Treatment-Refractory Schizophrenia

A Clinical Conundrum

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Preface

It is a far too frequent occurrence that patients with schizophrenia don't respond adequately or return to function using current pharmacological and non-pharmacological treatment approaches. As schizophrenia is fundamentally characterized by recurrent relapses, the extent to which a refractory treatment status represents a de novo, more severe form of psychosis or occurs in evolution over the course of a deteriorative illness is a fundamental consideration. Biological studies reveal a range of deficits and support, at least in part, the proposition that treatment-refractoriness worsens over time. Our field has struggled about when to introduce clozapine, the gold-standard antipsychotic medication for treatment-refractory schizophrenia, and at present this "drug of choice" is more often than not introduced too late in the course of illness. One reason for this is the highly variable efficacy of other antipsychotics in people where one anti-psychotic has already failed, with the sequential availability of each new antipsychotic seeming to relegate clozapine's position even further away from its use in early illness.

Once clozapine is tried, a proportion of patients will inevitably have an unsatisfactory outcome and how best to next treat these patients remains subject to clinical debate. A range of adjunctive medication strategies has been tried with variable success. The coming on line of new neuromodulatory approaches (e.g., repetitive transcranial magnetic stimulation) has provided more treatment options as well as renewed interest in the role of electroconvulsive therapy in this patient population. Cognitive and vocational approaches represent another avenue to bolster improved outcomes. Families play a fundamental role in advancing better outcomes in patients with recalcitrant schizophrenia. Unfortunately, one consequence of chronic and inadequately treated active psychosis is the propensity for poorer social outcomes. This remains a real source of concern, emphasizing just how far we have yet to travel on the journey toward effective, comprehensive, and well-integrated care for people with severe schizophrenia. Perhaps the emergence of pharmacogenetic approaches to individualized care might "move the dial" further toward better individual outcomes.

This book, with thirteen authoritative chapters by leading experts from across the globe, provides a timely overview of the current options for treatment of most severely ill patients with schizophrenia and a peek into future possibilities.

The book is clinically focused, with a view to helping the clinician apply the latest research evidence in both neurobiology and psychology to clinical practice. The content is wide-ranging, covering current pharmacological approaches to treatment nonresponse and treatment intolerance, various emerging add-on approaches, and a range of cognitive and psychosocial treatments. The contributors are highly regarded experts who have taken a translational approach, melding clinical experience with cutting-edge research to provide readers with an invaluable book on the fundamental aspects of clinical care for refractory schizophrenia.

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Psychotic illnesses affect between 2 and 3.5 % of the population (Perala et al. 2007) with schizophrenia accounting for 0.3–0.7 % (McGrath et al. 2008). The onset of schizophrenia is typically 3–4 years earlier in men, the incidence peaking at ages 21–25, with women showing a bimodal distribution with peaks at both 25–30 and perimenopausally (Falkenburg and Tracy 2014). Since the serendipitous discovery of chlorpromazine in the 1950s, the primary treatment of schizophrenia has been antipsychotic medication. Their introduction revolutionised the care of millions and heralded a process of enormous deinstitutionalisation and the end of the era of the asylum (Kirkby 2005). Nevertheless, it's becoming clear that they do not benefit everyone and the burden of treatment refractory illness remains an enormous personal, clinical and societal problem. There are several inherent difficulties in managing this treatment refractory patient group, including a lack of consensus on how to define the issue of refractory illness; uncertainty around which factors to give most attention to in the assessment; establishing treatment goals that are reasonable and rational; setting up a care plan when standard guidelines break down; and standardised monitoring for clinical changes.

It's not currently possible to predict those patients who will or will not respond to antipsychotic medication, and there is increasing interest in this area in order to better target our drug development of new compounds and also to establish better biomarkers for our existing medications. Reverse engineering of antipsychotic drug actions (Carlsson and Lindqvist 1963; Seeman et al. 1975) led to the dopaminergic

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hypothesis of schizophrenia and the conclusion that psychosis was caused by excess dopamine (DA) transmission in the brain. Whilst this was pragmatically useful—and all efficacious antipsychotics block DA D_2 receptors—subsequent developments showed such hyperdopaminergia was limited to the mesolimbic pathway, and there was a pathological dopamine deficit state in the mesocortical brainstem projections to the frontal lobes: 'positive' psychotic symptoms appeared correlated with the former over-active state and negative symptoms with the latter under-active one (Kapur 2003). In recent years, emerging evidence has accumulated for a putative primary glutamatergic deficit—with downstream effects on dopamine functioning—and there is considerable ongoing work trying to find effective medications that modulate the glutamate system (Papanastasiou et al. 2013; Sendt et al. 2012).

The push for novel antipsychotics has primarily been driven by the common problem of inadequate efficacy, compounded by adverse side effects, resulting in poor adherence to treatment. One in three patients with schizophrenia fails to show an adequate response to antipsychotic medication (Hasan et al. 2012). While newer 'atypical' or second-generation antipsychotics (SGA) offered diversity and improvements in the quality of patient care through decreased extrapyramidal side effects, the anticipated improvements in negative symptoms and cognitive symptoms—via a second pharmacodynamic action of pre-synaptic $5HT_{2A}$ antagonism—have not been supported by data. With the exception of clozapine, the SGAs were generally no more efficacious in managing positive symptoms than the older 'typical' or first-generation antipsychotics (FGA); had minimal effects on cognition and negative symptoms; and they demonstrated higher rates of metabolic side effects, with prominent impact on impaired glucose tolerance, dyslipidaemia and weight gain. The influential CATIE (Lieberman et al. 2005) and CUtLASS (Jones et al. 2006) studies clearly demonstrated that there was little to differentiate the efficacy of the atypical SGA antipsychotic drugs from the first generation and showed rather alarmingly high rates of medication discontinuation in both.

The impact of refractory illness is not just felt at the personal and family level but is also evident at the socio-economic level; exemplified by a mean reduction in life expectancy of between 15 and 20 years (Tandon et al. 2009), increased rates of substance misuse (Green et al. 2007) and suicide, and increased prevalence of physical comorbidities (Laursen et al. 2011), including some that are predominantly iatrogenic (Rummel-Kluge et al. 2010). Refractory illness does not only generate costs related to direct care but also exerts indirect influence on factors such as lost productivity—less than a third of sufferers attain employment (Marwaha and Johnson 2004)—and provision of informal care and carer burden: these social costs are considered to be significantly greater than the direct health-care costs (Zeidler et al. 2012). Indeed, Wu et al. (2005) estimated the costs in the USA in 2002 to be $62.7 billion, of which $22.7 billion was in direct health-care costs; in the UK Mangalore and Knapp (2007) estimated a total cost in 2004/2005 to be £6.7 billion, of which approximately £2 billion was in direct health-care costs.

1.1 Factors Affecting Outcomes in Schizophrenia

Schizophrenia is increasingly considered a spectrum dimensional disorder within a broader psychosis umbrella that includes bipolar affective disorders, with positive, negative, cognitive and affective symptom domains that—with the possible exception of negative and cognitive symptoms—are not significantly correlated with each other (van Os and Kapur 2009). This is supported by the genetic data—schizophrenia is a highly heritable but polygenetic disorder and can be conceptualised as a 'pathway illness' involving hundreds and possibly thousands of differing risk genes (Sullivan 2012). Fitting with this spectrum, the outcomes in schizophrenia are variable: routine treatment results in a consistent reduction in positive symptoms, but not in negative or cognitive symptoms; and half of first episode patients are still symptomatic a decade after initial assessment (Bromet et al. 2005). An international study (Harrison et al. 2001) evaluated outcomes of 1,633 subjects across 14 culturally diverse population groups: they reported that the frequency of psychotic symptoms in the first 2 years was predictive of outcome after 15 years. Episodic illness—defined as no episode lasting greater than 6 months—had a better outcome than continuous illness—defined as no recovery period greater than 6 months. However, overall the authors described the outcomes as displaying 'striking heterogeneity'. A recent systematic review and meta-analysis (Jaaskelainen et al. 2012) of 50 studies evaluating recovery—defined as showing improvement in both clinical and social domains, with at least one of these persisting for 2 years—demonstrated only 13.5 % of patients met this criteria (Jaaskelainen et al. 2012). There has been a movement, both patient and clinician led, to regard recovery as a highly individualised subjectively tailored process, though outcomes can then be more difficult to quantify empirically (Emsley et al. 2011; Harvey and Bellack 2009) (Table 1.1).

1.2 Treatment Resistance or Treatment Remission: What to Measure, What to Aim For?

1.2.1 Defining Treatment Resistance

Early guidelines for defining treatment resistant illness were predicated on persistent predominantly positive psychotic symptoms; lasting a significant period of time—e.g. 2 years of treatment—with an adequate dose and duration of antipsychotic treatment; at least 6 months on phenothiazines, with minimum doses of 600 mg/day for chlorpromazine and 80 mg/day for trifluoperazine (Itil et al 1966). However the most influential contemporary definition arose as a consequence of a landmark study using clozapine (Kane et al 1988), which defined treatment resistance as follows:

- Failure to respond to at least three periods of antipsychotic treatment in the preceding 5 years, with medications from at least two different classes and at doses greater or equal to an equivalent of 1,000 mg/day of chlorpromazine

Table 1.1 Factors affecting outcome in schizophrenia

Factors affecting outcome in schizophrenia			
Domain	Positive factors	Negative factors	Uncertain/no influence
Genetic/ epigenetic	Female gender	Morphological brain abnormalities	
Environmental	Good social support	Illicit drug use Physical ill-health Unfavourable family environment High expressed emotion	
Illness history	'Episodic' illness pattern	Greater illness in first two years 'Continuous' illness pattern Cognitive symptoms	
Medication	Continuous dosing	Intermittent dosing Medication discontinuation Interactions with other medications	High doses Polypharmacy

- No significant period of good functioning during that time
- Symptom severity $\geq$45 on the Brief Psychiatric Rating Scale (BPRS) with two of the subcategories of conceptual disorganisation, suspiciousness, hallucinatory behaviour, and unusual thought content $\geq$4.

These 'Kane criteria', or minor variations thereof, have been amongst the most commonly used definitions of treatment resistance. A recent systematic review (Suzuki et al. 2011b) of 33 studies (each with $\geq$40 participants) of antipsychotic use in treatment-resistant patients found that most studies defined such resistance as failure to respond to at least two antipsychotic trials at 'Kane' chlorpromazine doses for $\geq$6 weeks (although some studies included failure to tolerate a minimum drug dosage as a failed trial). Treatment *response* was defined as a change in a symptom scale, typically $\geq$20 % decrease in the Positive and Negative Symptoms of Schizophrenia (PANSS) or a post-treatment score of $\leq$35 in the BPRS. Whilst methodologically valid and reliable, such work generally based past treatment failures on retrospective recall—there were only a few prospective studies, e.g. Kane et al. (2011).

However, it has become clear that in addition to these broad pharmacological criteria, there is a need for attention to psychosocial factors and the issues of medication adherence and drug and alcohol use. Suzuki et al. (2012) have recently proposed broadening the definition to include such markers, and in addition to failure to respond to two adequate dosed and duration antipsychotics, they recommend that the definition of treatment resistance also requires:

- A score $\geq$4 on the Clinical Global Impression Severity Scale (which is ordinal from 1 = normal to 7 = most ill) *and*
- A score of $\leq$49 on the Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) scale *or*
- A score of $\leq$50 on the GAF

The FACT-Sz is more specific to schizophrenia than the commonly used Global Assessment of Functioning (GAF) and has been shown to have good reliability and validity when tested against other similar scales. The authors further proposed that treatment response be defined based on a CGI-Change score of $\leq$2, a $\geq$20 % decrease on total PANSS or BPRS and an increase of $\geq$20 points of the FACT-Sz or GAF. Specific data on the clinical outcomes of treatment-resistant cohorts, with a variety of definitions, is generally disappointing. A review and meta-regression analysis (Suzuki et al. 2011a) of 19 studies showed that most improvements that do occur from antipsychotic treatment occur early in treatment, with far fewer gains thereafter; improvements of 29 % were seen by week six, with approximately two-thirds of the gains occurring in the first 3 weeks. However, clozapine has been shown to continue to provide clinical gains up to 6 months after commencement of treatment (Breier et al. 1993).

1.2.2 Remission as a Clinical Marker

The high levels of heterogeneity in outcome studies tell us that a minority of individuals do fully recover, that there is a significant cohort who do not seem to respond to any intervention, but there has been relative neglect of the largest group—those who show a middle path of incomplete recovery. In this context the concept of illness *remission* is important, and in 2003 an expert working group was set up to establish appropriate operational criteria for thresholds of reached and maintained improvement (Andreasen et al. 2005). These criteria, sometimes referred to after the lead author as the Andreasen criteria for remission, are shown in Table 1.2. An attraction of this model is that rather than focusing on defining those treatment-resistant individuals who are not showing an adequate response to medication, or measuring percentage changes in symptom severity, the issue moves to establishing a more reasonable and real-world threshold one might aim for in the large group of patients falling between full recovery and non-response. The emphasis is a longer term heuristic one, based upon an individual's functioning despite having a serious mental illness and the persistence of some symptoms of schizophrenia. It also allows a standardised comparison across a wide range of therapeutic inputs, from pharmacological to sociological. A review by Lambert et al. (2010) of the 50 or so papers subsequently published utilising the working group's recommendations supported the validity of the initial criteria, specifically noting that they appeared both 'achievable and sustainable for a significant proportion of patients and are related to a better overall symptomatic status and functional outcome'. Overall findings included identifying that 45–70 % of patients met remission criteria at during the follow-up period, and about three quarters of those who attained this maintained a stable remission during the relevant study trials.

Table 1.2 Schizophrenia remission criteria as proposed by the Remission in Schizophrenia Working Group (Andreasen et al. 2005)

Proposed schizophrenia remission criteria items *Maintenance over a 6-month period of simultaneous ratings of mild or less on all items is required*						
	SAPS and SANS items		Positive and negative syndrome scale items		BPRS items	
DSM-IV criterion	Criterion	Global rating item no.	Criterion	Item no.	Criterion	Item no.
Delusions	Delusions (SAPS)	20	Delusions Unusual thought content	P1 G9	Grandiosity Suspiciousness Unusual thought content	8 11 15
Hallucinations	Hallucination (SAPS)	7	Hallucinatory behaviour	P3	Hallucinatory behaviour	12
Disorganised speech	Positive formal thought disorder (SAPS)	34	Conceptual disorganisation	P2	Conceptual disorganisation	4
Grossly disorganised or catatonic behaviour	Bizarre behaviour (SAPS)	25	Mannerisms/ posturing	G5	Mannerisms/ posturing	7
Negative symptoms	Affective flattening (SANS)	7	Blunted affect	N1	Blunted affect	16
	Avolition–apathy (SANS) Anhedonia–asociality (SANS)	17 22	Social withdrawal	N4	No clearly related symptom	
	Alogia (SANS)	13	Lack of spontaneity	N6	No clearly related symptom	

BPRS Brief psychiatric rating scale, *SANS* Scale for the assessment of negative symptoms, *SAPS* Scale for the assessment of positive symptoms

1.2.3 The Need for Better Psychosocial and Cognitive Markers

All the patients who fail to achieve remission can be conceptualised as being treatment refractory; thus in reality treatment response lies on a continuum of severity rather than a threshold and our assessments will need to incorporate a broader focus—beyond the traditional positive symptoms profile. In the past, there has been a primary focus on positive psychotic symptomatology, with less attention given to negative symptoms, cognition and social functioning. In the systematic review by Suzuki et al. (2011) none of the studies measured cognitive functioning or patients' subjective experiences. However neurocognitive deficits have been shown to predict worse functioning than positive symptoms in 'real-world'

domains of community and household activities, work skills and interpersonal relationships (Bowie et al. 2006).

The PANSS is the most commonly used symptom measure in schizophrenia research but the relatively long duration taken for its administration limits the number of additional symptom based scales that can be reasonably used. The Global Assessment of Functioning (GAF) tool (Hall 1995) has been perhaps the most commonly used social functioning measure in parallel to symptom scales: it offers a broad assessment across a range of domains including psychological, social and occupational, is easy and relatively quick to administer and is sensitive to change (Burlingame et al. 2005). However it remains rather generic and non-specific, with no consensus on cut-off or improvement measures and with some concerns about inter-rater reliability (Aas 2011).

Other widely used, and more specific and detailed, scales include the Camberwell Assessment of Need (CAN) (Phelan et al. 1995) and the University of California Performance-Based Skills Assessment (UPSA) (Patterson et al. 2001). Both are designed to assess functionality across a range of domains: 22 in the former, 5 in the latter. An exciting recent development in this regard has been the National Institute of Mental Health's MATRICS programme (http://www.matricsinc.org), which aims to standardise research into cognition in schizophrenia. This is a step towards redressing the lack of attention paid to the cognitive aspects of the disorder, and the use of a standardised battery will help address both the previous lack of consensus on which neurocognitive scales should be used and facilitate better comparison between study trials.

1.3 The Assessment of the Refractory Patient: Background Factors

1.3.1 Medication Adherence

A major problem when conceptualising response to antipsychotic medication is the high rate of suboptimal adherence frequently demonstrated. This has been linked to longer duration of inpatient treatment, poorer symptomatic outcome and has been identified as the strongest predictor of relapse in patients with psychosis (Caseiro et al. 2012). Relapses in turn predict poorer prognosis and longer time required to achieve future remission (Perkins et al. 2008), and medication gaps of even several days can have a significant impact on relapse risk (Masand et al. 2009).

A recent systematic review (Sendt et al. 2014) of studies evaluating adherence to antipsychotic medication in schizophrenia found rates ranging from 47 to 95 %. Two critical problems—a lack of consensus in what defines 'adherence' and varying study methodology—likely account for the large range in the findings and might account for some inconsistencies in literature. For example, there is data to support a negative correlation between symptom severity and adherence (Fenton et al. 1997; Marder 2003; Pinikahana et al. 2002), but the finding is not consistent. Interestingly the route of administration has not been shown to

Table 1.3 Factors affecting medication adherence in schizophrenia

Domain	Positive factors	Negative factors	Uncertain/no influence
Patient	Good attitude to medication Illness insight	Lack of insight	Sociodemographics Symptom severity
Medication	Simple drug regimen	Side effects Co-morbid substance misuse Complex drug regimen	Class (FGA v SGA) Administration route
Environmental	Good therapeutic relationship	Lack of trust in doctor	Family and social supports

From Sendt et al. (2014)

particularly impact upon adherence rates: long-acting injectable antipsychotics potentially facilitate adherence through less frequent administration, though such prescribing is often in patients with a history or assumed risk of poor adherence (Barnes et al. 2009; Kim et al. 2012). Similarly side effects to medication are found to be less of a factor than one might expect, with only three studies of thirteen studies in this particular systematic review identifying such problems as a barrier to medication adherence (Baloush-Kleinman et al. 2011; Jonsdottir et al. 2010; Karow et al. 2007). Naturalistic data from the CATIE study (Lieberman et al. 2005) demonstrated a disappointingly high 74 % of patients discontinuing their medication because of intolerable side effects before that trial's 18-month endpoint with few differences between specific medications. Overall the clinical problem of sub-optimal adherence is significant, but the area remains understudied (Table 1.3).

1.3.2 Pharmacokinetics

There are various pharmacokinetic factors that can affect an individual's metabolism of a drug. While gender and body build are the most obvious factors—men and larger individuals may need higher doses than women and those of smaller build—general physical health factors are also an important area to consider:

- Gastrointestinal problems can affect liberation and absorption of a drug
- Significant cardiovascular disease can affect drug distribution through the body
- Hepatic and renal problems can affect metabolism and excretion of medication.

Similarly, concomitant medication requires considerable thought; most drugs are predominantly bound to plasma proteins in the blood stream, with only the non-bound fraction pharmacologically active. The binding is a competitive process and the more drugs an individual is on, the greater the potential for a rise in the active component, e.g. if a drug had its plasma protein-bound fraction reduced from 99 to 98 % by administration of a second medication, this seemingly small change actually leads to a doubling of the pharmacodynamically active part (going from 1 to 2%). Most metabolism occurs in the liver through the cytochrome P450 class of enzymes: Table 1.4 gives the major subclasses and the drugs broken down therein.

Table 1.4 Liver cytochrome P450 enzymes relevant to psychiatric prescribing

CYP enzyme	1A2	2C9/19	2D6	2E1	3A4
Substance metabolised	Cigarettes Clomipramine Clozapine Duloxetine Fluvoxamine Haloperidol Insulin Olanzapine Warfarin	Amitriptyline Citalopram Clomipramine Diazepam Fluoxetine Fluvoxamine Phenytoin THC	Amitriptyline Aripiprazole Amitriptyline Chlorpromazine Clomipramine Desipramine Fluoxetine Fluvoxamine Haloperidol Imipramine Paroxetine Risperidone Thioridazine Venlafaxine Zuclopenthixol	Disulfiram Ethanol	Alprazolam Amitriptyline Barbiturates Carbamazepine Diazepam Fluoxetine Glucocorticoids Haloperidol Methadone Modafinil OCP Phenytoin Quetiapine Risperidone Sertraline Trazodone Venlafaxine Zolpidem Ziprasidone

Drugs are listed alphabetically in columns under their major metabolising enzyme sub-class. Compounds that significantly inhibit hepatic enzymatic function are coloured in red; those that induce the relevant enzyme are coloured blue. *OCP* oral contraceptive pill, *THC* tetrahydrocannabinol

The greater the 'burden' on any one enzyme class, by co-administration of other drugs, the greater the likelihood of increased serum levels and side effects. Some drugs are particularly likely to inhibit these liver enzymes and produce such a response, whilst others are enzyme 'inducers' that will speed up drug metabolism and might lead to lower serum and pharmacodynamically available levels. Of particular note is that cigarette smoking, which is more common in those with psychosis than the general population, will induce the 1A2 subclass of enzyme that is responsible for metabolising several antipsychotics including clozapine.

1.3.3 Pharmacogenomics and Interpreting an Individual's Past Response to Medication

While clinical trial data have shown that, with the exception of clozapine, there is little to distinguish the efficacy of other antipsychotic medication, most clinicians have had the experience of a patient, seemingly idiosyncratically, responding to one drug but not another. This raises an important issue: how do you evaluate the relative contribution of a patient's past individual responses to treatment with clinical trial data? There is a risk within randomised placebo-controlled clinical studies that so-called class size effects and will mask significant effects which are only evident within a subpopulations of full, partial and non-responders to any given treatment (Tracy et al. 2013).

The broad principle of individual variation in metabolism of, and response to, a given drug—referred to as individualised or stratified medicine—is well understood, but the therapeutic application to an individual's care, particularly in psychiatry, but also in most areas of medicine is a nascent field. Pharmacokinetically there

is data to suggest that some individuals are 'fast' hepatic metabolisers, with an above average metabolism of drugs, and conversely that some might be 'slow' metabolisers. The individual pharmacodynamics of why an individual will show benefit to one compound but not a pharmacodynamically very similar one remain uncertain beyond the principle that the two medications in question will be chemically different compounds, and there are genetic variations in individuals' expression of neurotransmitter receptors and the complex patterns of neurotransmitter recycling and intracellular messaging.

A question for future research might not be "is treatment X effective" for treatment-resistant schizophrenia, but rather "when and for whom might it work", with an improved knowledge of the consequences of varying clinical, pharmacodynamic, pharmacokinetic and psychosocial factors. The tantalising hope exists of prospective identification of such factors and more targeted prescribing, although early work on predicting genetic polymorphisms associated with favourable or unfavourable responses to psychotropic drugs has been somewhat mixed (Penn and Tracy 2012).

One common example of class effects may underlie the discrepancy in the evidence for the utility of high dose and polypharmacy in prescribing antipsychotics; the data at a population level (a research 'class-effect') shows that there is little benefit from these approaches, while individual case reports highlight patients who do respond to such prescribing, even if the majority do not. It is possible that 'fast' hepatic metabolisers might be breaking drugs down before they can be fully efficacious and might benefit from above maximum dose prescribing, whereas 'slow' hepatic metabolisers might develop side effects from even modest range doses and might benefit from prescribing more than one drug at a lower dose. One must inevitably be cautious and circumspect about any prescribing that goes contrary to guidelines or prescribing licenses, but it is nevertheless rational and appropriate to consider how the refractory patient compares with trial study populations and what can be learned from their unique pattern of past responses to treatment. One specific factor to be mindful of when considering apparent failure to respond to clozapine is the duration of treatment and clozapine levels attained as, unlike other antipsychotics, continued improvement on treatment has been shown to accrue up to 6 months after drug commencement.

1.4 Assessment and Treatment

More importantly than ever, the key medical tenets of an accurate and detailed history, with collateral information where possible, are essential in the treatment refractory patient. Open collaborative working, as far as is possible, and demonstrating an active interest in trying to improve the quality of the patient's life can hugely strengthen the clinician–patient relationship and facilitate care. An interesting aspect of many pharmacological trials in treatment resistant schizophrenia is the statistically significant rates of improvement of those in the *placebo* arm. Whilst this is a well-recognised research effect, a second pragmatic message

emphasises the dangers of therapeutic nihilism in patients who have not responded well to previous treatments–and the value of a positive engagement and the instillation of hope. A core data set will include the following:

- The illness history, including whether continuous or episodic
- Evaluation of historical changes in positive, negative, affective and cognitive symptoms
- Changes and current abilities and deficits in social functioning
- A developmental and psychosocial history exploring risk factors and precipitating and protecting environmental factors
- An open but frank appraisal of current and past alcohol and illicit drug use
- Past and current physical history and examination should be made, with appropriate investigations such as routine blood tests

With past medications it is important to get as precise a past treatment history as possible, with best estimates for duration, dosages and combination with other medication. A temporal chart or timeline can serve as a helpful visual historical guide—Fig. 1.1 gives a suggested model—especially if combined with information on drug(s) efficacy, side effects, and adherence and estimates on illness severity, perpetuating factors, and degree of social functioning.

Past psychological treatments, their efficacy and the patient's degree of engagement are important to establish: when documenting past 'failure' it is necessary to try ascertain why this occurred and if there are current factors or barriers that could be re-evaluated.

1.4.1 Commencing Treatment: Protocols and Documentation

Good documentation is essential, both for clinical reasons and for medico-legal purposes, especially when using medication in a non-standard manner. The rationale for a patient's care plan should be clearly stated, especially if prescribing is outside of guidelines or prescribing licenses. Good practice should include the patient and family or carers in this discussion or at least provide justification of why that was not possible. An explicit timeframe should be given to review and evaluate the effectiveness, and any problems or side effects, of the treatment plan. Clinical practice is often very busy and it can be difficult to find time to undertake symptom, side effect or social functioning scales. However these can be invaluable in accurately gauging any progress and are a worthwhile investment of time with refractory patients. A suggested protocol is provided in Fig. 1.2.

- Continuous, rather than intermittent, antipsychotic monotherapy is recommended, with guidelines usually stating *effective* treatment should last at least 2–5 years in those who have suffered at least one relapse and >5 years in multi-episode individuals (Hasan et al. 2013).
- Discussion on adherence and trying to understand the individual's reasons, supporting factors and difficulties taking treatment can be helpful, particularly if there are practical steps that can be implemented to help, for example, disorganised thoughts or cognitive difficulties.

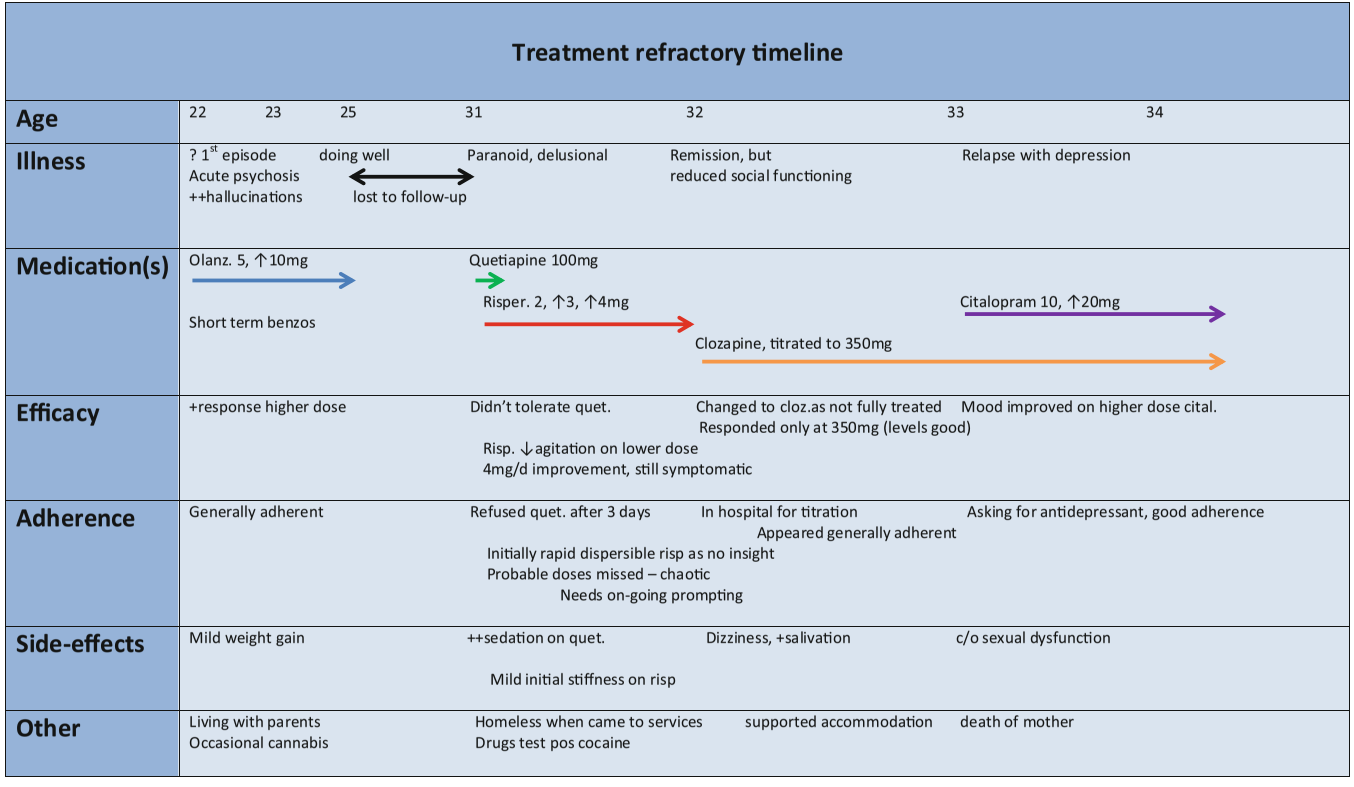

Fig. 1.1 Suggested model of a treatment refractory timeline to help gauge responses to treatment and the roles of associated factors

Treatment refractory schizophrenia medication chart

Name:			**DoB:**				**ID:**			
Current medication regimen										
Initial therapy			Change 1		Change 2		Change 3		Change 4	
	Drug	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose
1											
2											
3											
4											
5											
6											

Medication care plan

Rationale for medication plan: ☐ Past efficacy ☐ Proposed efficacy ☐ Patient choice ☐ Other
Comments:

Discussed with patient/carer:
Comments:

Follow-up reviews of care plan

	Date:	Date:	Date:	Date:
Rationale remains/changed				
Discussed with patient/carer				

Health checks (highlight abnormalities & changes)

1. **Physical**	Baseline	Follow-up 1	Follow-up 2	Follow-up 3
Date				
Cardiovascular				
ECG				
Weight/BMI				
Bloods				
Other (state)				
2. **Adverse events**, e.g. GASS, LUNSERS etc.				
Date				
Scale(s), score				
Comments				
3. **Mental state**, e.g. PANSS, PSYRATS etc.				
Date				
Scale(s), score(s)				
Comments				

Fig. 1.2 Suggested chart for documenting and monitoring treatment plans and changes

- If faced with a significant history of medication discontinuation due to side effects, it is important to consider common factors that are often less discussed due to patient or clinician embarrassment or discomfort, such as sexual dysfunction, excess saliva production and incontinence.

1.5 Evaluating Broader Team or Service Practice of Refractory Care

The difficult truth is that the natural history and outcomes of schizophrenia are not as favourable as one would wish for and refractory illness is relatively common. Good evidence-based guidelines for schizophrenia do exist; but the options and prognosis for those resistant to first- and second-line treatments are limited. It is a huge challenge to instigate sufficiently well-powered studies to detect statistically significant changes after a few generations of medication change. Refractory illness can be a source of frustration for both the patient and clinician—Shepherd et al. (2009) noted how clinicians can feel they "should" know how to manage such individuals—and it can be easy for both to lose hope and become somewhat fatalistic about progress.

While sociodemographic, structural and resource variations will mean that different teams work with different refractory populations in different ways, significant variation in clinical practice between services is not necessarily explained by these factors (Paton et al. 2008). Correll et al. (2011) assessed the treatment habits of psychiatrists using semi-structured interviews, and found, interestingly, that those with more clinical experience were more likely to undertake treatment plans unsupported by existing evidence and have fewer concerns about this. Individual doctors tended to have preferred medication combinations, but there was no clear pattern in this particular study (in a sample of 44 from a single site teaching hospital), and many had 'inherited' patients on such combinations with reluctance to change. Modern psychiatric practice can involve patient transfer between different clinical team with differing prescribing and treatment habits—from wards to community services to specialist services such as assertive outreach and crisis teams with the potential for 'accumulating' an assortment of medications and treatment plans on the way.

There is an onus on teams to evaluate and audit their own practice and compare to local parallel services and national guidelines. Any major deviation from the expected results needs thoughtful investigation: with open case discussions and cross-fertilisation of ideas across teams. This requires involvement of the entire multidisciplinary team including the prescribing physicians, the nurses who dispense them and the pharmacists responsible for medication governance. The existing evidence suggests that such educational directives can have effects on team clinical practice (Thompson et al. 2008), though these might only produce short-term changes in practice (Baandrup et al. 2010), and staff turnover is inevitable, so teams and wards need to think longitudinally about on-going teaching programmes on best practice and evidence-based care, as well as case-based discussions of refractory patients' care.

Table 1.5 Criteria for referral to a refractory psychosis service

Criteria for referring to a refractory schizophrenia service	
Generic complex/refractory criteria	Specific to a psychosis centre
Diagnostic uncertainty hampering treatment	Failure to respond adequately (or tolerate) two antipsychotics (at least one atypical)
Persistently high symptom burden	
Significant impact on functioning	Attempted adequate trial of clozapine, usually for a minimum of 6–9 months
Persisting (>2 years) pattern of incapacity despite appropriate treatment	
Multiple comorbidities increasing likelihood of chronicity	Appropriate psychological therapies such as cognitive behavioural therapy and family interventions should have been attempted
Need for specialised treatments, e.g. TMS	
Inpatient stay >6–12 months	

Based upon UK Department of Health guidelines (2010)

There will be times when "fresh eyes" are required, though there will be variation in the ability and mechanisms for either transferring care or seeking second opinions. Given the scale of the problem there is surprisingly little data on tertiary specialist care for treatment-resistant psychosis, though nascent data has shown such units can provide efficacious and cost-effective care that is valued by the patient, relatives and referrer alike (Sarkar et al. 2014). There is no consensus on what a specialist centre should look like or provide, though there are guidelines for when referral to a specialised psychosis services might be warranted (Specialised Services National Definitions Set 2010) (Table 1.5).

In summary, there is a considerable burden of morbidity in patients with schizophrenia which remains poorly treated. Often this does not lie with the highly visible patient with persistent positive psychotic symptoms despite treatment with a range of antipsychotic medication, but in the vast majority of patients who continue to suffer with cognitive and negative symptoms. This requires both an increased attention to the assessment and monitoring of these symptoms and contribution of iatrogenic and socio-cultural factors in maintaining them. Careful assessment and monitoring of the different symptoms profiles is essential, along with individualised management—this should routinely include discontinuation of ineffective interventions as well as evaluation of novel interventions. Following this approach, the eventual aim is to create a culture of positive therapeutic engagement—at the individual, team and service level.

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2 Biology of Schizophrenia: Is Treatment Refractoriness Synonymous with Severity of Illness [A.K.A. Is This a Drug Efficacy Problem or an Expression of Severe Illness?]

Helio Elkis and Peter F. Buckley

We would like to start this chapter by describing three severe cases of schizophrenia where treatment resistance developed at different time points of the evolution or natural history of disorder.

Case report 1—AB is a man of 34 years who developed his first psychotic symptoms at the age of 17 years. He has a history of neurodevelopmental abnormalities such as birth complications and motor and language retardation as well as use of cannabis which triggered his psychotic with concomitant mood swings. Due to this he was considered to have bipolar disorder and was admitted for the first time and treated according to such diagnosis, i.e., with antipsychotics and mood stabilizers but was discharged with no improvement. He was then subsequently admitted five more times due to the presence of clear persecutory delusions, auditory hallucinations, thought disorganization, and agitation without mood features. In one of the episodes he hit his mother in the chest and menaced his father with a knife. Patient was diagnosed as having paranoid schizophrenia due to the characteristics of the psychotic episodes and absence of concomitant mood symptoms.

He has been treated with six different antipsychotics during this period (haloperidol, trifluoperazine, olanzapine, risperidone, quetiapine, and aripiprazol) without satisfactory response with persistence of persecutory delusions and auditory hallucinations. The patient was again admitted and then defined as having treatment for resistant schizophrenia, and clozapine monotherapy was introduced with progressive doses, reaching 500 mg/day. The patient was discharged and after some weeks responded to treatment, achieving full remission at 6 months. He presently

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takes daily doses of 400 mg of clozapine and is studying law and the relationship with family is very satisfactory.

Case report 2—CD. This is a 45-year-old male patient who started showing first symptoms of schizophrenia by the age of 25. Patient has no history of birth complications or use of drugs. He had some mild difficulties during high school and especially during his university course, concluding a 4 years course on administration business in 7 years. The first symptoms and subsequent psychotic episodes were characterized by the presence of suspiciousness, paranoid ideas, and intense delusional perception. However, these episodes were of mild severity and the patient had never been admitted into a psychiatric hospital. He has been treated with a series of conventional antipsychotics (haloperidol, pimozide, trifluoperazine) as well as atypical antipsychotics (amisulpride and aripiprazol) with partial response, maintaining mild persistent psychotic symptoms, especially delusional symptoms, but with no substantial impact on patient's behavior. However, the patient developed predominance of negative symptoms characterized by blunted affect, avolition, and anhedonia which cause impairment of his social and occupational functions. Antidepressants such as imipramine and fluoxetine have shown evidence of efficacy over negative symptoms and therefore were added to antipsychotics (Singh et al. 2010).

Due to the exacerbation of his delusional perceptions it was decided that the patient should be treated with clozapine which reached 300 mg/day with remission of psychotic symptoms after a couple of weeks. However the severity of negative symptoms continues to represent a major issue in patient's life, who still complains about fatigue, anhedonia, and lack of drive. Due to this a trial with lamotrigine was recently started based on the evidence that it is an effective clozapine augmentation drug (Tiihonen et al. 2009).

Case Report 3—EF. This is a 50-year-old male patient with a history of schizophrenia which started when he was 15 years old, after heavy use of drugs such as cannabis, cocaine, and LSD. His aunt had a diagnosis of schizophrenia which was so severe that she was treated with leucotomy almost 60 years ago, when this surgery was allowed in Brazil. At the time of the first examination he weighed 90 kg and was 167 cm tall (MCI = 32.3).

He was treated only with conventional antipsychotics during 20 years and during this period was admitted four times into psychiatric hospitals. His disorder was characterized initially by auditory command hallucinations when he hit his own head and developed a traumatic cataract. He also showed disorganized behavior, laughing without reason and with outburst of pronounced aggressiveness towards members of the family. He also tried to cut his penis with a knife.

It was necessary to place the patient in a room outside his house with a person specially hired to take care of him. In terms of treatment he received atypical antipsychotics such as aripiprazol, due to his obesity, at doses of 40 mg/day, but he did not respond at all. Subsequently risperidone was introduced reaching 12 mg/daily for several weeks, but without substantial response as well. Clozapine was then initiated and patient responded partially with 800 mg/daily with reduction of aggressiveness and improvement of sociality. However command voices remained

present and it was decided to augment clozapine with ECT. He is presently much better taking 700 mg/daily of clozapine and receiving ECT sessions twice a week. Also, he had a substantial reduction in his weight (75 kg, MCI = 26.9).

In case number 1 resistance to antipsychotic developed early, with the patient showing an unsatisfactory response since the beginning of treatment. Case number 2 represents a classical chronic patient with schizophrenia who has predominance of negative symptoms and functional impairment but where psychotic symptoms represent an active dimension of psychopathology with important impact on his behavior. Case number 3 represents the extreme of resistance with patient responding partially to clozapine and developing what we call super-refractoriness (Buckley et al. 2001; Henna Neto and Elkis 2007).

Therefore such cases illustrate a spectrum of resistance which may appear in the beginning of the disorder as well as at the chronic phase of schizophrenia and can reach extremes of great severity and impairment of functioning.

Resistance to treatment continues to be one of the most important issues in terms of the treatment of schizophrenia, and the items discussed below represent an attempt to encompass this complex phenomenon.

2.1 Treatment Response and Treatment Resistance

It is well established that a certain proportion of patients with schizophrenia do not respond adequately to antipsychotic treatment and such patients are defined to have Treatment Resistance Schizophrenia (TRS). However, the definition of TRS proves problematic to this day, implying various connotations.

Generally TRS is mistaken by chronicity. In fact chronicity frequently is taken as a synonym of refractoriness, and, consequently, many clinicians believe that refractoriness is the inevitable outcome of schizophrenia. However epidemiological studies such as the International Study on Schizophrenia have shown that about 50 % of the cases of schizophrenia do respond to treatment and have a favorable outcome in terms of remission of symptoms and maintaining certain level of functioning (Harrison et al. 2001).

Schizophrenia is a chronic disorder and it is important to make a distinction between chronicity and refractoriness, since there are various chronic diseases, as for example, diabetes and hypertension, that, despite their chronicity, do in fact respond to treatment, with patients remaining stable using the same doses of hypoglycemic agents or antihypertensive drugs throughout their lives (Elkis 2010).

What is the meaning of response to treatment? A simple definition is the reduction in the severity of symptoms, as assessed by some sort of scale (Leucht and Kane 2006). This definition implies that a certain instrument must be chosen to measure the level of response as defined by a certain threshold or cutoff point (Leucht et al. 2009). For example, the first criteria which defined refractoriness in schizophrenia established that patients should be considered responsive to clozapine if there was a reduction of 20 % or more of the BPRS (Kane et al. 1988).

