first- and second-generation antipsychotics recommended for COS schizophrenia patients by clinicians, *clozapine* remains the drug of choice for treatment-resistant cases, with good short-term efficacy and bringing good response in long-term maintenance [53]. Particularly, clozapine was more effective in reducing positive symptoms and alleviating the negative symptoms compared to risperidone, fluphenazine, and olanzapine [53]. However, the side effects caused by clozapine remain severe and present more often in children than in adults [54–56]. A combination of antipsychotics (e.g., clozapine plus risperidone) has been suggested for treatment-resistant cases as well, while risperidone alone causes a high incidence of extrapyramidal side effects in children and adolescents [48, 57]. Among the second-generation antipsychotics, SGAs, olanzapine also showed good efficacy in treatment-resistant COS cases, with lower dropout rate [58–60] and less increases in plasma prolactin and cholesterol than seen with risperidone [61–63]. However, olanzapine has been shown to provoke the largest weight gain, which is critically important in terms of cardiometabolic risks, in comparison to clozapine, risperidone, and quetiapine, whereas the least weight gain was observed with aripiprazole [62].

As a general principle, the treatment choice should consider all data on *efficacy, safety, and tolerability of the treatment* [40, 64], and the indications should be made using the available knowledge on adverse effects. The more serious are metabolic side effects, which were less pronounced with molindone, ziprasidone, fluphenazine, haloperidol, and aripiprazole and higher with drugs such as clozapine, olanzapine, thioridazine, mesoridazine, sertindole, risperidone, and quetiapine [65]. The extrapyramidal side effects [48, 66] are also relevant factors in treatment choice, as is FDA approval for use in children during early interventions in COS [52]. Among FDA-approved SGAs, risperidone and aripiprazole serve as the first-line treatment strategy for children and adolescents, with a preference to weight-neutral aripiprazole [67, 68], which is also less apt to provoke extrapyramidal side effects.

The use of *electroconvulsive therapy (ECT)* in children and adolescents has not been systematically studied, but it may be indicated for severely impaired adolescents if antipsychotic medications are not helpful or cannot be tolerated [43]. In proposing ECT as a treatment option for a young patient, the clinician must balance the risks and benefits of ECT use, considering the severity of disorder and patients' attitude, and must obtain informed consent from parents or caregivers, predicated upon a detailed discussion of potential complications. There is emerging evidence that COS patients may benefit from *transcranial direct current stimulation* [30].

Non-medical treatments include cognitive remediation [21] and cognitive therapy focusing on the basic life, social, and communication skills [69], family-focused interventions, and therapy identifying the family members with high emotional expression [70]. Other approaches include rehabilitation and assertive community treatment, as well as other psychosocial interventions

focusing on adaptation in the educational system [45, 71, 72]. The outcome of COS is considered to depend on effective treatment strategies entailing the *combination of antipsychotic pharmacotherapy with psychotherapy, psychoeducation, and social support programs* [4, 43, 72], but there remains a need for well-designed, prospective studies to substantiate the optimal treatment approaches according to evidence-based criteria.

Evidence-Based Outcome of COS in Response to Pharmacological Treatment

The rate of prescriptions of antipsychotic drugs for children has significantly increased since its approval for use in the pediatric population, and this may prove to be a factor in COS outcome [36, 73]. Particularly, the SGA and TGA (third-generation antipsychotics) medications [61] have been used more often because of their better safety in COS patients compared to the FGA medications [40, 47]. The antipsychotic medication recipients in the USA—7% of whom were children and adolescents in 1996–1997—had risen to 15% in 2004–2005 [74]. Wong et al. [75] in a study of prescribing trends in nine countries in the period 2000–2002 found a significant increase in antipsychotics prescriptions for children in seven countries (Argentina, Brazil, Canada, France, Germany, Mexico, and Spain), beside the USA and UK. A longitudinal study of the dispensing in Australia from 2009 to 2012 demonstrated that the prescriptions of antipsychotics to children increased by 22.7% in that interval, with the most rapid increase occurring in children aged 10–14 (49.1%), a cohort including COS patients, with risperidone being the most common antipsychotic prescribed to children under 15 and quetiapine in adolescents and young adults (15–24 years) [76]. A survey of Medicaid claims in the USA from 2001 to 2005 reported that around 75% of young patients with schizophrenia-spectrum disorders discontinued their treatment with atypical antipsychotic drugs (1745 participants using aripiprazole, risperidone, quetiapine, olanzapine, or ziprasidone) within 1.5 years from the treatment start [77]. A randomized double-blind study called the Treatment of Early Onset Schizophrenia Spectrum Disorders Study (TEOSS) compared olanzapine, risperidone, and molindone in young COS patients, revealing that less than 50% of 119 patients responded over 8 weeks of acute treatment and no evident difference in efficacy between antipsychotics [78]. Depot forms of antipsychotics have not been studied in the category of children and adolescents, and thus their prescription should be avoided unless justified by chronic course and poor adherence to ordinary treatment [43].