In fact response is a key concept in defining resistance and a recent systematic review of 33 studies found that definitions of TRS vary extensively but have in common the following components or dimensions (Suzuki et al. 2011):

- Failure to respond to 1–3 previous antipsychotic trials, with therapeutic doses, within certain duration
- Prospective treatment with another antipsychotic
- Evaluation of treatment response of prospective treatment with certain instruments (e.g. PANSS or BPRS)

Definitions of TRS based on algorithms such as those proposed by the American Psychiatric Association (APA) (Lehman et al. 2004) or the International Psychopharmacology Algorithm Project (IPAP) (http://www.ipap.org) (Elkis 2007) simplify clinical decisions since they propose that a patient should be considered to have TRS if he or she does not respond to at least two trials with antipsychotics, with adequate doses, with 4–6 weeks duration.

It is also important to mention that response should not be confounded with remission since sometimes TRS is associated with the idea of lack of remission, generally conceived as a complete absence of symptom. Actually remission is defined as the presence of a group of symptoms within a certain level or threshold of severity, during a defined period of time (Leucht et al. 2009). In the case of schizophrenia, "remission" currently is defined as a minimum period of 6 months during which psychotic symptoms, symptoms of disorganization, and negative symptoms have low levels of clinical severity and impact on patient's behavior (Andreasen et al. 2005).

Finally TRS cannot be mistakenly confounded as the result from a lack of adherence to treatment since patients considered to be resistant can actually be non-adherent (Correll et al. 2011) and the distinction between treatment resistance and resistance to treatment must be carefully evaluated (Lambert 2010).

2.2 Is the Failure to Respond to Antipsychotics a Manifestation of Brain Neurodevelopmental or Neurodegenerative/Neuroprogressive Processes?

The neurodevelopmental model proposes that schizophrenia represents the end stage of abnormal developmental processes that began years before the onset of illness (Rapoport et al. 2012) with neurodevelopmental abnormalities giving rise to the symptoms of schizophrenia during adolescence or early adulthood through the interaction of genetic and environmental factors (Sheitman and Lieberman 1998; Murray et al. 2008).

Neurodegenerative processes otherwise represent progressive brain disease of the nervous system that are initiated by specific biochemical changes which have a genetic basis (Jarskog and Gilmore 2006). Schizophrenia was primarily regarded as a neurodegenerative process with a deteriorating course ("dementia praecox"); however, such processes are considered limited, leading to the concept of neuroprogression, which is defined as the pathological reorganization of the central nervous

system along the course of several mental disorders (Jarskog and Gilmore 2006; Gama et al. 2013).

Sheitman and Lieberman were the first to propose a model where TRS could be regarded as the result of neurodevelopmental and neurodegenerative processes through the lifespan. According to this model resistance to antipsychotic drugs would develop at certain time point of the evolution of schizophrenia based on three stages: cortical neuropathology and deficient neuromodulatory capacity, neurochemical sensitization, and subsequent neurotocixity (Sheitman and Lieberman 1998).

In this model, cortical neuropathology and deficient neuromodulatory capacity would be the result of genetic and/or epigenetic factors and would occur during the fetal gestation and early perinatal development. Neurochemical sensitization would be expression of a deficiency in neuromodulatory capacity which occurs in adolescence or early adulthood and would be triggered by environmental factors such as stress or substance abuse while neurotocixity occurs in the residual phase of the development of schizophrenia and is associated with neuronal changes or neuronal loss (Sheitman and Lieberman 1998).

Various levels of evidence have shown that some neurodevelopmental factors may be associated with treatment response, as for example, genes, lower levels of premorbid function, early age of onset, male gender, as well as brain abnormalities (Sheitman and Lieberman 1998). Some of them are summarized below.

2.3 Genetics

It is well known that response to drugs is mediated by genes. The ability of antipsychotics to improve the symptoms of schizophrenia is dependent on its antagonist and reverse agonist activities at different neuroreceptors, and some genetic association studies of resistant-schizophrenia have focused on different pharmacodynamic factors (Luca et al. 2010). Some genetic studies have shown an association between response to antipsychotics or TRS and candidate genes such as 5HT receptors, cytochrome families, and dopamine receptors (Inada et al. 2003; Cordeiro et al. 2006; Luca et al. 2010; Hotta et al. 2011).

The COMT (Catecol-Orto-Methyltransferase) is key enzyme in the metabolism of dopamine, which is known to be deregulated in schizophrenia. It is located in the cytogenetic band of 22q11.2 on chromosome 22. In terms of its polymorphisms it has been shown that a G–A transition in the codon 158 of the COMT gene results in the substitution of valine to methionine (Inada et al. 2003).

This COMT Val158Met polymorphism has been extensively studied in association with aggressive behavior, violence, suicide, and use of cannabis in patients with schizophrenia (Inada et al. 2003; Hosak 2007; Henquet et al. 2008). Using a very restrictive definition for TRS (patients hospitalized for 1 year and receiving daily the equivalent of 1,000 mg of chlorpromazine during this period), Inada et al. compared 100 patients with schizophrenia with 201 healthy controls and observed no association between COMT polymorphism or alleles (H and L) with

the diagnosis of schizophrenia, but the rate of TRS tended to be higher in patients with COMT L/L genotype than in those without TRS (Inada et al. 2003).

It is well known that the serotonin system (5HT) plays a key role in the mechanisms of action of antipsychotics and consequently in terms of treatment response as well as cognitive impairment (Meltzer et al. 2003, 2012; Meltzer 2010). The HTR3A, HTR2A, and HTR4 were investigated in 101 Japanese patients defined as having TRS based on the Inada's et al. stringent criteria (Inada et al. 2003) as compared with 239 non-TRS. The investigators found no association between the single marker analysis of those genes and in the haplotype analysis of HTR3A and HTR4. However, the daily neuroleptic dosage is higher in patients with T/T genotype of the HTR3A polymorphism (Ji et al. 2008).

Among these genes the DISC-1 (Disrupted-In-Schizophrenia), which, along with Neuregulin-1–ErbB4, plays a key role in neurodevelopment and is considered a candidate gene for schizophrenia (Jaaro-Peled et al. 2009), was investigated through four Single Nucleotide Polymorphisms (SNPs) in 32 patients diagnosed with TRS as compared with 95 non-TRS patients, but no association was found between DISC-1 and TRS (Hotta et al. 2011).

The association between 384 markers (SNPs) from candidate genes was investigated in 85 patients defined as having TRS, according to APA definition of treatment resistance (Lehman et al. 2004), and compared with 115 non-TRS. The investigators found a significant trend with the SNP rs2152324 in the NALCN gene, but after False Discovery Rate (FDR) correction, the *p*-value showed to be not significant (Teo et al. 2012).

The role of inflammation has been investigated for a long time in TRS (Lin et al. 1998; Maes et al. 2002), but recently the gene FAS, which plays a key role in this association, was investigated in 96 patients, defined as having TRS by Kane et al. criteria (Kane et al. 1988), in comparison with 77 non-TRS patients. The researchers found a significant association between the SNP rs7085850 and two haplotypes that were significantly associated with TRS in this sample (Jia et al. 2011).

2.4 Brain Abnormalities

Early studies with CT scans have demonstrated an inverse relationship between the degree of ventricular enlargement and treatment response (Weinberger et al. 1979). Many subsequent CT studies tried to replicate these findings, but a first meta-analysis of these early studies as well as a critical review of this subject found no relationship between ventricular enlargement and treatment response in patients with schizophrenia (Friedman et al. 1992; Borgio et al. 2010).

In an early MRI study Lawrie et al. compared patients responsive with resistant and found that poorly responsive patients had lower volumes of most brain structures than treatment responders, but no particular specific brain region was associated with poor response (Lawrie et al. 1995).

However, recent studies in patients whose illness is progressive and resistant to treatment—termed poor outcome patients or having "Kraepelinian schizophrenia"—have shown abnormalities such as ventricular enlargement and decrease in gray matter as well as in the corpus callosum size, internal capsule, and putamen (Buchsbaum et al. 2003; Mitelman et al. 2007, 2009a, b, c, 2010; Mitelman and Buchsbaum 2007).

Lack of response to clozapine was initially related to cortical atrophy in some computed tomography studies (Friedman et al. 1991), but such finding was not replicated in magnetic resonance imaging studies (Borgio et al. 2010).

2.5 Is the Failure to Respond to Antipsychotics a Manifestation of Abnormal Neurotransmission?

It is well known that dopaminergic dysfunction underlies the majority of symptoms of schizophrenia (Howes and Kapur 2009) and that efficacy of antipsychotic is related to the degree of D2 occupancy (Seeman 1995). Patients with schizophrenia show and increase amphetamine-induced dopamine release in the striatum, especially in those who are drug-naïve (Javitt and Laruelle 2006) and Single Photon Emission Computed Tomography (SPECT) studies showed that higher levels of dopamine at baseline were significantly associated with greater improvement of positive symptoms after 6 weeks of antipsychotic treatment (Abi-Dargham et al. 2000).

Demjaha and colleagues compared 12 TRS patients with 12 non-TRS patients (responders), as well as 12 controls, in terms of their capacity of dopamine synthesis using ^{18}F-DOPA Positron Emission Tomography (PET). All patients were treated with non-clozapine antipsychotics. Patients with TRS showed similar levels of dopamine synthesis compared with normal controls but a lesser capacity than patients who responded to treatment (Demjaha et al. 2012).

Conclusions

Although this brief overview enumerates diverse neurobiological changes in patients with treatment refractory schizophrenia, none of these represent—alone or collectively—a distinct "neurobiological" signature of refractory schizophrenia. While it appears intuitive that worsening and prolonged psychosis would over time lead to fundamental brain changes [in line with a "Kraepelinian" typology], in reality this is hard to either refute or confirm scientifically. The neuroplastic and also potentially neurotoxic effects of antipsychotic medications add another level of complexity to these considerations.

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Dopamine and the Biology and Course of Treatment Resistance

3

Arsime Demjaha and Oliver D. Howes

3.1 Introduction

A key question faced by any clinician is why some patients respond to standard treatments, whilst others don't. Understanding this is likely to be a prerequisite to developing better treatments for refractory patients. It will also help the development of biomarkers to identify these patients early so they can be fast-tracked to appropriate treatments, avoiding the current clinical merry-go-round of empirical trials with different antipsychotics. This chapter first considers the pathophysiology of schizophrenia and treatment response, focusing on the dopamine (DA) system as this is central to the mode of action of current drugs. It then considers the course of refractory schizophrenia and whether treatment resistance is present from illness onset or evolves during the course of illness. Finally, it considers whether we can answer the question posed at the start of this chapter.

3.2 The Role of DA in the Neurobiology of Schizophrenia

Whilst the neurobiology of schizophrenia is complex, it has become clear that dopaminergic alterations play a central role in the pathophysiology of the disorder and its treatment (Abi-Dargham 2004; Howes and Kapur 2009). The first evidence of this came from in vitro findings indicating that antipsychotics work by blocking DA D2/3 receptors and from psychopharmacological studies showing that drugs

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that activate the DA system such as amphetamine can induce psychotic symptoms (Abi-Dargham 2004; Howes et al. 2009a; Berman et al. 2009; Curran et al. 2004). Subsequent post-mortem studies have also identified elevations in DA levels and DA D2/3 receptor densities in patients with schizophrenia (Bird et al. 1979; Cross et al. 1978; Zakzanis and Hansen 1998). However, as the post-mortem findings were predominantly from patients who had been treated for schizophrenia for many years, it was not clear whether the DA abnormalities were primary or secondary to treatment or late stage sequelae of the disorder. Subsequent molecular imaging studies were able to clarify this by studying untreated patients at onset or relapse of the disorder. A recent meta-analysis of the now more than 50 molecular imaging studies of the DA system in schizophrenia has identified three important findings to come out of this work. First, alterations in D2/3 receptor availability are inconsistent and small at most (Howes et al. 2012). Second, DA transporter availability is unaltered (Howes et al. 2012; Chen et al. 2013). Third, there is robust evidence for presynaptic DA alterations, specifically elevated DA synthesis capacity (Table 3.1), increased DA release, and elevated baseline synaptic DA levels in schizophrenia. The effect sizes for these alterations are large (Cohen's $d > 0.8$) (Howes et al. 2012), much larger than that for ventricular enlargement, for example. In short, this pinpoints presynaptic dysregulation as the major locus of DA dysfunction in the disorder (Howes et al. 2009a, 2011a, b; Lyon et al. 2011). Moreover, it does not seem to be a non-specific mark of psychiatric illness—for example, presynaptic DA function is unaltered or reduced in people with depression, bulimia, addictions, anxiety disorders and non-psychotic bipolar disorder [see review (Howes et al. 2007)], although it may be elevated in people with psychosis linked to temporal lobe epilepsy (Reith et al. 1994) and people with schizotypal personality disorder, who have psychotic-like symptoms (amongst other schizophrenic traits) (Abi-Dargham et al. 2004) and increased DA synthesis capacity (Howes et al. 2011a). Molecular imaging studies that index DA release following amphetamine in patients with schizophrenia indicate that greater release is associated with greater induction of psychotic symptoms (Laruelle et al. 1999). This is also the case when DA levels are depleted with inhibitors of DA synthesis: greater depletion following inhibition of DA synthesis is directly associated with greater reduction in psychotic symptoms (Abi-Dargham et al. 2000). Moreover, DA release was greater in patients who are acutely psychotic than in remitted patients (Laruelle et al. 1999). Taken together these findings thus link presynaptic DA alterations to the expression of symptoms in schizophrenia.

However, whilst these findings implicated DA in the pathophysiology of schizophrenia, it was still unclear if DA abnormalities were leading to the disorder or were developing secondary to the onset of the illness. To address it was necessary to study the development of the first episode of illness. Schizophrenia is typically preceded by a prodromal phase of subclinical psychotic symptoms and subtle functional changes. People who present with these features indicating a high clinical risk of developing schizophrenia in the next year or so show a large effect size increase in DA synthesis capacity, similar to that seen in schizophrenia although not as large (Howes et al. 2009b; Egerton et al. 2013). However, not all

Table 3.1 The PET imaging studies of dopamine synthesis capacity in schizophrenia

Study	Patients (*N*)	Controls (*N*)	Age	Illness stage	Radiotracer	Medication status	Effect size
Reith et al. (1994)	5	13	38	Chronic	[^{18}F]-DOPA	4 MN 1 MF	1.52
Hietala et al. (1995)	7	8	26	FEP	[^{18}F]-DOPA	All MF	0.9
Dao-Castellana et al. (1997)	6	7	26	Chronic	[^{18}F]-DOPA	2 MN 4 MF	0.35
Hietala et al. (1999)	10	13	30	FEP	[^{18}F]-DOPA	All MF	1.02
Lindstrom et al. (1999)	12	10	31	FEP/ Chronic	[^{11}C]-DOPA	10 MN 2 MF	1.01
Elkashef et al. (2000)	19	13	36	Chronic	[^{18}F]-DOPA	9 MF 10 M	−0.13
Meyer-Lindenberg et al. (2002)	6	6	35	Chronic	[^{18}F]-DOPA	All MF	1.82
McGowan et al. (2004)	16	12	38	Chronic	[^{18}F]-DOPA	All M	1.55
Kumakura et al. (2007)	8	15	37	Chronic	[^{18}F]-DOPA	3 MN 5 MF	0.10
Nozaki et al. (2009)	18	20	36	FEP/ Chronic	[^{11}C]-DOPA	14 MN 4 MF	0.13
Howes et al. (2009a, b)	7	12	36	FEP	[^{18}F]-DOPA	3 MN 4 MF	1.18
Shotbolt et al. (2011)	7	10	43	Chronic	[^{18}F]-DOPA	All M	0.07
Demjaha et al. (2012)	12	12	44	Chronic-Responders	[^{18}F]-DOPA	All M	1.12

Abbreviations: *FEP* first episode psychosis, *MN* medication naïve, *MF* medication free

clinically high risk individuals are truly in the prodrome to schizophrenia. Follow-up of these individuals shows that elevated DA synthesis capacity is specific to those who go on to develop schizophrenia/similar disorder (Howes et al. 2011a). Moreover, DA synthesis capacity is directly associated with the severity of subclinical symptoms in these individuals but not in those who do not go on to develop a psychotic disorder (Howes et al. 2011a). These individuals show functional recovery, but many continue to experience subclinical psychotic symptoms. In this respect they are similar to people in the general population who experience subclinical psychotic symptoms (Hanssen et al. 2005). A study of such people who had experienced subclinical psychotic symptoms for many years without impairment or distress and without developing a psychotic disorder also found no evidence of DA elevation (Howes et al. 2013). Another group in whom subclinical psychotic symptoms and other schizophrenic traits are seen is relatives of people with schizophrenia, but here the findings are contradictory (Huttunen et al. 2008; Shotbolt et al. 2011).

Furthermore, a longitudinal study where patients were scanned in the prodrome and then again after they developed acute psychosis found an increase in DA synthesis capacity during the progression from the prodrome to the first psychotic episode, whilst DA synthesis capacity did not change in those "at risk" individuals who did not go on to develop psychosis (Howes et al. 2011b).

These findings indicate a link between greater DA dysfunction and the development of more severe psychotic symptoms and suggest that the DA dysfunction is dynamic, increasing with the worsening of the disorder. However, whilst DA dysfunction appears most marked in acute psychosis, it is not confined to schizophrenia per se, but is also seen in people with other psychotic disorders and people with subclinical psychotic symptoms and schizophrenic traits.

3.3 Drugs, Receptors and Treatment Response

Whilst antipsychotic drugs block D2 DA receptors, they also act at a number of other brain receptors, in particular other DA receptors and serotoninergic, histaminergic, norepinephrinergic and cholinergic receptors. This complexity meant it was initially far from clear where they were acting therapeutically in the brain. The studies in the 1970s showing the relationship between the affinity of antipsychotic drugs for D2 receptors and their clinical potency first made a clear link between D2 receptors and therapeutic outcome (Seeman and Lee 1975). However, these studies were in vitro, a very different system to a brain, not least because brains are protected by a barrier that effectively excludes many drugs. Molecular imaging studies since then have provided in vivo evidence to support the in vitro findings, first by showing that the drugs cross the blood–brain barrier in humans and secondly that they block D2/3 striatal receptors in vivo at doses in the usual therapeutic ranges (Howes et al. 2009a). This is also true of the newer drugs so far studied [e.g., (Kapur et al. 1999; Kegeles et al. 2008)]. Subsequent molecular imaging studies have gone on to characterise a number of aspects of the relationship between DA receptor occupancy and clinical response.

A key finding is that the relationship between antipsychotic D2 receptor occupancy and clinical response appears to be non-linear: there is little clinical response seen when occupancy is less than 50 % and little additional benefit for occupancy levels much greater than 80 % (Kapur et al. 2000). Thus, there appears to be a therapeutic window. Figure 3.1 illustrates this, showing there is a minimum level of D2 occupancy required for clinical response to antipsychotic drugs and a level above which there is little further advantage but increased risk of side effects. A study in first episode patients tested this using [11C]raclopride PET scans to measure D2 receptor occupancy after patients had received 2 weeks of antipsychotic treatment.(Kapur et al. 2000) Subsequent clinical response was assessed using the global clinical impression of how much the patients had improved. Responders were those who were much or very much improved, whilst non-responders were defined as those with little or no response. The study supported the idea there is a therapeutic window, finding that antipsychotic D2

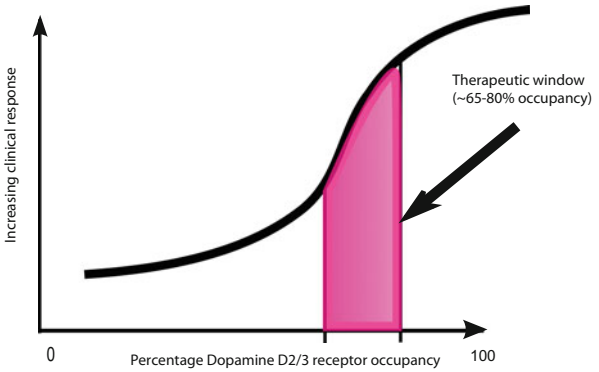

Fig. 3.1 The relationship between clinical response and dopamine receptor occupancy

occupancy of 65 % best distinguished responders from non-responders: 80 % of responders showed >65 % receptor occupancy, whilst 67 % of the non-responders had occupancy below the 65 % threshold. They also found that occupancy levels much above 80 % were associated with an increased risk of side effects. The notion of a therapeutic window of D2 occupancy for clinical response has subsequently been confirmed by a meta-analysis of imaging studies for a range of the most commonly used antipsychotics.(Yilmaz et al. 2012) However, it is important to note that in the first episode study, about one-third of the non-responders showed occupancy levels above the threshold.(Kapur et al. 2000) Thus, whilst some non-response may be due to inadequate receptor occupancy, there is still a proportion of patients who show inadequate response despite good D2 occupancy.

The role of other receptors has also been examined in vivo. The observation that clozapine, the only antipsychotic licensed for refractory schizophrenia, showed high levels of serotonin 2A receptor antagonism at clinical doses underpinned efforts to develop antipsychotic drugs that reproduced this aspect of clozapine's pharmacology without its tolerability issues. In the 1990s a number of second generation antipsychotics that showed high serotonin 2A receptor antagonism came to market. In vivo studies have subsequently investigated serotonin 2A occupancy in healthy volunteers and patients at clinical doses of these drugs. These studies have found that high levels of serotonin 2A occupancy is already apparent at low doses of these drugs, for example, risperidone at 2 mg and olanzapine at 5 mg (both generally sub-therapeutic doses) show serotonin 2A occupancy of >80 % (Kapur et al. 1999). Furthermore, a study that compared cortical serotonin 2A occupancy in patients randomised to either olanzapine or clozapine found that serotonin 2A occupancy was not significantly different between the patients on olanzapine (mean dose ~18 mg/day) and clozapine (mean dose ~325 mg/day) but, whilst both groups of patients improved with treatment, the patients on clozapine showed a significantly greater improvement in positive symptoms, suggesting that serotonin 2A occupancy alone does not explain clozapine's superiority (Moresco et al. 2004). Furthermore, even for an antipsychotic such as risperidone that shows high levels of serotonin 2A antagonism, there is a striking relationship between D2 occupancy and clinical response (r values

>0.75) (Catafau et al. 2006). It is also worth noting that chlorpromazine at higher doses (500–700 mg/day) shows high levels of serotonin 2A occupancy, similar to levels seen with clozapine (Trichard et al. 1998). In contrast, amisulpride, a second generation antipsychotic, shows almost no serotonin 2A receptor occupancy at clinical doses (Trichard et al. 1998). As amisulpride is as effective as drugs with high serotonin 2A occupancy, such as risperidone and olanzapine, this is further evidence that serotonin 2A occupancy does not explain antipsychotic efficacy. Other studies have investigated D1 receptor occupancy and clinical response. Here, again there are large differences between drugs at clinically relevant doses, suggesting that D1 occupancy is not a requirement for clinical response (Reimold et al. 2007).

In summary, D2 occupancy is needed for therapeutic response in general, and low levels of D2 occupancy are linked to inadequate response. Thus, in some patients increasing the dose will help. However, it is also clear that some patients do not respond despite high levels of DA D2 receptor occupancy. Thus, D2 receptor occupancy is not sufficient to guarantee response in a proportion of patients. This raises the question what is different about the biology of the DA system in refractory patients.

3.4 The Presynaptic DA System and Treatment Response

Given that presynaptic DA dysfunction is the major locus of dopaminergic abnormality in the disorder, this is the obvious contender for a difference in the DA system between responders and refractory patients. The first studies to investigate this were studies that measured levels of DA metabolites in plasma or cerebrospinal fluid in relation to antipsychotic response. The major DA metabolite examined is homovanillic acid (HVA). Higher baseline DA metabolite levels are generally associated with good subsequent response to antipsychotic treatment, whilst lower DA metabolite levels are associated with poor response (Yoshimura et al. 2003; Mazure et al. 1991; Pickar et al. 1984). Furthermore, there is some evidence that there is a bimodal distribution of HVA levels amongst patients with schizophrenia that is linked to subsequent response to antipsychotics (Ottong and Garver 1997; Bowers 1991). The first peak is higher than that seen in controls, and is seen in patients who respond to antipsychotics, whereas the second peak, at a similar level to control levels, is associated with non-response. A limitation of the plasma HVA measures used in many studies is that they are influenced by peripheral as well as central DA metabolism. Nevertheless, the same pattern of high HVA levels in responders and levels in non-responders is seen when cerebrospinal fluid is used (Pickar et al. 1992). Most of these studies examined non-response to one antipsychotic rather than resistance to multiple antipsychotics, but the same pattern is seen in studies of patients who met treatment resistance criteria (Pickar et al. 1992; Risch and Lewine 1993; Lieberman et al. 1994).

Of course, whilst elevated HVA levels in responders are consistent with the notion that DA levels are elevated in responders, there are alternative

explanations—they could reflect increased metabolism of DA, or reduced metabolism of homovanillic acid, for example—that could account for the differences between responders and non-responders.

Baseline synaptic DA levels in the striatum, indexed using a DA depletion paradigm, have been measured in relation to treatment response (Abi-Dargham et al. 2000). In this study Abi-Dargham and colleagues found that higher synaptic DA levels were associated with a better response to antipsychotic treatment. However, this study did not determine if the patients who showed a poor response were treatment resistant. A more recent imaging study examined DA synthesis capacity in patients who met rigorous treatment resistance criteria and compared them to patients who had shown a good response to antipsychotics, defined as meeting standardised criteria for remission. Interestingly, DA synthesis capacity in resistant patients was not significantly different from that in matched controls (Demjaha et al. 2012). Furthermore, a proportion of these patients then went on to have magnetic resonance spectroscopy to index glutamate levels in the anterior cingulated cortex. Here, the pattern was the opposite: the treatment-resistant patients showed elevated glutamate indices, whereas the responders showed lower glutamate levels that were not significantly different to those seen in matched controls (Demjaha et al. 2013a). These findings thus suggest that there is a double dissociation in DA and glutamate function between responders and resistant patients.

3.5 The Onset and Course of Treatment Refractory Schizophrenia

One issue that bedevils the interpretation of research into the biology of treatment resistance is that most of the studies are in chronic patients. Indeed, by definition patients will have had to have at least two treatment courses and so will have been ill for some time. It is thus not clear whether differences observed in treatment-resistant patients were present from illness onset or developed later. This links to the on-going debate in the field as to whether treatment resistance in schizophrenia evolves over time, perhaps as a consequence of untreated psychosis, or is manifest at the onset of illness. In line with a first notion, Wyatt (1991) reviewed the evidence derived from 22 studies of predominantly first episode patients that examined the effect of medication on the natural course of schizophrenia. Based on this he suggested that early psychopharmacological intervention improves outcome and prognosis, and proposed that a neurodegenerative process may be inherent to psychosis and thus unfavourably affect the clinical course in those who are non-compliant and subjected to multiple relapses. In a subsequent review of clinical studies, he synthesised the evidence showing that patients who received antipsychotic treatment early in the course of illness, specifically during their first or second hospitalisation, had a much better outcome than patients who did not receive any treatment (Wyatt 1995). This gave support to the "neurodegeneration hypothesis" suggesting that psychotic episodes have a neurotoxic effect on the

brain. However, numerous MRI studies have subsequently addressed this question and, whilst it is clear that brain changes do evolve in some patients, it remains possible that this is due to the effect of antipsychotic treatments (Zipursky et al. 2012).

Another possibility is that a proportion of patients become less responsive to pharmacological treatment as the illness progresses. Kolakowska et al. (1985) examined retrospective accounts of medicated patients 2–20 years after their first presentation to investigate this. However, the authors found that majority of 40 poor responders in their sample were unresponsive throughout the illness and thus concluded that treatment response is related to the "type" and not the "stage" of illness. The retrospective design of this study could have led to a measurement error leading to information bias. Still, as the authors rightly suggest, the bias would be towards "over-estimation" of remission particularly in cases were associated behavioural disturbance was not recorded. In addition, two other longitudinal studies have similarly observed that a refractory illness course is apparent in early stages of illness in a proportion of patients (Bleuler 1978; Huber et al. 1975). More recently, a large follow-up study of first episode patients that specifically examined the development of treatment resistance over the 10-year follow-up found that over 80 % of treatment-resistant patients were persistently resistant from the initiation of antipsychotic treatment (Demjaha et al. 2013b). Moreover, about 20 % of first episode psychosis patients appear to be resistant to medication at a very early stage of their illness, and at the time of initiation of treatment,(Agid et al. 2011; Robinson et al. 1999; MacMillan et al. 1986; Lieberman et al. 1996) which cannot be explained by the effects of medication, neurochemical sensitisation or neurodegeneration.

Thus, the longitudinal studies suggest that both models are right: a proportion, the clear majority, of treatment-resistant patients are resistant from onset, but there is a proportion who develop it later in their illness. Given that the clear majority of treatment-resistant patients are resistant from onset, the studies of treatment-resistant patients are likely to largely reflect the biology of treatment resistance from illness onset.

What, then, could underlie the development of treatment resistance in those patients who develop it during the course of their illness? There is evidence from animal studies that chronic treatment with DA blocking antipsychotics induces DA D2 receptor up-regulation, which could reduce the efficacy of antipsychotic treatment and lead to breakthrough DA supersensitivity. (Samaha et al. 2007; Ginovart et al. 2008) This implies that the development of DA supersensitivity may predispose some patients to becoming resistant following repeated and long-term exposure to antipsychotic treatment.

It should be noted that there is a third group of treatment-resistant patients who achieve spontaneous remission or start responding to treatment later in life (Meltzer 1997). Observations that older schizophrenic patients require much lower antipsychotic doses than their younger counterparts (Fenton and McGlashan 1987) suggest that the development of treatment responsiveness could be related to age-related reductions in dopaminergic transmission (Dreher et al. 2008; Reeves et al. 2002).

However, whilst this would explain the resolution of treatment resistance due to breakthrough DA supersensitivity, it would not account for resolution of resistance in patients who have been treatment resistant from onset.

Conclusion

The question raised at the beginning of the chapter was what underlies why some patients respond to antipsychotic treatment and others do not. Research over recent decades allows us to go some way to answer this. It is clear that presynaptic dopamine dysregulation is a consistent finding in schizophrenia and linked to the onset of psychosis. It would take a lot of new evidence to overturn this finding. This indicates that by blocking dopamine receptors, antipsychotic drugs are acting on the right system. It is also clear that adequate dopamine receptor blockade is central to the mode of action of all first-line (non-clozapine) antipsychotics, with D2 receptor occupancy greater than a threshold of 65 % or so linked to antipsychotic efficacy. Nevertheless, some patients do not respond despite adequate D2 blockade. The studies of dopamine metabolites in the 1990s and the more recent molecular imaging studies indicate that non-responders do not show the same dopamine abnormality seen in the majority of patients. This would explain why they do not respond to dopamine blocking drugs. Moreover, recent results suggest that treatment-resistant patients instead show altered glutamate function. However, this finding requires further testing, and there are questions that remain outstanding, not least whether these biological differences exist at illness onset or whether they develop during the course of the illness. The fact that treatment resistance is present early in the illness suggests that they are likely to be present at illness onset for the majority of treatment-resistant patients, but longitudinal imaging studies are required to definitively determine this.

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Medical and Psychiatric Comorbidities: Complicating Treatment Expectations

4

Brian J. Miller and Peter F. Buckley

There has been a renewed awareness in recent years of the long-standing association between schizophrenia and increased premature death from both unnatural and natural causes. Indeed, this well-documented finding antedates antipsychotic therapy (Harris and Barraclough 1998). Increased premature mortality in schizophrenia is an important public health problem. In 2004 in England, the indirect costs of schizophrenia, including those associated with premature death, were estimated at $7.6 billion (Mangalore and Knapp 2007). In 2002 in the USA, the indirect costs of death from suicide in patients with schizophrenia were estimated at $1.1 billion (McEvoy 2007).

The growth of research in mortality (and its associated risk factors) in schizophrenia has highlighted the complexity of this issue. The higher rate of suicide in schizophrenia—up to half of patients with schizophrenia attempt suicide, and the lifetime risk of completed suicide in the disorder is 5 %—contributes substantially to heightened mortality, but it is by no means the full story (Palmer et al. 2005). Cardiovascular disease is the leading cause of mortality in patients with schizophrenia (Saha et al. 2007). Metabolic abnormalities in first-episode drug-naïve patients with schizophrenia, coupled with findings of increased natural cause deaths in the pre-antipsychotic era, suggest that there seems to be something about the illness that contributes to this premature mortality. These findings are complemented by the heightened natural cause mortality risk in the antipsychotic era (Saha et al. 2007), driven in part by effects of antipsychotics, including cardiometabolic risks of antipsychotic-associated weight gain and glucose and lipid abnormalities, direct cardiotoxicity of antipsychotics (Reilly et al. 2000), and respiratory deaths associated with antipsychotic polypharmacy (Waddington et al. 1998).

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Germane to our focus on treatment-resistant schizophrenia (TRS) is the case of clozapine. Clozapine was initially hailed as a breakthrough ("life-saver") drug for the most severely ill patients. Moreover, it was actually shown to reduce suicide in patients with schizophrenia in a randomized controlled trial (Meltzer et al. 2003). Now, it is associated with the greatest risk of metabolic disturbances, as well as with potentially fatal thromboembolism and myocarditis (Annamraju et al. 2007; Coodin and Ballegeer 2000). Thus, the impact of appropriate management of treatment-resistant schizophrenia results in the need for the treating clinician to balance the apparent mitigating effect of clozapine on suicide risk with its potential exacerbating effects on natural cause mortality, over the longitudinal course of illness. Further complicating the clinical picture and treatment of schizophrenia is the substantial psychiatric comorbidity (Buckley et al. 2009). Depression, anxiety, and substance abuse are common accompaniments of the schizophrenia condition, and in turn their presence (and potentially their treatment) can impact on medical comorbidities, as well as mortality risk from both unnatural and natural causes.

The purpose of this chapter, framed within the context and set against the other findings illuminated in this comprehensive text on treatment-resistant schizophrenia, is to give a current account of both medical and psychiatric comorbidities in TRS, their impact on mortality risk, and treatment considerations for the practicing clinician.

4.1 The "Balancing Act" of Comorbidity in Schizophrenia

Consider the following scenario. A 45-year-old man presents for the first time to the outpatient clinic for an initial evaluation for schizophrenia. He reports a 15-year history of pervasive suspiciousness that his neighbors are spying on him. He tells the psychiatrist that he has overheard them numerous times over the years plotting to kill him. He endorses receiving special messages while watching television that reinforce these beliefs. He also endorses daily auditory hallucinations that tell him he is "a no good failure", and "you should just go ahead and kill yourself." He lives independently and is able to care of his basic needs, although he is generally isolated at home. He has been unable to work for the past 15 years due to the unremitting nature of his symptoms. He endorses periods of depression, and 6 years ago he was hospitalized following an overdose on medication in an admitted suicide attempt. He tells the psychiatrist that he was treated previously with risperidone 4 mg at bedtime, for several years, and quetiapine 400 mg at bedtime, also for several years. He states that he took both of these medications regularly because they helped him sleep better, but that he continued to hear the voices and feel suspicious of his neighbors, and "I stopped them because they made me gain weight." He was also tried briefly on ziprasidone, but "my doctor stopped it because of something to do with my heart." He smokes two packs of cigarettes daily.

The psychiatrist discusses with the patient the risks and benefits of a trial of clozapine, to which the patient ultimately agrees. Before starting clozapine, the patient is 69 in. tall and weighs 180 lb (body mass index = 27). Baseline fasting

blood work reveals a normal glucose and lipid panel. The patient has no known medical problems and does not take any other medications. Overall, the patient tolerates the clozapine trial well. The dose of clozapine is titrated up to 450 mg daily and the patient shows significant improvement in his psychiatric symptoms. He no longer hears the voices. He admits to fleeting thoughts that his neighbors talk about him behind his back, but he is not preoccupied with them. He joins a local church and makes some friends through a bible study. He is able to work part-time. He has increased contact with his family. However, the patient also gains 40 lb in the first year on clozapine (body mass index = 33). Subsequently, he develops hypertension, diabetes, and hyperlipidemia, diagnosed and managed by a primary care physician in the community, whom the patient sees no more than annually. These comorbidities are initially treated with diet and exercise, but ultimately medications are required. The patient cuts down on nicotine use but still smokes a pack per day. The risks of his physical health problems are discussed with the patient by the psychiatrist, but he is adamant that he wants to continue the clozapine because "it's the only medication that's ever helped me." The patient is treated with clozapine for 10 years, when he dies from a myocardial infarction at the age of 55.

Consider an alternative scenario. The same patient declines the clozapine trial, but agrees to a trial of perphenazine. He stops the medication after a month because "it made my arm twitch." In 3 months, he drops out of treatment altogether. The patient's hallucinations and delusions persist. He becomes increasingly depressed and isolated. He attempts to "self-medicate" with alcohol, typically 6–12 cans of beer daily. One evening after a period of heavy drinking, the voices become particularly loud and continue to berate the patient. He feels "trapped." In order to "get rid of the voices", the patient completes suicide by firearm at the age of 47.

The second scenario is obviously tragic, but can we consider the first scenario a treatment "success"? Knowing the metabolic risks of clozapine, would you start "prophylactic treatment"? If so, which treatment would you give? It's a very complex question, especially since these treatments might have their own side effects. And, even if you were able to blunt or decrease the weight gain and metabolic disturbance associated with clozapine, would the patient still have died prematurely from cardiovascular disease? What would you do if treatment with clozapine was also associated with the emergence of obsessive–compulsive symptoms? These are tough questions, too. Indeed, as we will describe in this chapter, managing the risks and benefits of clozapine amounts to a delicate "balancing act" for the practicing clinician.

4.2 Beyond Blood Monitoring: Other Serious Side Effects of Clozapine

Clozapine is recommended for positive symptoms in patients with treatment-resistant schizophrenia (Buchanan et al. 2010). While the need for white blood cell and neutrophil count monitoring due to the risk of bone marrow suppression and agranulocytosis with clozapine is well known, greater awareness and screening

are needed for other potentially life-threatening effects of clozapine, including diabetic ketoacidosis (DKA), gastrointestinal (GI) hypomotility, and myocarditis. Cohen et al. (2012) performed a systematic review of 16 studies that included data on these adverse effects. They found a 4–8 % incidence of clozapine-induced agranulocytosis, with a 2–4 % case-fatality rate. Clozapine was also associated with a 1–3 % incidence of DKA, which had a remarkable 20–31 % case-fatality rate. Similarly, there was a 4–8 % incidence of GI hypomotility, with a similarly high case-fatality rate of 15–28 %. The authors found a discrepancy in incidence of clozapine-induced myocarditis between Australia (7–34 %) and the rest of the world (0.1–0.6 %). In contrast to this finding, Haas et al. (2007) reviewed 116 case reports of suspected myocarditis associated with clozapine use in Australia during 1993–2003. They calculated an incidence 0.7–1.2 % in treated patients. Myocarditis occurred in relatively young patients (median age 30) with early onset after treatment initiation (median 16 days) and was associated with a >10 % mortality rate. Taken together, these findings underscore the need for vigilant monitoring for multiple comorbidities associated with clozapine treatment.

4.3 Treatment-Resistant Schizophrenia and The Metabolic Syndrome

According to the World Health Organization, the top six global mortality risk factors are hypertension, smoking, diabetes, physical inactivity/cardiorespiratory fitness, overweight or obesity, and dyslipidemia (WHO 2009). The metabolic syndrome is a constellation of metabolic risk factors associated with the development of atherosclerotic cardiovascular disease (Galassi et al. 2006; Grundy et al. 2005) and cardiovascular disease mortality (Galassi et al. 2006). As defined by the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (Grundy et al. 2005), subjects meeting three or more of the following five criteria are defined as having the metabolic syndrome: (1) waist circumference ≥102 cm in males or ≥88 cm in females, (2) fasting triglycerides ≥150 mg/dL, (3) fasting HDL <40 mg/dL in males or <50 mg/dL in females, (4) blood pressure ≥130/85 mmHg or on antihypertensive drug treatment in a subject with a history of hypertension, and (5) fasting glucose ≥100 mg/dL or on drug treatment for elevated glucose.

The prevalence of the metabolic syndrome in TRS is remarkably high. Among 84 patients in Ireland receiving clozapine, Ahmed et al. (2008) found that 46 % met criteria for the metabolic syndrome. Male gender and concomitant antipsychotic medication (in addition to clozapine) were significantly associated with the metabolic syndrome in this study. A similar prevalence was reported in a Swedish cohort of patients with schizophrenia treated with clozapine (Hägg et al. 2006). 48 % of 54 subjects on clozapine monotherapy had the metabolic syndrome, including 70 % with abdominal obesity, 57 % with hypertriglyceridemia, 39 % with low HDL, 43 % with hypertension or medication use, and 22 % with high fasting glucose or medication use.

Several other studies have described relationships between clozapine use and individual components of the metabolic syndrome. In a chart review of 82 clozapine-treated patients, Henderson et al. (2004) found significant increases in systolic and diastolic BP over 5 years. 27 % of these patients received treatment for hypertension following initiation of clozapine, compared to just 4 % of 56 patients treated with typical antipsychotics and 9 % of 102 patients treated with other atypical antipsychotics. In a 10-year naturalistic study of 96 patients following clozapine initiation by the same group, the Kaplan–Meier estimate for 10-year cardiovascular disease mortality was 9 % (Henderson et al. 2005). The authors found significant increased cardiovascular mortality risk in African and Hispanic American versus Caucasian patients. The Kaplan–Meier estimate of new-onset diabetes in the cohort was 43 %, and diabetes risk was also higher in African and Hispanic American patients.

What are the potential mechanisms by which clozapine contributes to the metabolic syndrome? One possibility is direct effects of the medication. For example, clozapine impedes glucose uptake by muscle cells, possibly through impaired cell surface glucose transporter proteins (Tovey et al. 2005). Three previous studies have found an increased prevalence of type 2 diabetes in the parents of patients with schizophrenia and related disorders (Fernandez-Egea et al. 2009; Mukherjee et al. 1989; Spelman et al. 2007). This association might be due to genetic or environmental risk factors (or both). For example, low birth weight and exposure to prenatal stress during gestation are environmental risk factors for both disorders. Likewise, the gene for tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine, is located on chromosome 6p21.3, a region associated with schizophrenia in numerous linkage studies (Zai et al. 2006). The type 2 diabetes susceptibility gene IGF2BP2 has also been associated with schizophrenia in a Han Chinese population (Zhang et al. 2013).