The evidence base to guide pharmacotherapy of very-early-onset schizophrenia is limited, but increasing efforts to rank different drugs in terms of their efficacy, tolerability, and safety—particularly regarding COS outcome—have not proven any particular drug to be superior; but see detailed reviews for comparison between antipsychotics in children and adolescents in Fraguas et al. [62] and Stafford et al. [13]. There is, at present, insufficient information on the impact of the specific pharmacological intervention on COS outcome, also because of ethical issues in research in children and adolescents; thus, most COS patients in the available studies received their treatment as usual [15]. Measuring *the outcome of COS in response to pharmacotherapy*, Stafford et al. [13] discussed the need to undertake:

1. Primary examination of psychotic symptoms (total, positive, negative), relapse at post-treatment, and follow-up
2. Secondary analysis of the symptoms of depression, anxiety, global state, discontinuation rates, weight gain, and other adverse effects

The literature reviews studies measuring the response of COS patients to different antipsychotic pharmacotherapy and efficacy using different clinical scales (e.g., BPRS, CGAS, GFS, PANSS, SANS, SAPS), more often classifying *the general outcome of treatment* as (1) good, (2) moderate, or (3) poor [15, 19, 20, 24, 25, 40, 53, 79].

Table 28.1 The safety profile related to the most common side effects caused by antipsychotics use in children and adolescents with schizophrenia

Drug name	Side effects		
	Extrapyramidal symptoms	Hormonal (prolactin level increase)	Metabolic (weight gain)
Aripiprazole	+/++[a]	+	+
Clozapine	+	+	++
Haloperidol	+++	+++	+
Olanzapine	+/++[a]	++	+++
Quetiapine	+	+	++
Risperidone	+/++[a]	+++	++
Ziprasidone	+	+	+

+ low, ++ moderate, +++ high
[a]dose-related (based on Amor [51]; Caccia et al. [80])

The antipsychotic drug choice should be based on their *safety profile*, which calls for priority for SGA and TGA versus FGAs (first-generation antipsychotics), due to the propensity of FGAs to cause more often acute side effects, notably extrapyramidal symptoms (EPS), as shown in Table 28.1 [46, 80]. Indeed, EPS are adverse effects frequently occurring in response to FGA treatment, especially in drug-naïve patients. These effects include mild to severe dystonias, manifestating with laryngospasm, cramps, and pain in the head, neck, and back muscles [68, 81], which are also observed in patients treated with high doses of risperidone. Life-threatening neuroleptic malignant syndrome has been reported in children in response to SGA treatment, including risperidone, olanzapine, and aripiprazole, starting during the first 2 weeks of treatment, with mean recovery between 7 and 10 days and mortality rates as high as 10–20% [67, 68]. Thus, antipsychotic drug safety profile is a red line in the treatment strategy of COS patients [68]. However, SGA and TGA are characterized by frequent and serious adverse effects including weight gain, metabolic complications, and elevated prolactin levels [56, 68]. Particularly, COS patients may experience more severe adverse effects from SGAs than do patients with adult-onset schizophrenia [82], so the individual drug choice is critical in COS and requires careful monitoring [56, 68]. Carmel and Gorman [65] proposed a classification of antipsychotics *according to their level of metabolic risks*, where:

1. The low metabolic risk antipsychotic drugs are *molindone*, *ziprasidone*, *fluphenazine*, *haloperidol*, and *aripiprazole*.
2. The higher metabolic risk antipsychotic drugs are *clozapine*, *olanzapine*, *thioridazine*, *mesoridazine*, *sertindole*, *risperidone*, and *quetiapine.*

Sedation, somnolence, and fatigue are also very important side effects causing school and learning difficulties in children and adolescents, occurring in 46–90% of patients using clozapine, 44–94% for olanzapine, 29–89% for risperidone, 25–80% for quetiapine, 42–69% for ziprasidone, and 33% with aripiprazole [56].

There is presently inadequate evidence from observational studies and randomized controlled trials of antipsychotic medication, mostly short-term studies in populations of children and adolescents. As such, the NICE guidelines for adults with schizophrenia adults (2009) should be also used, *faut de mieux* [56, 61, 83]. The treatment choice should be also based on the recommendations prepared by McClellan and Stock [43] as an AACAP official action called "Practice parameter for the assessment and treatment of children and adolescents with schizophrenia."