The metabolic syndrome is also associated with a state of chronic, low-grade inflammation (Devaraj et al. 2010). A recent meta-analysis found that high-sensitivity C-reactive protein (CRP), an acute phase protein that is a marker of inflammation, was an independent predictor of cardiovascular disease (Kaptoge et al. 2010). In a meta-analysis, we found that blood CRP levels were significantly increased in patients with schizophrenia versus controls, and 28 % of patients with schizophrenia had an elevated CRP levels (Miller et al. 2013). Several studies have found that blood CRP levels are correlated and/or predict metabolic syndrome (Fan et al. 2010; Miller et al. 2013; Shcherbakova et al. 1999) or components of the metabolic syndrome (Carrizo et al. 2008; Dieset et al. 2012; Fan et al. 2010; Fawzi et al. 2011; Miller et al. 2013) in patients with schizophrenia. It is important to note that most studies of CRP did not focus exclusively on subjects with TRS or clozapine-treated subjects. A notable exception is a study by Löffler et al. (2010a, b), who reported a statistically significant 600 % increase in hsCRP in eight subjects with chronic schizophrenia started on clozapine for the first time for 8 weeks. It was also reported in that study that a cross-sectional investigation of 25 patients on long-term clozapine and 25 psychiatric controls did not show an elevation of hsCRP with

clozapine after 1 year or more. Further longitudinal studies are needed to investigate these associations in TRS.

Schizophrenia is also associated with increased blood levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), TNF-α, and IL-1β (Miller et al. 2011), including studies in patients with first-episode psychosis and minimal exposure to antipsychotics, suggesting an association that may be independent of medication. The adverse metabolic effects of atypical antipsychotics, which increase metabolic syndrome risk, may potentiate aberrant blood levels of inflammatory markers (Beumer et al. 2012). In our cytokine meta-analysis, we also found significantly increased blood levels of the soluble interleukin-2 receptor in patients with TRS versus controls, suggestive of chronic immune activation in these patients (Miller et al. 2011). Similar to the literature for CRP, there is a paucity of longitudinal studies of the effects of clozapine on blood cytokines. One such study found a 1.3-fold elevation of blood IL-6 levels in 12 patients treated with clozapine monotherapy compared to 10 controls (Löffler et al. 2010b). This finding is internally consistent, as cytokines, particularly interleukin-6 (IL-6), are the primary inducers of CRP. Chen et al. (2008) found elevated TNF levels in clozapine-induced obesity in patients with chronic schizophrenia. Similarly, Kluge et al. (2009) found a significant positive correlation between increase in TNF and BMI during clozapine initiation. Other immune system-related effects of clozapine have been reviewed extensively elsewhere (Røge et al. 2012).

Telomeres, noncoding tandem repeat structures at the end of chromosomes, are thought to be markers of biologic aging. Critically shortened telomeres promote cellular senescence, and shortened telomeres are associated with type 2 diabetes (Sampson et al. 2006), coronary artery disease (Obana et al. 2003), and all-cause mortality in people aged >60 (Cawthon et al. 2003). Three studies have examined telomeres in patients with schizophrenia. Fernandez-Egea et al. (2009) found significantly decreased telomere content in 41 drug-naïve patients with first-episode non-affective psychosis compared to 41 well-matched controls, suggesting an association that is independent of antipsychotic medications. Patients with schizophrenia (versus controls) in this study also had increased pulse pressure and increased 2-h glucose on a glucose tolerance test—indices that have been linked to an increased risk of diabetes and hypertension. Yu et al. (2008) measured telomere length in 68 patients with schizophrenia—including 34 responders and 34 nonresponders to antipsychotics—and 76 controls. They found significant telomere shortening in peripheral blood leukocytes of patients with poor response to antipsychotics versus controls, but no difference between antipsychotic responders and controls. Lastly, Kao et al. (2008), in a study of 51 patients with schizophrenia and 52 controls, found a significant effect of diagnosis on shorter telomere length, after controlling for age and sex. Furthermore, there was no correlation between current or lifetime antipsychotic dose and telomere length. The authors estimated that the rate of telomere loss more than doubled in the 20 years following the onset of schizophrenia in their sample and that the lymphocytes had aged at least 25 years more than controls.

Table 4.1 Pharmacologic management of antipsychotic-induced metabolic disturbance in schizophrenia

Agent	Proposed mechanism of action	Trial results	Comments
Amantadine	Decrease appetite	[a]	
Atomoxetine	Appetite suppressant	(−)	
Betahistine	Satiety	(−)	
Fluoxetine	Decrease appetite	(−)	
Fluvoxamine	Decrease appetite	(+)	Decreased weight, glucose triglycerides
Metformin	Enhances insulin sensitivity	(++)[a]	Decreased weight (2 trials) Decreased insulin, triglyceride/HDL; Increased HDL (1 trial)
Nizatidine	Decrease appetite	[a]	
Orlistat	Decrease intestinal fat absorption	(−)	
Phenylpropanolamine	Appetite suppressant	(−)	
Reboxetine	Decrease appetite	[a]	
Sibutramine	Appetite suppressant	(−)	
Topiramate	Decrease appetite	(+)[a]	Decreased weight; No changes in glucose of lipids

(+) = significant findings
(−) = negative trial
(++) = significant findings in multiple trials
[a]Significant findings, but not studied in TRs

4.4 Pharmacologic Management of Antipsychotic-Induced Weight Gain

Given the above-detailed associations between clozapine and the metabolic syndrome or its components, and the impact on morbidity and mortality risks, it follows that there has been significant interest in pharmacologic strategies to prevent or reverse antipsychotic-induced weight gain. Several trials have been effective in mitigating this effect, although findings are limited by few randomized placebo-controlled trials and the fact that most were short duration trials lacking adequate statistical power (reviewed in Baptista et al. 2008). Despite these limitations, as well as contradictory results for some agents, there have been some promising results for patients with TRS, which are also described in Table 4.1.

Topiramate is an antiepileptic that is thought to decrease appetite through glutamatergic inhibition. Hahn et al. (2010) performed an open-label trial of 12 weeks of adjunctive topiramate (mean dose 167 mg/day) in 16 treatment-refractory patients with schizophrenia on clozapine. Patients had a mean weight loss of 2.6 +/− 3.7 kg 12 weeks, corresponding to a 2.5 % reduction in body weight. There were no significant changes in fasting glucose, lipids, hemoglobin A1c, or 2-h glucose challenge. Two other randomized controlled trials also found

significant weight loss with adjunctive topiramate (Narula et al. 2010; Ko et al. 2005), though these trials were not in treatment-resistant patients.

Lu et al. (2004) studied 68 inpatients with schizophrenia treated with either clozapine monotherapy (<600 mg/day), or the selective serotonin reuptake inhibitor fluvoxamine (50 mg/day) plus low-dose clozapine (<250 mg/day) ($n = 34$ in each group) for 12 weeks. At study endpoint, the fluvoxamine group had lower glucose, triglycerides, and norclozapine levels. Importantly, norclozapine levels were significantly positively correlated with changes in weight, glucose, and triglycerides. The authors concluded that fluvoxamine treatment can attenuate weight gain and metabolic disturbances; however, fluvoxamine can markedly increase plasma clozapine levels through cytochrome P450 activity, increasing the risk of adverse events.

Sibutramine is an appetite suppressant that blocks monoamine reuptake. Henderson et al. (2007) performed a 12-week trial of sibutramine (up to 15 mg/day) versus placebo in 21 patients with schizophrenia or schizoaffective patients treated with clozapine. They found that sibutramine did not reverse clozapine-induced weight gain ($p = 0.31$ vs. placebo), and there were no significant differences in changes in weight, BMI, abdominal and waist circumference, HgbA1C, fasting glucose, or cholesterol levels between subject groups.

Ball et al. (2011) studied 37 patients with schizophrenia or schizoaffective disorder who gained at least 7 % of their baseline body weight following treatment with clozapine or olanzapine. Subjects were randomized to a 24-week comparison of adjunctive atomoxetine or placebo, and all participants received structured support and an exercise group. They found a modest but nonsignificant weight loss (about 2 kg) in both groups.

The most extensively studied adjunctive agent for antipsychotic-induced weight gain to date has been the antidiabetic agent metformin, which enhances insulin sensitivity. Ehret et al. (2010) performed a meta-analysis of six randomized, placebo-controlled trials of metformin in patients taking atypical antipsychotics. They found that subjects treated with metformin had significantly reduced weight, BMI, waist circumference, and insulin resistance, but a nonsignificant reduction in diabetes risk. Two trials of metformin have focused on patients treated with clozapine. In an elegantly designed study, Wu et al. (2008) recruited 128 adults with first-episode schizophrenia who gained more than 10 % of their pretreatment weight, of which 31 % were treated with clozapine. Subjects were assigned to one of four treatment groups for 12 weeks: metformin 750 md/day +/− lifestyle intervention versus lifestyle intervention only versus placebo. They found that metformin plus lifestyle intervention showed the best effect on weight loss, but metformin alone was also efficacious for weight gain. Furthermore, metformin alone was more effective in weight loss and improving insulin sensitivity than lifestyle intervention alone. Carrizo et al. (2009) performed a 14-week placebo-controlled trial of extended release metformin (500–1,000 mg/day) in 61 patients receiving clozapine for more than three consecutive months. In an analysis of completers (there were seven dropouts in the metformin group, but none in controls), subjects on metformin had significantly more weight loss, a significant

decrease in insulin and the triglyceride/HDL ratio, as well as a significant increase in HDL.

There have also been positive trials of several other agents, though not specifically studied in TRS, including the H2 receptor antagonist nizatidine, the selective norepinephrine reuptake inhibitor reboxetine, and the dopamine agonist and NMDA receptor antagonist amantadine (reviewed in Baptista et al. 2008). While the 2009 Schizophrenia Patient Outcomes Research Team (PORT) psychopharmacological treatment recommendations (Buchanan et al. 2010) note the contribution "antipsychotic-induced weight gain is thought to be an important modifiable contributor to the high rates of obesity" in schizophrenia, which contributes to higher morbidity and mortality, "there is currently insufficient evidence to recommend a specific pharmacological intervention for the prevention or treatment of antipsychotic-induced weight gain. However, clinicians should monitor weight gain due to antipsychotic medications and consider the use of an evidence-based psychosocial weight loss intervention."

4.5 Non-Pharmacologic Management of Antipsychotic-Induced Weight Gain

In addition to pharmacologic management, there has been great interest in non-pharmacologic interventions to mitigate antipsychotic weight gain. As has been the case with pharmacologic trials, studies of behavioral interventions have been limited by relatively small sample sizes and study durations (reviewed in Das et al. 2012; Strassnig and Ganguli 2007). Despite these limitations, there are some promising results. Several trials have focused on patients treated with clozapine. As noted above, Ball et al. (2011) found modest, nonsignificant weight loss (about 2 kg) subjects treated with clozapine or olanzapine who received 24 weeks or structured support and an exercise group in addition to atomoxetine or placebo. Wu et al. (2008) found that metformin plus lifestyle intervention was more efficacious than metformin alone for weight loss in first-episode psychosis (of whom almost one-third were treated with clozapine). In a study of 53 clozapine-treated patients with schizophrenia and obesity, subjects treated with a dietary intervention (200–300 decreased calorie intake per day) and a 6-month regimen of regular physical activity (walking 3 days per week) had a significant decrease in weight, BMI, and waist and hip circumference at 3 and 6 months and decreased triglycerides at 6 months, compared to controls (Wu et al. 2007). In a sample of 35 patients who gained at least 20 lb during antipsychotic treatment and subsequently lost 10 lb, the most frequent weight loss interventions were regular dietitian visits, self-directed diet, and weight loss as a treatment goal (O'Keefe et al. 2003). In a meta-analysis of behavioral interventions in schizophrenia as a whole, nutritional counseling plus exercise showed the greatest benefit (Das et al. 2012). In this review, although improvements were modest, behavioral therapies showed the most consistent benefits (versus adjunctive pharmacotherapies) compared with controls. Taken

together, these findings suggest that non-pharmacologic interventions also play an important role in the treatment of antipsychotic-induced weight gain.

4.6 Treatment-Resistant Schizophrenia and Psychiatric Comorbidity

Psychiatric comorbidity is remarkably common in schizophrenia, and these comorbidities, in turn, can perturb the clinical picture. For example, depression can cause secondary negative symptoms, panic attacks can drive paranoia, and cannabis abuse can worsen positive and disorganization symptoms. In a previous review, we estimated a 15 % prevalence of comorbid panic disorder, 29 % for PTSD, and 23 % for OCD in patients with schizophrenia (Buckley et al. 2009). Comorbid depression occurs in 50 % of patients. Conservatively, 47 % of patients have a lifetime diagnosis of comorbid substance use disorder. Unfortunately, few studies have investigated the prevalence of psychiatric comorbidities in patients with TRS.

To our knowledge, there are no randomized controlled trials in the treatment of either panic disorder or PTSD. There is a case report of a 44-year-old male veteran with PTSD and psychosis, who experienced significant clinical improvement on clozapine (Hamner 1996). There is also a case series of clozapine treatment for adolescents with PTSD and psychotic symptoms, in which four of six subjects had significant improvement in psychiatric symptoms and behavior with a therapeutic dose of clozapine.

A significant proportion of patients with schizophrenia have comorbid OCD. It has been suggested the presence of obsessive–compulsive symptoms might constitute a distinct schizo-obsessive subtype that are generally considered highly treatment refractory. However, an important consideration in this relationship is the timing of the onset of obsessive–compulsive and psychotic symptoms relative to each other. In a case series and literature review, patients who begin to exhibit OCD symptoms within the course of the psychotic process are more likely to be successfully treated with clozapine monotherapy (Reznik et al. 2004). By contrast, clozapine may also be associated with de novo onset or reemergence of preexisting OCD symptoms (Reznik et al. 2004; Schirmbeck and Zink 2012). There are significant correlations of the severity of OCD symptoms with the duration, dose (especially for doses >600 mg/day), and serum levels associated with clozapine treatment. When OCD symptoms precede the development of schizophrenia, clozapine monotherapy appears to be inefficient and may worsen symptoms and requires treatment with concomitant anti-obsessive agents (Reznik et al. 2004). The authors recommended citalopram or sertraline, due to the absence of interactions with clozapine.

Comorbid substance use disorders might be considered the "rule" rather than the exception in patients with schizophrenia, and carries potentially devastating negative consequences on the course and outcome of the disorder. These consequences include more positive symptoms, illness relapse, heightened risk of suicide and

violence, more medical comorbidities, legal complications (including heightened risk of incarceration), and greater propensity to antipsychotic-related side effects (Buckley et al. 2009). Several reviews have documented the apparent superiority of clozapine, versus other antipsychotics, for decreased substance use and relapse of substance use in patients with schizophrenia and comorbid substance use disorder, including alcohol, cannabis, and cocaine (Brunette et al. 2006; Drake et al. 2000; Kelly et al. 2012; Murthy and Chand 2012). Clozapine may also reduce nicotine use in schizophrenia (Murthy and Chand 2012). The mechanisms by which clozapine reduces substance use in schizophrenia are not clear. However, one study of 123 patients with psychotic disorder and cannabis dependence found that patients treated with risperidone had significantly greater craving for cannabis than those treated with either clozapine or olanzapine (Machielsen et al. 2012). The authors postulated that the differences in D2 receptor occupancy and dissociation and the D1/D2 occupancy ratio between clozapine and risperidone contributed to the observed differences (Machielsen and de Haan 2009; Machielsen et al. 2012). Based on the available evidence, the 2006 Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia recommended (group consensus) that patients with comorbid substance use disorder should prompt earlier institution of clozapine in the algorithm (Moore et al. 2007).

4.7 Mortality in Treatment-Resistant Schizophrenia

The tremendous burden of premature mortality from natural and unnatural deaths in schizophrenia is well documented (Saha et al. 2007). Many studies have described mortality in schizophrenia and related disorders without regard to treatment resistance. Mortality data for TRS center around studies of the (short- and long-term) effects of clozapine, with a number of insightful findings. There is a substantial body of evidence regarding the anti-suicidal properties of clozapine, perhaps best summarized by the Schizophrenia PORT psychopharmacological treatment recommendation that "A trial of clozapine should be considered for people with schizophrenia who exhibit marked and persistent suicidal thoughts or behaviors. Clozapine is the only medication approved by the US FDA for preventing suicide in patients with schizophrenia" (Buchanan et al. 2010).

Hennen and Baldessarini (2005) performed a meta-analysis of six published studies contrasting rates of suicides or suicide attempts by patients treated with clozapine versus other agents. There was a significant, approximately threefold lower overall risk of both suicidal behaviors and completed suicides in patients on long-term treatment with clozapine. Of note, five of the six studies in this meta-analysis were registry studies. Meltzer et al. (2003) reported on the International Suicide Prevention Trial (InterSePT), the only randomized controlled trial of clozapine for suicide prevention. This trial was a 2-year study of 980 patients with schizophrenia or schizoaffective, considered high risk for suicide due to either previous attempts or current suicidal ideation, randomized to either clozapine or olanzapine. The authors found significantly less suicidal behavior, fewer suicide

attempts, hospitalizations, or rescue interventions to prevent suicide, and fewer patients treated with concomitant antidepressants or anxiolytics in the clozapine group. However, there was no difference in completed suicide between the two groups (5 in the clozapine and 3 in the olanzapine group). The "high risk status" of patients enrolled in this study may have contributed to the observed lack of differences.

The mechanisms by which clozapine decreases suicidality are not well defined. Spivak et al. (2003) studied 18 patients treated with clozapine and 26 patients treated with haldol decanoate in an open, prospective 6-month trial. In the clozapine group only, the reduction in measures of suicidality was significantly correlated with a reduction in impulsiveness and aggression. Indeed, the Schizophrenia PORT guidelines recommend a trial of clozapine for patients with schizophrenia who present with persistent symptoms of hostility and/or display persistent violent behaviors (Buchanan et al. 2010).

In a seminal study, Tiihonen et al. (2009) compared cause-specific mortality in 66,881 patients with schizophrenia versus the total population of Finland (5.2 million) between 1996 and 2006. They found that the lowest risk of death was for clozapine (versus perphenazine), and that clozapine had substantially lower all-cause and suicide mortality than any other antipsychotics. There was also a nonsignificant lower risk of death from ischemic heart disease in clozapine-treated patients. However, it has been argued that methodological and conceptual issues of this study make interpretation of findings problematic (De Hert et al. 2010). One possibility is that the findings for all-cause mortality were driven by the dramatic reduction in suicide mortality and that subjects were not followed long enough to accurately measure the potential increase in cardiovascular disease mortality due to the metabolic effects of clozapine. Indeed, Fontaine et al. (2001) estimated mortality due to clozapine-induced weight gain using data from the Framingham Heart Study. Interestingly, they found that the reduction in suicide mortality would be offset over 10 years by the increased mortality associated with a weight gain of 10 kg.

Several other studies have examined natural cause mortality in patients treated with clozapine. Walker et al. (1997) compared mortality rates in 67,072 current and former clozapine users. There were 396 deaths in 85,399 person–years of follow-up in patients aged 10–54. They found lower mortality during current clozapine use versus periods of nonuse. There was an almost sixfold decrease in suicide mortality in current versus past users, but there were also a greater than fivefold increase in mortality from pulmonary embolism and an almost threefold increase in mortality from respiratory disorders. There was a trend for a 1.7-fold increased risk of cardiovascular mortality as well. Kelly et al. (2010) performed a retrospective cohort study of 1,084 patients with schizophrenia who started clozapine and 602 patients never treated with clozapine (who were instead initiated on risperidone) between 1994 and 2000 and followed for 6–10 years. In patients who started treatment at age >55, patients treated with clozapine had nonsignificantly higher 5- and 10-year cardiovascular disease mortality, but overall there was no difference in cardiovascular disease mortality between clozapine and risperidone in this study.

Thus, more longitudinal studies are needed to evaluate the long-term impact of clozapine on cardiovascular disease mortality. Smith et al. (2013) performed a cross-sectional study of 314 primary care practices in Scotland, including 9,677 patients with a primary care record of schizophrenia or related psychosis and 1.4 million controls. They found that patients with schizophrenia are more likely to have multiple medical comorbidities, but are less likely than patients without schizophrenia to have a primary care record of cardiovascular disease, suggesting a systematic under-recognition and treatment, which might contribute to the associated increased premature mortality.

Interestingly, paternal age at birth, a robust risk factor for schizophrenia, may also be a risk factor for mortality. In a cohort of 529 subjects with non-affective psychosis born in Helsinki, Finland, between 1951 and 1960 and followed until 2006 (age 46–55), we found a significant increase in all-cause mortality and natural deaths (both greater than sevenfold) in female, but not male, offspring of fathers aged >40 compared to a reference paternal age of 25–29 (Miller et al. 2010a, b). The association between paternal age and mortality may extend to females in the general population as well (Miller et al. 2010b).

Several other recent studies also shed light on the issue of mortality in schizophrenia. In a study of all patients in England discharged from inpatient care with a diagnosis of schizophrenia, the absolute risk of death within a year of hospitalization was about 1.5 %, and circulatory and respiratory diseases were leading causes of death (Hoang et al. 2011). Similarly, we previously reported that 3 % of patients with serious mental illness in Ohio died within 5 years of inpatient psychiatric care, and cardiovascular disease was the leading cause of death (Miller et al. 2006). Thus, inpatient care for schizophrenia offers a critical window during which risk factors for mortality, particularly cardiorespiratory disease, can be recognized and modified. Systematic efforts to screen for and treat modifiable risk factors, including metabolic screening, smoking cessation interventions, and pneumonia and influenza vaccination programs are needed (Miller et al. 2011).

Conclusions

Medical and psychiatric comorbidity in TRS is extremely common. There is evidence, from the pre-antipsychotic era as well as studies of drug-naïve patients with first-episode psychosis, that some of this comorbidity (and/or liability to comorbidity) may be part of the pathophysiology of the disorder. Antipsychotic treatment, including clozapine, can exacerbate this vulnerability or induce comorbidities due to side effects or direct toxicities. Conversely, clozapine is extremely beneficial with regard to treatment-resistant (particularly) positive symptoms, and reducing suicidal thinking and behavior, impulsivity and aggression, and substance use. Furthermore, schizophrenia is a very heterogeneous disorder, with no two patients presenting with the same constellation of signs, symptoms, and comorbidities. The net result is the extremely delicate "balancing act" for the practicing clinician regarding the management of patients with TRS. A summary of potential risk and benefits of clozapine in TRS, with regard to medical and psychiatric comorbidities, and strategies to manage and mitigate

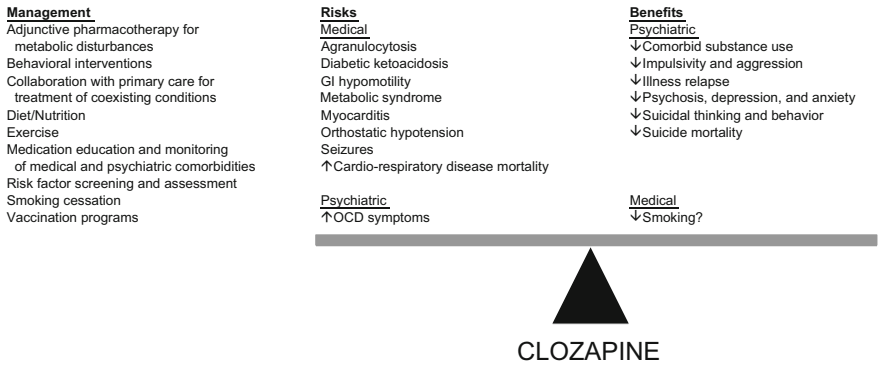

Fig. 4.1 Potential risk and benefits of clozapine, with regard to medical and psychiatric comorbidities, and strategies to manage and mitigate associated risks

associated risks, is presented in Fig. 4.1. Given the tremendous burden of comorbidity future research should focus on concerted, multimodal (e.g., screening and monitoring, pharmacologic and behavioral treatments) approaches to improve quality of life and decrease mortality in TRS.

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Overview of Pharmacological Treatments and Guidelines

5

Siobhan Gee and David Taylor

5.1 The Discovery of Clozapine

During the earlier part of the twentieth century, psychopharmacologists had worked with the belief that the antipsychotic properties and movement disorder side effects of drugs went hand in hand. The prevailing opinion was that without the often physically and socially disabling emergence of tardive dyskinesias and extrapyramidal side effects (EPSEs), an antipsychotic would lack therapeutic benefit. The development of clozapine marked a turning point.

Clozapine was one of a number of compounds synthesised by Wander Laboratories in the late 1950s. Chemically, it is a dibenzodiazepine, its ring structure differing from imipramine by the insertion of a nitrogen atom on one side of the "carbon bridge" of the seven-membered central ring. Its structural conformation suggested it would have antidepressant properties. In fact, a similar compound produced at this time (dibenzepin) was found to be an antidepressant and is still in use.

Clozapine was not active in animal screening tests for antipsychotic activity, but its effects in humans were reported to be profoundly antipsychotic and, uniquely, to occur in the absence of extrapyramidal adverse effects. The Wander Company was apparently reluctant to market clozapine as an antipsychotic because it did not fit the prevailing theories on antipsychotic action—all antipsychotics caused extrapyramidal side effects, and so these effects must be part of the antipsychotic action.

Open label studies of clozapine's effects in schizophrenia were published in German in the mid to late 1960s (Hippius 1999) and by the end of 1966, nearly 100 subjects had received clozapine (Crilly 2007). The original manufacturers,

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Wander AG, were acquired by Sandoz in 1967 and clinical testing was increased. Sandoz had already marketed thioridazine and had significant presence in Europe. By the end of 1969, patient exposures had risen to 2,200 despite mass prejudice against a drug which produced no extrapyramidal effects (Crilly 2007).

The first double-blind trial of clozapine (or HF 1854 as it was then known) was reported in 1971 (Angst et al. 1971). In this study of 64 subjects, clozapine was compared with levomepromazine. Subjects were diagnosed with schizophrenia or mania. Clozapine was more effective against psychotic symptoms than levomepromazine and appeared to act more quickly. Both drugs were sedative; adverse effects noted for clozapine were lowered blood pressure, tachycardia, weight gain and constipation. No extrapyramidal effects were observed.

In the following few years, a series of small (and so, underpowered) studies was reported showing that clozapine was broadly equivalent in efficacy to perphenazine (Rodova et al. 1973; Van Praag et al. 1976), haloperidol (Gerlach et al. 1974) and chlorpromazine (Ekblom and Haggstrom 1974) but with some minor advantages for clozapine noted (against negative symptoms and conceptual disorganisation). Studies reported in the later 1970s were often similarly underpowered, but clozapine's superiority over chlorpromazine with respect to speed of onset and magnitude of positive and negative symptom score reduction was nonetheless detected (Chiu et al. 1976; Shopsin et al. 1978, 1979). In none of the studies conducted in the 1970s did clozapine show any signs of extrapyramidal adverse effects.

5.2 Clozapine and Treatment-Resistant Schizophrenia

Kraepelin described the deteriorating course of his patient's "dementia praecox" as being progressive and severe (Keefe et al. 1987, 1996), with active symptoms requiring continuous hospitalisation. This is in contrast to a more relapsing and remitting disease state, where periods of illness may be interspersed with at least partial remission. "Kraepelin-type" patients have been shown to respond less completely to antipsychotic medication (Keefe et al. 1987), leading to a suggestion that there may be more than one type of schizophrenia. This non-medication responsive cohort of patients is termed "treatment-resistant".

Five trials form the foundation on which clozapine was licensed for treatment-resistant schizophrenia. In 1987, Claghorn et al. (1987) compared clozapine therapy to chlorpromazine in the treatment of patients who were suffering with tardive dyskinesias or extrapyramidal effects induced by antipsychotic medications. Clozapine was demonstrably superior to chlorpromazine not only in amelioration of extrapyramidal side effects but also in magnitude of therapeutic efficacy and the speed at which this was achieved.

This result was repeated by Kane et al. (1988) and Kane et al. (1989). For patients with schizophrenia that was unresponsive to other antipsychotics, clozapine provided symptom relief in 30 % of cases, compared to 5 % of patients who were given chlorpromazine (Kane et al. 1988). Honigfeld (1984) produced a

strikingly similar result in comparison to haloperidol—therapeutic benefit was demonstrated in 31 % of the clozapine group, compared to 10 % of the haloperidol-receiving patients.

Kuha and Miettinen (1986) published the first trial demonstrating long term efficacy of clozapine. In a retrospective review over 7 years, patients (all of whom had previously failed on antipsychotics, and had a mean duration of illness of 15 years) experienced improvement in 33 % of cases. The longer trials conducted by Juul Povlsen et al. (1985) and Lindström (1988), both retrospective studies over 12 year periods, showed improvement on clozapine in 51 % and 40 % of patients respectively.

5.3 Definitions and Clinical Guidelines

Kane's trials in 1988 and 1989 (Kane et al. 1988, 1989) aimed to establish the effectiveness of clozapine in treatment-resistant patients—and so a definition of "treatment-resistant" was required. The criteria chosen by Kane et al. were: patients (with a diagnosis of schizophrenia) must have had at least three periods of treatment in the preceding 5 years with neuroleptic agents (from at least two different chemical classes) at dosages equivalent to or greater than 1,000 mg/day chlorpromazine for a period of 6 weeks, each without symptomatic relief, and no period of good functioning within the preceding 5 years (Kane et al. 1988).

The assertion that two failed antipsychotic trials are sufficient to define treatment resistance is supported by Kinon et al. (1992, 1993); a third antipsychotic trial was found to confer less than 7 % chance of response in patients who had already failed to respond to two prior antipsychotics.

In the face of what was considered overwhelming evidence for clozapine being the gold standard treatment for neuroleptic-resistant schizophrenia, guidelines in the USA (Conley and Buchanan 1997; Noel 2007; Moore et al. 2007), UK (National Institute for Health and Clinical Excellence 2010; Barnes 2011), and internationally (Brenner et al. 1990; Gaebel et al. 2005) were developed. All recommend the use of clozapine after two failed trials of other antipsychotics.

5.4 Clozapine and Toxicity

Whilst there is clear evidence for the effectiveness of clozapine, there is also a clear history of toxicity. In 1975, nine cases of fatal blood dyscrasias secondary to clozapine were reported in Finland (Idänpään-Heikkilä et al. 1975). Following this, clozapine was withdrawn from the market. Close analysis of the individual cases of agranulocytosis and neutropaenia suggested that in most cases, the reaction was reversible (on stopping clozapine) and, if detected early and before infection had taken hold, survivable (Anderman and Griffith 1977). This recognition of clozapine-induced blood dyscrasias being detectable and the risk modifiable,

along with the lack of any comparable successor to clozapine being identified in the intervening years, led to its re-introduction in 1990.

After clozapine was retrieved from the pharmaceutical sin bin, it was hoped that as well as improving the symptom control of many treatment-refractory patients, it would also lead to the production of other antipsychotics that would be effective for the treatment of this neglected group of patients (Marder and Van Putten 1988). Many antipsychotics since then have attempted to emulate the success of clozapine, but have failed.

Clozapine has been repeatedly shown to be superior to typical antipsychotics in treatment-resistant schizophrenia (Claghorn et al. 1987; Kane et al. 1988, 1989; Honigfeld 1984; Kuha and Miettinen 1986; Juul Povlsen et al. 1985; Lindström 1988; Fischer-Cornelssen and Ferner 1976; Breier et al. 1993). As atypical antipsychotics were introduced to the market, their potential as haematologically safer alternatives to clozapine in treatment-resistant schizophrenia was proposed. Randomised trials of risperidone (Cavallaro et al. 1995, 1998) found it to be effective in 33 % of treatment-resistant patients. However, switching the risperidone non-responsive patients to clozapine provided symptom relief for a further 56 %. Short trials found risperidone to be non-inferior but faster acting (Bondolfi et al. 1998; Lindenmayer et al. 1998), but longer trials demonstrated superiority for clozapine (Flynn et al. 1998; Sharif et al. 2000). Non-inferiority studies of olanzapine in treatment-resistant schizophrenia found it effective (Tollefson et al. 1998), but others found clozapine remained superior (Kumra et al. 2008). Studies where clozapine responders were switched to olanzapine were inconclusive—some showing response to olanzapine in 90 % of cases (Littrell et al. 2000) others decompensation for 58 % of patients (Henderson et al. 1998). It is worth noting that several of these trials were sponsored by the company marketing the new atypical medication, used low comparator clozapine doses, or included treatment "intolerant" patients, as well as true "treatment-resistant" patients (Meltzer 1999).

In 2006, the influential CATIE trials (Clinical Antipsychotic Trials of Intervention Effectiveness) compared switching treatment-resistant patients to either an atypical drug or clozapine (McEvoy et al. 2006). Switching to clozapine was more effective than switching to a different atypical drug, both in terms of time to treatment discontinuation and positive and negative symptom severity. A recent meta-analysis has even demonstrated clozapine's superiority over both atypical and typical drugs in non-treatment-resistant illness (Leucht et al. 2013).

5.5 Augmentation of Clozapine

The drug of choice for use in refractory schizophrenia is clozapine, and for around 60 % of patients (Breier et al. 1993), no further pharmacological input is required. For the remaining third however, symptom relief is absent or incomplete and other treatment options are sought.

Where residual symptoms are distressing or disabling, persevering with clozapine as the sole prescription is often not considered a viable option. Non-drug augmenting treatments, such as cognitive-behavioural therapy (Valmaggia et al. 2005) or electro-convulsive therapy (Kales et al. 1999), have been shown to be of benefit, but may not be available or acceptable to patients.

Co-prescription of multiple antipsychotics remains, unfortunately, a common phenomenon despite a paucity of evidence for benefit and abundant evidence of harm (Grech and Taylor 2012; Barnes and Paton 2011). Reasons for adding a second antipsychotic to clozapine may however extend beyond a desire for more complete symptom control. Adding a second drug may allow for dose reduction of clozapine and relief of dose-dependent side effects (Nielsen et al. 2011). Some drugs have been shown to have a specific benefit in preventing longer term complications of clozapine therapy—aripiprazole, for example, is effective in attenuating weight gain (Fleischhacker et al. 2008).

Prescribing of multiple antipsychotics is not without risk. The addition of a second antipsychotic to clozapine may compound side effects such as sedation, weight gain or other metabolic effects, as well as causing increased serum prolactin or akathisia. An informed analysis of the potential benefits to be gained by adding additional antipsychotics to clozapine therapy is clearly essential.

Paton et al. (2007) conducted a meta-analysis of randomised, placebo-controlled studies of antipsychotic augmentation of clozapine treatment. They found no overall advantage to adding a second antipsychotic to therapy. A larger meta-analysis by Taylor and Smith (2009) found only a marginal therapeutic benefit to co-therapy, and this was updated recently with the same outcome (Taylor et al. 2012).

Before considering adding a second agent to augment the clinical effects of clozapine, the current medication regimen must be carefully considered and optimised (Fig. 5.1).

Table 5.1 outlines the pharmacological approaches which have been used to augment clozapine. Although the evidence base is developing, many questions remain unanswered and many negative results are reported. Augmenting agents with which there are the most published data are lamotrigine, aripiprazole, risperidone and sulpiride. This does not mean that these are the preferred agents, only that they are the best studied. Augmenting clozapine with any antipsychotic shows a small but significant benefit (effect size −0.239), (Taylor et al. 2012) but data are lacking to confirm which antipsychotic combination confers the most benefit (Taylor et al. 2012; Cipriani et al. 2009).

5.6 Alternative Options for Treatment-Resistant Schizophrenia

Pharmacological strategies employed in treatment-resistant schizophrenia instead of clozapine are frequently ineffective and harmful. Antipsychotics may be prescribed in doses above those that have been licensed (“high dose” prescribing), or in

- Poor adherence should be investigated and addressed.
- Clozapine monotherapy should be tried for at least 3-6 months to evaluate efficacy.
- Clozapine plasma levels of at least 350mcg/L should be achieved.
- Additional medication may have pharmacokinetic or pharmacodynamic interactions with clozapine
- Combinations may require additional physical health monitoring (we recommend 6 monthly ECGs, as well as routine monitoring of blood pressure, weight, and lipids when combining antipsychotics)
- Efficacy should be assessed using recognised scales
- Always time-limit any trial (e.g. 3-6 months) and discontinue the augmenting agent if response is unsatisfactory.

Fig. 5.1 Factors to consider before clozapine augmentation

combination with other antipsychotics. Neither of these options is without risk. The compounding of side effects such as sedation, weight gain or other metabolic effects, increased serum prolactin or akathisia is inevitable.

For some patients, however, treatment with clozapine is just not possible. This may be due to non-compliance with oral therapy or with the necessary blood tests, intolerable side effects or physical complications that contraindicate clozapine use.

It is important to reiterate here that clozapine is the only medication that is effective in treatment-resistant schizophrenia. All efforts should be made to facilitate treatment wherever possible. The majority of common side effects are short-lived (e.g. Hypotension, tachycardia, drowsiness) and/or treatable (e.g. Constipation, hypersalivation, weight gain). Before ceasing treatment with clozapine, all options for continuing therapy must be exhausted.

Some adverse effects of clozapine present more complex challenges for the clinician wishing to continue clozapine treatment, and a detailed assessment of these and strategies for continuation of therapy is beyond the scope of this chapter. Further reading is recommended on the management of myocarditis (Ronaldson et al. 2011) and benign ethnic neutropaenia (Whiskey et al. 2011; Spencer et al. 2012).

Where clozapine treatment is impossible, other strategies may be employed but these are likely to be of limited effectiveness. Supra-maximal doses of other antipsychotics, principally olanzapine (up to 60 mg/day), have been trialled with some benefit. Case reports (Reich 1999; Sheitman et al. 1997) suggest moderate efficacy, but at the expensive of increased emergence of extrapyramidal side effects. Conley et al. (2003) compared 50 mg/day of olanzapine to 450 mg/day of clozapine in a cross-over study design, and found higher rates of discontinuation and poorer symptom control in patients on high-dose olanzapine. A larger study found the same to be true in adolescent patients (Kumra et al. 2008), although a longer, 6 month comparison to clozapine in adults suggested that the two treatments may be comparable (although this was a small sample size) (Meltzer et al. 2008).

Table 5.1 Pharmacological approaches to clozapine augmentation

Drug/type of studies	Typical daily dose	Total Nos in RCTs	Duration	Comments
Antiepiletics				
Lamotrigine Six RCTs and one meta-analysis (Tiihonen et al. 2009).	100–400 mg	195	Up to 24 weeks	Meta-analysis suggests a moderate effect size although several negative RCTs exist (Goff et al. 2007; Vayisoglu et al. 2013). When effective, benefits in both positive and negative symptoms are demonstrated. Generally well tolerated. Monitor closely for a rash during the initial titration of lamotrigine.
Topiramate Four RCTs (Tiihonen et al. 2005; Afshar et al. 2009; Hahn et al. 2010; Muscatello et al. 2011a), multiple case series (Tiihonen et al. 2005).	50–400 mg	117	Up to 24 weeks	Two positive (Afshar et al. 2009; Hahn et al. 2010) and 2 negative RCTs (Tiihonen et al. 2005; Muscatello et al. 2011a). Associated with weight loss, impaired cognition, visual disturbances, depression and psychosis.
Antipsychotics				
Amisulpride One RCT (Assion et al. 2008), one open label study (Munro et al. 2004) and case series (Agelink et al. 2004).	400–600 mg	72	Up to 8 weeks	Trend to improvement seen but failed to reach significance in one small RCT (Assion et al. 2008). Greater improvement seen with amisulpride augmentation than quetiapine–clozapine augmentation (Genc et al. 2007). An open label study ($n = 33$) reported the benefit continued to 6 months (Munro et al. 2004). Occasionally used for clozapine-induced hypersalivation (Kreinin et al. 2006).
Aripiprazole Four RCTs (Chang et al. 2008; Muscatello et al. 2011b; Barbui et al. 2011; Fleischhacker et al. 2010), many case series and open-labelled studies.	15–30 mg	407	Up to 12 months follow up.	Limited evidence for an improvement in symptoms. One RCT demonstrated an improvement in positive symptoms only (Muscatello et al. 2011b), another reported only improvements in negative symptoms (Chang et al. 2008). May be as effective as haloperidol and

(continued)

Table 5.1 (continued)

Drug/type of studies	Typical daily dose	Total Nos in RCTs	Duration	Comments
				clozapine in combination but better tolerated (Chang et al. 2008). May reduce the metabolic risks associated with clozapine (Fleischhacker et al. 2010).
Haloperidol One RCT (Barbui et al. 2011)' and case series (Kapur et al. 2001).	2–4 mg	106	Up to 12 months follow up.	Shown to be as effective as clozapine and aripiprazole but less well tolerated (Barbui et al. 2011).
Olanzapine Case reports only (Gupta et al. 1998).	15 mg	–	Up to 1 year follow up	Poorly supported and likely to exacerbate metabolic adverse effects.
Paliperidone Case series (Chang et al. 2011).	6–12 mg	–	8 weeks	A subjective improvement in symptoms was observed.
Pimozide Two RCTs (Friedman et al. 2011; Gunduz-Bruce et al. 2013)	2–8 mg	85	Up to 12 weeks	Two well conducted RCTs failed to demonstrate any improvement in symptoms. Pimozide is associated with QTc prolongation.
Risperidone Five RCTs (Taylor et al. 2012), multiple open studies and case reports (Kontaxakis et al. 2006).	2–6 mg	114	Up to 18 weeks	Two negative RCTs (Freudenreich et al. 2007; Honer et al. 2006). A lower risperidone dose and longer duration of trial may improve outcome (Kontaxakis et al. 2006). Comparable efficacy to ziprasidone and clozapine combination but with a greater rise in serum prolactin (Zink et al. 2009).
Sertindole One RCT (Nielsen et al. 2012).	16 mg	50	Up to 12 weeks	No benefit over placebo shown and associated with QTc prolongation.
Sulpiride Four RCTs and a Cochrane review (Wang et al. 2010).	200–1,000 mg	221	Up to 12 weeks	Short-term data favoured sulpiride combination over placebo. The overall effect was modest. Mostly Chinese studies.
Ziprasidone One RCT (Zink et al. 2009), one open study (Ziegenbein et al. 2005) and case series (Kaye 2003).	80–160 mg	12	Up to 6 weeks	Comparable efficacy to risperidone and clozapine combination but associated with QTc prolongation (Zink et al. 2009).