Lachman [48] recommends the following steps within the treatment algorithm for the special category of children with first-episode psychosis:

1. Comprehensive assessment, including different kinds of risks, the initial duration of then

symptomatic period, and comorbidities occurring before the psychosis onset.
2. Embrace diagnostic uncertainty.
3. Treatment in the least restrictive setting (premorbid diagnosis of post-traumatic stress disorder, minimization of adverse experiences in acute psychiatric wards, evaluation of the degree of family support).
4. Concurrent psychosocial interventions (cognitive behavioral treatment in individual format and group therapy, with structured exercises addressing insight about emotions of self and others, management of temper outbursts, problem-solving, social skills training, cognitive rehabilitation, and family interventions, aimed to reduce the rates of relapse and re-hospitalization).
5. Pharmacotherapy (treatment with antipsychotic drugs). According to the Schizophrenia Patient Outcomes Research Team recommendations, patients with first-episode psychoses should be treated with lower doses of antipsychotics than patients with schizophrenia in general, suggesting that lower doses are as effective as higher doses in first-episode patients [84].

Kendall et al. [83] recommend that the choice of antipsychotics should be made not only by healthcare professionals but also by the parents or caregivers of children and adolescents, considering *all the side effects of each drug*:

- Metabolic, including weight gain and diabetes
- EPS, including akathisia, dyskinesia, and dystonia
- Cardiovascular, including prolonging the QT interval
- Hormonal, including increasing plasma prolactin
- Others, including unpleasant subjective experiences

Following the 2009 NICE guidelines, Kendell et al. [83] provide a list of important points *necessary to monitor and record* during the treatment of children and adolescents with schizophrenia, especially during the period of drugs titration:

- Efficacy, including changes in symptoms and behavior
- Side effects of treatment, considering overlap between certain side effects and clinical features of schizophrenia (e.g., the overlap between akathisia and agitation or anxiety)
- The emergence of movement disorders
- Body weight, weekly for the first 6 weeks, thereafter at 12 weeks, and then every 6 months (plotted on a growth chart)
- Height every 6 months (plotted on a growth chart)
- Waist and hip circumference every 6 months (plotted on a centile chart)
- Heart rate and blood pressure (plotted on a centile chart) at 12 weeks and then every 6 months
- Fasting blood glucose, HbA_{1c}, blood lipids, and prolactin levels at 12 weeks and then every 6 months
- Adherence
- General physical health

All these measures might be also included as endpoints in further studies of antipsychotic treatment in COS.

As mentioned above, it is formally necessary to consider the list of *FDA-approved antipsychotics* with indication of schizophrenia (Table 28.2). To ensure a safer treatment course, it is important to use antipsychotics approved for the category of children and adolescents [51, 80]. In terms of FDA approval, risperidone and aripiprazole constitute the first-line treatment in children and adolescents with schizophrenia [67, 85]. The weight gain effect is much greater with risperidone, compared to weight-neutral aripiprazole [67]. Though the experience using aripiprazole is insufficient to support firm conclusions, its efficacy and tolerability properties favor its use in COS patients [68]. Clinical guidelines by McClellan and Stock [43] state that children and adolescents with schizophrenia may benefit from adjunctive medications addressing the side effects of antipsychotics (e.g., antiparkinsonian

Table 28.2 FDA-approved antipsychotics for children and adolescents with schizophrenia indication[a] [52]

First-generation antipsychotics		Atypical antipsychotics		
Drug name	Age group	Drug name	Age group	Dosage
Chlorpromazine	1–12 years	Aripiprazole (Abilify)	13–17 years	2–10 mg/day; max 30 mg/day
Loxapine	≥12 years			
Perphenazine	≥12 years	Olanzapine (Zyprexa)	13–17 years	Start 2.5–5 mg/day; target 10 mg/day
Prochlorperazine	>2 years, >9 kg	Paliperidone (Invega)	12–17 years	Weight < 51 kg: 3–6 mg/day; ≥51 kg: 3–12 mg/day
Thiothixene	≥12 years			
Thioridazine	Children	Quetiapine (Seroquel)	13–17 years	400–800 mg/day
Trifluoperazine	≥6 years	Risperidone (Risperdal)	13–17 years	1–6 mg/day

[a]Haloperidol is not FDA-approved for children and adolescents with schizophrenia but used in COS patients (2.5–10 mg/day); clozapine is not FDA-approved for children and adolescents with schizophrenia but widely used (150–400 mg/day), especially in treatment-resistant COS cases

agents to cope with extrapyramidal side effects, β-blockers for akathisia, mood stabilizers for aggression, benzodiazepines for anxiety, insomnia, initial stages of catatonia) or alleviating associated symptomatology (e.g., agitation, mood instability, depression, explosive outbursts), but further trials should be performed.