(continued)

Table 5.1 (continued)

Drug/type of studies	Typical daily dose	Total Nos in RCTs	Duration	Comments
Antidepressants				
Duloxetine One RCT (Mico et al. 2011).	60 mg	33	16 weeks	Some benefit in negative symptoms and general psychopathology shown.
Fluoxetine One RCT (Buchanan et al. 1996).	20–60 mg	33	8 weeks	No significant differences were found between fluoxetine and placebo augmentation. Fluoxetine may increase clozapine plasma levels.
Mirtazapine One RCT (Zoccali et al. 2004).	30 mg	24	8 weeks	Some improvements in negative symptoms reported. Associated with weight gain and sedation which may be exacerbated in combination with clozapine.
Others				
Donepezil One small RCT (Stryjer et al. 2004).	10 mg	8	18 weeks	A trend to an improvement in positive symptoms was seen, but this did not reach significance.
Glycine Three RCTs (Potkin et al. 1999; Evins et al. 2000; Diaz et al. 2005).	30–60 mg	61	28 weeks	All three RCTs failed to show any improvements in symptoms. One reported a greater improvement in the clozapine monotherapy group (Potkin et al. 1999).
Ginkgo Biloba One RCT (Doruk et al. 2008).	120 mg	42	12 weeks	A significant improvement in negative symptoms was reported. No effect on positive or overall symptomology.
Memantine One RCT (de Lucena et al. 2009).	20 mg	21	12 weeks	Significant improvements in negative and positive symptoms and cognition demonstrated.

Anticholinergic side effects and weight gain (3.4 kg over 8 weeks, compared to 1.2 kg for clozapine) are worse for high-dose olanzapine than clozapine (Kelly et al. 2003). As for all treatment regimens involving high-dose or multiple antipsychotics, contraindications to the prescription must first be ruled out (ECG abnormalities, hepatic impairment), regular physical monitoring is essential (ECG, weight, U&Es) and recognised rating scales must be used every 3 months, with cessation of treatment if no response is measured.

Combining two non-clozapine antipsychotics is a persistently common practice (Grech and Taylor 2012), despite the evidence supporting it being largely

theoretical (Stahl 2012) or based on small studies or case reports (Chan and Sweeting 2007). Again, physical risks abound with additive side effects and regular assessment of benefit must be made. In one year-long study looking at the effects of switching patients on poly-pharmacy to monotherapy, 60 % of patients that were switched did so successfully, and with the added benefit of weight loss (Essock et al. 2011).

The use of electroconvulsive therapy for psychosis is often reserved as a last line treatment, although both anecdotal reports and larger, open studies do suggest a moderate benefit. A meta-analysis of 26 trials found benefit with ECT, but medication was more effective when directly comparing the two interventions (Tharyan and Adams 2005). The combination of antipsychotics with ECT may be more effective than ECT alone, and it may be best reserved for patients with catatonic features (Pompili et al. 2013).

5.7 Summary

- Clozapine is the only treatment with repeated proven effectiveness for treatment-resistant schizophrenia.
- All major national and international guidelines advise its initiation after two adequate trials of different antipsychotics (one of which should ideally be an atypical).
- Augmentation of clozapine with other antipsychotics is unlikely to deliver anything other than a small clinical benefit, but certainly increases the risk of long-term side effects.
- Where clozapine cannot be prescribed, other options are unlikely to be of more than moderate benefit and are supported by a very limited evidence base.
- High-dose or combination antipsychotic regimens must be regularly reviewed to ensure continued benefit, and patients must have regular physical health checks.

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Clozapine: Gold Standard Treatment for Refractory Schizophrenia: Now or Never?

6

P.F.J. Schulte and James H. MacCabe

The atypical antipsychotic drug clozapine is the only evidence-based treatment for treatment of refractory schizophrenia (Essali et al. 2009; Mortimer et al. 2010). It is also probably superior in reducing suicidality (Meltzer et al. 2003) and all-cause mortality (Tiihonen et al. 2009). In comparison, the role of antipsychotic polypharmacy and other augmentation strategies remains unclear, at best (Kane and Correll 2010).

Many patients with treatment of refractory schizophrenia are reluctant to accept a trial with clozapine. Their most frequent objections are the mandatory blood tests, the risk of agranulocytosis, which reinforces a perception of clozapine as a life-threatening drug, and the more common adverse effects, particularly weight gain, diabetes and hypersalivation. In addition, many doctors are reluctant to prescribe clozapine, although their concerns are more often focused on the risk of life threatening adverse reactions, such as agranulocytosis and myocarditis, and the medicolegal implications of these risks.

6.1 The Decision to Use Clozapine

A full review of the patient's medication history, including doses, durations and responses to drugs, is essential. The UK National Institute of Health and Clinical Excellence (NICE) guidelines recommend that clozapine should be offered to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic

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drugs, where at least one of the drugs was a non-clozapine second-generation antipsychotic.

6.2 Initial Discussions With the Patient and Their Carers

Patients are more likely to accept clozapine if they are given adequate time and opportunity for discussion. It is important to explore together with the patient any concerns about clozapine and its adverse effects. Clinicians should provide up to date information regarding the probability of adverse effects and what can be done to alleviate them. Some patients and carers find it helpful to speak to another patient who uses clozapine. The online resources listed at the end of this chapter may also be useful.

It's very important to communicate all the potential problems to people, but it can make the idea of clozapine quite daunting. Where patients and carers perceive clozapine as dangerous, it may be helpful to draw attention to the emerging evidence that patients on clozapine have a reduced mortality in comparison to users of other antipsychotics, which may be the result of lower suicide rates and better use of somatic health services (Walker et al. 1997; Tiihonen et al. 2009).

6.3 Requirement for Blood Monitoring

The national regulations on the frequency of blood monitoring vary, but most agree on continuous monitoring of the full blood count, beginning before initiation and continuing for 4 weeks after discontinuation of clozapine treatment. The white cell count (WCC) should remain $\geq 3.5 \times 10^9$/l and the absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/l). If counts fall below certain threshold levels, blood tests must be performed more frequently and in most countries, clozapine treatment must be stopped if the ANC drops below 1.5×10^9/l.

The requirement for regular blood tests is frequently given as a reason for reluctance to take clozapine. Therefore, the rationale for these controls should be explained: if a substantial drop of the white blood cell is seen, clozapine will be discontinued to prevent agranulocytosis. As a result of these controls the safety of clozapine is increased—now the risk of dying from this haematological complications is reduced 1–3 in every 10,000 patients treated with clozapine (Cohen et al. 2012). Any potential risk must be weighed against the potential benefits of taking clozapine.

Where the patient is concerned about the blood draw itself, careful exploration and reassurance may be enough to allay these fears and talking to other clozapine users sometimes also helps. A consistent approach from the clinical team is important. In practical terms, a topical analgesic, such as lidocaine/prilocaine cream, placed under an occlusive dressing for 60 min prior to venipuncture, can be very helpful. For some people, the use of a butterfly cannula can appear less threatening than a needle. In some cases of needle phobia, the use of anxiolytic

drugs prior to venipuncture can reduce distress. Sometimes people may decline blood tests for clozapine because of features of their psychosis, for example, paranoid ideas about the use of the blood; this requires an individualised approach, if necessary referring to relevant legislation. In all cases, it is important to ensure that other blood tests, such as clozapine plasma monitoring, are taken at the same time as much as possible, to avoid unnecessary blood tests.

6.3.1 Benign Ethnic Neutropenia

In some populations (particularly in those of African descent or Yemenite Jews), mean population levels of WCC and ANC are lower than those in Caucasian populations, a condition termed benign ethnic neutropenia (BEN) (Whiskey et al. 2011). The lower limits for WCC and neutrophil granulocytes imposed by clozapine monitoring services can be reduced in cases where a haematologist has diagnosed BEN. In the UK the cut off points for patients with benign ethnic neutropenia are 0.5×10^9/l lower than normal (Rajagopal 2005).

6.4 Switching to Clozapine

In many countries patients are hospitalised during the initiation phase of clozapine. This may discourage patients from taking the drug, and pressures on psychiatric beds may provide a disincentive to clinicians. However, the initial titration is feasible and safe in an outpatient setting in low-risk patients, and there are protocols available for this (Taylor et al. 2012).

Many prescribers choose to cross-titrate clozapine and the last antipsychotic to avoid a temporary deterioration of the patient. On the basis of sex, weight, and smoking status, a prediction can be made about the dose which will result in most cases in a clozapine plasma level around the 0.35–0.5 mg/l threshold (Rostami-Hodjegan et al. 2004). Below this threshold 30 % of therapy refractory patients respond, but above the threshold the response rate is 73 % (Schulte 2003). After 8 weeks at a stable plasma level without any improvement in symptoms, the dosage/plasma level should be increased. In rare cases (especially young male smokers), off-label dosages may be necessary to reach a therapeutic drug level.

Depending on tolerability, a titration scheme can be developed to titrate up to a target dose over 2 weeks to 1 month. Clozapine is generally prescribed twice daily in the UK, although in some patients once daily dosing at night is used to avoid daytime sedation. Dose escalation in daily steps of 12.5–25 mg is tolerable for most patients. In case of emerging side effects the dosage may be reduced and the titration scheme slowed down. In rare cases of severe sedation or orthostasis several months may be needed, but the majority of patients can be titrated to an effective dosage or at least a plasma level in the therapeutic range (3.5–5.0 mg/l) within 2–4 weeks.

6.5 Sedation

If sedation occurs and the patient still takes sedative drugs, these may be reduced and stopped. In the case of benzodiazepines this should be done very slowly because clozapine lowers the epileptic threshold (especially during the titration phase). In clinical practice, aripiprazole 5–10 mg/day can improve sedation for some people but may sometimes cause agitation.

6.5.1 Myoclonus and Seizures

The risk of seizures increases with increasing clozapine dose (Pacia and Devinsky 1994). A first seizure is not usually a reason to discontinue clozapine treatment (Wong and Delva 2007). Often for patients without other risk factors reducing the clozapine dose by 30 % and increasing it more gradually is an adequate solution. If a second seizure occurs, or if the plasma level is consistently above 0.5 mg/l, valproate or lamotrigine can be added in order to continue clozapine treatment. Valproate should always be used with caution in women of childbearing age because of the very high rates of teratogenicity.

Myoclonic jerks in a patient on clozapine often herald the onset of seizures (Sajatovic and Meltzer 1996) and should prompt a reduction in dosage or the addition of an anticonvulsant such as sodium valproate, although it should be noted that lamotrigine may in some people induce myoclonic jerks (Crespel et al. 2005).

6.6 Postural Hypotension

In case of orthostasis the patient should be advised to be cautious when rising from sitting or lying down and to drink at least 2 l a day. The clozapine titration should be slowed down. In rare instances a time-limited course of fludrocortisone, with tapered dose reduction, can be used to increase blood pressure.

6.7 Pyrexia

Benign transient hyperthermia sometimes occurs during the first 3 weeks of clozapine treatment. The temperature elevation is usually not more than 1.5 °C. If there are any signs of infection (temperature $\geq$38 °C, sore throat, flu-like symptoms) during the first 18 weeks, WCC and ANC should be performed the same day/within 24 h to exclude agranulocytosis. An infective screen and assessment of the results by a doctor on the same day are recommended.

Acute infection may lead to toxic clozapine concentration levels, sometimes with delirium (Van der Molen-Eijgenraam et al. 2001; De Leon 2004; Raaska et al. 2001). There is evidence that cytokines may inhibit the liver enzymes

responsible for the metabolism of clozapine, CYP1A2 and CYP3A4 (Raaska et al. 2002; Renton 2004; Aitken et al. 2006; Crawford et al. 2004). Moreover, a patient confined to bed or hospitalised will smoke less or not at all, which can also lead to increased clozapine levels. Therefore, in the event of infections it is important to monitor for sedation or other signs of raised clozapine concentrations and to monitor plasma levels if indicated. A temporary dose reduction may be required, while monitoring plasma levels, especially if there has been an alteration in smoking habit.

6.8 Tachycardia

Tachycardia may occur secondary to hypotension or via vagal inhibition as a result of the drug's anticholinergic properties. Tachycardia is common and usually settles after a few weeks of treatment. However, persistent tachycardia, especially if it does not normalise during sleep, may be associated with increased cardiovascular mortality (Borer 2008). A cardioselective β-blocker (such as atenolol, bisoprolol or metoprolol) may be a solution for severe tachycardia if the patient's blood pressure permits it. Alternatively, Ivabradine is a selective blocker of the "funny" ion channel which has been shown to reduce heart rate significantly without any adverse effects on myocardial contractility or left ventricular dysfunction, and without reducing blood pressure. It has been used in clozapine patients in whom beta blockers are not tolerated or contraindicated and is effective and well tolerated (Lally et al. 2013).

6.9 Myocarditis

Tachycardia and fever may, however, also be a symptom of myocarditis, a rare but dangerous complication with an incidence rate of 0.06 % (Canada), 0.015 % (United States) or 0.029 % (Germany plus Switzerland) (Cohen et al. 2012). In Australia, uniquely, much higher figures (0.7 %–3.4 %) have been reported. 80 % of cases occur during the first month of clozapine treatment. Exertional dyspnoea, chest pain, arrhythmia, fever, leukocytosis, weakening and dizziness are suggestive of myocarditis. An ECG and a cardiological consultation must be considered if such symptoms occur, especially during the first month of clozapine treatment. In two-thirds of these early cases, the ECG or echocardiogram shows abnormalities. Checking troponin and CRP levels is useful. Increased troponin levels of twice normal limits are present in 90 % of cases, so this should be monitored daily in patients showing these signs (Ronaldson et al. 2011). CRP may also be indicative—a CRP >100 mg/l is seen in clozapine-induced myocarditis patients without a clinically relevant rise in troponin (Ronaldson et al. 2011).

6.10 Constipation

Constipation occurs in 34 % of patients and is due to clozapine's anticholinergic effect (Yusufi et al. 2007). Depending on the severity, there is a danger of intestinal obstruction and even ileus, which can be fatal. Early detection of constipation and symptomatic treatment is therefore very important. The clinician should enquire directly as only 8 % of patients complain spontaneously about a change in bowel habit (Yusufi et al. 2007). The first step in treatment of constipation is adequate hydration (at least 2 l of fluid per day), sufficient exercise and a fibre-rich diet. Since reduced gut motility is the usual cause, stimulant laxatives such as senna should be considered early. If this is not enough, bulk-forming laxatives such as psyllium fibre (also known as Ispaghula husk) 3.6 g 1–2 daily doses of one sachet can be prescribed. These are preferable to osmotic laxatives such as lactulose (maximum of three doses of 30 ml) which often lead to abdominal cramps and flatulence. The importance of maintaining an adequate fluid intake must be emphasised with bulk-forming agents. Psyllium fibre, for example, must be taken with at least 2 l of water. This may be problematic for some patients and requires proper instruction, because if taken without enough fluid, psyllium fibres will increase constipation.

6.11 Hypersalivation

Hypersalivation occurs in over half of patients, particularly during sleep (Sockalingam et al. 2007). Tolerance may develop, but not always. Dose reduction or chewing gum may help somewhat. Swallow training has been used in intellectually disabled people with hypersalivation for daytime drooling with some effect and may be worth consideration (Van der Burg et al. 2007, 2009). A systematic overview of the pharmacological treatment of clozapine-induced hypersalivation came to the conclusion that there is no clear-cut recommendation (Syed et al. 2009). Anticholinergics seem to be effective, but it must be borne in mind that clozapine already has an intrinsic anticholinergic effect and that anticholinergics may exacerbate other side effects such as constipation. Hyoscine (scopolamine) 300 mcg nocte is commonly used in the UK, and anecdotally is helpful, although there remains no RCT evidence of its effectiveness. In other medical conditions sometimes accompanied by hypersalivation, such as amyotrophic lateral sclerosis and Parkinson's disease, hyoscine (scopolamine) patches have been used (Hockstein et al. 2004), and a successful treatment with these patches for a patient on clozapine has been described (Gaftanyuk and Trestman 2004). Another alternative may be intranasal or sublingual administration of ipratropium bromide 0.03 mg/ml in a nasal spray or sublingual atropine [one drop 1 % solution (0.5 mg atropine per drop, a maximum of two drops a day)] (Calderon et al. 2000; Freudenreich et al. 2004; Hyson et al. 2002; Comley et al. 2000; Fischer and Eichhorn 2001; Tessier and Antonello 2001; Christiaens and Pieters 2005). Another possibility is oral glycopyrrolate 1 mg once or twice daily (Liang et al. 2010; Arbouw et al. 2010) Glycopyrrolate has the advantage of having no central effect, because it does not

pass the blood–brain barrier. The advantage of all these remedies is that they can be administered locally.

6.12 Weight Gain and Diabetes

Clozapine may have a greater liability for weight gain and diabetes than other antipsychotics, although the evidence with regard to diabetes is inconsistent (Moisan et al. 2013). The fellow dibenzodiazepine, olanzapine, causes at least as much weight gain as and more binge eating than clozapine (Meltzer et al. 2003; Kluge et al. 2007), although the non-dibenzodiazepines tends to have a lesser effect on weight. There is some evidence that lower clozapine plasma levels cause less weight gain (Simon et al. 2009).

Two treatment strategies may be helpful for unwanted weight gain. The usual recommendations about a healthy lifestyle are very worthwhile as an intervention to prevent and reverse clozapine-induced weight-gain, namely (a) a healthy, balanced diet and (b) increased exercise, which may form part of an occupational therapy programme. In addition, a cautious reduction of the dose can be considered, accompanied by careful monitoring of the patient's mental state.

Metformin 1,500 mg/day has recently been shown to reduce body weight and reverse metabolic abnormalities in patients on clozapine (Chen et al. 2013). Where conservative management has failed, aripiprazole at a dose of 5–15 mg/day has been shown in some studies to be effective in reducing weight, BMI and waist circumference with associated benefits on lipid levels and therefore can help overall tolerance of clozapine (Fleischhacker et al. 2010; Fan et al. 2013).

6.13 Clozapine Re-Challenge

Clozapine re-challenge has been attempted in patients with a history of myocarditis, cardiomyopathy and severe neutropenia on clozapine. Previous adverse reactions should be taken into account and a careful risk–benefit analysis undertaken involving the patient, carers and specialists from relevant disciplines such as haematology or cardiology.

For treatment-resistant patients who responded well to clozapine but had to stop the treatment because of neutropenia, re-challenge may be considered, provided that no agranulocytosis has occurred (Whiskey and Taylor 2007). The American prescribing information for clozapine keeps the option of restarting clozapine open, even with a WBC count of $<3.0 \times 10^9$/l and granulocyte count $<1.5 \times 10^9$/l, provided these counts have never been lower than 2.0×10^9/l and 1.0×10^9/l, respectively. However, with an initial drop in the WBC count to less than 3.0×10^9/l, the risk of agranulocytosis on re-challenge is 12 times higher than in patients taking clozapine for the first time. Weekly blood tests throughout the first year after restarting is recommended by the FDA. Add-on therapy with lithium or, in certain circumstances, G-CSF may be considered after neutropenia following

careful risk–benefit analysis (Kanaan and Kerwin 2006; Whiskey and Taylor 2007; Rajagopal et al. 2007; Conus et al. 2001; Sperner-Unterweger et al. 1998; Hägg et al. 2003; Ghaznavi et al. 2008). However, response to GCSF can be idiosyncratic (MacCabe et al.), so does need careful monitoring for safety and at present is only used as a last resort. There is no evidence that GCSF or lithium will reduce the risk of a recurrence of a true clozapine induced agranulocytosis. There is some evidence that lithium elevates G-CSF and potentiates its effect (Petrini and Azzarà 2012).

Reintroduction of clozapine after cardiac problems including cardiomyopathy, myocarditis or pericarditis may be attempted in exceptional circumstances, provided the risks, benefits and other options have been carefully explored with patients, carers and physicians. Of four patients reported in the literature re-challenged following myocarditis, three were successful (Manu et al. 2012). One patient was successfully re-challenged after pericarditis (Crews et al. 2010).

Because of the high risks of recurrence, and medically dangerous nature of these conditions, clozapine re-challenge after stopping previously because of low WBC counts or cardiac problems should only take place in specialist settings, with the informed consent of the patient or the patient's legal representative and in collaboration with an experienced haematologist or cardiologist.

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Online resources

NHS patient information leaflet on clozapine. http://www.nhs.uk/medicine-guides/pages/MedicineOverview.aspx?condition=Schizophrenia%20and%20Psychosis&medicine=clozapine

The following documents may provide useful information about clozapine: the European summary of product characteristics (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Leponex_30/WC500010966.pdf), the American prescribing information (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019758s067s068s070lbl.pdf)
Dutch guideline for the use of clozapine with its explanatory supplement which contains much practical advice (http://www.clozapinepluswerkgroep.nl/wp-content/uploads/2013/07/Guideline-for-the-use-of-Clozapine-2013.pdf)

What Can We Do If Clozapine Fails? Pharmacologic Choices and Differential Outcomes

7

David J. Castle and Nicholas Keks

As outlined elsewhere in this book, clozapine has earned its place as the "go to" medication in people who prove "resistant" to other antipsychotic medications. However, not all such individuals have an adequate response to clozapine, with anything from 40 to 60 % of patients having residual symptoms at the completion of an adequate trial of clozapine (Chakos et al. 2001). This chapter outlines pharmacological strategies that might be employed to enhance outcomes for this group, who we shall henceforward refer to as "clozapine resistant," albeit the use of such a term does not do justice to the heterogeneity in terms of which symptoms (e.g., positive, negative, disorganization) and associated issues (e.g., depressive and anxiety symptoms, cognitive problems) are "residual." Where possible, distinctions are made about which symptoms are targeted by the various strategies outlined.

At the outset, it is important to note that a distinction needs to be made between clozapine resistance and clozapine intolerance. Clozapine is associated with a range of potential adverse side effects. Some of these are potentially fatal (e.g., agranulocytosis, myocarditis) and mostly preclude clozapine rechallenge. Other side effects are less dangerous but might be a reason for the patient to decide to discontinue clozapine. These include sialorrhoea, constipation, and seizures. Table 7.1 outlines some simple strategies to help ameliorate some of these side effects (see Castle et al. 2013).

As it is, the literature on clozapine resistance is relatively scant and bedeviled by numerous methodological problems that makes it difficult to draw definitive conclusions and makes comparison across studies difficult. For example, while there is general consensus that a serum clozapine level of 350–450 μg/ml is therapeutic, not all studies have assessed levels and this may have particular implications with augmentation strategies due to drug–drug interactions. Also,

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Table 7.1 Side effects of clozapine and how to deal with them (from Castle et al. 2013) (with permission)

Problem	Response
Weight gain	Diet, exercise advice; monitoring; consider adding metformin or aripiprazole
Hyperlipidemia	Dietary advice; monitoring; if persistent add statin
Emergent or worsening diabetes	Monitoring; dietary advice; add metformin; liaise with endocrinologist if persists
Myocarditis, cardiomyopathy	Clinical monitoring especially during initial phase of treatment; baseline ECG, troponin, CRP and cardiac echo: repeat as clinically indicated; any concerns liaise with cardiologist urgently
Neutropenia, agranulocytosis	White blood count (WBC) and neutrophil count (NC) weekly for first 18 weeks, then monthly. If: • WBC >3.5 and/or NC >2.0: continue normal FBC monitor • WBC 3.0–3.5 and/or NC 1.5–2.0: twice weekly FBC • WBC < 3.0 and/or NC <1.5: halt clozapine and arrange urgent hematology review For persistent mild neutropenia consider lithium augmentation
Constipation	Dietary advice: high fiber diet, ensure adequate exercise and noncaffeinated fluid intake. If ineffective, try laxatives
Sialorrhoea	Towel over pillow at night; atropine drops under tongue or hysocine hydrobromide tablets
Seizures	Neurology review; EEG; add lamotrigine or sodium valproate
Sedation	Take at bedtime, if persists augment with aripipazole and try to decrease clozapine dose

there are varying views about what an adequate trial of clozapine entails: some authorities argue that this should be of 12 months duration (Conley et al. 1997; Wilson 1996). Further methodological concerns include: varying definitions of "resistance"; many studies have small numbers of participants; many are open studies and lack controls; and outcome measures lack uniformity across studies. Furthermore, most studies are of relatively short duration and arguably do not give some interventions sufficient time to maximize effects.

Given the relatively small number of studies in the area, we have elected to include not just double blind randomized controlled trials but also open studies without controls, but not single case reports. The problems associated with unblinded studies and the difficulties interpreting uncontrolled studies are acknowledged. We also note that this review is of pharmacological interventions, with only brief mention being made of other biological parameters such as transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT). We do not cover psychosocial interventions, albeit acknowledge that the care of a person with schizophrenia requires a multifaceted multidisciplinary approach and that psychosocial interventions such as cognitive behavior therapy, acceptance commitment therapy, and cognitive remediation can play an important role in ameliorating residual symptoms in people with schizophrenia.

7.1 Pharmacological Augmentation Strategies

The majority of trials in clozapine-resistant patients are of medication augmentation. In this area we have relied mostly on two recent reviews, one by Porcelli et al. (2012) which included RCTs and open, uncontrolled studies and the more restrictive review of Sommer et al. (2012) which considered only double blind RCTs and which used meta-analytic techniques where possible.

7.1.1 Antipsychotics

A number of different antipsychotics have been employed as clozapine augmenters, as summarized in Table 7.2. Some of these agents seem to have been chosen on the basis that they are "tight" binders to the dopamine D2 receptor and thus hypothesized to work synergistically with clozapine, which is a "loose" D2 binder. These medications include haloperidol and risperidone. Sommer et al. (2012) could find only one RCT of haloperidol augmentation of clozapine, with only six subjects: the findings were negative on both positive and negative symptom scores, but clearly the study was underpowered and few definitive conclusions can be drawn. Risperidone has been much more extensively studied as a clozapine augmenter, but despite initial excitement regarding outcomes, subsequent studies have produced a very mixed picture. Porcelli et al. (2012) found 11 pertinent studies, six of which were positive; their meta-analysis showed no overall benefit, a finding confirmed by the meta-analysis of Sommer et al. (2012). Both reviews comment on the heterogeneity of outcomes. This begs the question whether there are some particular subgroups of clozapine-resistant patients who respond differentially to risperidone augmentation, and many clinicians report individual patients who do seem to benefit, perhaps most notably in terms of positive symptoms amelioration. However, precisely which patients will respond has not been determined. It is also not clear whether some patients might respond at higher doses of risperidone, albeit higher doses would be expected to carry a higher risk of side effects such as worsening cognition, hyperprolactinaemia, postural hypotension, and impaired glucose tolerance (see Porcelli et al. 2012).

Amisulpride is also a tenacious dopamine D2 receptor blocker, but which also targets D3 receptors. It, like risperidone, has some currency as an augmenter of clozapine and Porcelli et al. (2012) found five studies of this agent, all of which were positive. However, only one was an RCT ($n = 20$) and for that study there was null result for both positive and negative symptoms. Side effects such as hyperprolactinaemia and extrapyramidal side effects (EPSEs) are also concerning with amisulpride, albeit the high inherent antimuscarinic properties of clozapine might theoretically at least limit the latter problem. Of particular interest is the single RCT of sulpride (also a D2/D3 antagonist) which, despite only 28 participants, showed benefit for both positive and negative symptoms (Shiloh et al. 1997): more studies are required to confirm or refute these results.

Table 7.2 Studies of antipsychotic agents as adjuncts to clozapine in schizophrenia [adapted from Porcelli et al. (2012)]

Authors	Agent	Daily dose (mg)	*n*	Duration	Outcome	Side effects
Freudenreic et al. (2007)[a]	Risperidone	4	14	6w	– (PANSS)	Nil
Honer et al. (2006)[a]	Risperidone	3	38	8	– (PANSS)	↑ Glucose
Anil YagcJoglu et al. (2005)[a]	Risperidone	≥ 6	30	6	– (PANSS)	Sedation,↑ prolactin
Akdede et al. (2006)[a]	Risperidone	≥ 5	30	6	– (PANSS)	↓ Cognition
Josiassen et al. (2005)[a]	Risperidone	≥ 6	40	12	+ (BPRS)	Nil
Weiner et al. (2010)[a]	Risperidone	4	65	16	+ (BPRS)	↑ Prolactin
Taylor et al. (2001)	Risperidone	3	26	4.28	+ (PANSS)	Nil
Henderson and Goff (1996)	Risperidone	2–6	12	4	+ (PANSS)	Nil
de Groot et al. (2001)[a]	Risperidone	5.3	12	4	– (PANSS)	Nil
Zink et al. (2009)[a]	Risperidone	3.8	12	6	+ (PANSS)	↑ Prolactin
	Ziprasidone	134	12	6	+ (PANSS)	↑ QTC
Kuwilsky et al. (2010)[a]	Risperidone	3.8	12	6,26,52	+ (PANSS)	Akatisia
	Ziprasidone	134	12		+ (PANSS)	Akatisia
Chang et al. (2008)[a]	Aripiprazole	5–30	61		+ (SANS only)	Nil
Mitsonis et al. (2007)	Aripiprazole	15	27		+ (PANSS)	Nil
Henderson et al. (2006)	Aripiprazole	15–30	10		– (PANSS	Nil
Ziegenbein et al. (2006)	Aripiprazole	26.4	11		+ (PANSS)	Nil
Benedetti et al. (2010)	Aripiprazole	6.8	6		+ (BPRS)	Nil
Bachmann et al. (2009)	Aripiprazole	8.2	15		+ (BPRS)	Nil
Assion et al. (2008)[a]	Amisulpride	400–600	16		+ (GAF, CGI)	Akathisia, EPSE, ↑ prolactin
Munro et al. (2004)	Amisulpride	7,800	28		+ (PANSS)	↑Prolactin
Kampf et al. (2005)	Amisulpride	11.5	14		+ (CGI)	Nil
Lerner et al. (2005)	Amisulpride	800–1,200	5		+ (CGI)	Nil
Zink et al. (2004)	Amisulpride	527	15		+ (Clinical)	Nil
Shiloh et al. (1997)[a]	Sulpiride	7,600	28		+ (BPRS)	↑Prolactin

Abbreviations: *PANSS* Positive and negative symptom scale, *SANS* Scale for the assessment of negative symptoms, *BPRS* Brief psychiatric rating scale, *HAM-D* Hamilton depression scale; + = study positive on main outcome measure; – = study negative on main outcome measure
[a]Placebo controlled

Ziprasidone was effective in two open trials as a clozapine augmenter, with a particular effect on negative symptoms. However, the studies had small numbers and high dropouts, and there are no published RCTs with this agent. Another potential issue is the propensity for ziprasidone to prolong the QTc interval, an effect also seen with clozapine.

The dopamine partial agonist aripiprazole is increasingly being used by clinicians in some jurisdictions not so much to enhance the efficacy of clozapine, but to try to ameliorate the sedation and weight gain which can be so troublesome for some patients. Of the six studies included in the review of Porcelli et al. (2012), all but one showed benefit for aripiprazole, notably on negative symptoms; there were also gains in terms of the metabolic side effects of clozapine. However, Sommer et al. (2012) meta-analyzed the two published RCTs of aripiprazole augmentation and reported marked heterogeneity of effect on negative symptoms, and an overall null result.

In conclusion, augmenting clozapine with other antipsychotics, while common in clinical practice, has little consistent research support, with marked heterogeneity being found amongst published studies. There is also the potential for the augmenting agent to be associated with untoward side effects as well as pharmacokinetic and pharmacodynamic interactions. Having said this, some patients do seem to benefit from such augmentation, but what features predict responders is not clear. Aripiprazole augmentation might have a particular place in ameliorating the metabolic side effects of clozapine.

7.1.2 Antidepressants

The literature on antidepressant augmentation of clozapine is complex to interpret as it is not always clear which symptoms are being targeted. For example, there is an association between clozapine and the emergence or worsening of obsessive–compulsive symptoms (OCs), and serotonergic antidepressants are a legitimate therapeutic intervention in patients who experience this. However, it can be difficult to disentangle change in OCS from change in psychotic symptoms, and vice versa. Likewise, depressive symptoms are common in people with schizophrenia and can be difficult to differentiate from negative symptoms. Another issue is that those antidepressants that are metabolized by the P450-1A2 pathway (notably fluvoxamine) can impede the metabolism of clozapine, resulting in substantial rises in serum clozapine levels: this is not always accounted for in studies of these agents as augmenters.

These issues aside, the number of studies of antidepressant augmentation of clozapine is small. Fluoxetine in doses of up to 80 mg/day has uniformly shown no benefit on either positive or negative symptoms (Buchanan et al. 1996; Spina et al. 1998). All three published studies of fluvoxamine augmentation (Silver et al. 1996; Wetzel et al. 1998; Lu et al. 2000) were positive, but this might have been influenced by the increased serum levels of clozapine due to the pharmacokinetic interaction discussed above, and no RCTs have to our knowledge been

published. A single RCT of citalopram augmentation ($n = 61$) showed an impressive effect size of 0.81 (CI 0.30–1.33) with the major impact being on negative symptoms (Lan et al. 2006): again, replication is required.

Mirtazapine is an antidepressant with an unusual mechanism of action, with presynaptic alpha blockade leading to increased serotonin release in the synaptic cleft and postsynaptic serotonin 5HT-2C and histamine H1 antagonism. Of the three published studies of this agent as a clozapine augmenter, two were positive (Zoccali et al. 2004; Delle Chiaie et al. 2007; Berk et al. 2009). However, a meta-analysis of the two RCTs ($n = 35$) showed substantial heterogeneity of effect on negative symptoms and an overall effect size of 2.91 (CI −2.69–8.52). Weight gain and sedation are troublesome side effects of mirtazapine and are obviously expressly concerning in people already experiencing such effects from clozapine itself.

7.1.3 Mood Stabilizers

Mood stabilizers are used fairly commonly as a clozapine augmenter in people with associated mood instability, and again it is not always clear from studies whether it is primarily mood or psychotic symptoms which are being targeted. Also, some studies have included patients who probably have schizoaffective disorder, but they are not generally differentiated from those with schizophrenia in the analyses.

Lithium has a long history of use in clinical settings as an adjunct to clozapine, but Porcelli et al. (2012) could identify only three studies of this agent: two were positive (Bender et al. 2004; Kelly et al. 2006) and one negative (Small et al. 2003), but side effects were common and included hypersalivation, orthostatic dysregulation, weight gain, and oral dyskinesias. Another use of lithium is to boost white cells in those patients who, on clozapine, experience persistently low neutrophil counts. It seems that lower doses of lithium can be effective for this indication than for usual clinical use, and tolerability is not as problematic.

Sodium valproate or divalproex sodium is used commonly as an anticonvulsant in clozapine patients who experience seizures, or as a prophylactic anticonvulsant in patients on high doses of clozapine. However, Porcelli et al. (2012) found only a single published study of the use of divalproex sodium for persistent psychotic symptoms in patents on clozapine. This study (Kelly et al. 2006) was a retrospective review of 25 patients on clozapine alone, 15 on clozapine plus divalproex sodium (750–2,000 mg/day), and 9 on clozapine plus lithium (900–1,800 mg/day). The authors reported therapeutic effects with the divaproex sodium for psychotic symptoms as well as a reduction in anxiety, depression, and hostility: there was no analysis as to how these symptom changes might interact with each other. Problems with valproate in the setting of clozapine include weight gain, sedation, and suppression of white blood cells.

Lamotrigine in doses of 100–400 mg/day has been investigated in six published studies with mixed results (Dursun and Deakin 2001; Tiihonen et al. 2003; Kremer et al. 2004; Zoccali et al. 2007; Goff et al. 2007). Sommer et al. (2012) performed a

meta-analysis of five RCTs of lamotrigine as a clozapine augmenter ($n = 143$). The overall effect size for psychotic symptoms was 0.53 (CI 0.03–1.04) but one study was an outlier, and once this study was excluded from the analysis the effect size was reduced to a non-significant 0.27 (−0.10–1.04).

Finally amongst the mood stabilizers, topiramate has been used in a number of studies to try to reduce weight in people on clozapine and has also been evaluated as an augmenter for psychotic symptoms in three studies (Dursun and Deakin 2001; Tiihonen et al. 2005; Muscatello et al. 2011). In their meta-analysis of these latter studies, Sommer et al. (2012) reported an effect size of 0.75 (CI −0.05–1.56), but exclusion of a single outlier study reduced this to 0.38 (−0.13–0.89). Furthermore, side effects such as asthenia and sedation can be troublesome, and topiramate can exacerbate psychosis in some individuals.

In summary, mood stablizers as augmenters of clozapine have been understudied, expressly in terms of large RCTs. Published studies are disappointing, with little consistency in beneficial effects and some agents producing problematic side effects in a number of patients. It might be that mood stabililzers should be reserved for clozapine non-responders who have substantial associated mood instability or meet criteria for schizoaffective disorder. Adjunctive use of valproate might have particular benefits for hostility, but more studies are required to draw definitive conclusions.

7.1.4 Other Agents

A number of other agents have been investigators as clozapine augmenters. These have been reviewed by Porcelli et al. (2012). Of particular note are those agents that are associated with the glutamatergic system, given the substantial interest in this system in trying to understand the pathogenesis of schizophrenia (Papanastasiou et al. 2013). Studies of these agents are summarized in Table 7.3. Unfortunately, the findings with a number of different gluatamatergic agents as adjuncts to clozapine have been very mixed. Sommer et al. (2012) calculated the combined effect size of the three RCTs using glycine, as −0.18 ($p = 0.50$). Problems with these studies in general include small numbers of participants and short duration (mostly 6 weeks). The only longish-term study, that of Diaz et al. (2005) assessing 60 mg of glycine vs placebo over 28 weeks, had only six subjects in each arm and delivered a nul result. Worryingly, glycine might even worsen negative symptoms in some patients (Goff et al. 1999). Having said this, the complexity of the glutamatergic system and the fact that many of the different glutamatergic agents investigated have different mechanisms of action means that we should not close the door on a potential role in clozapine-resistant patients. Indeed, Goff et al. (2008) reported the agent CX-156, which binds to an allosteric site of the AMPA receptor, was associated with a reduction in negative symptoms in a group of patients with clozapine resistance; side effects included insomnia, fatigue, and abdominal discomfort, and these might limit the agent's clinical utility.

Table 7.3 Studies of glutamatergic agents as adjuncts to clozapine in schizophrenia [adapted from Porcelli et al. (2012)]

Authors	Agent	Daily dose	*n*	Duration	Outcome	Side effects
Evins et al. (2000)	Glycine	60 g	27	8w	+ (4 % ↓ PANSS)	Nil
Potkin et al. (1999)	Glycine	30 g	19	12w	− (BPRS)	Nil
Diaz et al. (2005)	Glycine	60 g	12	28w	− (PANSS)	Nil
Heresco Levy et al. (1999)	Glycine	60 g	26	6w	+ (30% ↓ PANSS)	Nil
Goff et al. (1999)	D-Cycloserine	50 mg	11	6w	− (13.5% ↑ SANS)	Nil
Lane et al. (2006)	N-Methylglycine	2,000	10	6w	− (PANSS)	Nil
Tsai et al. (1999)	D-Serine	30 mg/kg	30	6w	− (PANSS, HAMD)	Nil
de Lucena et al. (2009)	Memantine	20 mg	21	12w	+ (PANSS)	Nil
Goff et al. (2001)	Ampakine CX-516	900–2,700 mg	18	4w	+ (↓ 10 points on PANSS)	Hypertension, headaches, abdominal discomfort
Goff et al. (2001)	Ampakine CX-516	2,700 mg	51	4	− (PANSS)	

Abbreviations: *PANSS* Positive and negative symptom scale, *SANS* Scale for the assessment of negative symptoms, *BPRS* Brief psychiatric rating scale, *HAM-D* Hamilton depression scale

Berk et al. (2008) assessed the efficacy of the glutathione precursor N-acetyl cysteine (NAC) as an adjunct to antipsychotics in people with schizophrenia. Of the 140 enrolled patients, 45 % were on clozapine. Results were very encouraging, with significant improvements on the CGI-S (effect size 0.43; $p < 0.05$) and PANSS-negative (effect size 0.52; $p < 0.05$) and general (effect size 0.46; $p < 0.05$) but not positive symptoms. The agent was extremely well tolerated. However, there was no sub-analysis for clozapine patients specifically, and we are not aware of any replication studies.

The stimulant modafinil has intuitive appeal as a clozapine augmenter in that it could theoretically ameliorate some of the fatigue and lassitude seen in some schizophrenia patients on clozapine. However, the single published RCT of this agent (doses up to 300 mg/day) was negative for both positive and negative symptoms (Freudenreich et al. 2009). There is also the potential risk of aggravation of psychotic symptoms in some patients, with modafinil.

There has been considerable interest in EPA (omega-3-fatty acid) as a therapeutic modality in a number of psychiatric disorders, including schizophrenia. The RCT of Emsley et al. (2002) included nine patients in each arm and a total dose of 3 g daily over 12 weeks; it showed significant benefit in terms of symptom

reduction. A similar finding was reported by Peet and Horrobin (2002) with up to 4 g daily of EPA in 31 patients (there were seven controls); interestingly, the effect seemed most robust at a dose of EPA of 2 g daily. However, the much larger ($n = 75$) 16-week study of Fenton et al. (2001) failed to show significant separation between EPA and placebo. It is difficult to interpret these disparate findings.

Benzodiazepines are frequently useful in addition to clozapine for treatment of comorbid anxiety/panic, insomnia, and agitation, although the possibility of inducing abuse and dependence from longer-term use is a concern. Clonazepam should be avoided with clozapine due to the potential for increasing risk of agranulocytosis. However, epidemiological findings suggest that mortality may be increased with long-term adjunctive use of benzodiazepines in schizophrenia (Tiihonen et al. 2012). Pregabalin has also been observed to help anxiety in patients with treated schizophrenia, though not specifically those who were clozapine-resistant (Engllsch et al. 2010).

The use of hormones such as estrogen, testosterone, and related agents for augmentation of the effects of clozapine is a largely unexplored area. Adjunctive therapy with estrogen has shown some promise in limited studies in women and now men, but more research is needed. Augmentation of antipsychotic therapy (not specifically clozapine) with the selective estrogen receptor modulator raloxifene 120 mg daily has been compared to placebo in postmenopausal women with schizophrenia, demonstrating reductions in psychopathology (Kulkarni et al. 2012).

7.2 Other Modalities

A recent pilot study suggests that transcranial magnetic stimulation (TMS) may be useful as adjunctive therapy for schizophrenia. In a small four week study, TMS was administered to patients, some of whom were taking clozapine. Benefit for working memory was observed (Barr et al. 2013).

Electroconvulsive therapy has long been employed in the treatment of schizophrenia, albeit its use for this indication has waned with the advent of antipsychotics. It is still at times utilized by clinicians in treatment-resistant patients. In a review, Pompili et al. (2013) found 31 studies of ECT in schizophrenia, the most common indication being to augment antipsychotics, mostly targeting catatonia, aggression, and suicidality. In terms specifically of clozapine augmentation with ECT, Flamarique et al. (2012) performed an observational study of 28 adolescents with schizophrenia or spectrum disorders: compared to patients receiving the ECT-clozapine combination, those with other antipsychotics had more hospitalizations over the 12 month follow-up, but there was no difference between the groups in symptoms score. In a separate study, Kupchik et al. (2000) reported a 67 % improvement in psychotic symptoms in a sample of 36 patients treated with ECT and clozapine; adverse reactions, including prolonged seizures and tachycardia, affected 16 % of their patients. A single RCT (Masoudzadeh and Khalilian 2007), showing benefit for ECT in combination with clozapine compared to clozapine alone or ECT alone, is bedeviled by a small sample size (six in each

group) and other methodological concerns. Thus, there is little in the way of supportive evidence for the use of ECT in people on clozapine, but some studies suggest that it might be beneficial for some such patients.

Conclusions

Clozapine can be a highly effective agent in people with schizophrenia who are unresponsive to other antipsychotics. However, it is not always optimally effective. A range of augmentation strategies has been investigated in people who have 'failed' clozapine, including other antipsychotics, antidepressants, mood stabilizers, and glutamatergic agents. Strategies that have seemed encouraging in case reports and small case series have generally been disappointing in more rigorous studies. This inconsistency of outcomes probably speaks to the heterogeneity of the schizophrenia construct and should not stop clinicians from employing such interventions (carefully and sequentially and with clear outcome assessments) in individual patients.

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Therapeutic Brain Stimulation in Treatment-Resistant Schizophrenia

8

Peter B. Rosenquist, Anthony O. Ahmed, and W. Vaughn McCall

8.1 ECT

The initial conceptualization and rationalization of ECT were as an antipsychotic, antischizophrenia treatment. In the absence of good therapeutics, psychiatrists at the turn of the twentieth century had to content themselves with observational studies on the course of serious mental illness and histological studies of their patients' brains. The efforts produced two complimentary findings. First, that among those individuals with both epilepsy and chronic psychosis, when the epilepsy was active, then the psychosis became less problematic, and when the epilepsy was less active, the psychosis became more intense. Second, histologic examinations of the brains of normal, epileptics, and schizophrenics led to the conclusion that while the brains of epileptics had more glial density than the brains of normal, the brains of persons with schizophrenia had less glial density than the brains of normal. Together, these two findings led to a theory of antagonisms between epilepsy and psychosis and the search for a means to induce seizures in persons with psychotic mental illness who did not have epilepsy.

The initial techniques for inducing seizures were intramuscular injection of camphor, which was replaced by intravenous metrazol (a GABA antagonist). The approaches were problematic as they did not reliably produce seizures, or sometimes produced more than one seizure, and had a lag between injection and seizure onset that was terrifying for patients. ECT replaced metrazol, as ECT was reliable in seizure induction, produced one and only one seizure, and produced immediate unconsciousness with no terrifying lag period.

ECT was introduced in 1938 in Rome, and the first patient treated was thought to have what today might be called undifferentiated schizophrenia. Of course, modern nomenclature and diagnostic criteria did not exist at that time; thus much of the early inference of ECT's therapeutic effects could be clouded by what we now view

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as diagnostic uncertainty. Still, many of the early cases of schizophrenia seemed to respond to ECT, although the response was acknowledged as uneven across patients. ECT came to the USA in the 1940s, which ushered in a period of diagnostic trial and error. ECT at one time or another was applied to persons with eating disorders, dementia, alcoholism, substance abuse, and serious mood disorders.

Now, 75 years later, in the Western hemisphere ECT is largely considered a treatment for major depression and bipolar disorder, and is rarely used to treat schizophrenia. The most recent usage rates from the USA show that 72–92 % of patients receiving ECT have a diagnosis of depression, 0–25 % with bipolar disorder, and 8–29 % with schizophrenia or schizoaffective disorder (Leiknes et al. 2012). The role of ECT in the care of schizophrenic patients declined in the West in the 1960s with the advent of effective antipsychotic medication, relegating the role of ECT in schizophrenia to the care of treatment-refractory cases. This is not the case in the Eastern hemisphere, as ECT is viewed as a first-line treatment of severe psychotic symptoms in India, China, parts of Africa, and other developing nations when symptoms require hospitalization. In many of these countries, schizophrenia is the primary indication for ECT.

The efficacy of ECT in treatment-resistant schizophrenia has been clarified in the last 20 years by the work of Petrides and Chanpattana. Chanpattana studied a group of patients who had failed in the present episode a minimum of two antipsychotics from at least two different classes, each equivalent to 750 mg chlorpromazine equivalents daily (Chanpattana et al. 1999). Other inclusion criteria included a baseline BPRS score of at least 35, over 2-year duration of illness, and a presentation during an acute psychotic exacerbation.

The study employed a unique two-phase design. The first phase was an open label acute trial of ECT/antipsychotic medication in combination, followed by a 3-week stabilization period during which ECT was tapered. Responders who sustained improvement during the stabilization period were then randomized in a 6-month continuation phase to receive either treatment alone or in combination. In the acute phase 114 patients with schizophrenia were enrolled. All received flupenthixol 12 mg in the first week and increased as tolerated to 24 mg in the second week, while receiving bitemporal brief pulse ECT at threshold three times a week. ECT was continued until patients achieved the response criteria (defined a priori as a reduction in the BPRS to 25 or less) or received a maximum of 20 treatments at which time they were declared nonresponders. 101 patients completed the study with 58 responders and 43 nonresponders. Baseline BPRS scores before/after treatment were 49.1 (+/−9.6) / 18.7 (+/−7.2) in responders and 51.4 (+/−9.4) /39.4(+/−8.3) in nonresponders. It is worth noting that this treatment trial employed more ECT in the index course than would typically be used in the Western hemisphere in the treatment of major depression. The average number of ECT treatments for responders was 13.9 (+/−4.8) while nonresponders received 20.4 (+/−0.8) treatments.

In this second phase, continuation ECT was given weekly for 1 month (4 treatments) and then biweekly for 5 months (10 treatments). Fifty-one patients

were enrolled and 45 completed the second phase of the study. Among the completers, 60 % maintained remission after 6 months in the combined continuation ECT + flupenthixol group, while 93 % relapsed in both the continuation ECT alone and the flupenthixol alone groups, which represented a significant difference between groups.

In this study, and a subsequent larger study by the same authors ($N = 293$, 54.6 % responders), responders tended to be younger and had shorter durations of illness, and of the current episode, more psychiatric admission, less extensive family history of schizophrenia, more paranoid type, lower baseline negative symptoms, and higher baseline GAF compared to nonresponders (Chanpattana and Chakrabhand 2001).

Petrides pursued a complimentary line of research in treatment-resistant schizophrenia, but with a focus on comparisons with clozapine (Petrides 2012). They identified treatment-resistant patients with schizophrenia on a stable dose of clozapine and serum levels >350 meq/ml for at least 8 weeks, with persistent psychotic symptoms (>/= 12 in the BPRS psychosis subscale) and no current mood symptoms. Patients were randomized to receive 8 weeks of bitemporal ECT in addition to clozapine or to continue with clozapine treatment for 8 weeks.

Patients in the pharmacotherapy arm who did not respond after 8 weeks were crossed over to the ECT arm and received the combination treatment for another 8 weeks in an open trial. Petrides defined two different response criteria: 20 %, and 40 % reduction in the psychosis items of BPRS. There were no responders in the pharmacotherapy group who realized a 20 % reduction of the psychosis subscale, compared to 12 of 20 (60 %, $p < 0.001$) in the ECT + clozapine group. There were 10 of 20 (50 %, $p < 0.001$) responders in the ECT + clozapine group meeting the 40 % reduction criterion. Those who did not respond to 16 weeks of clozapine treatment crossed over to the combination. There were 11 of 15 (73.3 %) responders when response was defined as 20 % reduction and 6 of 15 (40 %) when 40 % was used.

Perhaps the best controlled comparison study of clozapine and ECT alone and in combination to date was conducted by Masoudzadeh and Khalilian (2007) They reported on 18 treatment-resistant schizophrenic patients randomized to clozapine alone (with sham ECT), ECT alone with clozapine placebo, and clozapine plus ECT in combination. Treatment resistance was defined by failure to respond to two antipsychotic agents at adequate dose and duration, and there was a 2-week medication free washout period. Patient groups were matched on age, gender, type of schizophrenia, and baseline PANSS scores. In each group there were 3 men and 3 women; 3 with paranoid subtype, two disorganized and one undifferentiated.

Interestingly, all ECT was administered with right unilateral electrode (RUL) placement, given three times weekly for 12 sessions. Sham ECT consisted of drug-induced sedation without seizure induction in the ECT treatment room. Outcome was measured by a blinded rater using the PANSS at baseline and twice weekly thereafter for a total of 5 scores. All treatments were well tolerated, and there were no dropouts from any treatment arm. All groups showed improvement. However,

combination therapy was superior to either treatment given in monotherapy. The reduction of PANSS scores was 46 % in the clozapine group, 40 % in the ECT groups, and 71 % in the combination group ($p < 0.05$). The reduction in positive symptoms was also superior for the combination treatment. In the clozapine group, mean positive symptom score decreased 31 %, in the ECT alone group by 51 %, and by 80 % for the combination group. For negative symptom scores, the clozapine and combination groups achieved a greater reduction than the ECT group, but this difference was not statistically significant. Mean negative symptom scores decreased by 63 % in the clozapine group, 61 % in the combination group, but only 29 % in the ECT group. The authors also state that patients receiving the combination treatment had a more rapid response compared to the two monotherapies.

The available literature suggests that the combination of ECT with antipsychotic medications is superior to either treatment in monotherapy. While each treatment contributes uniquely and has the potential for significant adverse effects, the combination appears to be safe, without generating unusual, additive effects in adults or adolescents with schizophrenia (Braga and Petrides 2005; Flamarique et al. 2012).

The therapeutic mechanism of action for ECT in schizophrenia is not fully understood, as is the case in its mechanism in mood disorders. Still, it seems likely that ECT's benefit in schizophrenia is not a specific "antischizophrenia" effect per se, but rather is a more general antipsychotic effect. This is illustrated in the fact that ECT has antipsychotic effects in both psychotic mood disorders and in psychosis related to Parkinson's Disease. In the case of mood disorders, the presence of psychotic symptoms usually denotes marginal response to combined antidepressant plus antipsychotic medication, but exquisite sensitivity to ECT. Of note, the psychotic symptoms of mood disorders are usually so thoroughly addressed by ECT that an antipsychotic drug is not necessarily required to keep psychotic symptoms at bay during the post-ECT continuation time frame. The antipsychotic effect of ECT in Parkinson's Disease is equally fascinating. It is well known that late stage Parkinson's Disease may be associated with both mood symptoms and psychotic symptoms, especially in the presence of dopamine agonists. The application of ECT in such circumstances will usually produce simultaneous improvement in both the motor symptoms and reductions in psychotic symptoms. The simultaneous improvement of motor and psychotic symptoms defies the easy explanation of a simple, monolithic increase in dopamine function, as antipsychotic action is usually assumed to include a downregulation of dopamine transmission. Yet in animal models, and in some human studies, there is evidence that ECT [or electroconvulsive shock (ECS) in animals] enhances CNS dopamine transmission. Perhaps ECT has a differential effect on dopamine in the nigral-striatal tract as opposed to the meso-limbic tract. At any rate, there is some evidence that ECT has general antipsychotic properties, not just antischizophrenia properties, and the mechanism for this is more complicated than simple dopamine blockade.

While the total body of work in the world's literature is small on the topic of ECT and treatment-resistant schizophrenia, the message is clear that it has value,

although it may be difficult to know which patients will benefit. Published treatment guidelines and comprehensive reviews generally parallel this perspective, but the emerging picture is that catatonic as well as paranoid and other positive symptoms are most likely to respond (Zervas et al. 2012).

Practitioners who refer patients with treatment-resistant schizophrenia for ECT should be prepared for potentially lengthy courses of treatment. Patients who are severely incapacitated by treatment-resistant schizophrenia may lack capacity to understand the nature of their illness, and the relative risks and benefits of pursuing ECT versus alternative courses of action. Therefore, all patients with treatment-resistant schizophrenia should be examined for their capacity to consent, and surrogate consent for ECT should be pursued from a legally responsible person if the patient lacks capacity. Also, it is acceptable to pursue ECT for treatment-resistant schizophrenia even if the goal of treatment is less than full remission from schizophrenia. In fact, ECT may have worthwhile humanistic value even if its application does not lead to discharge from psychiatric hospitalization, as illustrated in this vignette:

8.1.1 Case

A young man in his mid-twenties is referred for ECT at a state psychiatric hospital. The man has been continuously hospitalized for 3 years. He had remote history of head trauma, having gone through the windshield of his automobile in a motor vehicle accident. His injury had led to epilepsy. In the subsequent months after the accident, he developed severe thought disorder with verbigeration, word salad, and neologisms. Although he spoke fluently and without dysarthria, his communications were entirely nonsensical. He was inclined to unprovoked aggression against the staff of the hospital, so much so that he was in the most secure ward of the hospital, with a 1:1 staffing ratio for 10 of the most severely disturbed patients out of a hospital census of 700 patients. This patient further distinguished himself as being the only patient among the 700 who required continuous "ambulatory restraints" (i.e., a strait jacket) to contain his violence. He was diagnosed with undifferentiated schizophrenia and epilepsy, although his epilepsy was under good control and thought to not contribute in a meaningful way to his dominant symptoms. His treatment included robust doses of antipsychotics and anticonvulsants over long periods of time with no response to his core psychopathology.

He was referred for ECT three times and was refused by the ECT treatment team on the first two occasions, because no one on the treatment team had ever provided ECT for a similar case. The team accepted the patient after the third referral by the patient's primary psychiatrist. The patient did not have capacity to consent, so consent was obtained from the legally responsible person. ECT commenced with brief pulse constant current stimuli using bitemporal electrode placement, with a treatment frequency of three times per week. The first 12 sessions did not produce any meaningful change and the treatment team was considering abandoning the

course, but the referring psychiatrist prevailed upon the team to continue. After 15 ECT sessions, the team received reports from the non-doctoral ward staff that the patient "was getting smarter." Upon further investigation it was learned that what the staff was reporting was a clearing of the patient's thought disorder. After 21 consecutive session the patient was coherent (but still bizarre), his aggression had abated, he was able to come out of ambulatory restraints, and he was able to go on an excursion outdoors for the first time in 3 years. However, he did not improve enough to be discharged from the hospital over the subsequent year of follow-up.

This case teaches that ECT can produce meaningful improvements in the life of a patient with treatment-resistant schizophrenia, even if the improvement falls short of full remission, and that the course of ECT can be long for these individuals.

We conclude that the data for ECT is strong enough that no patients with treatment-resistant schizophrenia should be declared "untreatable" if they have not had a course of ECT, especially a course of ECT combined with an antipsychotic, or better still, specifically ECT combined with clozapine.

8.2 Transcranial Magnetic Stimulation

There is a small but growing literature on TMS for treatment-resistant schizophrenia, and consonant with the relatively recent development of this modality, there is no consensus on its effectiveness or the best way to apply TMS for schizophrenia at this time. On the plus side, its side effects are negligible, with no important cognitive side effects and no requirement for anesthesia. Compared to ECT, TMS is decidedly a more focal treatment employing a small electromagnetic coil placed on the scalp. The electromagnet converts electrical charge from a bank of capacitors into a pulsed magnetic field of approximately 1.5 Tesla which passes without impedance through the skull. The varying magnetic field induces an electrical field in the underlying cerebral cortex penetrating to approximately 3 cm in depth. The strength of the magnetic field diminishes with distance from the electromagnetic coil. Cortical neurons with axons at right angles to the electrical field depolarize and generate action potentials where there is sufficient intensity.

Pulses administered can be single, paired, or in a series (also called a "train," which in turn can vary in its duration). When TMS is delivered in a series of pulses, or a train, this is termed repetitive TMS (rTMS). Generally, single and paired pulse-type TMS are used for neurodiagnostic purposes, whereas rTMS is the modality that is believed to have therapeutic potential in psychiatric disorders. The shape of coils also varies and may ultimately have some bearing on the depth and intensity of neurostimulation and clinical effect.

TMS delivered at frequencies of less than or equal to 1 Hz is termed low frequency or slow rTMS and tends to have an overall inhibitory effect on the underlying cortex. TMS at frequencies above 1 Hz (generally from 10 to 20 Hz) is termed high frequency or fast rTMS and tends to be excitatory. Correspondingly, fast or high-frequency rTMS increases brain perfusion, and metabolic activity, whereas low-frequency rTMS has the opposite effect (Pascual-Leone et al. 1994).

This differential effect on brain activity allows the targeting of different cortical regions whose increased or decreased metabolic activity is implicated in the pathophysiology of neuropsychiatric conditions.

rTMS has been employed with mixed results in a number of clinical trials directed towards the amelioration of the primary symptoms of schizophrenia, including auditory hallucinations, negative symptoms, and neurocognitive deficits.

8.2.1 TMS Treatment of Auditory Hallucinations

Hoffman et al. (2003) conducted the first double-blind sham-controlled treatment of treatment-resistant auditory hallucinations in 24 patients using low frequency 1 Hz TMS administered over the left temporoparietal area hypothesized to be overactive in the production of auditory hallucinations (AH). The center of the coil was positioned midway between T3 and P3 as per the international electroencephalographic electrode placement corresponding to the posterior border of Wernicke's area, associated with auditory processing.

Medication resistance was defined as daily AH despite two adequate trials of antipsychotic medication for at least 6 weeks at 1,000 mg chlorpromazine dosage equivalents for typical agents and daily minimum of atypical agents of 6 mg risperidone, 15 mg olanzapine, 500 mg quetiapine, or 400 mg clozapine. Four 15-min treatment sessions of active rTMS treatment with figure-eight coil at 90 % of motor threshold in this study produced a significant and sustained improvement in AH compared with the sham treatment, as measured by a 7 item Auditory Hallucinations Rating Scale. Importantly, there was neither improvement nor worsening of negative symptoms or cognition.

Subsequent studies employing similar rTMS protocols for treatment-resistant AH continued to be safe and well tolerated by patients, but achieved mixed results. In the most recent meta-analysis of 17 randomized trials and 337 patients (209 active and 197 sham), the mean weighted effect size of rTMS in improving auditory hallucinations by a number of outcome measures was modest at 0.44 (95 % CI 0.19–0.68, $I2 = 35.7$) (Slotema et al. 2012). Five studies with 61 active and 57 sham patients combined reported outcomes at 1-month posttreatment, producing a mean weighted effect size of 0.40 (95 % CI − 0.23–1.02) which raises questions about the durability of effect.

Although the mechanism of action of TMS in the treatment of AH remains uncertain, a recent fMRI study of ten sessions of low frequency TMS directed towards the sylvian parietotemporal region demonstrated decreases in cerebral blood flow in the posterior auditory cortex, Boca's area, and the cingulate cortex, indicative of a widespread inhibition of structures implicated in AH (Kindler et al. 2013a, b).

The 2009 schizophrenia PORT guidelines (Buchanan et al. 2010), recommended 1-Hz TMS as treatment for patients with auditory hallucinations (AH) that have not responded to pharmacological treatments, perhaps based upon the more promising meta-analyses available at that time. However, the treatment is not yet approved for

this indication by the FDA in the USA. A large and more definitive multisite trial will likely be required as was the case with rTMS treatment of major depression in order to optimize treatment parameters and further evaluate the clinical role of rTMS in the treatment of AH.

8.2.2 TMS Treatment of Negative Symptoms

Whereas AH appear to be a result of overactive auditory cortex, negative symptoms of schizophrenia have been hypothesized to be related to decreased cortical activation, as evidenced by reductions in frontal and temporal gray matter volumes as well as diminished or anomalous activation of these regions in functional neuroimaging studies. The first published study investigating rTMS for negative symptoms was an open label examination of rTMS treatment of six patients with chronic schizophrenia for 10 days of 20 Hz delivered at 80 % of motor threshold, and directed towards left dorsolateral prefrontal cortex (DLPFC) (Cohen et al. 1999). Negative symptoms as measured by the negative symptom subscale of the PANSS were decreased in this group of patients by 12 %. The study failed to show any change in activity from baseline in 99mTc-HMPAO SPECT scanning. Subsequent open label and double-blind-controlled studies of high-frequency rTMS (10–20 Hz, given for 1–4 weeks) stimulation of DLPFC have shown beneficial effects on patients with drug resistant and prominent negative symptoms. (Sachdev et al. 2005; Hajak et al. 2004). However, other controlled studies failed to demonstrate improvements (Holi et al. 2004; Novak et al. 2006) and correspondingly, recent meta-analyses have yielded divergent results. A review of eight double-blind studies found that rTMS had a mild to moderate ($d = 0.58$) effect size on alleviating the negative symptoms of schizophrenia (Freitas et al. 2009). A subsequent meta-analysis evaluated nine double-blind studies (Dlabac-de Lange et al. 2010) indicated a possible mediating effect of stimulus frequency. For studies with any high-frequency stimulation of the left DLPFC, the effect size of the treatment was low ($d = 0.43$); when the analysis included only studies with a 10 Hz frequency, the effect size of the treatment was intermediate ($d = 0.63$).

Based upon the observation that patients with schizophrenia have reduced EEG alpha activity (power and coherence) which may improve along with negative symptoms when successfully treated with clozapine, Jin et al. (2012) performed a double-blind crossover trial employing four different rTMS frequencies. Twenty-seven patients with predominantly negative symptoms stable on antipsychotic regimen were assigned to one of two study groups, each of which included two blinded treatments from one of four possibilities: sham rTMS, or rTMS delivered at one of three frequencies—3 Hz, 20 Hz, or "alpha rTMS" delivered at the individual's alpha frequency (8–13 Hz). Stimulation was at 80 % of the motor threshold, and the coil was placed over the DLPFC. As measured by PANSS negative symptom scores, the alpha rTMS produced a significantly greater reduction (29.6 % +/− 0.27) compared with sham (8 % +/− 0.2) and both low (9 % +/− 0.12) and high (−4 % +/− 0.18) frequency stimulation. Using a response criterion

of a 30 % reduction or < 16 endpoint in PANSS negative symptom score, 6 of 11 patients responded to the alpha rTMS vs. 1 responder to the low frequency, 1 to sham, and none to the high-frequency stimulation.

In light of divergent methodologies and the small number of controlled trials on the efficacy of the treatment for negative symptom schizophrenia, without further research it is difficult to recommend rTMS for clinical settings.

8.2.3 TMS Treatment of Cognitive Dysfunction

Cognitive dysfunction is a core feature in schizophrenia, exerting a negative influence on quality of life, occupational and social outcomes. The profile of deficits in schizophrenia includes critical functions of attention, memory, executive function, and processing speed, and these remain incompletely treated with antipsychotic medications. Data on the effects of rTMS on cognition in schizophrenia have been reported primarily as a secondary outcome from studies targeting AH or negative symptoms. Stimulation of auditory cortex appears to have little effect on cognition in either direction.

A recent review identified 6 RCTs, 5 open trials, and two crossover studies that reported cognitive outcomes of rTMS treatment of schizophrenia, although the primary focus for the majority of studies was to improve negative symptoms (Demirtas-Tatlidede et al. 2013). A wide range of cognitive measures were performed, limiting generalizability of results. Similarly, there were a number of different brain areas that were the focus of stimulation—seven trials focused on left DLPFC, while three stimulated DLPFC bilaterally, and one each for the auditory cortex and the cerebellum. No effect on cognition was found in seven studies, and no studies showed a worsening of cognitive performance. Cognitive enhancing effects were found in six studies and included improvements in delayed visual memory in two studies, an auditory imagery test, verbal learning at 2-week follow-up, working memory and other measures of executive function in two studies, sustained attention, and visual motor tracking in female subjects only. No consistent predictor of positive cognitive outcome can be discerned from the stimulation intensity or frequency parameters of treatment.

In summary, rTMS has shown modest efficacy in the treatment of AH, with some promising preliminary work showing some effect on negative symptoms and cognition. The success of TMS in the treatment of schizophrenia will likely mirror technical developments as the methods are refined for the treatment of all neuropsychiatric conditions. Accurate neuroanatomical registration to ensure that the treatment is delivered to the appropriate cortical structures remains an ongoing challenge. The original "5 cm rule" for localizing the site of stimulation anteromedially in prefrontal cortex based upon the known location of motor cortex has been amended to 5.5 or 6 cm after studies of MRI registration showed that some patients received stimulation in the prefrontal cortex as a result of the original procedure (Johnson et al. 2012). MRI is costly but may prove necessary depending upon the degree of focality required. Areas of active research and development

include the search for greater depth of stimulation, as with the so-called H-Coil (Bersani et al. 2013) and novel patterns of stimulation, such as alpha EEG synchronized (Jin et al. 2012) and theta burst TMS (Kindler et al. 2013a, b).

8.3 Transcranial Direct Current Stimulation *tDCS*

tDCS is the application of low-level, constant unidirectional electrical current to the scalp in order to produce relatively long-lasting hyperpolarization or depolarization of underlying regions of the brain cortex. It is not approved for use in the USA, where it is viewed as experimental. Sessions typically last 20–30 min, do not require anesthesia, do not produce seizures, and are well tolerated with no major side effects. There are two types of stimulation with tDCS: anodal and cathodal stimulation. Anodal stimulation acts to excite neuronal activity while cathodal stimulation inhibits or reduces neuronal activity. These effects are analogous to the stimulation and inhibition associated with high and low frequency rTMS, respectively. Unlike ECT and TMS, tDCS does not result in neuronal depolarization, but rather affects resting membrane potential. The regional specificity of the treatment effect implies that the applied location of the stimulating electrodes will be critical to determining its effect.

While there remains a relative paucity of systematic studies of tDCS in schizophrenia, a few case reports have documented its use to treat treatment refractory schizophrenia and represent the majority of articles published on its application for schizophrenia (e.g., Andrade 2013; Nawani et al. 2013; Palm et al. 2013; Rakesh et al 2013; Shiozawa et al. 2013a, b). These studies demonstrated the use and benefits of tDCS to treat auditory hallucinations, catatonia, and negative symptoms in schizophrenia. In the treatment of catatonia in a 65-year-old woman who was receiving a regimen of 400 mg of clozapine, Shiozawa and colleagues provided ten consecutive sessions of once daily tDCS. The treatment was configured such that the cathode electrode stimulated the right DLPFC, and the anode stimulated the left DLPFC. The stimulation was provided for 20 min using a direct current of 2.0 mA. The authors reported that the patient demonstrated improvements in catatonia during the 10-day course of treatment and after a month of treatment demonstrated improvements in basic social skills and independent living skills. Rakesh and colleagues provided a 5-day treatment of tDCS to a 24-year-old patient with treatment-refractory auditory hallucinations, who had become opposed to continuing medication treatment. The patient's tDCS treatment comprised twice-daily stimulation with at least a 3-h interlude between sessions. Whereas the anode electrode was placed over the left DLPFC, the cathode electrode was placed over the left temporoparietal junction. The stimulation was provided for 20 min using a direct current of 2.0 mA. Rakesh and colleagues reported that reductions in auditory hallucinations were almost immediately apparent by the end of the second session of the first day of tDCS treatment. At the end of the fifth day of treatment, the patient endorsed no auditory hallucinations, obtaining a score of zero on the AHRS. There were also apparent improvements in social interactions, insight,

concentration, and overall treatment engagement following tDCS. Subsequently, the patient was initiated on 5 mg/day of olanzapine to address residual psychotic symptoms such as delusions of reference. Palm and colleagues provided tDCS treatment to a 19-year-old man with Paranoid Type Schizophrenia, who demonstrated severe negative symptoms such as avolition, social withdrawal, flat affect, and anhedonia. The patient had been unresponsive to an 8-week treatment of 20 mg/day olanzapine treatment but remained on the regimen during the course of tDCS treatment. The patient received once daily tDCS for 10 week days within a 2-week period. The anode electrode was placed over the left DLPFC whereas the cathode electrode was placed over the contralateral supraorbital region. As with other case reports, stimulation was provided for 20 min using a direct current of 2.0 mA. The patient completed the PANSS, Scale for the Assessment of Negative Symptoms (SANS), the Calgary Depression Rating Scale in Schizophrenia (CDRSS), Self-Ordered Pointing Task (SOPT), and the Trail Making Test (TMT) at baseline, after five sessions of tDCS, and after 10 sessions of tDCS had been completed. Following the 2-week tDCS treatment, the patient demonstrated a 37 % reduction in the severity of positive symptoms and a 25 % reduction in negative symptoms on the PANSS. The patient also demonstrated a 28 % reduction in the severity of negative symptoms as measured by the SANS, an 82 % reduction in depressive symptoms, and an improved performance on the TMT.

Andrade (2013) reported on a 25-year-old patient with a 7-year history of schizophrenia whose treatment-resistant auditory hallucinations had previously responded and were kept at bay with 1 Hz rTMS, and who relapsed due to an interruption in the availability of this treatment. Subsequent daily treatment with tDCS between 2 and 3 mA with cathode placement over auditory cortex and the anode over left DLPFC was successful in reducing the intensity of auditory hallucinations and restoring functional abilities. The author reports that the patient's brother, being medically qualified, has been able to continue this treatment over a 3-year period to maintain clinical gains. Attempts to wean to frequency of tDCS below once to twice daily resulted in clinical deterioration, but were easily restored with restitution. Patient and family agree that this treatment was superior to the less frequent rTMS she had earlier received.

To our knowledge, there has been only one published clinical trial of tDCS for the treatment of schizophrenia. Brunelin et al. (2012) conducted a clinical trial to evaluate the efficacy of tDCS for 30 patients with medication-refractory auditory hallucinations. The patients were randomized to receive either sham stimulation or 2 mA tDCS in which the anode stimulated the left dorsolateral prefrontal cortex and the cathode stimulated the left temporoparietal cortex. Stimulation was provided 5 days a week, twice daily for 20-min sessions with at least 3 h between sessions. The sham stimulation condition was designed to provide 40 s of 2.0 mA stimulation and small current pulses periodically (550 ms) while displaying the configurations for "real" stimulation. Study participants completed the Auditory Hallucinations Rating Scale (AHRS) as a measure of the severity of auditory hallucinations and the PANSS for the severity of schizophrenia symptoms. Outcome measures were completed at baseline, after completing 5 days of tDCS, and at a 1 and 3-month

follow-up to determine if any putative treatment benefits were sustained. Following 5 days of tDCS, the treatment group obtained greater improvements in auditory hallucinations as measured by the AHRS with large effect sizes. The tDCS group demonstrated a 31 % decrease in the severity of auditory hallucinations compared to 8 % for the sham stimulation group. The benefits on positive and depressive symptoms overall as measured by the PANSS were in the medium range whereas the benefits on disorganization and grandiosity/excitement were in the small and minimal range, respectively. Interestingly, they obtained effect sizes on negative symptoms as measured by the PANSS that were larger than those obtained from positive symptoms. Brunelin and colleagues also found that gains in the severity of auditory hallucinations were maintained at the 1-month and 3-month follow-up periods.

It is clear that tDCS is more tolerable than ECT, and its tolerability has been reported in several case studies. Several studies have systematically examined the safety and tolerability of tDCS in adult patients which have found no indication that it negatively impacted brain function or motor abilities. tDCS has however been commonly associated with minor side effects such as tingling or skin irritation at the site of stimulation, or more rarely fatigue, nausea, insomnia, and mild headache (Poreisz et al. 2007; Tadini et al. 2011). In one study, Mattai et al. (2011) sought to evaluate the tolerability of the intervention in a pediatric sample with childhood onset schizophrenia that may inform the possible practice frontiers of tDCS. Childhood onset schizophrenia is very debilitating, a rare form of the illness that is often treatment refractory given the persistence and severity of the symptoms (Nicolson and Rapoport 1999). Mattai and colleagues recruited 12 children receiving services in an inpatient setting who were assigned to either bilateral cathode stimulation of the superior temporal gyrus or bilateral stimulation of the DLPFC. The most consistently reported side effects were tingling (37.5 %) and itching (50.0 %) from the electrodes, but no participants asked to end the study due to side effects.

Unlike rTMS that has been evaluated for possible cognitive enhancing benefits for patients with schizophrenia, the putative procognitive benefits of tDCS in schizophrenia remains speculative. There is reason to believe that tDCS may foster neurocognitive benefits as this has been demonstrated in patients with major depressive disorder and Alzheimer's disease (Demirtas-Tatlidede et al. 2013; Oliveira et al. 2013). Moreover, the impact of tDCS on the expression of BDNF and the efficiency of NMDA signaling suggests that tDCS may influence processes directly implicated in neurocognitive impairments in schizophrenia. In the absence of clinical studies, the impact of tDCS on neurocogntion and neurobiological change remains speculative.

Conclusions

For patients with schizophrenia who have responded poorly or are intolerant of antipsychotic medication, therapeutic neurostimulation may provide another series of options. Though often neglected, ECT has the advantage of an extended track record with an often robust clinical response and demonstrated synergy

with antipsychotic medication, particularly clozapine. TMS and tDCS are promising but relative newcomers, with significant advantages over ECT in terms of safety, tolerability, and the capability to excite or inhibit specific regions of the brain. Both emerging technologies are awaiting further research to refine the techniques and ultimately define their role in the care of the treatment-resistant patient.

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Cognitive Therapies for Refractory Schizophrenia

9

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Cognitive difficulties are a central feature of schizophrenia in all diagnostic systems and have been since they were first identified by Kraepelin and Bleuler more than a century ago. This chapter focuses on these difficulties, with particular reference to their effects on social and vocational functioning, but also quality of life and ultimately recovery. Whilst positive symptoms remain the primary target of interventions in schizophrenia, cognitive symptoms are more persistent over time and have greater resistance to conventional treatments. Evidence suggests, however, that these processing deficits may not be refractory, but may respond to relatively new treatment options that have not yet had their full potential fulfilled. The development of new cognitive therapies collectively known as "cognitive remediation therapies" has given cause for optimism and will be detailed in this chapter.

9.1 Cognitive Deficits in Schizophrenia

Cognitive difficulties are a core feature of schizophrenia (Fioravanti et al. 2005; Heinrichs and Zakzanis 1998; Joyce and Huddy 2004), independent of drug use (Bilder et al. 2000; Joyce et al. 2002; Mohamed 1999), and are strongly linked to poor recovery. Studies of patients in chronic phases of the disorder indicate that cognitive impairment is the primary mediator of poor functional outcome (Green 2006; Wykes 1994) and more strongly related to clinical outcome than positive and negative symptoms (Aylward et al. 1984; Neuropsychology 2003). There is evidence to suggest that the onset of cognitive deficits precedes the onset of the illness (Fuller et al. 2002; Häfner et al. 2003; O'Carroll 2000) and persist even after positive symptoms (such as delusions and hallucinations) are ameliorated (Leeson et al. 2009a, b), making cognition a key target for assessment and treatment in those

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with a diagnosis of schizophrenia or at high-risk of developing the disorder (Green 1996).

9.2 Global Cognitive Deficit Profile in Schizophrenia

Although Kraeplin and Bleuler's original description of the cognitive profile was recognised in a disorder known as "dementia praecox", the profile of cognitive deficits found in people with schizophrenia is distinct and very different to that found in patients with dementias. Alzheimer sufferers, for example, have severe impairments in recalling recently learned information, whereas those with late life schizophrenia find this function relatively uncompromised. In comparison with other psychiatric disorders, such as bipolar or delusional disorder, there seems to be only quantitative differences on cognitive problems, with schizophrenia patients being the most significantly impaired.

Many areas of cognitive function have been found to be affected in patients with schizophrenia, with research consistently showing that people with schizophrenia perform significantly worse than healthy controls on various neuropsychological tests of cognition. These deficit domains broadly fall under six categories: Working memory, attention, perception, executive function, long-term memory and social cognition (Carter et al. 2008). There is a vast array of research on these individual cognitive domains, their measurable deficits in schizophrenia and their ability to predict functional outcome. A meta-analysis of cognitive function in patients with schizophrenia versus healthy controls found moderate to large effect sizes on 22 neurocognitive test variables with varying degrees of disability in all domains (Heinrichs and Zakzanis 1998). Individual studies have attempted to identify the most pivotal deficits in schizophrenia, finding, for example, the presence of a particularly pronounced impairment in executive function (Reichenberg and Harvey 2007) or greater impairment in working memory than long-term memory, (Sullivan et al. 1997) but the specificity of the key cognitive impairments continues to be difficult to elucidate, in part due to a lack of refinement in the variable measurement tools used. Whilst there is still some debate over the key cognitive deficits, what is becoming increasingly apparent is that people with schizophrenia usually have profound global cognitive impairment (Dickinson et al. 2011; Keefe et al. 2006) and that specific cognitive impairments exist within the context of a wider global impairment. This view of global impairment has been supported by neuroimaging studies which have found wide-ranging structural and functional abnormalities present in those with a diagnosis of schizophrenia. It must be stressed that it is not always the case that those with schizophrenia experience significant cognitive difficulties, although it is the majority who do. Research suggests that of people who continue to be involved with psychiatric services, 85 % perform below normal levels on one or more cognitive domains (Aylward et al. 1984) and that overall cognitive performance is between 1.0 and 2.0 standard deviations below the normal population in those with a diagnosis of schizophrenia (Reichenberg and Harvey 2007; Bilder et al. 1995).

Global impairment is frequently measured by Intelligence Quotient (IQ) tests. One particularly interesting facet is that variability in intellectual ability in schizophrenia remains wide ranging and comparable to that of healthy controls. Though IQ impairment has been found to be only mild (approximately 10 IQ points below average) in people with schizophrenia, (Aylward et al. 1984) research has shown that those with schizophrenia and cognitive performance apparently intact are likely to have had a higher premorbid IQ than control subjects with similar current intelligence. This indicates that a diagnosis of schizophrenia is associated with a decline in functioning from pre-morbid IQ levels (Holthausen et al. 2002; Kremen et al. 2000). Importantly, Leeson et al. (2009a) showed that IQ is the best predictor of functional outcome in schizophrenia, more so than individual measures of memory or executive function. This suggests that global cognition rather than any individual cognitive domain should be the target of remediation and that IQ may be an important measure to identify the onset of the disorder in those deemed most vulnerable. Keefe et al. (2005) found that when cognitive function decrement is defined as the failure to meet the expected levels of cognitive functioning (estimated by maternal and paternal education), 98.1 % of patients with schizophrenia fall below their overall expected level of cognitive functioning.

9.3 Are Cognitive Deficits Static of Progressive?

There has been conflicting findings in the literature about whether cognitive impairment is static or progressive over the duration of the disorder. There is little doubt that cognitive difficulties begin before the onset of symptoms; this notion has been further supported by population and birth cohort studies (Lewandowski et al. 2011; Reichenberg et al. 2010). Lewis et al. (2000) showed, in a cohort of Swedish military, that those with a lower IQ were more likely to develop schizophrenia spectrum disorders than those with higher IQs. These results were replicated by Reichenberg et al. (2006) showing that schizophrenia spectrum disorder risk increased with decreasing IQ score. It is also clear that there is a substantial worsening of cognitive performance with the onset of the disorder in a range of patients. Mild impairments that were evident before the first episode often progress into severe cognitive deficits in the months before and during the first episode and remain relatively stable throughout the course of the illness (Leeson et al. 2011) and after remission (Bozikas and Andreou 2011; Shrivastava et al. 2011). Further evidence that cognitive impairments are relatively stable over time come from cross-sectional studies, which show no significant difference in cognitive functioning between adolescent and chronic patients (Goldberg and Weinberger 1988), first episode and chronic patients (Greenwood 2000) and young patients with a short duration of illness, old patients with a short illness duration and old patients with a long illness duration (Lewandowski et al. 2011; Jeste et al. 1995). Some studies have found a relationship between duration of untreated

psychosis and cognitive outcomes, but findings have been inconsistent (Rapp et al. 2013).

9.4 Cognitive Difficulties, Symptoms, Rehabilitation and Life Skills

9.4.1 Symptoms

One might assume that cognitive difficulties in schizophrenia are strongly correlated with hallucinations and delusions (positive symptoms), but a large number of studies have found that cognitive dysfunction share only a small amount of variance with symptoms (Frith 1995; O'Leary et al. 2000; Ventura et al. 2010). Some studies have found neurocognitive correlates with positive and negative symptoms (Berenbaum et al. 2008; Kerns et al. 1999; Kerns and Berenbaum 2002; Morrison et al. 2000; Spitzer et al. 1993), but direct and causal links have not been conclusively established. However, it seems likely that cognitive impairment has a causal relationship with positive symptoms, perhaps affecting the interpretation of abnormal events (Gray et al. 1991; Hemsley 2005) such as hallucinations, which may therefore result in delusional ideas. Various theoretical explanations for the causal role of cognitive impairment and positive symptoms have been developed over the years. Frith (1995) hypothesised that positive symptoms such as hallucinations may occur when cognitive system breaks down, causing actions and thoughts one would normally know were self-generated, to appear external or persecutory. Hemsley (1993) also proposed that hallucinations and delusions may be the result of "weakening of the influences of stored memories of regularities of previous input on current perception," leading to aberrant sensory input which one cannot integrate and structure. Bentall et al. (2001) suggested that paranoia, a common delusional theme in patients with schizophrenia, may be the result of an attributional bias to assigning negative events to the external world. Garety and Freeman (1999) and Speechley et al. (2010) suggest hyper-salience results from cognitive impairment, with Harvey et al. (1990) suggesting that this may lead to premature decision making and "jumping to conclusions" thinking. Another import aspect to consider when determining causality is temporality (Hill 1965). Cognitive problems occur first, suggesting that cognitive dysfunction plays a causal role in the positive and negative symptoms which follow.

With these hypotheses, it is important to understand why there have been few studies so far identifying direct relationships between cognition and symptoms. One possible explanation is that the failure to identify relationships between cognition and symptom severity is the fault of limitations in the measurement of positive symptom severity itself. Abnormal beliefs and delusions can prove difficult to measure and require refined psychological measures. A lack of subtlety of symptom severity measures is apparent, for example, where individual items on measurement scales often confuse severity (disruption to everyday life) with frequency, thus inaccurately measuring individual variability. Without an accurate measure of

individual variability, it is not possible to identify subtle links between cognitive variables and positive symptoms. More refined symptom severity measures may allow us to explore these potentially more subtle relationships and have proven successful in identifying relationships when employed in carefully designed studies such as those by Harvey et al. (1990) and MacDonald et al. (2005). Another possible scenario is that cognitive problems may represent a distal risk for symptoms and only the interaction with the environment, such as the onset of a stressful event, is responsible for specific symptoms. Refining and developing these measures is likely to shed light on the specific nature of this relationship.