There are several newer antipsychotics, which have not yet been approved for the treatment of COS and early-onset schizophrenia due to their side effects, including iloperidone (Fanapt), asenapine (Saphris), and lurasidone (Latuda) [86]. Some SGAs have not been approved by the FDA for pediatric patients, but are prescribed off-label and used in research involving children and adolescents with COS [47, 80]. For example, clozapine is not approved by the FDA for children with schizophrenia, but several studies show its efficacy in COS patients [53]. Considering the preference for SGA and TGA versus FGA medications regarding the safety profile and differences in side effect profiles encountered in COS patients, we below describe the features of COS outcomes in response to the most commonly used antipsychotics in this category of patients.

Clozapine

A number of short-term studies lasting from 6 to 8 weeks have demonstrated better efficacy of clozapine compared to risperidone, fluphenazine, and olanzapine in relation to the reduction of positive symptoms and alleviating negative symptoms in COS patients [53, 87]. Two randomized studies have shown the superiority of clozapine over typical and atypical antipsychotics in COS patients' treatment [81, 88]. The comparison of clozapine efficacy over other antipsychotics demonstrated the effect size to be 0.848 (85 participants, CI 0.748–0.948), demonstrating that clozapine was distinctly more efficacious [89]. A parallel randomized double-blind study by Kumra et al. [90] including 39 COS patients with treatment-refractory schizophrenia of mean age 11.8 ± 2.9 years old at the time of onset compared treatment using clozapine (403 ± 202 mg/day) and high-dose olanzapine (26.2 ± 6.5 mg/day) and found better efficacy for clozapine in relation to negative symptoms as measured by SANS after 12 weeks (Scale for the Children's Global Assessment Scale, Assessment of Negative symptoms), $p = 0.02$, Cohen's $d = 0.92$. Two small sample studies, including 11 and 2 COS patients, demonstrated association between high plasma concentration of clozapine and better clinical response [81, 91]. Another double-blind and open-label study by Sporn et al. [55] including 55 COS patients reported on clinical improvement measured with BPRS and SAPS after 6 weeks; improvement was strongly associated with the ratio of the clozapine metabolite N-desmethylclozapine (NDMC) concentration to clozapine, which serves as a predictor of

treatment response. Sporn et al. [55] also found a higher rate of side effects (6% neutropenia, 15% akathisia) than in adult patients (1–2% neutropenia, 3% akathisia), but these side effects were not related to clozapine dose or the plasma concentrations of clozapine or NMDC. In that study, long-term outcome (Children's Global Assessment Scale) at 2- to 6-year follow-up was associated with lesser illness severity at baseline and greater improvement during the first 6 weeks of therapy using clozapine.

Treatment-resistant cases of COS can benefit from clozapine therapy due to its high antipsychotic efficacy in acute episodes, more prominent improvement in adolescents with chronic course of the disorder, and better safety in terms of EPS [5, 54]. Clozapine is reported to be more effective in relation both to positive and negative symptoms improvement in COS and to the decreased incidence of EPS and tardive dyskinesia compared to conventional antipsychotics [81, 92]. Nevertheless, electroencephalographic monitoring is recommended at the start and at every 6 months of treatment after reaching the optimal clozapine dose, as it brings a dose-dependent risk of epileptic seizures in children and adult patients [68]. Centorrino et al. [93] point to the higher risk of electroencephalographic abnormalities during the clozapine treatment pine (47%), compared to olanzapine (39%), risperidone (28%), FGA (15%), and quetiapine (0.1%).

Hematological side effects, including greater risk of early- (during first weeks of therapy) and late-onset neutropenia and agranulocytosis, are described in adolescents treated with clozapine, which requires careful monitoring [67, 68, 94]. However, the study by Midbari et al. [95] demonstrated that clozapine is rather safe for COS patients, with incidence of hematological side effects not much higher compared to that from other antipsychotics. Furthermore, these events were transient, allowing resumption of clozapine treatment after their resolution. This study included 17 COS inpatients treated with clozapine and 19 COS inpatients receiving other antipsychotics with follow-up of less than 1 year. Moderate and mild transient neutropenia was observed in two children (12%) in the clozapine group and one child (6%) in the non-clozapine group, with only one clozapine-treated patient discontinuing the therapy. There were no cases of agranulocytosis registered in the clozapine group, while two children (11%) in the non-clozapine group had developed this complication. One patient (6%) in the clozapine group demonstrated hyperlipidemia. On the other hand, Kim et al. [96] reported that neutropenia developed in 27% patients with very-early-onset schizophrenia at 1-year follow-up of clozapine treatment, but agranulocytosis was not registered. However, cardiological side effects were significant in response to clozapine, with 47% of clozapine-treated children experiencing tachycardia compared to 5% in the non-clozapine group ($p < 0.05$) [95].

Kasoff et al. [53] reported a long-term clozapine maintenance rate of 87 of 12 (72.5%) COS patients treated with dosages ranging from 50 to 900 mg/day (median 500 mg/day), which is higher than in adult-onset schizophrenia patients. The authors argued that clozapine demonstrated better efficacy in COS patients than in patients with adult-onset and that COS patients were significantly more responsive to clozapine treatment. In a 20-year follow-up open study, the mean duration of clozapine treatment was 6.9 ± 5.0 years, ranging from 1.0 to 23.5 years, and only 8.3% (10/120) of treatment-resistant, chronic COS patients discontinued the clozapine treatment [53]. The study of COS cases refractory to treatment found that 96% (25) patients showed a significant reduction in hospital days per year with clozapine compared to their previous medication [96]. The long-term benefit was also confirmed by further decrease in hospitalization rates during 3 years of therapy with clozapine, and most patients who experienced side effects nonetheless maintained the treatment with clozapine.

Haloperidol

Typical neuroleptics were recognized as effective in children and adolescents, and many of the FGAs are FDA-approved for children (see Table 28.2). A study including 16 children and

adolescents with schizophrenia aged from 5.5 to 11.7 years found haloperidol to be superior compared to placebo [97]. Meta-analysis by Sarkar and Grover [89] reported that haloperidol had the highest effect size in comparison to placebo followed by risperidone, olanzapine, and paliperidone prescribed at medium doses, aripiprazole and quetiapine at higher-than-usual doses, lower-dose aripiprazole, high-dose paliperidone, lower-dose quetiapine, and lower-dose paliperidone. Comparison of FGA such as haloperidol versus placebo demonstrated an effect size of 2.9 (31 patients, CI 1.368–4.528), while SGA versus placebo had an effect size of only 0.45 (1308 participants, CI 0.414–0.542). On the other hand, haloperidol has shown lesser efficacy in reducing psychotic symptoms than did atypical antipsychotics including clozapine [81]. In a 6-week parallel randomized double-blind study, COS patients had significantly worse improvement when treated with haloperidol (16 ± 8 mg/day) compared to clozapine (176 ± 149 mg/day) in relation to positive symptoms measured by SAPS (p = 0.01, Cohen's d = 0.675), negative symptoms by SANS (p = 0.002, Cohen's d = 1.156), general clinical symptoms by BPRS (p = 0.04, Cohen's d = 0.258), and global functioning by CGAS (p = 0.01, Cohen's d = 1.370) [81].

Seventy percent of children and adolescents with schizophrenia experienced significant EPS when treated with haloperidol [67]. A small-sample non-randomized study by Gothelf et al. [98] also demonstrated that haloperidol was associated with a higher frequency of depressive symptoms and more severe EPS in COS patients than in those treated with olanzapine and risperidone. However, haloperidol at a dose of 2.5–10 mg/day did not provoke any significant weight gain side in adolescents [99].

Olanzapine

A 1-year open-label study of olanzapine in COS patients demonstrated improvement in positive psychotic symptoms after 6 weeks of treatment and significant improvement in negative symptoms after 1 year of follow-up [100]. In a 12-week study of olanzapine administration to nine chronic COS treatment-resistant patients, there was a preliminary washout period lasting 2 weeks followed by a gradual increase of drug dose from 5 mg/day on day 5 to 10 mg/day in week 3 (five patients received 20 mg/day). These patients showed only mild side effects and no EPS, but had a significant mean weight gain of 6.10 ± 3.25 kg, and showed somnolence [59]. After attaining the mean olanzapine dose 15.6 ± 4.6 mg/day, the mean BPRS scores had decreased from 54.9 ± 12.2 to 37.3 ± 18.6 and mean total PANSS scores from 123.6 ± 20.3 to 96.7 ± 27.0, including both positive and negative scales. The CGI score decreased by 23.5%. At 1-year follow-up of treatment with olanzapine, there was still a significant improvement in psychotic symptoms in eight of nine patients. In this group, four children were well-integrated in families, communities, and schools for special education, four were placed in special rehabilitation boarding schools, and one was re-hospitalized with relapse after enjoying 6 months of stable improvement [59]. However, another study by Kryzhanovskaya et al. [101] reported about a lower (38%) response rate for olanzapine and no difference compared to placebo in adolescents with schizophrenia.

Kumra et al. [58] investigated response of COS patients to olanzapine treatment, reporting various side effects, including increased appetite, nausea, headache, somnolence, insomnia, nocturnal enuresis, transient elevation of liver transaminase levels, agitation, insomnia, tachycardia, and difficulty concentrating. The prospective study of 50 adolescents with schizophrenia demonstrated a mean 11% weight gain in 91% of patients over 12 weeks of olanzapine treatment at a dose of 2.5–20 mg/day [99]. The retrospective study by Mandoki [102] included COS patients who switched from clozapine treatment to olanzapine; both antipsychotic drugs had similar efficacy, but olanzapine caused fewer side effects of lower severity than did clozapine. An open-labeled nonrandomized uncontrolled treatment using olanzapine at a dose of 5 mg/day over 8 weeks in 15 children aged 9.4 ± 2.0 years (of whom nine were under the age of 10 years) with

acute-onset schizophrenia reported on predictors of better response and safety with this treatment [103]. They found that sedation was the most common side effect occurring during the first 2 days of treatment, while weight gain was not registered during short-term inpatient course, and that greater initial sedation was associated with better clinical response. They also found that younger age and de novo treatment with olanzapine correlated with better clinical response.