9.4.1.1 Rehabilitation Outcome

Patients with schizophrenia are supported by a range of services from accommodation to therapeutic interventions and at considerable costs. The outcome of rehabilitation interventions and, more generally, illness prognosis is influenced by a number of prognostic factors. Evidence shows that those with the greatest impairments in a number of cognitive domains including working memory, vigilance, executive function and verbal memory are those who show the least improvement on rehabilitation programmes (Liddle 2000). Cognitive impairments in the area of memory or attention may limit the learning and application of skills taught by rehabilitation programmes. Conversely, studies have found that levels of positive and negative symptoms of schizophrenia do not correlate with rehabilitation progress (Harvey et al. 1990) despite the assumption that these symptoms play a disruptive role in rehabilitation programmes. Also, unsurprisingly, the presence of cognitive difficulties correlates with the degree to which individuals are reliant on psychiatric services, with those with the most severe cognitive impairment requiring the most restrictive forms of care. A longitudinal follow-up of care requirements following the closure of a large psychiatric hospital found that cognitive process (i.e. processing speed) was a predictor of service dependence (Wykes 1994). There was also a direct relationship between overall cognitive impairment (as measured on tests of response inhibition, verbal working memory and cognitive shifting) and care costs (Patel et al. 2006).

9.4.1.2 Life Skills

Increasingly, patients live outside of inpatient settings, but many do not achieve independent living status and are frequently reliant on support in numerous life domains. These service users remain less likely to attain and maintain personal relationships or employment than those who have not experienced illness. A study conducted by Hegarty et al. (1994) found no improvement in the living status of people with schizophrenia in the preceding 100 years, prompting a reflection on the little progress that this area of care has experienced.

Cognitive performance has been demonstrated to be the best predictor of functional outcome in schizophrenia, with research showing significant correlations between cognitive impairment and work performance, attainment and maintenance (Green 1996; Green et al. 2000; Kaneda et al. 2009; Mcgurk 2004; Midin et al. 2011; Tan 2009; Tsang et al. 2000), financial competency (Niekawa

et al. 2007), involvement in community activities (Bowie and Harvey 2006) and social skills and independent living (Green 1996, 2006; Green et al. 2000). Furthermore Gold et al. (2002) have shown that IQ, memory and speed of processing were the primary mediators of gaining competitive paid employment following a rehabilitation programme.

9.5 Treatments and Treatment Issues

Although it seems clear that cognitive deficits remain stable throughout the course of the illness, this does not necessarily mean they are immutable. The identification and acceptance of cognitive difficulties as core symptoms and barriers to social and functional recovery in schizophrenia have led to the research and development of a number of innovative treatment approaches, which give cause for optimism. Caution must be taken, however, as studies have shown that a patient's current cognitive state may interact negatively with a treatment strategy. It has been shown, for example, that when patients with schizophrenia who are currently experiencing high levels of cognitive difficulties were moved into community placements where there was more burden on them to make decisions, their positive symptoms worsened. In contrast, those without severe cognitive difficulties improved both their social functioning and showed a reduction in symptoms upon their move to community placements (Wykes 1994). Defining the most suitable time to tackle cognitive difficulties and the most suitable approach to be taken still requires some further thought and investigation.

The possibility of preventing poor prognosis has stimulated the idea of early interventions. Increased neural plasticity (associated with younger age and shorter duration of untreated psychosis) is thought to be important to achieve better prognostic outcomes. Nonetheless, individuals with a long mental health illness and more marked impairment may experience larger gains when offered treatments. This provides optimism for those with treatment refractory schizophrenia who are unlikely to have received interventions primarily targeting cognition.

9.5.1 Treatment Approaches

With cognitive improvements correlated closely with social, functional and occupational outcome, addressing cognitive dysfunction in schizophrenia is a critical target in facilitating recovery. There is no standardised psychological treatment programme targeting cognitive dysfunction in schizophrenia, and pharmacological approaches are yet to be proven effective. Antipsychotics do not primarily target cognition, and evidence for their effect in this domain has been contradictory thus far. There is some evidence that atypical antipsychotic medications have moderate positive effects on cognition, with research implicating different medications with improvements on different psychological tests (Davidson et al. 2009; Woodward et al. 2005); others have shown no effects (Goldberg et al. 2007) and few have

shown a global improvement in cognitive functioning or translational improvements to functional outcomes. Some antipsychotics are even associated with worsened cognitive problems (Elie et al. 2010).

New pharmacological approaches targeting cognitive improvements are currently being investigated but are still some way from clinical practice, with many early trials being underpowered. Pharmacological interventions aim to target the neurotransmitter systems most commonly associated with cognitive function (e.g. glutamatergic, dopamingergic, cholinergic and serotonergic) but have so far yielded limited or non-replicable results. Cognitive enhancing nicotine and psychostimulant drugs such as those used to treat attention deficit hyperactivity disorder are being trialled and show promise, particularly in improving attention (Levin and Rezvani 2006; Scoriels et al. 2012). A trial of an antibiotic in an early intervention group offers some optimism (Levkovitz et al. 2008) but to date there have been relatively few studies of cognitive enhancers suggesting significant benefits and many have shown no effects. The short- and long-term side effects of many pharmacological interventions are also unknown, and more research must be done in this area before new approaches can be validated.

At present, psychological approaches fare much better, with manual (pencil and paper) or computerised cognitive remediation training programmes showing replicable moderate cognitive improvements, which are currently unmatched by pharmacological interventions.

Psychological approaches to ameliorating cognitive dysfunction in schizophrenia usually take one of three approaches.

- Directly changing cognition
- Compensatory approaches
  - Adapting rehabilitation programmes to fit strengths
  - Cognitive adaptation training

9.5.2 Directly Changing Cognition: Cognitive Remediation

Various psychological interventions have been adopted in order to directly enhance individual or global cognitive systems. The most robustly effective approach to date is called cognitive remediation therapy (CRT) (Wykes and Reeder 2005; Wykes and van der Gaag 2001). CRT for schizophrenia is a behavioural, training-based intervention with the objective of improving cognitive function (attention, memory, executive functioning and social cognition), teaching global and transferable strategies and improving motivation and metacognition (Twamley et al. 2003; Wykes and Spaulding 2011; Cella et al. 2012). In general, CRT training programmes employ one of more of the following techniques, supplemented by practice of tasks, in order to improve automatisation and task efficiency. These techniques are as follows:

Scaffolding: It is essential for the participant to undertake an effortful learning process, without associating frustration or failure with the therapeutic experience. To achieve this, CRT provides tasks where the patient learns to achieve goals

through self-efficacy; that is to say, through their own efforts. This requires that the tasks are challenging but remain inside the patient's level of competence, so that they have to make some learning effort but are able to succeed (called scaffolding).

Errorless Learning: This technique first described by (Terrace 1963; Cella et al. 2012), aims to minimise errors in learning, most commonly by employing a slow and gradual increase in difficulty of cognitive tasks (Medalia et al. 2001; Fisher et al. 2010) and providing easy discrimination of the part of the task to be learnt, sometimes with therapist intervention. Errorless learning in CRT is based on the concept that people experiencing cognitive difficulties often find it difficult to distinguish (in memory) between responses that were correct and those that produced errors (Pope and Kern 2006); thus, if they frequently make errors, they will find it difficult to carry out the task successfully in the future. By ensuring the user maximises their correct answers, it subsequently maximises their ability to remember the correct strategies to use in everyday situations.

Self-monitoring: Self-monitoring involves allowing the user to not only develop a technique for completing a task but also for rehearsal of the task instructions. Programmes employing self-monitoring may include in-built hints or reminders of instructions or alternatively may rely on the therapist for reminders or hints about the task requirements. Self-monitoring may be more effective at improving performance of more difficult executive tasks such as planning and problem solving rather than more basic and intuitive tasks (Harvey et al. 2009).

Despite the common principles employed by CRT programmes, there is some divergence in their procedural application and assessment. The primary differences are the frequency of sessions, the medium of delivery (pencil and paper or computerised) and the context of delivery (group, one to one or without a therapist). There is a consensus that an intensive training period is required (Keefe et al. 2006) and increasing practical preference for computerised versions of the therapy which offer improved attractiveness, comprehensibility, user acceptability and therapist adaptability. These procedural differences were not found to have a significant effect, if within a certain range, on the efficacy of the therapy (Wykes and Spaulding 2011). Research regarding the optimum and more efficient method of delivery is ongoing. Alternative to the traditional one to one sessions are groups sessions. Further remote delivery and the possibility of conducting independent sessions are currently under evaluation to meet the demands of different mental health services.

A more substantial difference in the development of CRT programmes is the strategy through which cognitive improvements are achieved. The literature suggests two different approaches: Drill and practice, or drill and strategy. Drill and practice approaches focus on training on many trials of the same task, increasing gradually in difficulty. The theory behind this approach is that repetition and the gradual increase in difficulty will prompt neuronal reorganization in intrinsic learning systems (Koch et al. 2007). This method of enhancing cognition has a repetitive nature which may be detrimental to participant engagement and offers no strategy for the more effective completion of tasks. In contrast, drill plus strategy approaches focus on teaching more efficient methods of solving tasks which are

applicable to everyday problems but at the same time practising these strategies so that they become over-learnt. Clearly individuals need therapy to provide them with much more than improvement on abstract neuropsychological tasks that are used to measure cognitive performance. Drill and strategy approaches therefore place emphasis not only on alleviating the cognitive difficulties but also promote the transfer of cognitive improvement into functional improvement (Wykes and Reeder 2005). These strategies are then practised and transferability is emphasised. This method is often personalised to target each individual's cognitive problems (Wykes and Spaulding 2011) and may rely more on engaging and maintaining the motivation of the participant (Medalia and Choi 2009). Wykes et al. (2011) in a meta-analytic study found that patients show a greater improvement on a range of tasks when given the chance to practice, but that improvement in everyday life function is more closely related to the therapy teaching new strategies. This study considered data from 40 controlled or randomised controlled trials and found a cognitive remediation effect size of about 0.45 on global cognition. This effect size was shown to be durable, with a significant global cognitive and functional improvement at follow-up. These findings were consistent with a previous meta-analysis which showed an effect size on cognitive improvement of 0.4 and on functional outcome (McGurk et al. 2007). Although various studies (Bell et al. 2001; Eack et al. 2011; McGurk et al. 2005; Spaulding et al. 1999; Wykes et al. 1999) have shown that cognitive improvement resulting from psychological therapies led to functional improvements (Patel et al. 2006; Reeder et al. 2004), not all cognitive improvements have been shown to enhance functional outcome. A good example of a study in which cognitive improvements can be independent of functional improvements was carried out by Velligan et al. (2003). They found that cognition could be enhanced by quetiapine alone but that this did not result in functional improvement. Analyses have confirmed that random changes apparent in the control conditions of trials also do not consistently lead to functional improvements (Reeder et al. 2006).

9.5.2.1 Mechanisms and Moderators of Treatment Success

CRT is a relatively new intervention and although clinical efficacy is established, the theory behind its mechanisms of success and the process by which cognitive deficits disrupt daily living, are still unclear.

Wykes and Reeder (2005) suggest that a person's ability to implement cognitive resources is influenced by three pathways, with different levels of cognitive load required for each. These three pathways are: *routine actions, routine controlled actions* and *non-routine actions*. Routine actions require minimal cognitive control, and behaviour is governed by existing schema (mental structure of preconceived ideas) automatically at the occurrence of an environmental trigger. These actions are unlikely to be affected by small changes in cognitive functions. Routine controlled actions, similarly, are governed by existing cognitive schema but may require some adaptation in order to successfully complete the action. This may be, for example, deciding to attend to the appropriate part of the schema in order to complete the action required. Improving cognitive function may improve the

efficiency of these actions (e.g. more quickly attend to the necessary part of the schema) but this effect is unlikely to be profound. Non-routine actions are those which occur most frequently and require the greatest level of flexibility. These actions may require the development of new and efficient cognitive schemas, which require reflection on one's own current knowledge. This reflection of one's own knowledge or "thinking about thinking" has been termed "metacognition" (Flavell 1979). Wykes and Reeder suggest that in order to successfully translate cognitive skills into successful actions, metacognition is essential. For this reason, metacognition training techniques are implemented in some CRT programmes, using, for example, a feedback process by which the user reflects upon the strategies they used in order to solve a problem and are asked to think about their own perception of task difficulty in relation to the difficulty it actually causes them. Research by Verdoux et al. (2010) found support for this theory, finding that better cognitive self-awareness leads to better functional outcomes following CRT. Lysaker et al. (2010) and Stratta et al. (2009) have also highlighted the role of metacognition as a mediator between cognitive improvement and functional outcome. A recent meta-analysis on cognitive treatment in traumatic brain injury also suggests that for improvements in neural plasticity in this group, and particularly for functioning, including metacognition as a target is also essential (Cicerone et al. 2011). Other mediators and moderators of transfer which have been evidence in the literature are:

- Learning potential (Green et al. 2000)
- Social cognition (Schmidt et al. 2011)
- Motivation (Nakagami et al. 2010)
- Cognitive reserve (Kontis et al. 2013)

There has been some research into neurobiological changes that occur during the course of treatments, with evidence pointing to a role of neural plasticity. A neuroimaging study by Wykes et al. (2002) showed for the first time that brain activation changes could be clearly associated with a psychological intervention (CRT), as opposed to a pharmacological intervention. Eack et al. (2010) later showed that those receiving cognitive enhancement therapy had a greater preservation of grey matter over a 2-year period in cortical areas associated with cognitive functioning, than those receiving an alternative therapy (enriched supportive therapy). Evidence that cognitive remediation therapy may offer neurobiological protective or enhancing effects is an exciting prospect and provides further optimism that the cognitive difficulties associated with schizophrenia may not be refractory.

9.5.3 Compensatory Approaches

Compensatory approaches do not aim to improve cognition directly, but rather find ways to circumvent cognitive difficulties in order to achieve the desired outcome. There are two general methods described below.

9.5.3.1 Adapting Rehabilitation Programmes

This is an approach regularly adopted in learning disability programmes. It seems clear that cognitive difficulties will be a barrier to any therapeutic programme and must be taken into account at the outset. Rather than directly improve cognition, this approach creates an individualised rehabilitation programme to suit one's cognitive capabilities, by first obtaining an extensive cognitive ability profile of the individual, and then altering the intervention to suit their strengths. Where, for example, outcomes of social skills training programmes are restricted by poor verbal memory (Nakagami et al. 2010), it may be possible to adapt this programme to instead use visual memory cues, for those who are particularly impaired on verbal memory, but have been found to have better performance on visual memory tasks. Despite showing some success in the learning disability literature, little research on this technique with populations with diagnoses of schizophrenia has been carried out.

9.5.3.2 Cognitive Adaptation Training

Cognitive Adaptation Training (CAT) (Velligan et al. 1996) is an approach for managing cognitive impairment which involves using environmental cues and supports to achieve tasks by alleviating demand on dysfunctional cognitive processes. This is based upon the premise that executive functioning impairments inhibit correct behaviour and limit functioning.

This intervention is similar to interventions used for people with dementia and is usually a last resort to manage, rather than remediate cognitive impairment. CAT involves first assessing an individual's level of cognitive impairment, behaviour and environment, and then making adaptations to facilitate their functioning. It involves the use of audio and visual cues (e.g. signage or alarmed medication packaging) and encourages organisation and sequencing of behaviour (such as putting clothing for each day in individual boxes) with those who experience greater executive function impairment often receiving more salient cues (more brightly coloured signs, louder alarms). A preliminary randomized control trial of CAT in outpatients with schizophrenia showed it was successful in improving global functioning, motivation and psychotic symptoms (Velligan et al. 1996). However, this intervention is usually seen as a last resort in treating cognitive impairment, owing to the invasive nature and heavy reliance on resources. Improved performance on tasks and preventing some learning errors have been found, but this approach does not support a return to premorbid levels of functioning.

9.5.3.3 New Approaches in CRT

With CRT proven as an efficacious treatment for cognitive difficulties in schizophrenia, the focus is now on the optimization of transfer to real-world gains. In order to achieve this, investigative studies are examining CRT together with other treatments in order to maximise functional gains. Bowie et al. (2012) have shown that combining cognitive remediation with functional skills treatment elicited increased functional competence compared with cognitive remediation alone.

Bell et al. (2001) have found that computer training for cognitive dysfunction in adjunction with work therapy (paid work activity in job placements) demonstrated a significant improvement in work quality of participants, over those who had work therapy alone, and Kidd et al. (2012) found that cognitive remediation appears promising when embedded in a supported education programme. Recent research by Lindenmayer and colleagues showed promising results by combining cognitive remediation with social cognition interventions (Lindenmayer et al. 2013). This approach seems a fruitful avenue to pursue particularly in light of the strong association found between social cognition deficits and poor functional outcomes in schizophrenia (Schmidt et al. 2011). Future research is likely to reveal the optimum method and context of CRT delivery.

Conclusions

Cognitive deficits are an enduring and global feature of schizophrenia, closely mediating the functional outcome and quality of life those who experience the disorder. Pharmacological and psychological interventions to target cognitive difficulties have recently undergone investigation and development, with psychological interventions currently faring favourably. Combinatory approach (psycho-social and pharmacological) may prove most favourable, but more research is needed in this area (Michalopoulou et al. 2013). The heterogeneity of schizophrenia points to the need for individualised and adaptive cognitive remediation programmes. CRT currently shows the clearest benefits, evidencing significant and durable improvements in both cognition function and functional outcome. A focus now becomes the method and context of delivery in order to maximise functional gains.

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Cognitive Behavioural Therapy for Psychosis

10

Elaine C.M. Hunter, Louise C. Johns, Juliana Onwumere, and Emmanuelle Peters

Cognitive Behavioural Therapy for psychosis (CBTp) and Family Interventions (FIp) are two psychological approaches to working with psychosis[1] that are valuable adjunct therapies, especially for those who remain symptomatic despite optimal pharmacological treatment. Both CBTp and FIp have solid empirical evidence bases and are recommended by national UK and US treatment guidelines (National Institute for Health and Clinical Excellence (NICE 2002, 2009); US Schizophrenia Patient Outcomes Research Team (PORT), (Kreyenbuhl et al. 2010). This chapter will outline the current evidence for CBTp (see Chap. 13 for Family Interventions in Psychosis), give an overview of its key clinical components, and describe some of the latest initiatives in the development of CBTp.

[1] We use the term 'psychosis' rather than 'schizophrenia' in this chapter as in therapy we are referring to a spectrum of phenomena rather than a specific diagnostic category.

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10.1 Introduction

Cognitive Behavioural Therapy (CBT) is a highly effective talking therapy that has been used across a wide spectrum of clinical disorders, age groups, intellectual abilities, settings and cultures. At its most simple, the CBT model proposes that in any given situation, a person's cognitions (such as thoughts, beliefs, and mental images) will directly influence their emotional, physiological and behavioural responses. However, cognitions are highly susceptible to both past and present experience, so if a person is having current difficulties or has had previous adverse life events, this can lead to biased, exaggerated and/or inflexible thinking patterns and processes. Interactions between the four component parts of the CBT model (cognitions, emotions, physiology and behaviour) can lead to the creation of a 'vicious cycle', which acts to exacerbate and maintain the initial problem. CBT aims to assess and formulate vicious cycles in the 'here and now', in order to identify and implement effective interventions that will bring change in each domain, and in doing so, alleviate distress and allow the person to function better and achieve their goals. CBT can also help a person understand how their past experiences may continue to influence their current cognitions though systematic biases. By increasing understanding of these links, re-evaluating past events and working to change ingrained, less adaptive thinking patterns and behaviours, CBT can move beyond simply working in the 'here and now' to preventative therapy to reduce the likelihood of further occurrences of distress.

CBT initially focussed on the treatment of emotional disorders (Beck et al. 1979). Although Beck published a case study of CBT for psychosis in 1952, it was not until the 1990s and early 2000s that the first books on the application of CBT to psychosis were published (Fowler et al. 1995; Kingdon and Turkington 1994, 2005; Chadwick et al. 1996; Nelson 2005) and empirically based cognitive models of psychosis were developed (Birchwood and Chadwick 1997; Freeman et al. 2002; Garety et al. 2001, 2007; Morrison 2001; Bentall et al. 2007). Although these models differ in some regards, they share the basic tenet that it is not the presence of unusual or anomalous experiences per se which cause the distress and disability associated with psychosis, but the person's appraisal of these experiences as external, personally significant and/or threatening, that results in a significant increase in negative emotions (e.g. anxiety, depression, hopelessness, anger) as well as behaviours that the person believes help prevent the feared outcome (i.e. 'safety seeking behaviours'), but which serve to maintain and perpetuate the negative appraisals by preventing disconfirmation. The aims of CBTp therefore are to work collaboratively with the person with psychosis to help them gain a better understanding of their experiences and the factors that might have contributed to these, enhance ways of coping with psychotic symptoms to improve functioning, learn adaptive strategies to manage emotional distress, recognise how certain cognitive processes and overt behaviours might be contributing to maintaining the problem, test out alternative responses and see if individuals might be open to considering different, less distressing, ways of appraising their experiences.

10.2 The Evidence Base for the Efficacy of CBTp

Over the past few decades a substantial number of clinical research trials of CBTp have been conducted and evaluated. There are several useful ways to review these data: overall effect sizes of CBTp from meta-analyses and analyses of the efficacy of CBTp in terms of client groups, target symptoms, as well as client and therapist factors.

10.2.1 Meta-analyses of Randomised Controlled Trials of CBTp

To date, there have been eight meta-analyses reviewing different number of trials (Jauhar et al. 2014, $n = 52$; Jones et al. 2004, $n = 19$; Jones et al. 2012, $n = 20$; Lynch et al. 2010, $n = 9$; Pfammater et al. 2006, $n = 17$; Sarin et al. 2011, $n = 22$; Wykes et al. 2008, $n = 33$; Zimmermann et al. 2005, $n = 14$). The two largest of these meta-analyses (Wykes et al. 2008; Jauhar et al. 2014) found a 'moderate' effect size on the targeted primary outcome of 0.40 (33 studies; Wykes et al. 2008), and on overall psychotic symptoms of 0.33 (34 studies; Jauhar et al. 2014). These results are mainly consistent with other meta-analyses whose effect sizes ranged from 0.37 (Zimmermann et al. 2005) to 0.47 (Pfammater et al. 2006). A more conservative estimate of 0.19 was reported in the meta-analysis with the smallest sample size of nine trials (Lynch et al. 2010), but this excluded a number of relevant trials and received some criticism of the methodology used.

Despite the consistency of positive outcomes in the meta-analyses of randomised controlled trials (RCTs), the effect sizes remain modest, and are significantly reduced in trials where blinding of the assessors did not occur (Wykes et al. 2008; Jauhar et al. 2014). One other recent review (Jones et al. 2012) compared CBTp to other types of psychological interventions with psychosis and concluded that CBTp did not show a convincing advantage over other therapies. However, the authors suggest that there might be some longer term advantage in CBTp for dealing with emotions and distressing feelings, and some initial findings indicated that CBTp may be of greater benefit to people with depression and managing its symptoms. In part the modest research evidence could be due to issues inherent in research designs. RCTs of CBTp tend to be comprised of composite CBT approaches for heterogeneous groups of patients and attempt to address psychotic symptoms, affective disturbance, schemas, social functioning and relapse, while measuring multiple outcomes. This approach is necessary given the selection of participants for most trials by broad diagnostic group rather than for particular problems, but this approach can limit any assessment of what works for whom, and potentially masks what is, and what is not, being dealt with effectively in therapy (Jolley and Garety 2011). Trials of CBTp delivered in routine practice have demonstrated effectiveness (Krakvik et al. 2013; Lincoln et al. 2012; Morrison et al. 2004; Peters et al. 2010) and there is some evidence that clients continue to improve after therapy has ended (Sensky et al. 2000; Turkington et al. 2008), which was not taken into consideration by some of the meta-analyses (Jauhar et al. 2014).

It has been argued (Birchwood and Trower 2006; Slade and Priebe 2001) that the design of most current RCTs, based on those designed originally to test the efficacy of pharmaceuticals, may not be directly translatable for therapy trials. RCTs of CBTp are expected to include the reduction in psychotic symptoms as outcome measures, and some meta-analyses have excluded all other outcomes, regardless of the target of therapy (Jauhar et al. 2014). However, in routine therapy outcomes are often client led, recovery orientated, and focussed on achieving personally significant functional goals which may not always involve the removal of, or reduction, in positive symptoms. Trials that have used more psychological outcomes, such as compliance with command hallucinations (Trower et al. 2004) or global functioning (Grant et al. 2012) have reported larger effect sizes. Moreover, in a planned analysis of the most effective elements of CBTp of a recent RCT (Dunn et al. 2012) where the overall effect of CBTp in the full sample was limited to improvement in depression at 24 months (Garety et al. 2008), it was found that the clients who engaged with the active techniques in therapy and received a full course of CBTp had gains that were both clinically and statistically significant. Those who dropped out of therapy or whose therapy never progressed past the engagement/assessment stages did not benefit on the reported measures of change. Clearly more research is needed to identify these clients with whom CBTp is most efficacious and cost effective on which specific outcomes.

10.2.2 Efficacy in Different Client Groups

Another useful way to review the empirical literature on CBTp is to analyse what works best for different client groups. By far the strongest evidence is for the effectiveness of individual CBTp in people with treatment-resistant psychosis (e.g. Grant et al. 2012; Klingberg et al. 2011; Kuipers et al. 1997, 1998; Lincoln et al. 2012; Peters et al. 2010; Rector et al. 2003; Sensky et al. 2000; Tarrier et al. 1998, 1999; Turkington et al. 2008; Valmaggia et al. 2005). There are some client groups where the evidence so far is limited and/or equivocal, such as in 'dual-diagnosis' clients, where CBTp is combined with motivational interviewing (Barrowclough et al. 2001; Haddock et al. 2003); forensic populations and those with a history of violence (with positive outcomes for aggression and self-esteem: Haddock et al. 2009; Laithwaite et al. 2007), older adults (in terms of increasing social functioning and cognitive insight: Granholm et al. 2002, 2005), and clients from minority ethnic groups in the UK (Rathod et al. 2013). In terms of CBTp helping to prevent relapse, the evidence is mixed with some studies showing a good outcome (Barrowclough et al. 2001; Drury et al. 1996; Gumley et al. 2003; Dunn et al. 2012) but others not (Barrowclough et al. 2006; Drury et al. 2000; Garety et al. 2008; Tarrier and Wykes 2004). Although the evidence for CBTp so far is almost exclusively as an adjunct to medication, a recent pilot found that it may also help people who have chosen not to take medication (Morrison et al. 2012) with a full-scale multi-site RCT underway (Morrison et al. 2013).

10.2.3 Efficacy in Different Symptom Types

In terms of outcomes for specific symptoms of psychosis, the strongest evidence is for positive symptoms of psychosis (Wykes et al. 2008), although to some extent this is because the majority of trials have had positive symptoms as their primary outcome measure. Of these studies, the largest effect size of any trial of CBTp was for the pilot study targeting command hallucinations (Trower et al. 2004), with a multi-centred trial underway (Birchwood et al. 2011). CBTp has also been found to help alleviate negative symptoms in several studies (e.g. Grant et al. 2012; Johns et al. 2002; Klingberg et al. 2011; Rector et al. 2003; Sensky et al. 2000; Turkington et al. 2008).

As well as improving symptoms of psychosis, CBTp has been found to be effective at reducing depression (Garety et al. 2008; Morrison et al. 2004; Peters et al. 2010; Rector et al. 2003; Sensky et al. 2000), social anxiety (Halperin et al. 2000; Kingsep et al. 2003), suicidal ideation (Bateman et al. 2007; Peters et al. 2010) and improving levels of self esteem (Barrowclough et al. 2006; Hall and Tarrier 2003; Knight et al. 2006; Laithwaite et al. 2007; Lecomte et al. 2008) and social functioning and recovery (Cather et al. 2005; Fowler et al. 2009; Granholm et al. 2005; Grant et al. 2012; Rector et al. 2003; Startup et al. 2004).

10.2.4 Client and Therapist Factors Affecting Outcomes

There is some evidence that client factors may affect the outcome of CBTp. An important finding for chronic and treatment refractory groups is that neither cognitive impairments nor low IQ are contra-indicated for CBTp (Garety et al. 1997; Granholm et al. 2008; Premkumar et al. 2011). However, CBTp is more effective in those with some degree of cognitive flexibility and/or cognitive insight at the start of therapy (Brabban et al. 2009; Garety et al. 1997; Naeem et al. 2008; Perivoliotis et al. 2010) as well as better coping skills (Premkumar et al. 2011) and functioning (Allott et al. 2011), and the presence of a carer (Garety et al. 2008). Perhaps not surprisingly, therapist factors affecting outcomes include training and competence in CBTp (Steel et al. 2012; Wykes et al. 2008), although not generic CBT skills (Durham et al. 2003). A good outcome is predicted by a good therapeutic alliance (Bentall et al. 2003) as well as having a longer course of therapy (Sarin et al. 2011) and better engagement with the therapy process (Dunn et al. 2012), which itself may be influenced by the client having a view of their problems as psychological in origin (Freeman et al. 2013).

10.2.5 Recommended National Treatment Guidelines

In summary, there appears to be a small, but clear effect size for CBTp on psychotic symptoms as well as depression. This evidence has led to national UK and US clinical guidelines recommending that CBTp is offered to all patients with a schizophrenia diagnosis (National Institute for Health and Clinical Excellence (NICE 2002, 2009); US Schizophrenia Patient Outcomes Research Team (PORT), (Kreyenbuhl et al. 2010). The current NICE guidelines (NICE 2009) recommends

delivery of CBTp on an individual basis, for at least 16 sessions over a minimum of 6 months and the NICE guidelines (2014) update will not be changing this.

10.3 Overview of CBTp

Given the scope of this chapter, we can only give an overview of CBTp and suggest that more interested readers refer to the comprehensive treatment manuals for detailed guidance on the practice of CBTp (Beck et al. 2009; Fowler et al. 1995; Chadwick et al. 1996; Kingdon and Turkington 1994, 2005; Morrison 2002; Steel 2013). In theory, CBTp progresses through the stages of engagement, assessment, coping, formulation, intervention and relapse prevention. However, in practice therapists may need to be highly flexible in order to meet changing needs and to keep the client engaged in the therapy process. There are specific interventions for working with hallucinations, unusual/delusional beliefs, reasoning biases and negative symptoms. As well as working with psychotic symptoms, the CBTp therapist is also likely to work directly with emotional distress. These will be covered in more detail in the sections below.

10.3.1 Therapeutic Approach

The therapeutic approach of CBTp is worthy of elaboration in order to help dispel some of the misperceptions that often perpetuate. CBTp is not necessarily focussed on getting rid of psychotic symptoms, nor is it about 'challenging' and changing the client's delusional beliefs in order to increase 'insight', nor a way of improving compliance with medication. These outcomes may all occur as indirect by-products of therapy, but are not the main focus of CBTp as they run the risk of, respectively, setting up unrealistic expectations of what therapy can achieve or of creating ruptures in the therapeutic alliance due to differences of opinion. In CBTp, the aims of therapy are more likely to be helping the client cope better with their experiences, alleviate distress and to work towards achieving client generated, specific behavioural goals that improve general functioning and social engagement. In CBTp, therapists may work 'within' the client's belief system; that is, not attempt to refute delusional beliefs if it would be detrimental to the client (e.g. if this were to have a significant impact on the client's level of risk, depression and/or self esteem), or to the therapeutic relationship. Some clinicians unfamiliar with CBTp may initially feel uncomfortable with this stance as they see themselves as colluding with a client's unhelpful beliefs if they do not explicitly state that they do not share these views. However, novice therapists who take too direct an approach or try to challenge a client's beliefs before a strong therapeutic alliance is formed, or before they have a clear understanding of the role played by the belief and implications of belief change, are likely to find this simply leads the client into defending, rather than changing, these beliefs. Instead, CBTp requires the therapist to maintain a neutral, non-judgemental, but genuinely curious style to create an environment that facilitates open discussion of the client's concerns, minimises

Table 10.1 Summary points about therapeutic style

A good therapeutic relationship is absolutely crucial, and all work in psychosis must be done within the context of the therapeutic relationship
General
Empathy, warmth, genuineness, listening skills
Use of person's terminology (avoid psychiatric jargon)
Offer structure
Need to be sensitive to
Mental state (apologise about yet another assessment, ask permission to take notes, check if voices are present, be aware of fluctuations)
Beliefs about therapist
Expectations (client's and your own)
Need to be flexible with
Structure and length of assessment
Contact (length of sessions, frequency)
Therapy demands (e.g. not everyone will manage homework or self-generated alternatives)
Style (from concrete to philosophical) depending on client
To facilitate engagement
Empathise whenever possible
Normalise whenever possible
Use of humour if appropriate
May need to give specific reassurances
Honesty (about yourself, role within team/service, what you can offer)
Agree goals
Build on existing strengths
To facilitate assessment
'Columbo' technique (see Fowler et al. 1995)
Be open-minded and interested
Take client seriously (regardless of content)
See client as reasonable, struggling to understand difficult experiences
Take non-committal stance if necessary
Persevere (keep going even if confused/overwhelmed, or therapy looks unlikely, or client hostile, etc.)
Aim to understand, not change
To facilitate intervention
Set goals
Need creativity
Be gentle (be prepared to back off)
Collaborative, not confrontational
Containment (don't over-arouse/elicit too much emotion, leave things till later)
Agree to differ (but your version not necessarily right)

conflict and reduces arousal, and allows the client to feel understood and that their concerns are taken seriously (see Table 10.1 and chapter by Johns et al. 2013, for further guidelines on the therapeutic approach).

10.3.2 Differences Between CBTp and CBT for Other Disorders

CBTp is the same as generic CBT in many ways: it is based on a collaborative partnership, uses Socratic questioning so the client is guided to find their own solutions to their problems, has structured sessions starting with agenda setting and encourages 'homework' tasks between sessions, and therapy is orientated towards agreed goals. However CBTp differs in that it requires the therapist to be much more flexible in approach. This may mean adjusting the content, level of complexity and pacing of sessions to the client's abilities and arousal levels; offering a choice of location and/or shorter sessions; giving the client more support in sessions (e.g. by gently 'floating' some suggestions if the client struggles to generate their own) and greater tolerance around session structure and homework (which may be difficult for some clients with psychosis to complete) as well as being prepared to move between the standard stages of therapy (e.g. offering some initial coping strategies early in therapy to facilitate engagement or deferring some assessment to later sessions). There may be a longer duration of assessment and therapy overall but smaller and/or more specific goals. Moreover, the therapeutic style in CBTp is significantly more tentative and empathic than in standard CBT given the increased fragility and sensitivity of these clients, and therapists must be acutely aware of changes in their client's presentation and be prepared to quickly back down or change tack, as well as to provide direct reassurance if the client is anxious or paranoid, in order to maintain a good working relationship.

10.3.3 Engaging Clients in Therapy

It is important in CBTp to start with a period of engaging the client to address therapy interfering issues that may be directly (e.g. voices, paranoia, thought disorder) or indirectly (e.g. hopelessness about the possibility of change, difficulty attending sessions) related to psychosis. Any paranoia may also include therapists and trust may be slow to gain. Voices may interfere with the therapy process through direct threats, making undermining comments or distracting the client (e.g. "don't speak to her ....you can't trust her"). Giving explicit reassurances to the client about your role early on in therapy can be helpful especially if the client has a tendency to incorporate clinical staff into any delusional beliefs. Similarly, directly asking about voices interfering will normalise this process to the client and demonstrate therapist experience in this area.

10.3.4 CBTp Assessment

The primary aim of a CBTp assessment is to gather sufficient relevant information to create an individualised, detailed formulation of the client's problems. In order for CBTp to be effective, therapists need to achieve a balance of both breadth of assessment so that vital information is not missed, as well as depth so that the

current symptoms of psychosis as well as other associated problems are understood in sufficient detail to make accurate hypotheses about the mechanisms that might be maintaining these problems. Information from clinical interviews can be supplemented by the judicious use of standardised assessment measures and self-report questionnaires selected to suit the client's needs and which allow for the tracking of progress over the course of therapy (e.g. PSYRATS; Haddock et al. 1999; CHOICE; Greenwood et al. 2010; CORE; Connell and Barkham 2007). Questionnaires can be given as between-session homework for some clients or completed together in the therapy sessions.

Given the complexity of problems in the majority of people with psychosis, the assessment phase of CBTp is likely to be longer than in standard CBT. However, a lengthy assessment stage can be frustrating to the client who is eager for change and who is overwhelmed by symptoms, so it is important that therapists are pragmatic. Assessment in CBTp is best conceptualised as an on-going process throughout therapy, and assessment of past personal history, factors around the onset of psychosis and previous relapses can be left until later sessions, if required. An initial focus on gaining a list of current problems is a good starting point, alongside developing 'SMART' goals for therapy (i.e. specific, measurable, achievable, relevant and time sensitive), which are best framed in terms of things the person would like to do rather than how they will feel. Keeping these goals in mind will help orientate therapy, as the key problems to work on should be those that are preventing the client from achieving their goals. Table 10.2 lists some useful areas to cover in assessments and readers are directed to the chapter on CBTp assessment by Peters (2010) for more information.

10.3.5 Formulation

The cornerstone of effective CBTp lies in the quality of the therapist's 'formulation' of the client's problems, i.e. what has led to these, what are the factors contributing to keeping these going and what needs to change. This formulation is at the heart of the therapy process as this will inform the selection of interventions. During assessment, eliciting recent, typical examples of the client's problem in terms of specific triggers, cognitions, emotional and behavioural responses will provide more useful information for CBTp than discussions about general patterns. Drawing simple diagrams of these examples in the sessions helps the client understand the CBT model, see how these factors interact and contribute to maintaining their problems as well as showing how these vicious cycles can be broken. Figures 10.1 and 10.2 show examples of vicious cycle, maintenance formulations for, respectively, paranoia and voices. These illustrate the range of possible interventions strategies that would be derived from these formulations.

These initial, maintenance formulations can be developed by adding in past, relevant life events, specific triggers, circumstances and emotions around the first onset, and tracking how these difficulties may have changed over time. However, it is important that sharing parts, or all, of a formulation is *only* done if helpful to the

Table 10.2 Areas for assessment in CBTp

Delusion specific
Content
Conviction, preoccupation, distress
Typical, recent, day to day examples
Triggers/thoughts/emotions/behaviours
Maintenance factors (including other psychotic symptoms, emotional processes, safety behaviours, environment, drug and alcohol abuse)
Meaning of belief (for self and others)
View of self without delusions (e.g. being persecuted may be better than being mad)
Consequences—impact on life
Circumstances around onset
Change over time (including adaptation to symptoms)
Develop hierarchy of distressing beliefs (if necessary)
Voices specific
Triggers—situational/temporal/emotional
Voice form—number of voices, frequency, duration, volume, location, language spoken, whether recognised, age and gender of voices, source
Voice content—positive/negative, specific examples, intrusive nature—culturally/personally unacceptable, commands
Beliefs about voices—identity, benevolent/malevolent, omnipotence (power, control, omniscience), metacognitive beliefs
Relationship with voice—subordinate? Inferior?
Behaviour—resistance/engagement, compliance, coping strategies
Typical, recent, day to day examples
Triggers/thoughts/emotions/behaviours
Consequences—Impact on life
Cause and origin (Where do they come from? What causes them?)
Psychosis specific
Cognitive biases (jump-to-conclusions, theory of mind deficits, attributional biases (i.e. personal, externalising bias)
Cognitive deficits (difficulties in concentration, memory, planning, ability to manage complex information)
Model of understanding
Person specific
Personal beliefs (e.g. religion)
Relationship with services
Social support and social relationships
Short- and long-term goals and plans
Core beliefs, dysfunctional assumptions and schemas (sometimes)
Life history (sometimes)
Secondary disturbances
Other emotional problems (low mood, anxiety, worry, intrusive thoughts)
Cognitive distortions (as found in depression and anxiety)
Look out for
Cognitive flexibility (i.e. greater openness to consider alternatives)
Strengths and resilience

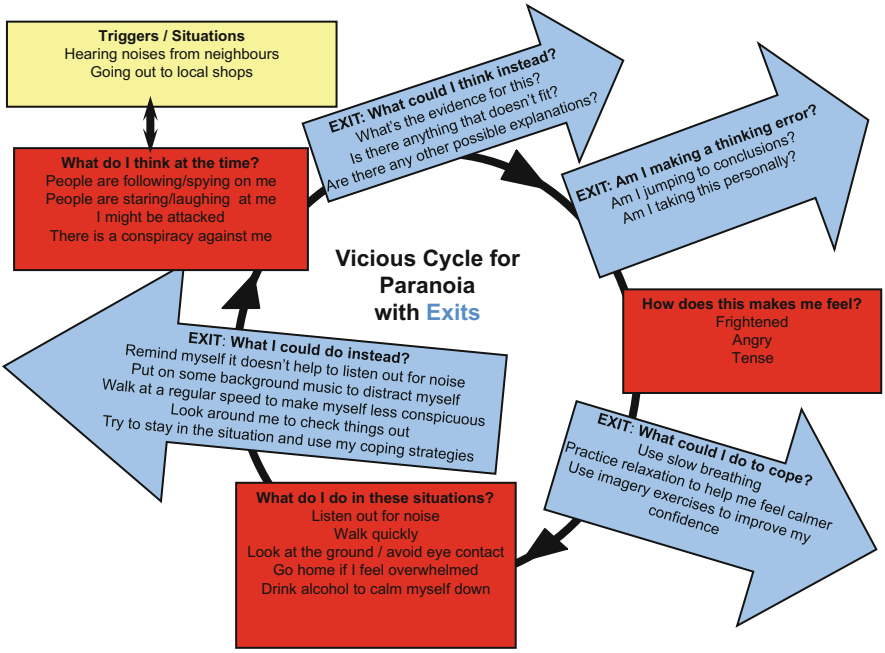

Fig. 10.1 Example vicious cycle for paranoia with possible interventions

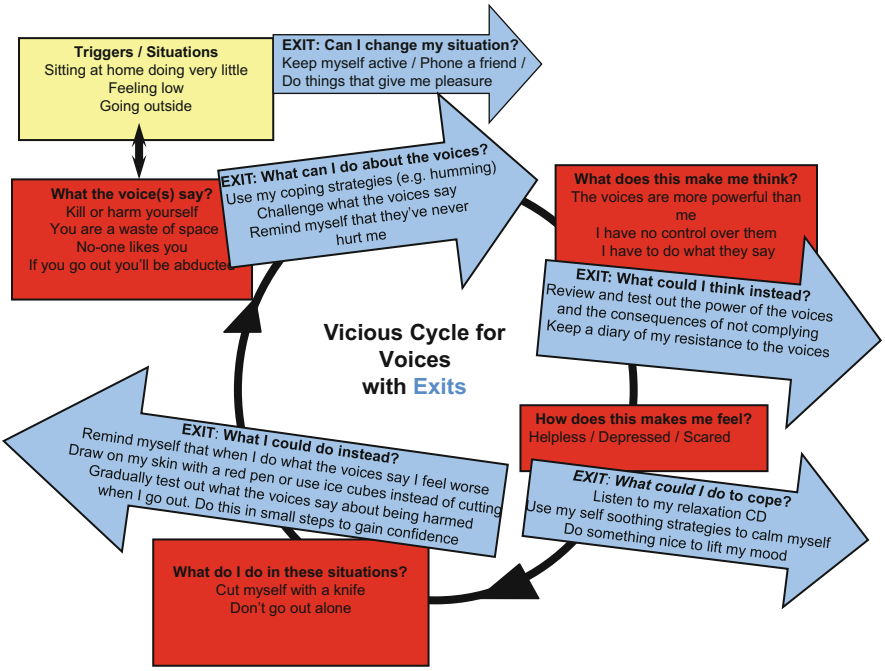

Fig. 10.2 Example vicious cycle for voices with possible interventions

client and by gathering feedback from the client. It is always better to err on the side of simplicity, as presenting overly complex formulations to clients can be unhelpful (Chadwick et al. 2003; Morberg Pain et al. 2008). In most cases the therapist keeps a comprehensive, detailed formulation for their own use, based on one of the cognitive models of psychosis (Bentall et al. 2007; Birchwood and Chadwick 1997; Freeman et al. 2002; Garety et al. 2001, 2007; Morrison 2001) and shares only the essential parts of this with the client.