There was no global effect on gray matter development and cortical thickness in COS patients treated with clozapine or olanzapine, but there was with some evidence of increased gray matter volume in the medial prefrontal cortex with olanzapine [104]. However, since 2010, the official Ziprexa black box states that "clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents."

Risperidone

Use of risperidone in combination with carbamazepine may decrease the serum level of risperidone, presumably due to induction of hepatic enzymes [105]. Treatment with risperidone (0.5–6 mg/day) provoked an increase in body weight of 6.6 ± 8.6%, whereas olanzapine caused an even greater weight gain, and haloperidol did not alter weight in a study of 50 adolescent patients [99]. An open-label study of risperidone in adolescents with schizophrenia reported that 14% of adolescents experience a gain weight of 9 kg after 8 months of treatment, with the most abrupt increase after the first 2 months of therapy [105]. The elevation in prolactin levels was significantly greater in the group of children and adolescents receiving risperidone (2.2 ± 2.0 mg/day), olanzapine (7.8 ± 4.2 mg/day), and quetiapine (283 ± 223 mg/day), but the duration of this side effect was not reported [106]. A study of COS patients by Gothelf et al. [98] reported that risperidone had similar efficacy against positive and negative psychotic symptoms as haloperidol and olanzapine, but with lesser incidence of fatigue.

A 12-week-long comparative study by Mozes et al. [60] included 25 COS patients aged 11.1 ± 1.6 years treated with risperidone (mean dose 1.6 ± 1.0 mg/day) or olanzapine (8.2 ± 4.4 mg/day). Both patient groups demonstrated a significant decrease of PANSS scores and similar scores in the Barnes Akathisia Rating Scale (BAS). Here, akathisia was observed in three olanzapine-treated children and one risperidone-treated child and EPS in seven olanzapine- and eight risperidone-treated children. There were similar Simpson-Angus Scale (SAS) scores and weight gain (5.8 ± 3.1 kg for the olanzapine-treated and 4.5 ± 2.9 kg for the risperidone-treated children). However, only 69% of patients treated with risperidone completed the study, compared to 92% of olanzapine group, indicating a higher dropout rate in the risperidone group.

Other Important Antipsychotics: Aripiprazole, Paliperidone, Quetiapine, and Ziprasidone

Aripiprazole, paliperidone, and quetiapine are FDA-approved for COS patients, and ziprasidone has been used off-label. A multicenter randomized double-blind placebo-controlled study of oral aripiprazole in 302 patients by Findling et al. [107] supported the prescription of aripiprazole in adolescents with schizophrenia and demonstrated its efficacy in COS-diagnosed patients. EPS occurred in 25% of adolescents treated with aripiprazole, compared to 7% for placebo and 13% in adult patients. There is also a strong caution about the need for careful monitoring for any increase in suicidal thoughts in children and adolescents treated with aripiprazole [108].

According to a meta-analysis by Sarkar and Grover [89], paliperidone efficacy was of lowest effect size (0.13) among the list of FGAs and SGAs used in COS when compared to placebo. Periodic monitoring of weight gain (mild to moderate increase is registered), HbA1c level, blood glucose level, and lipid panel is recommended according to clinical trial results with paliperidone [109]. However, there were few EPSs, and

cardiac monitoring is not required, as only mild QT prolongation was seen in clinical trials. Dizziness, orthostatic hypotension, tachycardia, and dry mouth may occur with paliperidone.

In clinical trials, quetiapine brought increased risk of hypertension in children and adolescents, such that periodic blood pressure monitoring is recommended [110]. Also, quetiapine may increase suicidal thoughts in children and is notable for the high level of sedation, dry mouth, and orthostatic hypotension, although no renal adjustment is necessary and drug-drug interactions are not common. Quetiapine is almost without effect on electroencephalographic recordings, compared to the moderate-to-severe electroencephalographic effects associated with clozapine, olanzapine, and risperidone [93].

In an open-label prospective trial of low-dose ziprasidone (≤40 mg/day) in 20 pediatric outpatients treated for up to 6 months, there were significant deviations from the baseline heart rate and pronounced QT interval prolongation, which was not related to the antipsychotic drug dose [111]. Therefore, close electrocardiographic monitoring is required when prescribing ziprasidone to children.

Evidence-Based Outcome of COS in Response to Psychosocial Treatment

Remschmidt [5] analyzed 18 follow-up studies in relation to the course and outcome of early-onset schizophrenia and concluded that psychological, family, and social factors indeed influence schizophrenia outcome. Several studies reported that children and adolescents who were socially active, intelligent, and well-integrated during their premorbid phase experienced better prognosis than those who were introverted, shy, or cognitively impaired [79, 112]. Children without any family anamnesis of schizophrenia and with good cooperation within the family demonstrated more rapid improvement during hospitalization [113]. Van Winkel et al. [114] have reported that environmental factors (psychosocial factors, expression of emotion in the family) may interact in a bidirectional manner with biological risk factors and moderate such parameters as the time of onset, features of disease course, relapse rates, and the severity of disorder. A healthy home environment may serve as a protective factor for children with a familial risk of schizophrenia [115]. These data support the importance of family and cognitive and psychosocial interventions during COS patients' treatment. It is important that children and their families receive early interventions to influence "the course of the illness and to allow for more normal development, less significant psychotic episodes, and the possibility of complete or partial remission" [70, 116].

There are insufficient studies available to evaluate the evidence-based effect of psychosocial interventions in children and adolescents with COS [13, 43]. Stafford et al. [13] have analyzed eight clinical trials studying psychological interventions (mostly cognitive behavioral therapy, i.e., CBT) in patients under the age of 25 years, but there was no such data for children and adolescents. The meta-analysis found only scant evidence that CBT together with family interventions had statistically significant effect on extending the relapse time. Jackson et al. [117] demonstrated the benefits of cognitive recovery interventions over treatment as usual in 66 patients with first-episode psychosis with different age of onset in reducing trauma and enhancing improvement at 6 and 12 months of follow-up. Linszen et al. [118] demonstrated that inpatient therapy in combination with psychoeducation for parents, followed by an outpatient psychosocial intervention program, has a good impact on protecting against relapse at follow-up of 12 months, albeit that additional family interventions may increase stress in families with low emotional expression and consequently increase risk of relapse. Wykes et al. [119] reported that a 3-month cognitive remediation therapy, compared to standard therapy, improved the planning ability and cognitive flexibility in adolescents with psychosis. Lower rates of re-hospitalization were registered in response to psychoeducation (patients' and parents' seminars), problem-solving sessions, milieu therapy during inpatient treatment, and community networking at the stage of returning to school [120]. Significant improve-

ments in visual information processing were observed after the course of psychoeducation in combination with cognitive remediation at the long-term 1-year follow-up [121, 122].

Practice parameters developed by AACAP emphasize the necessity of combining antipsychotic medications with psychoeducational, psychotherapeutic, and social and educational support programs [43] such as (1) family-focused interventions, (2) individual psychotherapy, (3) skills training, (4) cognitive remediation, and (5) rehabilitation and assertive community treatment. Interventions addressing comorbid states are very important to reduce the risk of relapse and enhance the quality of functioning. In order to deliver psychological interventions properly in children and adolescents with schizophrenia, Kendell et al. [83] recommend taking into account the patient's developmental level, emotional maturity, and cognitive capacity, including existing learning disabilities, sight, hearing impairments, and language delay.

Work with the family is very important, both because abnormal emotional communication within the family may influence the COS psychosis onset and because family communication is dramatically changed after the onset of psychosis in a young family member [70]. These authors also state that it is necessary to educate culturally competent therapists, suggesting that a biopsychosocial culture of schizophrenia and specific schizophrenia family culture do indeed exist, although this controversial notion was long rejected. Interactions in the family with members suffering from psychosis are characterized by a high level of disruption [9] and are diversely impacted when parents experience violence, verbal aggression, and withdrawal from their child, and they will feel loss of self due to the necessity of concentrating on their ill child, often requiring them to change their working schedules and social community activities [123]. Family members experience a high emotional burden, confusion about what to do, and difficulty in thinking optimistically about the future, while siblings of COS patients often experience feelings of loss and sadness [124, 125]. Chaotic experiences of disintegration in families with schizophrenia may be rescued through treatment strategies of structural family therapy offering the concepts of boundaries, coalitions, and hierarchy, as well as classic family system models, and multi-family therapy can also be helpful [70, 126, 127]. Kuipers [128] reported that reducing the high levels of expressed emotions (criticism, hostility, intrusiveness, over-involvement in relationships of family members) protects against relapse of symptoms in a child with COS [10].