10.3.6 Enhancing Coping Strategies

Early in therapy therapists can introduce coping strategies to help clients achieve some respite from, and a sense of control over, their symptoms. Many clients will already use some forms of coping, but often these are not used regularly, or for long enough, to be effective, or they can be counterproductive (i.e. they are functioning as safety behaviours). Building on these strategies in therapy can be helpful (Tarrier et al. 1990). Asking the client about when their symptoms are better (or if possible, asking the client to complete a diary where they rate this) and what they are doing at this time will allow for the creation of a coping strategy list. A shared analysis of why, and how, these strategies might be helping can lead to hypotheses about other possible coping strategies they might try and in this way the client's current coping strategies can be enhanced and supplemented. Coping strategies may include shifting attention from symptoms, relaxation, mindfulness and behaviours designed to self soothe and promote social support. New strategies should be practised in therapy sessions before trying them elsewhere. Regular use should be encouraged, so that clients become skilled and techniques become more effective. Clients can use a coping strategy diary where they note the effectiveness of each strategy by rating the severity of symptoms before and after use. Any success in coping with symptoms should be framed as an increase in the client's control to increase empowerment and counter hopelessness. Although coping strategies are often too effortful to be used all the time, an important outcome of their effective, even if occasional, use is to modify the person's beliefs about the degree of control they have over their experiences and power beliefs about their voices/persecutors (see below).

10.3.7 Working with Emotional Distress

The important role of emotional distress in not just the sequelae, but the formation and maintenance of psychotic symptoms, has been recognised (Birchwood 2003; Freeman and Garety 2003) and is included in all the main CBTp models (e.g. Bentall et al. 2007; Birchwood and Chadwick 1997; Freeman et al. 2002; Garety et al. 2001; Morrison 2001). Often working with distressing emotions is a good place to start as it is easier to find common ground, while the therapeutic alliance is formed. In addition, the techniques and strategies covered in this phase,

adapted from CBT for other disorders, especially anxiety and depression, will socialise the client to the process of CBTp in later work on psychotic symptoms. Furthermore, addressing emotional processes may also have a 'crab-like' effect on psychotic symptoms, e.g. decreased anxiety may lead to a reduction in voices and paranoia if it was acting as a trigger.

10.3.8 Working with Hallucinations

Most CBTp interventions with hallucinations have focussed on voices given their high prevalence in psychosis. It is helpful if clients can complete diaries at the start of this work to identify internal and external triggers for voices (such as negative emotions, social situations or isolation, drug/alcohol use) in order to intervene to modify these. Coping strategies that interfere with inner speech, such as reading aloud, humming or conversing appear most helpful and can be used to gain brief periods of respite. Therapist and client can work together to evaluate the *content* of the voices (in a similar way to reframing negative automatic thoughts in anxiety and depression) and the *interpretation* of the voice hearing. However it may take a while for the client to be ready to disclose the content of their voices, especially if it is highly distressing or perceived to be shaming. Psycho-education about the prevalence of these experiences (Johns et al. 2004; van Os et al. 2009), especially in situations of extreme stress, bereavement or sleep/sensory deprivation, is helpful in normalising the experience, and making links with the client's personal history, especially past experiences of psychological trauma, bullying and victimisation in order to reframe voices as re-experiencing phenomena, can be powerful to some clients. Similarly, discussions about other explanatory theories (such as misattributed inner speech) and psychological processes such as intrusive thoughts can offer alternative explanations (unless the content is too ego-dystonic, in which case it may be best to steer clear of such explanations).

Research into voice hearers' beliefs about voices (Chadwick and Birchwood 1994) has led to highly effective therapy protocols for voices (Chadwick et al. 1996) and for command hallucinations specifically (Byrne et al. 2006; Meaden et al. 2013). These approaches emphasise how working to reduce the perceived power of the voice is a key component of therapy, as this is an important predictor of distress (Birchwood et al. 2004; Peters et al. 2012a, b) and of acting on such commands (Hacker et al. 2008), together with beliefs about the voice's identity, intent and consequences of resisting (Brahan et al. 2004). Reducing motivation to comply with commands can be achieved by redressing the power imbalance between any voice(s) and the hearer. Therapy aims to increase the perceived control of voice hearer, weaken the conviction that the client is, or will be, punished, and weaken any unhelpful convictions about the identity of the voice as well as minimising the perceived omniscience and omnipotence of voices through the setting up of experiments to test out the voice's predictions, knowledge and threats. This approach also aims to alter the person's relationship with their voices. Voice hearers tend to be submissive to their voices and this is mirrored in their other social

relationships (Birchwood et al. 2000a). Higher levels of distress are found when the voice is perceived as having a dominant style of relating (e.g. bullying, critical, hostile) and the client has a submissive and distancing style of relating to voices (e.g. withdrawal) (Vaughan and Fowler 2004; Sorrell et al. 2010). This can be remedied by teaching the client to set boundaries with their voice, assertiveness training and working to improve the client's self esteem. Table 10.3 provides some summary points about working with voices (See Hayward et al. (2012) "Overcoming Distressing Voices" for a Useful Self-help Guide to Recommend to Clients).

10.3.9 Working with Unusual/Delusional Beliefs

There are many levels at which the therapist can intervene with unusual beliefs, all of which are potentially helpful. Although there may be some clients where CBTp can effect a complete change in the client's delusional belief system, therapy can still be deemed successful if clients achieve only partial change (e.g. maintain their delusional beliefs about the past but see the future as improved; perceive an increase in exceptions; or a reduction on the extent of the delusional beliefs) or maintain their delusional beliefs intact but achieve change to distress levels, preoccupation and behavioural impact. Before any direct work on delusions starts, it is important for the therapist to assess the implications of belief change with the client through questions such as 'If it were at all possible to find another explanation for what is happening, how would this make you feel?' For some clients changing their unusual beliefs may be more detrimental than maintaining them, as they might provide psychological protection (e.g. from past traumas), or it may be that the recognition of the impact their delusional belief system has had on their life leads to increased depression and suicide risk. With these clients, an emotional and behavioural change route is indicated. However, if cognitive work is undertaken, listing the advantages and disadvantages of belief change can increase motivation for looking at alternatives. Therapy can start to look at alternative explanations for small, specific day-to-day examples that are likely to be less challenging to the client. Highlighting and building on any inconsistencies or uncertainties that the client may already hold may facilitate discussion of alternative explanations. Therapists need to give clients space to consider their own alternatives, but can assist by proffering some tentative suggestions if clients struggle to generate alternatives (Freeman et al. 2004). If several beliefs need to be addressed, these can be organised into a hierarchy, and therapist and client can gently examine the evidence for and against each of these, starting with those held with least conviction. Behavioural experiments can be incorporated into this work, where the specific predictions derived from a thought, belief or assumption are directly put to the test and the outcomes evaluated. These can start out very small, may be conducted with the therapist and slowly build into a series of tests as the client increases in confidence. Behavioural experiments can be highly effective interventions but need careful, and collaborative, planning (see Bennett-Levy

Table 10.3 Summary points about working with delusions and voices

Delusions (and beliefs about voices)
Goals
Assess consequences of belief change carefully (e.g. grandiose delusions: meaning of life without belief/secondary gains?)
Do not push for change (evaluate advantages and disadvantages)
Aim for distress, preoccupation/interference over conviction
Aim for evidence for belief rather than belief itself
Work with hierarchies
Focus on maintenance cycles
Help person discover own best way of coping
Early on
Timeline (sometimes)
Psycho-education (stress-vulnerability model, cognitive model, information processing)
Normalisation (continuum of experiences, of cognitive biases)
Problem-solving
Coping strategy enhancement
Take the line of least resistance
Proceed to
Sharing formulations
Reframing (of day to day events, past events)
Behavioural techniques (e.g. graded exposure, distraction, relaxation, coping cards, etc.)
Cognitive techniques (e.g. Socratic questioning, adapting NAT thought records, alternative explanations (be prepared to float alternatives), de-catastrophise, working with continua, historical tests, data logs)
Metacognitive (cognitive biases, positive and negative metacognitive beliefs, e.g. positive beliefs about paranoia)
Reality-checking and behavioural experiments (modifying or dropping safety behaviours)
Voices
Coping strategy enhancement
Understanding negative cycle and triggers
Working with beliefs—power, control, omniscience, positive beliefs
Working with self-schema—bad me, poor me, social rank
Working with the relationship between the voice and voice-hearer
Working with attention
Working with command hallucinations
Working with illness model—normalisation
Working in groups—peer support, challenging stigma
General points
Work within client's model of understanding
Work with what is distressing, not what is abnormal
Don't rush
Promote homework
Often work with process rather than content
May need to work within delusion

(continued)

Table 10.3 (continued)

Delusions (and beliefs about voices)
Therapy often crab-like (e.g. targeting anxiety/worry may impact on delusion/voices without addressing psychotic symptoms directly)
Do not underestimate power of psychotic experiences (confirmatory evidence)
Always preserve the person's self-esteem

et al. 2004). Throughout all of this cognitive structuring work it is useful to ask the client for regular conviction ratings on the target beliefs to track change. For clients with 100% conviction, who are not able to tolerate contemplating alternative beliefs, therapy may focus instead on working to reduce emotional distress and disability. This may be through helping the client recognise the impact of their struggle on their emotional wellbeing, encouraging them to let go of the past and by increasing activities that fit with their valued goals *despite* their on-going situation. Table 10.3 presents some summary points about working with delusional beliefs (See Freeman et al. (2006) "Overcoming Paranoid and Suspicious Thoughts" for a Useful Self-help Guide to Recommend to Clients).

10.3.10 Working with Reasoning Biases

For many clients reasoning biases and/or metacognitive beliefs (beliefs about thinking; see Morrison 2002; Morrison et al. 2011) will be included in the formulation and will be addressed as part of the work on reframing unhelpful appraisals of experiences and reducing emotional distress. For some clients who present with examples of distressing events that are too numerous to be addressed individually, it is useful to notice the pervasive patterns of responding and to concentrate on working with these biases and metacognitive beliefs, rather than with specific content. Common reasoning and attentional biases in psychosis (Freeman 2007; Garety and Freeman 1999; Peters et al. 2013) include 'jumping to conclusions', hypervigilance, externalising attributional style and confirmatory bias. Therapists can normalise these biases, agree with the client that they may be useful *in some instances* (i.e. 'better safe than sorry'), use shared formulations to link over-usage and being overly inclusive to increased distress and help clients practise noticing their personal biases and problem solving ways to rectify these, such as by pausing and deliberately looking for alternatives. Effective, innovative computerised interventions have been developed to help clients in the recognition and re-training of reasoning biases such as 'jumping to conclusions' and an external attributional style (Moritz and Woodward 2007; Ross et al. 2011; Waller et al. 2011), again providing evidence for the usefulness of working at the 'process' rather than 'content' level for delusional beliefs.

10.3.11 Working with Negative Symptoms

Clients with negative symptoms often express cognitions about failure and hopelessness (Rector et al. 2005; Grant and Beck 2009) so it is important to set small, achievable goals in therapy to prevent confirming these predictions. Generating a list of pleasurable and rewarding activities with the client, and slowly but surely scheduling these into their routine is helpful. Moreover, it is important to identify, and address, negative and self-defeating cognitions and use problem solving to overcome obstacles to activity (Grant et al. 2012). Much of the work with negative symptoms will be similar to working with depression, although sessions may be shorter and the work may progress more slowly [approximately 50 short sessions over 18 months in the Grant et al. (2012) trial].

10.3.12 Relapse Prevention

Relapse prevention can be either a part of a longer course of CBTp or the main issue that is addressed in therapy. Clients differ in their early warning signs of relapse so much so that the term 'relapse signature' has been coined to highlight the individual nature of the pattern of symptoms. Many clients are adept at recognizing relapse indicators and therapy often simply involves formalizing this, with symptoms categorized into early, middle and late stages accompanied by appropriate actions at each of these stages. This work can be supplemented by looking at lists of common warning symptoms (Birchwood et al. 2000b). Moreover, for clients who have had multiple relapses, it is helpful to complete a timeline in sessions, where relapses are plotted on a graph with the various factors (e.g. situational, emotional, specific stressors, negative life events) that might have impacted on these relapses can be charted. This timeline can include periods where the client has stopped medication, which may help with compliance. If clients are willing, other people can be recruited to contribute to the relapse warning signs list. For all clients ending therapy, it is valuable to review progress and the techniques in therapy that have contributed to any recovery and to compile handouts, shared formulations and worksheets into a folder for them to keep.

10.4 Recent Developments in CBTp

10.4.1 Innovations in the Delivery of CBTp

There have been several interesting developments in the delivery of CBTp in recent years. A series of brief intervention studies targeting specific, common problems in the context of chronic persecutory beliefs [i.e. worry (Foster et al. 2010; Freeman et al. 2012); insomnia (Myers et al. 2011); and emotional processing (Hepworth et al. 2011)] have found positive results not only for the target symptoms but for the persecutory beliefs too. Although these studies are small, they provide evidence for

the 'crab-like' approach advocated by the original CBTp manuals (e.g. Fowler et al. 1995). Waller et al. (2013) have also piloted targeted, manualised interventions of graded exposure to feared situations (for anxious avoidance) and increasing activity levels for those with depression in psychosis, with good results. It is hoped these interventions will enable significantly more patients to access help, as these interventions can be carried out by front-line clinical staff in routine practice, under supervision.

A growing body of evidence is highlighting the prevalence and potential causal role of childhood and/or adult trauma in clients with psychosis (Mueser et al. 2004; Read et al. 2005; Varese et al. 2012; Hardy et al. 2013). It has been suggested that unrecognised, and untreated, post-traumatic-stress disorder (PTSD) symptoms may contribute to treatment refractory psychosis given the potential interactions between the two disorders, leading to the development of integrative models (Morrison et al. 2003; Mueser et al. 2002; Read et al. 2001; Steel et al. 2005). Emerging evidence from early research trials in the USA using CBT to treat residual trauma symptoms in clients with psychosis is promising (Frueh et al. 2009: Mueser et al. 2008), and European trials are just out (van der Berg & van der Gaag, 2012) or underway (Steel et al. 2010; de Bont et al. 2013).

Third wave or contextual approaches, such as mindfulness and person-based cognitive therapy (Chadwick et al. 2006, 2009) and Acceptance and Commitment Therapy (ACT; Bach and Hayes 2002; Morris et al. 2013), have similar goals to CBTp i.e. disrupting the associations between the presence of psychotic experiences and their emotional and behavioural sequelae, thereby changing the way people relate to their distressing experiences. However the 'road-map' to achieving these changes is different between CBTp and third wave approaches. Contextual therapies deemphasise the importance of changing the nature and content of difficult experiences, using instead acceptance and mindfulness processes to help people disentangle from difficult thoughts and feelings in order to facilitate engagement in behavioural patterns that are guided by personal values (Hayes et al. 2011). This contrasts to more traditional cognitive approaches in which interventions might target the meaning of thoughts or appraisals in order to reduce distress and increase functioning.

Compassion Focused Therapy (CFT) was developed specifically to build the capacities to experience compassion in high shame and self-critical individuals (Gilbert 2010). There is preliminary evidence that it can help people with psychosis (Braehler et al. 2012). Again the goals are similar to CBTp, i.e. reducing threat and distress, but the road map is different: CFT specifically aims to reduce shame, stigma and self-blame by helping people to 'self-soothe'.

Conclusions

To conclude, there is evidence for modest but significant effects for CBTp; newer trials assessing psychological outcomes rather than a symptom reduction focus have found larger effect sizes. Therapeutic techniques targeting psychotic experiences need to be implemented within the context of a good therapeutic

relationship and derived from a formulation (preferably developed in collaboration with the client). Recent developments are targeting specific psychological mechanisms, such as emotional processes and reasoning biases.

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Vocational Rehabilitation for Severe Mental Illness

11

Susan R. McGurk and Kim T. Mueser

Work is an important part of the society in which we live. Work is associated with financial security, self-respect and that of others, and structure in one's daily life. It is so integral and meaningful to people that they often define themselves in terms of the work they do. However, schizophrenia often has a dramatic effect on the ability of people to work, and the result is that employment rates are often very low. Although schizophrenia adversely impacts employment, with the assistance of rehabilitation programs, people with schizophrenia can find meaningful work. This chapter describes vocational rehabilitation programs for people with schizophrenia and other severe mental illnesses aimed at helping them return to the workforce.

11.1 Unemployment and Schizophrenia

Employment rates for people with schizophrenia are generally below 20–30 % (Lindamer et al. 2003; Salkever et al. 2007). However, despite the low employment rates, most people with schizophrenia and other severe mental illnesses express a desire to work (Mueser et al. 2001b; Rogers et al. 1991). Work provides people with a broad range of benefits and is an important part of recovery for many individuals with a mental illness (Provencher et al. 2002), as described below.

11.1.1 The Meaning and Importance of Work

Work means many different things to different people, whether or not they have a mental illness. Work gives people something that they need to do and thus helps

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structure their time. The stress-vulnerability model of schizophrenia indicates that structured, meaningful, but not overdemanding activities can minimize stress and improve functioning (Mueser and Gingerich 2011; Nuechterlein and Dawson 1984). In fact, research shows that when people with schizophrenia or other severe mental illnesses get work or are engaged in other structured activities, the severity of their symptoms decreases (Bell et al. 1996; Bond et al. 2001; Mueser et al. 1997).

Involvement in meaningful activity can be a very important benefit of work. Everyone has a need for meaning in his or her life, and such meaning is often provided by a combination of activities, including interpersonal relationships, spirituality, recreation, and work. Work often gives people something important to look forward to, since people feel that they are contributing to meeting a particular need. Having a job that fulfills some basic function helps people feel that they are contributing to society and are part of the work-a-day world.

Another important benefit of work is the extra money it can bring into someone's life. People with schizophrenia often receive a modest amount of disability income, which can force them to live in substandard housing with limited material possessions or the ability to pursue certain leisure activities (Gureje et al. 2002; Heider et al. 2007). Work can have a dramatic effect on one's financial standing by increasing the amount of money at one's disposal.

A final benefit of work is that it provides people with social opportunities. People often meet other people at their workplace, and these connections can serve as a basis for the development of closer relationships. While it is important to learn the boundaries between social relationships at work and other closer relationships, contact with coworkers provides a useful way of getting to know people better. Many of these relationships may be rewarding, even when they do not extend beyond the workplace (Rollins et al. 2011).

11.1.2 Concerns About Loss of Disability Entitlements

People with schizophrenia and other major mental illnesses are often afraid to return to work because they believe that it will threaten their medical insurance and any disability income they receive (Gettens et al. 2012; MacDonald-Wilson et al. 2003). Addressing these concerns is a critical aspect of vocational services. Most federal and state benefits programs in the USA have work incentive provisions designed to encourage people to go to work. Depending on which benefits programs the person is enrolled in, he or she can work part-time or even full-time and still retain some cash benefits and/or health insurance coverage. In most cases, people are financially better off working than not.

However, benefits programs are complex and difficult to understand, and the specific rules concerning disability insurance and income differ across states and also across individuals, depending on a host of factors. Therefore it is very important to get expert advice. This can be accomplished most effectively by arranging a meeting with a disability benefits counselor, who can explain specific rules regarding disability entitlements, and how work may affect them. Benefits counseling is

provided at most community mental health centers and also as part of vocational rehabilitation services.

11.2 Vocational Rehabilitation Programs

A wide variety of different vocational rehabilitation programs have been developed for people with mental illness. The core philosophies and approaches to rehabilitation can differ significantly across the different programs. We describe several programs here and then provide a more detailed description of the most empirically validated approach to vocational rehabilitation and supported employment.

11.2.1 Psychosocial Clubhouses and Transitional Employment

One of the oldest and most widely used approaches to psychiatric rehabilitation was developed over fifty years ago at Fountain House, a psychosocial clubhouse devoted to helping persons with severe mental illness reclaim their lives (Beard et al. 1982; Norman 2006). A fundamental tenet of the clubhouse approach is that work is an important part of daily life and that everyone can benefit from working. To prepare people for the demands of work, many psychosocial clubhouses are based on the work ordered day in which each member who joins the clubhouse is given specific work assignments involved in running the clubhouse. Such work assignments may include duties such as food preparation and serving, maintenance of the clubhouse, answering phones and responding to inquiries regarding clubhouse services, hosting visitors, or working in the accounting office.

As an individual becomes accustomed to performing jobs at the clubhouse, he or she becomes prepared to take the next step of working in transitional employment jobs in the community (Macias et al. 1995; Malamud and McCrory 1988). These jobs are secured by the clubhouse and involve working at a regular job that pays competitive wages. Individuals may work at a transitional job for a limited period of time, such as 3 months to 6 months, before moving on to another transitional job or to an independent competitive job. A variety of different transitional jobs may be available, such as working as a cashier, clerical work in an office, delivering interoffice mail, or janitorial work. These jobs are usually entry level.

The transitional employment approach has a number of positive features. By familiarizing individuals to work at the clubhouse, people get into a routine of work, which can prepare them for paid employment. Many individuals with psychiatric disabilities have not worked for a long period of time and they are insecure about their ability to work in a paying job. Transitional employment positions offer people the opportunity to build their work experience while providing a safety cushion of backup staff if they have difficulties completing their job responsibilities. They also can offer people a variety of different work experiences, which may be useful in selecting the type of job they would like on a more permanent basis.

11.2.2 Work Enclaves

Work enclaves are jobs in which a person with a disability works together with other individuals with disability in a community setting. Work enclaves are usually developed by a vocational rehabilitation agency that obtains contracts to provide specific services for companies and then fulfills the terms of these contracts by employing individuals with disabilities. For example, a work enclave might focus on providing janitorial services to a number of office buildings, with persons with psychiatric disabilities working in supervised crews to provide those services. Most work enclaves pay competitive wages and offer a degree of community integration because the work takes place in the community. At the same time, work enclaves sometimes protect people from stressful demands on their work performance, because the terms of the work are negotiated between the vocational rehabilitation agency and the contractors.

11.2.3 Consumer-Operated Businesses and Social Firms

In some communities, individuals with mental illness ("consumers" of psychiatric services) own and operate businesses that employ other consumers (Solomon and Draine 2001). A wide variety of such businesses exist, such as coffee shops and clothing stores. Consumer-operated businesses offer the unique opportunity of working for and with other individuals with psychiatric disabilities, who share the goal of promoting positive public attitudes toward mental illness, including the ability of such persons to work.

Social firms (or affirmative businesses) are businesses that are developed for the purposes of employing people with a disability, for the purposes of creating a needed product or service (Warner and Mandiberg 2006). Social firms provide valuable employment opportunities to people with a mental illness that pay competitive wages, in integrated community settings. These types of businesses are unique in that they also provide high levels of support and build a sense of community within the organization, in part driven by a shared endorsement of the vision, and promotion of self-empowerment.

11.2.4 Vocational Training Programs

One approach to helping people with psychiatric disorders join the workforce is to provide them with prevocational (i.e., pre-employment) training (Bond 1992). Training involves a variety of different activities, such as teaching interviewing and job-related skills, developing a regular daily schedule, identifying job-related areas of interest and strength, and training in basic social skills for interacting with coworkers, customers, and supervisors. Following the training in these programs, individuals may then be provided with support in seeking competitive work or may

be provided with work opportunities in sheltered workshops (see below) where additional training may be provided.

An advantage of vocational training programs is that they provide opportunities to strengthen particular skills and to develop specific plans for pursuing one's vocational goals. A disadvantage of training programs is that they are often time consuming and do not necessarily lead to gainful employment. As discussed in more detail below in the description of supported employment, many individuals who express a desire to work want to work now and not later and may therefore not be best served by vocational training programs, which tend to significantly delay the process of finding a job.

11.2.5 Sheltered Workshops

Sheltered workshops (or sheltered employment) is work that is conducted in a protected environment under the supervision of a vocational employment agency or mental health agency and that is free from many of the stresses associated with competitive employment in the community. In sheltered workshops, people typically work at their own pace, are provided with lots of support and encouragement, and are often paid based on the amount of work they produce rather than on an hourly wage. In most cases, sheltered workshops pay below minimum wage.

Most sheltered workshops provide some ongoing training and supervision with the goal of helping people move onto competitive employment. The advantages of sheltered workshops are that they provide an opportunity to work in a low-stress environment that is supportive and structured. The disadvantages include the lack of community integration, the low wages usually paid, and the fact that sheltered work rarely leads to competitive jobs (Bond 1992).

11.2.6 Department of Vocational Rehabilitation Services

All states have departments of vocational rehabilitation (or departments with similar names, such as the "Bureau for Rehabilitation Services") that provide employment services to people with physical handicaps or medical conditions, individuals who have been injured on the job and require retraining, persons with psychiatric disorders, and others with vocational needs. Depending on the state, local department of vocational rehabilitation may provide programs such as sheltered workshops, vocational training programs, enclave jobs, and supported employment. In addition, these agencies often have funding to support specialized educational programs, such as enrollment in a culinary arts program, an auto mechanics program, or a computer class.

The primary advantage of state departments of vocational rehabilitation is that they are widely available and they often have funds to support a range of different programs, including educational programs. The major disadvantages are that these programs are often not geared toward people with a mental illness; they frequently

have long waiting lists and require assessment before the person gets a job, and there is often limited coordination between the vocational rehabilitation and clinical treatment.

In the next section we discuss the supported employment approach to vocational rehabilitation. We describe this approach in more detail because of the extensive research supporting it compared to other models of vocational rehabilitation.

11.3 Supported Employment

Supported employment is based on the philosophy that people with schizophrenia and other severe mental illnesses are capable of working regular jobs in the community that pay competitive wages, provided that they are given sufficient supports. In contrast to other approaches to vocational rehabilitation, supported employment does not assume that people with a mental illness require either extensive prevocational training or "protected" employment experiences before getting an independent competitive job. Rather, supported employment programs are based on the premise that people can acquire and keep competitive jobs relatively quickly after joining the program.

In the early 1990s, Becker and Drake developed and evaluated a program for supported employment in people with severe mental illness, called Individual Placement and Support (IPS) (Becker and Drake 1993), subsequently revised a decade later (Becker and Drake 2003). Several of their early studies involved conversions of day treatment programs to IPS and showed that many people who had formerly attended day treatment programs were capable of working competitive jobs in the community if they were given the opportunity and necessary supports (Bailey et al. 1998; Becker et al. 2001; Drake et al. 1994; 1996).

Since this early work, multiple controlled studies have been completed comparing the IPS approach to a variety of other vocational rehabilitation models, throughout both the USA and the world (Bond et al. 2012). In each study, people with a psychiatric illness who participated in the IPS program were more likely to work, earned more money, and worked more hours than people in other vocational programs. Two longer term follow-up studies (up to 12 years) of persons enrolled in IPS demonstrate the effectiveness of IPS in improving vocational functioning (Salyers et al. 2004; Becker et al. 2007). The use of a standardized scale that measures the consistency of the practice of IPS with the model has facilitated dissemination of IPS nationally and internationally (Bond et al. 1997).

11.3.1 Principles of Supported Employment

IPS is the most comprehensive and standardized approach to vocational rehabilitation for persons with SMI (Drake et al. 2012). According to the IPS model, supported employment is defined by a core set of principles that are reflected in all of the services provided. These principles include zero exclusion criteria, rapid

job search, focus on competitive employment, provision of a follow-along supports, attention to client preferences, integration of vocational and clinical services, and benefits counseling, all of which are supported by empirical research (Bond 1998, 2004). We describe each of these principles below.

11.3.1.1 Focus on Competitive Work

Most people with SMI want competitive jobs in integrated community settings, rather than shelter jobs that often pay below minimum wage. The Substance Abuse and Mental Health Services Administration has defined competitive employment as work in the community that pays at least minimum wage and that has not been specially reserved for people with a disability (Cook et al. 2005a). In contrast to other vocational rehabilitation programs which may divert people interested in working into prevocational training, sheltered or transitional work-supported employment focuses on competitive work.

Supported employment programs help people find competitive jobs in the community, rather than volunteer work or work paying less than minimum wage, such as sheltered workshops. Working at a competitive job in the community helps people feel better about themselves (Torrey et al. 2000) and improves their satisfaction with their financial resources (Mueser et al. 2004). It is also something that people with psychiatric disabilities are capable of.

11.3.1.2 Rapid Job Search

The goal of a supported employment program is to begin the job search with each person as soon as possible after he or she is referred to the program. Rapid job search is one of the most defining characteristics of supported employment programs; research indicates that competitive job rates and vocational rehabilitation tenure are attenuated in programs requiring prevocational training or lengthy prevocational assessment prior to beginning a job search never seek (Bond et al. 1995; Bond 2004).

The process of rapid job search usually involves meeting with the individual, learning about his or her job experiences, skills, and interests, and beginning to explore prospective jobs, usually within a few weeks of beginning the program. The speed for starting the job search is determined by the individual. Some people start right away and others want to take a slower pace to allow time to visit different job settings to become more familiar with the work world. Rapid job search is crucial to capitalizing on a person's motivation to work.

11.3.1.3 Attention to Individual Preferences

Each individual has his or her own personal preferences about work that need to be taken into consideration. For example, some people like to work with other people, while others do not. Some individuals like to work in an office doing clerical activities, others prefer library work, others like cleaning, while still others like a job in the service industry, such as at a fast-food restaurant or customer services. Matching a job to an individual's preferences can optimize the fit between the individual and the job. While it is not always possible to find a job that exactly

matches an individual's preferences, research has shown that people in supported employment programs who get jobs in their areas of interest stay on those jobs an average of twice as long as people who get jobs that do not match their areas of interest (Becker et al. 1996; Mueser et al. 2001a).

Individual preferences regarding the type of support provided are also important. Some individuals are willing to allow prospective employers to know about their psychiatric disorder, while others prefer not to disclose this information. Some individuals appreciate it when their employment specialists talk directly with prospective employers and help them land jobs and negotiate accommodations. Others prefer the employment specialist to play a "behind the scenes" role to help them find possible jobs, prepare them with job interviewing, and support them in maintaining those jobs.

11.3.1.4 Follow-Along Supports

In many other approaches to vocational rehabilitation, the role of the program stops when the individual gets a competitive job. In contrast, follow-along supports are a critical component of supported employment programs that contribute to longer job tenure (Bond and Kukla 2011). Follow-along supports refer to the provision of a variety of different services designed to help people retain their jobs or to help them make a transition to a new job if needed or desired. A wide range of follow-along supports may be provided, such as on-the-job training, negotiating job accommodations with the employer, doing problem-solving with the individual to resolve difficulties at work, providing temporary logistical support in getting to and from work, skills training for handling social situations on the job, and consultation with the employer to address work-related difficulties. Over time, the intensity of supports declines for many people, and some move on to competitive work without supports, while others continue to need some level of support over the long term (Salyers et al. 2004).

11.3.1.5 Integration of Vocational and Mental Health Services

Not surprisingly, mental health issues and vocational functioning are often related to one another. For this reason, supported employment services are integrated with mental health treatment services. The integration of mental health and supported employment services is most effective when it occurs at the level of the treatment team, in which both mental health and employment specialists meet together on a regular basis (such as weekly) to discuss both mental health and employment concerns.

The evidence indicates that integration of clinical and vocational services improves work outcomes (Cook et al. 2005b; Mueser et al. 2004). The integration of vocational and clinical services provides several advantages for the support of the client's work goals. These advantages include enhanced support of the clinical treatment team for the client's pursuit of his or her vocational goals, employment specialists education about issues pertinent to the clinical management of the client's psychiatric disorder, improved clinical management to reduce the effects of symptoms and medication side effects on job performance, and improved coping

strategies that employment specialists can teach clients for dealing with illness-related problems at the workplace. In addition, treatment team members can be important sources of job leads.

11.3.1.6 Benefits Counseling

Benefits counseling is critical to supported employment to address clients' concerned about the effects of work on their benefits (MacDonald-Wilson et al. 2003). An employment specialist (or trained benefits counselor) can allay fears people have about losing disability insurance and income and help individuals make informed decisions about how much they want to work. Providing information about the effects of work on benefits can also relieve concerns family members may have about their relative working, which can ensure their fullest support for pursuing this important goal. There is good evidence that clients with psychiatric disabilities who receive personalized counseling on the impact of earnings on their benefits accrual more earnings from employment (Delin et al. 2012; Tremblay et al. 2006).

11.3.1.7 Recovery

As work is a common personal recovery goal for many clients (Le Boutillier et al. 2011; Provencher et al. 2002), the principles and practice of supported employment, more than any other vocational model, aids in the process of recovery. Recovery has been defined as "the process in which people are able to live, work, learn, and participate fully in their communities" (President's New Freedom Commission on Mental Health 2003). The emphasis in supported employment on community-based services, competitive employment, zero eligibility exclusion criteria, and respect for client preferences and self-determination are all compatible with the philosophy of recovery.

Also consistent with recovery is the emphasis of supported employment on client strengths rather than deficits and viewing the community as a potential resource rather than a barrier to the client's employment goals (Rapp and Goscha 2006). The identification of client strengths plays an important role in building up clients' self-confidence and helping them selling themselves to prospective employers. Employment specialists are always on the lookout to engage natural supports for the client in the community, including both of the workplace (e.g., supervisor, coworkers), at home (e.g., family or friends), as well as the client's treatment team. Capitalizing on natural supports in the client's environment takes advantage of the spontaneous opportunities these individuals may have to help the client, often at times when the employment specialist cannot be available, thereby avoiding unnecessary dependence on the employment specialist for providing all the needed supports (Zito et al. 2007).

11.3.2 Cognitive Remediation and Supported Employment

Cognitive functioning is often impaired in people with SMI, especially those with schizophrenia and is associated with poor vocational functioning (McGurk and Mueser 2004). In addition, impaired cognitive functioning is related to less benefit from psychosocial rehabilitation approaches such as social skills training (Smith et al. 2009) and vocational rehabilitation (McGurk and Mueser 2004), including supported employment (McGurk et al. 2003). Cognitive remediation involves systematic efforts to improve cognitive functioning using strategies such as computer-based drill and practice exercises and teaching more effective strategies aimed at improving cognitive performance (Wykes et al. 2011). Several controlled studies have shown cognitive remediation can improve employment outcomes in clients enrolled in vocational rehabilitation programs (Bell et al. 2001, 2003; Lindenmayer et al. 2008; McGurk et al. 2009; Vauth et al. 2005), including supported employment programs (McGurk et al. 2005; McGurk and Mueser 2006). Although these findings are promising, they need to be regarded as preliminary, and more research is needed to evaluate the impact of cognitive remediation in supported employment programs that have high fidelity to the IPS model.

11.3.3 Finding Supported Employment Services

Supported employment services can often be accessed through local community mental health center. Some mental health centers provide supported employment services within their own program. Other mental health centers may have working relationships with separate vocational rehabilitation agencies that provide supported employment. Many mental health centers have a director of vocational rehabilitation who can help direct individuals to an appropriate supported employment program.

Conclusions and Future Directions

Work plays an important role in defining who we are, both to ourselves and to others. Although it was once believed that people with schizophrenia were incapable of working, there is now overwhelming evidence that people who want to work can get meaningful jobs, contribute to society, and be rewarded for their efforts. The rewards of working are many and include increased self-esteem and financial resources, meaningful activities, and greater integration into the community. The rehabilitation field has made important strides in improving employment outcomes for people with SMI over the past two decades. The IPS model of supported employment is an evidence-based practice for vocational rehabilitation and the most effective vocational approach available in helping people with SMI reach their work goals.

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Pharmacogenetics and Treatment-Resistant Schizophrenia

12

Adriana Foster and Peter F. Buckley

12.1 Introduction

Many patients with schizophrenia (5–25 %) fail to respond to adequate trials of various antipsychotics (Brenner et al. 1990), even after they successfully control drug comorbidities and environmental stressors, fully adhere to treatment, and participate in comprehensive psychosocial approaches. National Institute for Clinical Excellence in UK (NICE) defines treatment-resistant schizophrenia as "*the presence of poor psychosocial and community functioning that persists despite trials of medication that have been adequate in terms of dose, duration and adherence*" (NICE guidelines 2010). Both NICE and the American Psychiatric Association (APA) guidelines (2004) recommend treatment with clozapine for people who meet this definition. However, only 30–60 % of the treatment-resistant patients respond to clozapine (Iqbal et al. 2003). Which patients will benefit of clozapine and, of these patients, who can tolerate clozapine without life-threatening agranulocytosis or severe metabolic consequences? A reliable and affordable pharmacogenetic test would be a major advantage for practicing physicians. Since Vogel (1959) defined pharmacogenetics as inherited variability in response to treatment with drugs, the research in this area progressed quickly and translated into the introduction of information about pharmacogenetic variability of drug response and adverse effects in the product labeling by the US Food and Drug Administration (FDA). For warfarin Lesko (2008), for example, which displays both pharmacokinetic and pharmacodynamic variations polymorphisms in the cytochrome P450 2C9 and respectively vitamin K epoxide-reductase gene

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(VKORC1) single nucleotide polymorphisms (SNPs- see Glossary of terms used in this article), FDA informs of testing availability while for carbamazepine, which is likely to induce Stevens Johnson Syndrome in people of Asian descent who carry the human leukocyte antigen (HLA) haplotype HLA-B*1502, they recommend pharmacogenetic testing prior to initiation of treatment.

This chapter is not meant to be a comprehensive review of pharmacogenetic studies in schizophrenia. The reader is referred to excellent reviews on this matter (Arranz and de Leon 2007; Arranz et al. 2011; Chowdhury et al. 2011). We focus here on pharmacogenetic studies involving patients with treatment-refractory schizophrenia and particularly on response and adverse effects from clozapine, which remains the "gold standard" somatic intervention for this patient population. Treatment-refractory schizophrenia is a high stakes area, where pharmacogenetics research can really make a difference in identifying people who have the highest likelihood to respond to clozapine and those who are more likely to develop metabolic syndrome and agranulocytosis.

Clozapine pharmacology and therapeutic action are covered extensively in Chaps. 5 and 6. We will briefly mention here that clozapine shows only 20–67 % binding to dopamine D2 receptors on raclopride PET at therapeutic doses, as opposed to first-generation antipsychotics' binding of approximately 80 %; however, clozapine binds highly to D4 receptor, which has lower distribution in the striatum and higher distribution in the cortex. Clozapine's lack of motor side effects is thought to be related not only to a lower D2 receptor binding, but also to fast dissociation from the D2 receptor (Marder and Ames in Essentials of Clinical Psychopharmacology, 2013). Clozapine also binds to D1, D3, and D5 as well as 5HT2A, 5HT1C, and 5-HT3 subtypes of serotonin receptors and to alpha 1–2 and B1–3 adrenergic, muscarinic cholinergic, M1–5, and histaminergic H1 and H3 receptors. Thus, many candidate genes could contribute to the variability of drug response to clozapine.

The challenges of pharmacogenetic studies in schizophrenia and the comparative advantages of such studies in patients with treatment-resistant schizophrenia are summarized in Fig. 12.1. While studying the association of genetic markers with drug response and adverse effects in schizophrenia in general is challenged by the illness stage and heterogeneity and medication dosing and adherence (Foster et al. 2010). The criteria for treatment-refractory schizophrenia were established early (Kane et al. 1988 or Brenner et al. 1990). The application of these criteria in pharmacogenetic studies increases the chance that samples are genetically homogenous (Liou et al. 2012). Among other advantages of pharmacogenetic research in treatment-resistant schizophrenia, the data from drug registries which ensure blood monitoring for agranulocytosis make it possible for researches to contact patients for potential research participation. Challenges common to both areas of pharmacogenetic research are ethnicity and small number of patients available to participate, particularly patients with relatively rare side effects like tardive dyskinesia and agranulocytsis.

Fig. 12.1 The challenges of pharmacogenetic studies in schizophrenia and advantages of conducting such studies in treatment-refractory disease

12.2 Pharmacogenetics of Response to Clozapine

12.2.1 Dopamine

Despite the fact that clozapine does not have a strong dopamine D2 blockade in its pharmacological repertoire, D2 and other receptors are believed to be involved in clozapine effect (Table 12.1). An early study by Potkin et al (2003) studied dopamine D1 receptor gene DRD1 and found the 1,2 genotype to be associated with poor response to clozapine response in a small cohort of patients with schizophrenia. Ota et al. (2012) studied ***rs4532*** in 124 patients with schizophrenia, of whom 59 met criteria for treatment resistance and found that the G allele was significantly associated with treatment resistance. Malhotra et al. 1999 studied dopamine D2 receptor gene (DRD2) promoter region −141 Ins/Del polymorphism in a population of patients treated with clozapine and showed that the Del – carriers had 5 times greater symptom reduction on clozapine than the Del + carriers. Hwang et al. (2005) studied 12 D2 receptor gene SNPs, which are thought to contribute to the D2 receptor density and function, in 2 different ethnic samples of people with TRS. He showed that in the Caucasian sample, no individual SNPs but 2 haplotypes located in the SNP 5–8 region were identified as protective. In the African-American sample, SNPs Taq1A (−), Taq1B, and ***rs1125394*** alleles significantly associate with clozapine response and the haplotype containing all 3 alleles is more strongly associated with the clozapine response status than each individual allele. Kohlrausch et al. (2008) found that cytochrome CYP3A5 low expression genotype and the haplotype T/A/G/C of DRD3 receptor gene are associated with lack of response to antipsychotics in a sample of Brazilian patients with schizophrenia, of European descent.