According to recommendations in NICE 2013 clinical guidelines for children and young people with schizophrenia [129], work with the patient's family should:

- Include the child or adolescent, if practical
- Be carried out during at least 3 months and up to 1 year
- Include at least ten planned sessions
- Take account of each family member's preference for the choice of either single-family or multi-family group therapy
- Take account of the relationship between the child/adolescent and parent/caregiver
- Provide a specific supportive, educational, or treatment function
- Include negotiated problem-solving strategies
- Include a component of crisis management work

In particular, during the process of family therapy, doctors should (1) be aware of their own feelings regarding the patient and the disorder and view the personality rather than the severe mental illness in order to provide proper support; (2) help the patient and family members to externalize the disorder and relationships in the family; (3) identify important life goals of family members distinct from the treatment of severe mental disorder; (4) avoid using terms of double-bind theory like "schizophrenic mother" and "schizophrenigenesis," which provoke blame and are not helpful in maintaining the treatment; (5) avoid the biased stance toward either the patient or family members, but rather take into account the family as a whole functioning system and work toward building trust between the therapist and the family unit by establishing a safe environment for the interactions; (6) find a balance helping the family to adapt together to the disor-

der, without treating family members like helpless victims, while not over-protecting them from their familial responsibilities; (7) not pathologize religious perspectives, as this may affect the delusional system of symptoms; (8) work as a grief counselor to help patient and family with feelings of grief, loss, sadness, depression, anxiety, and doubts about the future, aiming to foster appropriate hope and support an ability to cope with potential disappointments in the future; (9) work as an educator to explain the issues of pharmacotherapy and side effects and facilitate the opportunities to join rehabilitation and social support programs; and (10) be supervised by other experienced professionals working with families with psychoses to help them feel more confident with interventions and to be protected from health provider burnout syndrome and from adopting the role of savior [70, 130, 131].

A cognitive therapy approach, particularly for first-episode patients, should include an individual recovery plan, involving the components of:

- Engagement and formulation, trauma processing, and appraisals of psychotic illness [117, 132]
- Relapse prevention strategies [133]

Behavioral family management must consist of:

- Psychoeducation
- Communication training
- Development of problem-solving skills [118, 134]

CBT course should include learning strategies to enhance control of affective and psychotic symptoms and to reduce associated distress, suggesting the modules of:

- Stress management
- Depression and negative symptoms
- Positive symptoms
- Other comorbid states [135, 136]

The 2013 NICE clinical guidelines [129] state that CBT should be "delivered on a one-to-one basis over at least 16 planned sessions (although longer courses may be needed) and:

1. Follow a treatment manual so that:
   (a) Children and young people can establish links between their thoughts, feelings, or actions and their current or past symptoms and/or functioning
   (b) The re-evaluation of the child or young person's perceptions, beliefs, or reasoning relates to the target symptoms
2. Also include at least one of the following components:
   (a) Normalizing, leading to understanding and acceptance of the validity of their experience
   (b) Helping children and adolescents to monitor their own thoughts, feelings, or behaviors with respect to their symptoms or recurrence of symptoms
   (c) Promoting alternative ways of coping with the target symptom
   (d) Reducing distress
   (e) Improving functioning".

Cognitive therapy in COS patients includes psychoeducation about schizophrenia, pharmacotherapy, relapse prevention, social, basic life and self-care (grooming, hygiene, cooking, basic money management) skills training, vocational training, communication skills training (eye contact, self-advocacy, conversation skills, coping strategies), problem-solving strategies, and anger management [43, 69]. Many of these skills could be also trained during the process of education in schools [71]. Sometimes special tutoring services and school personnel support are necessary in addition to special education, depending on the level of cognitive deterioration of the child. Thus, open communication between school services and families should be organized, and the school psychologist may play a vital role in mediation and management of COS cases [71].

Summary

COS is a severe mental disorder leading to poor outcome in most patients. The age of onset and relapse rates depend on early detection and interventions in children in a (prodromal) state of high-risk developing psychosis. The first-line therapy

remains an antipsychotic pharmacological treatment with the preference given to SGA and TGA due to their better safety and side effect profiles compared to FGAs. The choice of antipsychotic drug is based on the individual patient's conditions and on the opinion of the patient's caregivers about the range of adverse effects of each drug. Pharmacotherapy should be carefully integrated into the whole system of treatment, including all available psychotherapy options (CBT, family therapy), psychoeducation, family interventions, and skills training. Healthcare professionals should enable the basic algorithm in treatment choice for COS patients and take the following steps within the treatment decision-making to improve a patient's clinical and social outcome:

1. Give priority to early detection and intervention according to clinical guidelines.
2. Check the safety profile of the intended drug in children and adolescents.
3. Check the adverse effects profile of the drug in children and adolescents.
4. Check the level of metabolic effects of the drug in children and adolescents.
5. Check the FDA approval of the drug for the indication in children and adolescents.
6. Consider the opinion of parents or caregivers related to the side effects of each drug.
7. Combine antipsychotic treatment with psychotherapy, psychoeducation, and social support programs.
8. Monitor and record all important aspects related to safety, tolerability, and efficacy of therapy at every successive stages of the follow-up.

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Index

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