Table 12.1 Selected studies demonstrating association of pharmacogenetic factors with drug response in patients with treatment-refractory schizophrenia

Gene, study author and characteristics	Sample ethnicity and size	Treatment resistance (TRS**) definition	Treatment response definition	Gene variants and their association
DOPAMINE D1 Ota et al. (2012)	European, African, Native American $N = 124$	International Pharmacological Criteria = no response to two adequate dose antipsychotic trials (4–6 weeks each)	Andreasen remission criteria score ≤ 3 on 8 PANSS items	D1 ***rs5432*** A-48G G allele is risk factor for treatment resistance $P = 0.001$, OR 2.85
DOPAMINE D2 Malhotra et al. (1999)	Caucasian, African American, Japanese $N = 72$	Patients treated with clozapine	≥ 20 % BPRS* reduction	D2 -141C Ins/Del Del + allele leads to poorer response $P = 0.02$
DOPAMINE D2 Hwang et al. (2005) Prospective study, clozapine plasma concentration, 6 months	183 Caucasian and 49 African American	Kane criteria (no response to three different antipsychotics)	≥ 20 % BPRS reduction	D2 2 haplotypes in Caucasians and Taq1A (−), Taq1B ($P = 0.03$), and ***rs1125394*** allele 1 ($P = 0.029$) SNPs as well as four haplotypes predict response in African Americans
CYP3A5 AND DOPAMINE D3 (DRD3) Kohlrausch et al. (2008)	$N = 186$ $N = 121$ TRS***	No response to adequate dose of first-generation antipsychotic for 3–6 months + continuous symptoms 2 years before study	≥ 20 % BPRS reduction	The low expression variant CYP 3A5*3 (6986G) ($P = 0.003$ OR = 3.16) and DRD3 T/A/G/A/C haplotype ($P = 0.021$, OR = 1.75) were associated with refractory status
DYSBINDIN (DTNBP1) Zuo et al. (2009) Prospective study 3 months	$N = 181$ veterans randomized to haloperidol or clozapine	TRS = no response to $\geq$ 2antipsychotics at 1,000 mg chlorpromazine equivalents + severity on BPRS and CGI*****	≥ 20 % improvement on PANSS	Diplotype ACCCTC/GTTGCC, genotypes T/T + T/C, or allele T of ***rs742105*** predict better response to clozapine ($0.005 \leq P \leq 0.049$) and

		+ social dysfunction + high inpatient care utilization	A<u>C</u>CCTC/<u>G</u>CCGCC, genotype A/G, or allele A of ***rs909706*** ($0.007 \leq P \leq 0.080$) predict better response to haloperidol in European Americans, African Americans, or the combined sample patients
Disrupted in schizophrenia gene (DISC) Mouaffak et al. (2011) Clozapine plasma concentration ≥ 350 ng/ml	$N = 25$ URS**** $N = 99$ respondent group	Ultra-resistant schizophrenia = patients who do not respond to clozapine = persistent positive symptoms, BPRS 18 ≥ 45, and CGI-S ≥ 4, ≥2 prior trials of antipsychotics at 600 mg chlorpromazine equivalents	DISC1 ***rs3738401*** variant is associated with URS
Metabotropic glutamate receptor (GRM3) Bishop et al. (2011)	$N = 95$ TRS	Persistent psychosis for 2 years despite 2–3 antipsychotic trials at 1,000 mg chlorpromazine	***rs1476455***_CC and ***rs198796***_CC genotypes significantly associated with higher BPRS scores ($P = 0.0071$ and $P = 0.0091$, respectively)

**BPRS* Brief psychiatric rating scale
***PANSS* Positive and negative symptom scale
****TRS* Treatment-resistant schizophrenia
*****URS* Ultra-resistant schizophrenia
******CGI* Clinical Global Impression

12.2.2 Serotonin

Clozapine's therapeutic effect in schizophrenia is attributed to its neurotransmitter receptor activity profile, among which serotonin plays a major role, particularly due to its modulatory effect on dopamine neurons in substantia nigra (Marder and Wirshing 2009) (Table 12.1). In a prospective study, Souza et al. (2010a, b) studied the effect of serotonin receptors 3A and 3B variants on clozapine response in 140 patients treated with clozapine for 6 months, after a washout period 2–4 weeks. Treatment response was defined as improvement $\geq$20 % BPRS (Kane et al. 1988). The authors found a significant association with treatment response for 3 alleles on 5HT3A, ***rs2276302-rs1062613-rs1150226***; however, only one polymorphism, ***rs1062613,*** remained significant after permutations (permutated $P = 0.04$). Same polymorphism was reported not to associate with clozapine response by Arranz et al. (2000) who used a different outcome measure (Global Assessment Scale) to determine response. Kohlrausch et al. 2010 studied the association of HTTLPR (serotonin transporter promoter region) with response in 116 stable outpatients with schizophrenia treated with clozapine. Response in 64 patients and nonresponse in 52 are classified as $\geq$30 % reduction in BPRS with a mean daily clozapine dose of 540.91 mg/day. In the HTTLPR ***/rs25531*** 5' regulatory region of the human 5 HTT, the S'-allele was more frequent in the nonresponder patients, when compared to those who responded ($P = 0.01$). The S (short) variant of the 44-base pair insertion/deletion decreases the expression of the activity of the serotonin transporter twofold in vivo. The study shows that carriers of the low expression genotypes have poorer response to clozapine. Rajkumar et al. (2012) used a logistic regression model to combine clinical predictors of treatment response: history of catatonia, being a current smoker, cognitive dysfunction and excessive sedation, and the 5HTR3A polymorphisms ***rs1062613 and rs2276302*** in 101 patients with treatment-resistant schizophrenia, on stable doses of clozapine. Both polymorphisms were associated with response, defined as BPRS total score $\leq$35 but could only explain 13.8 % of the variability of response in this TRS patient population while the combination of 5HTR3A polymorphisms and clinical response predictors explained 38 % of the variability.

12.3 Neuromodulators and Other Genes Thought to Contribute to Treatment Response in Refractory Schizophrenia

Bishop et al. (2011) studied the potential association with treatment-refractory schizophrenia of the metabotropic glutamate receptor (GRM3), which codes for a G-protein coupled receptor, mGluR3, with important role in brain glutamate signaling. The authors found that two GRM3 markers were associated with the refractory global BPRS scores, but there was no marker association with negative symptoms of schizophrenia (Table 12.1).

Mouaffak et al. (2011) analyzed disrupted in schizophrenia (DISC1), a schizophrenia susceptibility gene, in a sample of people with "ultra-resistant

schizophrenia" (URS) defined as persistent moderate-to-severe positive symptoms and lack of social remission in spite of treatment with clozapine with levels ≥350 ng/ml and prior treatment with at least 2 other antipsychotics. Remission criteria were BPRS ≤30, Clinical Global Impression Scale—severity (CGIS) <3, and GAF ≥61. The study included 222 patients and 151 healthy controls. Forty patients met criteria for URS (Mean BPRS score 59) and 99 were responders (mean BPRS 25). The authors found that the minor allele A of ***rs3738401*** was significantly associated with the URS group ($P = 0.01$) and was overrepresented in males with URS. The minor allele T of ***rs6675281*** was associated with the responder group, showing the potential role in treatment response in schizophrenia. The marker ***rs3738401*** is part of the HEP3 haplotype, previously demonstrated to be associated with cognitive function in schizophrenia. These results support prior animal data suggesting that the DISC1 pathway alters expression levels of other genes which modulate antipsychotic-induced brain changes.

In addition to the discovery that BDNF is involved in the neuroprotective role of antipsychotics, other neuromodulators, like glial-derived neurotrophic factor (GDNF), synthetized in striatal cells, increase the survival of dopaminergic neurons. Souza et al. (2010a, b) studied GFRAs, glycoproteins that are co-receptors for GDNF binding on the RET receptor (receptor protein tyrosine kinase) in 140 patients with treatment-resistant schizophrenia, treated with clozapine for 6 months, with monitored clozapine drug levels. Response was a dichotomous variable defined as ≥20 % improvement on BPRS. Receptors GFRA1, 2, and 3 from the GDNF family of receptors alpha associated nominally with schizophrenia and clozapine response (an association that did not survive permutation analysis).

Zuo et al. (2009) studied the effect of the dysbindin gene (DTNBP1), thought to be important in glutamate release, on response to clozapine in US veterans with refractory schizophrenia. Their study took into account the ethnic composition of the sample by estimating the ancestry proportions of the Caucasian and African Americans in the sample. Patients with diplotypes and genotypes containing allele T of the ***rs742105*** had better response to clozapine and patients with allele A of the rs909706 marker have better response to haloperidol in European Americans, African Americans, and the combined sample, suggesting that dysbindin alleles influence the response to antipsychotics.

A genome-wide association study (GWAS) performed in a sample of 795 Han Chinese people with schizophrenia suggested an association between a variant (***rs 28362691***) of NFKB1 (nuclear factor of Kappa light polypeptide gene enhancer in B cells 1), a gene that codes for NF kappa B, an important transcriptional factor in regulation of inflammatory factors like cytokines and adhesion molecules. This gene was previously reported to be associated with schizophrenia.

Attempts were made to combine pharmacogenetic markers to predict response to clozapine. Arranz and de Leon (2007) used logistical regression to predict response to clozapine using a combination of 19 genetic polymorphisms in the serotonergic and histaminergic systems yielding a sensitivity of 95.89 % and a specificity of 38.3 %. Lin et al. (2008) used a predictive model called artificial neural network to

study a combination of clinical variables (gender, age, height, body weight, body mass index) and polymorphisms in serotonin 5HT2A, adrenergic α2a, β3, and G-protein genes and defined treatment response as scores of 1 (very much improved) and 2 (much improved) on CGI in a sample of 93 Chinese patients with schizophrenia between 20 and60 years, who took clozapine for ≥3 months. The model rendered a sensitivity of 100 % and a specificity of 76.5 %, superior to logistic regression performed for comparison.

As opposed to the data accumulated about the importance of CYP2D6 and CYP1A2 genetic variants contributing significantly to adverse effects from risperidone and other second-generation antipsychotics, CYP2D6 variations do not appear to be relevant in the efficacy or adverse effects from clozapine. CYP3A5 and CYP1A2 genetic variants have been associated with clozapine efficacy (Kohlrausch et al. 2008).

12.4 Pharmacogenetics of Clozapine Adverse Effects

12.4.1 Weight Gain

Approximately 30 % of patients treated with second-generation antipsychotics develop weight gain which can progress to metabolic syndrome (Table 12.2). Antipsychotic-induced weight gain is a biologically complex phenomenon. Serotonin, dopamine, and adrenergic receptor genes, histamine, leptin, apolipoproteins, brain-derived neurotrophic factor, tumor necrotic factors, cytochromes, neuropeptide Y receptors, and other genes were studied as candidate genes in pharmacogenetic studies exploring associations with weight gain, but only few of these involved treatment-refractory patients on clozapine (Lett et al. 2012). Serotonergic system genes, particularly 5HT2C receptor, are implicated in weight gain as demonstrated in various ethnic populations (Reynolds et al. 2002). Miller et al. (2005) showed in a 6-month prospective study that the -759 T polymorphism of 5HT2C receptor gene protects against body mass index increase of ≥7 % in treatment-refractory patients treated with clozapine ($p = 0.0026$). Leptin, a hormone implicated in the pathophysiology of food and energy regulation, was studied in relation to antipsychotic-induced weight gain and the -2458G allele was associated with weight gain induced by clozapine (Chowdhury et al. 2011). A variant of the alpha 2A adrenergic receptor (−1291-C/G) was associated with clozapine-induced weight gain (Arranz and de Leon 2007). Tumor necrosis alpha (TNF), a cytokine which is overexpressed in people who are obese and is correlated inversely with insulin sensitivity, was studied by Wang et al. (2010) in Chinese patients with treatment-refractory schizophrenia. The authors demonstrated that the patients with GG homozygote of the −308 G > A polymorphism were more likely to gain weight than the −308 A allele carriers.

Table 12.2 Selected studies demonstrating association of pharmacogenetic factors with clozapine adverse effects

Gene, study author and characteristics	Adverse effect studied	Sample ethnicity and size	Treatment resistance (TRS) definition	Treatment response definition	Gene variants and their association
Serotonin receptor 5HT2C Miller et al. (2005) Plasma clozapine conc.	Weight gain	$N = 41$ Caucasian, African American, Hispanic	No response to ≥ 2 antipsychotics; $\geq$1,000 mg chlorpromazine equivalent; taken > 6 weeks*,**,*** BPRS 18 score ≥ 45	Not reported	-759 T allele in a significantly higher percentage of people who gained ≤ 7 % BMI on clozapine ($P = 0.0026$).
Tumor necrosis factor (TNF) alpha Wang et al. (2010) Prospective study Medication administered in the hospital	Weight gain	$N = 55$ Chinese	No response to $\geq$2 first-generation antipsychotics	CGI*** 1 and 2 (very much improved and much improved) = response at 14 months treatment	People with TNF α-308 GG gained significantly more weight than the -308 A carriers ($P = 0.008$)
HLA markers Yunis et al. (1995)	Agranulocytosis	10 Jewish 21 non-Jewish	n/a	n/a	Markers HLA DRB1*0402, DQB1*0302 and DQA1*0301 in Jewish and HLA-DR02, DQB1*0502, and DQA1*0102 in non-Jewish individuals associated with clozapine-induced agranulocytosis
HLA markers Valevski et al. (1998)	Agranulocytosis	61 Jewish, on clozapine 11 with clozapine-induced agranulocytosis 50 without agranulocytosis	n/a	n/a	HLA B38 antigen was present significantly more frequently in people with agranulocytosis ($P < 0.0001$)
HLA markers Dettling (2001)	Agranulocytosis	31 German patients clozapine-induced agranulocytosis and	n/a	n/a	HLA DQB-0201, HLA-Cw-7, HLA-DQB*0502,

(continued)

Table 12.2 (continued)

Gene, study author and characteristics	Adverse effect studied	Sample ethnicity and size	Treatment resistance (TRS) definition	Treatment response definition	Gene variants and their association
		77 without agranulocytosis			-DRB1*0101, and DRB3*0202 associated with clozapine-induced agranulocytosis
Tumor necrosis factor (TNF) alpha Turbay et al. (1997)	Agranulocytosis	33 (12 Jewish and 21 non-Jewish) people on clozapine who developed agranulocytosis	n/a	n/a	TNF α loci variants were significantly associated with clozapine-induced agranulocytosis in Jewish and non-Jewish patients

**BPRS* Brief Psychiatric Rating Scale
***BMI* Body Mass Index
****CGI* Clinical Global Impression

12.4.2 Agranulocytosis

Chowdhury et al. (2011) summarized the potential causes of neutropenia (<1,500 neutrophil cells/mm^3) and agranulocytosis (<500 neutrophil granulocyte cells/mm^3), which occur in 0.8 % of people treated with clozapine and lead to requirements for periodic blood cell monitoring while taking this medication. Given that approximately 25 % of people with schizophrenia are treatment-refractory (Brenner et al. 1990) and that clozapine is the gold standard treatment for this population, being able to predict who is at risk of agranulocytosis would be a major advantage and would potentially increase access and decrease burden of adverse effects from clozapine treatment. It is believed that clozapine contributes to agranulocytosis by bioactivation of a chemically active nitrenium ion. This reactive species is either directly toxic or it causes immune-mediated toxicity, which may negatively affect stromal bone marrow cells function and arrest neutrophil production from precursor myeloid cells (Pereira and Dean 2006). Since agranulocytosis occurs in a small number of people on clozapine, a genetic mechanism was proposed to cause it. Human leukocyte antigen system (HLA) alleles or haplotypes from the major histocompatibility system (MHS) were identified as being associated with agranulocytosis induced by clozapine in Europeans of Jewish descent. HLA-B38 alone and the haplotype HLA B38, -DR4, and -DQ3 were associated with clozapine-induced agranulocytosis in Jewish individuals (Table 12.2). HLA DQB1 variant 6672 G > C was associated with 16.9 times increased risk of agranulocytosis from clozapine. After a genome-wide association study confirmed HLA region HLA DQB1 as being associated with agranulocytosis (Athanasiou et al. 2011), a commercial test was developed utilizing this variant. Further, non-HLA areas in the major histocompatibility complex were identified as having potential contribution to clozapine-induced agranulocytosis (Turbay et al. 1997).

Conclusions

The data on neurotransmitter, neuromodulator, and drug-metabolizing enzyme gene variants, as well as the data from genome-wide analyses on clozapine response and adverse effects in treatment-refractory schizophrenia, need replication in larger samples. Although researchers started including clinical predictors, along with pharmacogenetic markers in combined algorithms to foresee treatment response, the efforts to create such a test will only gain momentum with support from regulatory agencies, industry, academic, and physician organizations, as well as consumers. McMahon and Insel (2012) bring up the challenge of proving the clinical utility of a pharmacogenetic test. They call for all stockholders to pursue widespread DNA collection in ongoing clinical trials and develop a central repository of anonymous samples to support large enough pharmacogenetic studies. Lastly, even after a reliable test has been created, how will it impact the physician and patient decision-making process? Efforts to aid physicians in integrating categorical information generated by such a test in their decision-making about treatment for individual patients will have to occur in parallel with consumers' involvement in the test approval and implementation. And lastly, ethical considerations occur in having such a test,

particularly if the results imply a patient's nonresponse status. Will this make an already vulnerable patient population even more exposed to insurance and healthcare access disparities and stigma?

Although still somewhat speculative, it is illustrative to consider the potential of pharmacogenetics to shape the care of patients with treatment-refractory schizophrenia. If for instance, a genetic marker was available to test "illness severity" or likelihood to have a "treatment-refractory illness," then clozapine might be used in such patients preferentially as a first choice agent. Similarly, greater understanding of the underlying biology of treatment response could lead to more targeted new drug treatments. Indeed, in keeping with targeting symptom domains, one could envisage different treatment strategies for individuals with demonstrated genetic susceptibility toward cognitive deterioration and then another targeted strategy for individuals with genetic predisposition toward a more negative symptom "deficit syndrome" form of illness. Then, addressing actual clozapine response, genetic markers of treatment response could predict who might respond best to clozapine. Such information could inform (1) whether the patient is selected for clozapine treatment in the first place, then (2) whether clozapine could be given at low dose, thereby minimizing risk of side effects, and (3) quitting clozapine early and not giving a prolonged treatment trial when the likelihood of response is low according to a "pretreatment" pharmacogenetic evaluation. There could also be considerable impact on clozapine use based upon pharmacogenetic information about side effects. If we could predict risk to serious life-threatening side effects like clozapine-induced myocarditis or pulmonary embolism, then we would avoid giving clozapine to patients who are at high genetic risk for such adversities. Likewise, we would exercise even greater caution if we could predict the genetic susceptibility for clozapine-induced agranulocytosis. Another impact of that strategy would be to minimize or do away altogether with the blood monitoring system for patients who were predetermined to have a low risk to develop agranulocytosis. Imagine how that information would radically alter the areas and use of clozapine for patients. Similarly, a real breakthrough on the pharmacogenetics of clozapine-induced weight gain and metabolic disturbances could profoundly influence who gets clozapine, how long they remain on treatment, and how aggressive a clinician should be in adding statin or other interventions. The potential of pharmacogenetics is substantial. Realizing that potential is both the challenge and the promise for our field.

Glossary of Terms Used in This Chapter

Allele One of several alternative forms of a gene at a given locus (a SNP has 2 alleles)

Diplotype Combination of two haplotypes

Exon Segment of a gene that contains the genetic code for an amino acid

Haplotype Combination of alleles at two or more closely linked gene loci on the same chromosome (for example, the human leukocyte antigen system)

Heritability **R**atio of additive genetic variance

Intron Sequence of DNA that does not contribute to the genetic information translated into the amino acid sequence of a protein molecule

Linkage disequilibrium Same block of DNA containing the SNP as well other polymorphisms in the same block, which are not independently inherited but "travel together"

Non-synonymous = functional polymorphism Genetic variance that produces changes in protein function

Pharmacogenetics Role of genetic factors in predicting drug response and potential side effects

Pharmacogenomics Relationship between whole genome factors and drug response and potential side effects

Polymorphism **G**enetic variation that occurs with a frequency of 1 % or more in population

Promoter Region of a gene that controls the initiation of protein production

SNP (single nucleotide polymorphism) Substitution from one nucleotide into another (for example, cytosine to timine) creating a mutation in DNA

Synonymous SNPs in coding regions that don't influence the structure of the protein.

p Short arm of chromosome

q Long arm of chromosome

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Family Interventions in Psychosis

13

Juliana Onwumere, Elaine Hunter, and Elizabeth Kuipers

13.1 Introduction

Cognitive models of caregiving (e.g. Kuipers et al. 2010) and neurobiological models of psychosis (e.g. Garety et al. 2007) both highlight the impact of familial relationships and environment independently, and in combination, on patient outcomes. Understanding the interplay between family relationships and patient and carer functioning remains of significant importance in research and treatment initiatives in psychosis. This chapter seeks to provide an overview of the clinical needs of patients who have regular contact with families and the role of cognitive behavioural family-based interventions in addressing patient and family needs and facilitating optimal outcomes.

13.1.1 Caregiving as a Resource

Schizophrenia has a lifetime prevalence of 0.87 % (Perälä et al. 2007) with the first onset typically falling during adolescence and young adulthood (Harwood et al. 2004). For many, the condition will prove to be long term and disabling, exerting a profound and negative impact on their functioning and their family. The

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global burden linked to schizophrenia spectrum conditions is well documented (Rossler et al. 2005; The Schizophrenia Commission 2012).

In recent decades, several countries have implemented a programme of mental health de-institutionalisation that has, in turn, placed a much greater emphasis on service provision within the community. Clinical and research evidence confirms that a significant proportion of people with psychosis continue to maintain close contact with informal carers (Foldemo et al. 2005). This contact is particularly evident during the first few years following the initial onset of difficulties (Addington et al. 2003; Parabiaghi et al. 2007) and amongst some black and minority ethnic groups (Guada et al. 2009). Informal carers are mainly first-degree relatives such as parents and are predominately female. Thus, a common clinical picture is of a middle-aged mother providing care for an adult male son. However, we also know that many carers are the spouses, siblings, or adult offspring of the service user (Grandon et al. 2008; Kuipers et al. 2006; Onwumere et al. 2013; Bowman et al. 2013).

There is a large body of evidence linking feelings of loneliness to mental health problems (Meltzer et al. 2013). People with psychosis tend to have very small social networks (Gayer-Anderson and Morgan., 2013; Sündermann et al. 2013; Berry et al. 2007; Harley et al. 2011) and few become parents or have adult romantic relationships (Fleury et al. 2008). Carers can therefore provide a vital source of social contact and support to patients (Lester et al. 2011; Parabiaghi et al. 2007) and find themselves in a key role to facilitate their recovery and re-integration within their local community. Carers will often respond to different areas of unmet need for patients including providing financial assistance, advocacy, and accommodation (Lester et al. 2011). They can take an active role in encouraging patient engagement with treatment plans, including pharmacological treatments, identifying and responding to early signs of relapse (Herz et al. 2000), and ensuring patients are able to access appropriate clinical services once the first signs of psychosis emerge (Fridgen et al. 2012; Bergner et al. 2008; Morgan et al. 2006). Recent evidence suggests that patients with carers, when compared to those without, obtained better outcomes from psychological therapies (Garety et al. 2008) and received less intensive interventions from mental health services (Catty et al. 2011; Wilks et al. 2008). We also know that patients with carer support can experience fewer inpatient admissions, shorter inpatient stays, and an improved quality of life (Schofield et al. 2001; Fleury et al. 2008; Norman et al. 2005; Tempier et al. 2013). Further, contrary to some misconceptions, patients themselves often welcome greater opportunities for their carers to be involved in their care (Walsh and Boyle 2009; Askey et al. 2009).

13.1.2 Understanding Caregiving: Impact of Role on Well-being

Carers of those with psychosis provide significant levels of unpaid care. The aggregate unpaid cost to society of the care provided by informal caregivers of individuals with schizophrenia in the UK alone falls in excess of one billion per

annum (The Schizophrenia Commission 2012). Approximately 15 % of carers have taken an average of 12.5 days off from employment and nearly 5 % of carers have terminated their employment due to the ongoing demands of their caregiving role (Mangalore and Knapp 2007).

The carer role is often taken on with little time to decide or prepare, and without a manual of what one should do (Kuipers 1992; Sawatzky and Fowler-Kerry 2003). It relies heavily on on-the-job training, and due to the characteristic relapsing–remitting nature of schizophrenia spectrum disorders (Harrow et al. 2005; Emsley et al. 2013), the role can be a long-term commitment. For many carers, their role will be incorporated into existing duties, which for some can include additional caregiving duties for other family members (Raune et al. 2004).

Supporting a relative with psychosis can have a negative impact on carer well-being (Kuipers et al. 2010; Kuipers and Bebbington 2005). The negative impact has been traditionally described as 'carer burden' or in recent years, the 'impact of care'. Several studies attest to high levels of burden in carer populations across the globe including those from Asia, Europe, and Africa (Awad and Voruganti 2008; Ukpong 2006; Igberase et al. 2010; Tang et al. 2008; Karanci and Inandilar 2002; Ostman and Hansson 2004) and in different carer subgroups such as siblings (Friedrich et al. 2008; Bowman et al. 2013), spouses (Jungbauer and Angermeyer 2002), and carers who are young children under 18 years old (Cooklin 2010). As part of their role, carers can report significantly smaller social networks and derive less satisfaction from their contact (Gouva et al. 2012). They can also experience a broad range of negative emotional reactions including loss, stigma, worry, guilt, and fear (Lauber et al. 2003; McCann et al. 2011; Kuipers et al. 2010). Many carers can express concerns about different aspects of their relative's functioning and well-being such as poor self-esteem, a lack of social relationships, financial and budgeting concerns, limited access to leisure and structured activities, and the impact of prescribed medications (Iyer et al. 2011).

Caregiving, in general, is frequently linked to a higher rate of common mental disorders, and significantly higher rates are associated with higher amounts of caregiving duties (Smith et al. in press). In carers of people with psychosis, high rates of emotional disturbance are found (Harvey et al. 2001) which can peak in carers of recent onset or recently admitted groups (Boydell et al. 2013; Martens and Addington 2001; Boye and Malt 2002). At least one-third of carers report clinical levels of depression (Kuipers and Raune 2000; Lowenstein et al. 2010) and trauma type symptoms (Hanzawa et al. 2013; Loughland et al. 2009; Barton and Jackson 2008), and many have found themselves the victims of physical and verbal aggression from their relative (Loughland et al. 2009; Belli et al. 2010). Indeed, family members and carers are more likely than non-family members and general public to be the targets of patient violence (Ural et al. 2012). Further, mental exhaustion and burnout, which are commonly found in paid mental health staff such as psychiatric nurses, have equally been observed in carers (Angermeyer et al. 2006).

Carers who are more socially isolated record greater levels of distress and burden (Magliano et al. 2002). Patient symptoms have been directly linked to reports of carer burden (Roick et al. 2006), although research findings are divided

over which type of symptoms prove most burdensome. In some studies, positive symptoms are associated with higher levels of carer burden (Wolthaus et al. 2002) whilst in others negative symptoms, particularly those characterised by inactivity and poor self-care, have been linked to greater reports of carer burden and distress (Ukpong 2006; Dyck et al. 1999). However, there have also been studies that have observed links between carer burden and both positive and negative symptoms (e.g. Addington et al. 2003).

The negative impact of psychosis on a carer's own physical health is also increasingly recognised within the literature. Results from a large sample of carers of schizophrenia spectrum and bipolar conditions ($N = 264$) found that two-thirds reported having one medical condition such as arthritis and hypertension, with one-third also reporting experiencing at least two conditions (Perlick et al. 2005). In addition, sleep difficulties in carers are not uncommon (Phillips et al. 2009).

13.1.3 Understanding Family Relationships: The Role of Expressed Emotion

The family environment and relationships can play an important role in the illness course for patients with psychosis (Bebbington and Kuipers 1994). The expressed emotion (EE) framework has been used over the last 60 years to assess and quantify the family environment. EE is said to reflect a carer's appraisal of the patient and the quality of their relationship; it provides a snapshot of the family's usual pattern of communication and behaviour (Miklowitz et al. 1984; Scazufca and Kuipers 1996). The gold standard measure of EE is the Camberwell Family Interview, a semi-structured interview completed with a carer that was initially developed in the mid-1960s and later revised (CFI: Brown and Rutter 1966, Vaughn and Leff 1976). EE is measured across five subscales with ratings derived from both the content and prosodic aspects of speech (e.g. tone, emphasis): (1) *Criticism*, which refers to unfavourable remarks about a patient's behaviour and/or personality. (2) *Hostility*, an extreme form of criticism that can manifest as a rejecting remark or global negative expression about the patient. (3) *Emotional over involvement (EOI)* comprises a range of different carer behaviours including self-sacrifice, overprotection, and over-identification with the patient. (4) *Positive comments* which reflect unambiguous positive statements about the patient's personality, skills, and attributes. (5) *Warmth* comprising carer reports of empathy, sympathy, and concern expressed towards the patient. Carers defined as being high EE report above threshold levels of critical, hostile, and/or emotionally over involved behaviours (King and Dixon 1999). Conversely, low EE carers have failed to reach that threshold. Although warmth and positive remarks form part of the EE framework and play a key role in clinical interventions with families, they are not included in the computation of high or low EE classification.

13.1.4 Expressed Emotion and Patient Outcomes

The relevance and importance of EE have continued since its original conception by George Brown and colleagues (Brown 1959; Brown et al. 1958, 1962, 1972) due to its ability to predict patient outcomes across different conditions including psychosis (Wearden et al. 2000; Hooley 2007).

In a meta-analytic review of 25 EE prospective studies from across the globe, Bebbington and Kuipers (1994) examined data from 1,346 cases and recorded a 50.1 % relapse rate for people with psychosis living in high EE households. The relapse rate in high EE households was more than twice the rate for patients in low EE homes. Similar findings were reported by Butzlaff and Hooley (1998) as part of their meta-analysis of 27 EE patient outcome studies. High EE, particularly criticism, has been linked to poorer patient outcomes in psychosis including a greater number of relapses and admissions over a 20-year follow-up period (Cechnicki et al. 2013).

The predictive links between high EE and poorer patient outcomes have also been found in diverse cultural groups in psychosis (Kopelowicz et al. 2006; Marom et al. 2002) but with some contrary findings (e.g. Singh et al. 2013; Kopelowicz et al. 2002; Lopez et al. 2004; Rosenfarb et al. 2006).

13.1.5 Expressed Emotion and Carer Functioning

As reported earlier, EE ratings are said to reflect the usual carer–patient communication and engagement patterns (Miklowitz et al. 1984). Available evidence suggests that carers rated as high EE have a tendency to exhibit poorer communication patterns with patients. Overall, they are likely to talk more and present as less effective listeners (Kuipers et al. 1983; Wuerker et al. 2001). Such carers can also have difficulty in expressing their thoughts in a coherent and supportive manner (Kymalainen et al. 2006). This compares to low EE carers who appear more able to take a step back and remain silent, a style that can often lend itself to being perceived as a good listener (Berkowitz et al. 1981). The research findings suggest that high EE caregivers can frequently find themselves entangled in a sequence of negative interactions with their relative with psychosis, unlike low EE carers, who are more likely to withdraw from challenging situations with patients before they escalate or have greater skills at being able to defuse them (Rosenfarb et al. 1995; Simoneau et al. 1998).

High EE components are linked to particular beliefs that carers report about the illness. For example, reports of carer criticism and hostility towards patients are more likely to be made by carers who attribute the patient's symptoms to the individual and their personality, instead of an illness. These carers will tend to express beliefs that their relative is able to control their symptoms and behaviour if they wanted to (Hooley and Campbell 2002; Barrowclough and Hooley 2003) and are more likely to engage in behaviours designed to directly change the patient's behaviour (Vasconelos et al. 2013). These carer attributions are more commonly

observed for negative symptoms rather than positive symptoms (Harrison and Dadds 1992; Weisman and Lopez 1997), although carer criticism has been linked to positive symptoms of psychosis (Shimodera et al. 1998). A lack of knowledge about the illness and greater pessimism about its course and impact have also been associated with carer criticism (Bentsen et al. 1998; Lobban et al. 2005).

In contrast, carers with high levels of emotional over involvement (EOI) tend to report more self-blaming (rather than patient blaming) attributions and perceive the patient as having very little control over their illness and experiences (Peterson and Docherty 2004). Carers rated as high EOI have a tendency to engage in more patient controlling behaviours through actively assuming control of events and completing tasks for the patient, in contrast to low EE carers who tend to attribute more positive events to patients (Grice et al. 2009). Though understandable and normative in many cultures in the short term, in the long term high EOI carer behaviours can invariably lead to a loss of confidence, roles, and independence for the patient and the carer. Evidence suggests that high EE, in general, is likely to be predicted by feelings of shame and the guilt/self-blame of having a relative with psychosis (Wasserman et al. 2012).

In the caregiving literature, coping styles are often categorised in terms of 'emotion'- and 'problem'-focused coping (Folkman and Lazarus 1980). Emotion-focused strategies comprise behaviours specifically designed to reduce the negative emotional impact of the stressor and can incorporate strategies based on avoidance and denial. In contrast, problem-focused coping refers to the direct attempts an individual makes to alter the situation such as seeking social support and problem-solving. Carers of people with psychosis employ a broad range of emotion and problem focused coping strategies to cope with the impact of the illness on their lives and relationships (Birchwood and Cochrane 1990). High EE, burden, and distress have all been associated with poorer carer coping styles (Scazufca and Kuipers 1999; Birchwood and Cochrane, 1990), specifically, coping styles based on avoidance (Cotton et al. 2013; Raune et al. 2004; Onwumere et al. 2011; Scazufca and Kuipers 1999).

13.1.6 Caregiving Relationships: Specifying the Mechanisms leading to Poorer Patient Outcomes

With regard to understanding the mechanism by which negative family relationships can lead to patient relapse, the current body of evidence identifies a key role for emotional dysfunction in patient impacting negatively on psychosis symptoms (Kuipers et al. 2006; Docherty et al. 2009). For example, Barrowclough et al. (2003) found that patients reporting negative self-evaluation were more likely to have carers with higher levels of EE. Kuipers et al. (2006) assessed a large sample of patients who had recently experienced a relapse in their positive symptoms; patients with high EE carers were more likely to report having a lower mood. Carer criticism was also predictive of patient anxiety in these settings. In a novel study that exposed patients with positive symptoms of psychosis to high EE and low EE

proxy speech samples, emotional dysfunction in patients, including reports of anger, significantly increased following their exposure to high EE criticism (Finnegan 2011). Recent findings from studies using functional magnetic resonance imaging (*f*MRI) have identified neural correlates of exposure to criticism and praise in people with mental health problems, including psychosis (e.g. Choi et al. 2013; Hooley et al. 2012; Rylands et al. 2011). Using a sample of patients with a diagnosis of schizophrenia, Rylands et al. (2011) assessed patterns of brain activation after participants had listened to critical comments from a key relative. High EE comments were linked to increased activation in brain regions focused on the processing of aversive social information (e.g. rostral anterior cingulate, left inferior frontal gyrus). It was argued that a neural network of responses may have a role to play in mediating the poor patient outcomes linked to high EE. Similar methods and findings have been observed in non-clinical schizotypal populations (Premkumar et al. 2013).

13.1.7 Positive Family Interactions and Outcomes

In recent years our understanding of the important contribution of positive and warm relationships to patient outcomes in psychosis has slowly increased. Data from long-term adoptee studies attest to the protective roles conferred by positive familial relationships and environment in reducing the risk of developing psychosis in genetically high-risk young people (Schiffman et al. 2002; Ierago et al. 2010; Tienari et al. 2004; Gonzalex-Pinto et al. 2011). Positive family relationships, in terms of caregiver warmth and expression of positive comments, have been linked to improvements in patient symptoms including social functioning (O'Brien et al. 2006). As part of their aggregate analyses of EE outcome studies, Bebbington and Kuipers (1994) reported how carer warmth and positive comments were predictive of improved patient outcomes in psychosis. Bertrando et al. (1992), for example, found that carer warmth was linked to significantly fewer relapses in patients in low and high EE households. There is evidence to suggest that the protective qualities of carer warmth and positivity may impact differently in different cultural groups (Lopez et al. 2004; Breitborde et al. 2007). In a study of EE and relapse in Anglo-American and Mexican-American groups of individuals with psychosis, it was Mexican-American patients returning to live in households characterised by high levels of carer warmth who displayed lower rates of relapse. Warmth, however, did not impact on the relapse rates of Anglo-American groups (Lopez et al. 2004).

13.1.8 Patient Perceptions of Carer EE

Running parallel to the literature on carer EE has been a developing body of literature on a patient's appraisal of the family environment and its link to patient outcomes in psychosis (Renshaw 2008; Tomlinson et al. 2013; Bachmann

et al. 2002). Patient appraisals of carer attitudes are reported to provide key information about the quality of the caregiving relationship and the extent to which carer appraisals about the patient may impact on or 'get through' to the patient (Hooley and Teasdale 1989). In psychosis, there have been a handful of studies confirming that patient appraisals of carer attitudes towards them overlap with a carer's reported attitudes (Cutting et al. 2006). Onwumere et al. (2009) found that patient perceptions of carer criticism towards them correlated positively with carers' reported ratings of patient criticism, hostility, and high EE. The positive links remained independent of the patient's affective and psychosis symptoms. Earlier work from Tompson et al. (1995) reported that it was patient perceptions of carer criticism instead of carer reports of EE that proved to be a significant predictor for patient outcomes over a 12-month follow-up. This finding was specific to black and ethnic minority participants and perhaps highlighted an important role for patient appraisals in this group.

13.2 Family Interventions in Psychosis

We know that individuals with a diagnosis of psychosis can be sensitive to stress (Myin-Germeys and van Os 2007) and that their recovery is vulnerable to the type of care they receive (Bebbington and Kuipers 1994). It therefore seems reasonable to assume that carers who may find themselves struggling with their own physical and mental health concerns will be less likely to provide optimal support and care for patients, which has negative implications for both patient and carer outcomes (Perlick et al. 2001).

Family interventions (FI) for psychosis were developed as a result of a body of evidence detailing the relationship between patient outcomes and family relationships, the impact of psychosis on carer functioning and well-being, and the unique care needs faced by patients with psychosis who maintain regular contact with carers. The provision of evidence-based family interventions has been included in schizophrenia treatment guidelines in the UK and USA (i.e. National Institute of Clinical Excellence updated guidelines 2009; PORT, Kreyenbuhl et al. 2010). For example, the UK NICE 2009 guidelines recommend that FI should be on offer to families of service users with psychosis who are in close contact and should include a minimum of ten sessions delivered over a three- to 12-month period. Similar recommendations exist in USA, although the intervention length is recommended at 6–9 months. The interventions are recommended as an adjunct to routine treatment packages including medication.

13.2.1 FI Evidence Base

There is a long and strong evidence base with more than 50 controlled trials reporting on outcomes from family interventions in psychosis with mainly longer term psychosis populations. Family interventions have proven efficacy (Pilling

et al. 2002; NICE 2009; Pharoah et al. 2010; Marshall and Rathbone 2011; Pfammatter et al. 2006) and are cost effective (Mihalopoulos et al. 2004; NICE Schizophrenia, Update, 2009; Xiong 1994). The main findings drawn from a recent Cochrane review of 53 randomised controlled trials undertaken within community settings across Europe, North America, and Asia show that FIs are efficacious in significantly reducing rates of patient relapse and readmission in psychosis (Pharoah et al. 2010). Family interventions can significantly improve levels of social functioning and medication compliance in patients (NICE 2009, Update; Pharoah et al. 2010) and reduce EE levels in high EE families (Pfammatter et al. 2006; Pharoah et al. 2010). The evidence on efficacy is stronger for longer term compared to brief interventions (Pfammatter et al. 2006; Mari and Streiner 1994; Pitschel et al. 2001).

In terms of effect size, Pharoah et al. (2010) reported fixed-effect OR of 0.55 for FI reducing relapse at 12 months compared to standard treatment. In an earlier meta-analysis, Pfammatter et al. (2006) observed effect sizes at 6–12 months of 0.42 for relapse reduction; 0.22 for reduction of readmission, and 0.51 for a reduction in readmission at 18–24 months in favour of FI when compared to standard care. Similar findings from Pilling et al. (2002) yielded a fixed-effect OR of 0.37 for FI compared to standard care at 12 months.

13.2.2 Early Psychosis Outcomes in FI

The early illness phase is generally considered to lend itself much better to undertaking family work since service users are more likely to be resident in families and/or be in regular contact with their families and caregivers. However, despite this picture, the number of published studies evaluating the efficacy of FI within early illness groups remains significantly fewer compared to the longer term groups, though the evidence base is increasing. Moreover, where studies have been completed these have tended to evaluate the impact of FI when delivered as part of an overall service approach to working with early intervention, which has complicated attempts to isolate the specific contribution of family interventions to patient and carer outcomes (Grawe et al. 2006).

Some of the earliest FI studies in early psychosis tended to yield equivocal findings about its impact (e.g. Leavey et al. 2004). Linszen et al. (1996) assessed 76 early phase (first episode) families following their receipt of individual psychosocial interventions. The authors failed to observe any significant benefit on outcomes (relapse) when families received a further 18 sessions of a 12-month behavioural family intervention. Moreover, families initially recorded as low EE showed poorer outcomes at the end of the intervention. Five-year follow-up data suggested that family interventions reduced inpatient admission times, although participants did not have an overall better illness course (Lenior et al. 2001). Zhang et al. (1994) examined the efficacy of family interventions using a male-only sample and where, for most of the intervention, the service user was not included within the session. The intervention offered a positive impact on relapse rates and

social functioning at 18-month follow-up. Using a sample of 106 first episode carers randomised to a brief (seven session) family intervention compared to standard care, no significant differences in levels of carer satisfaction or inpatient days were observed between carers in both arms of the study (Leavey et al. 2004). Gleeson et al. (2009) have argued that optimal interventions for early psychosis service users, following a period of symptom remission, should include a combination of individual cognitive behavioural therapy (see previous chapter from Elaine Hunter and colleagues) and family work that particularly targets relapse prevention. Bird et al. (2010) published data from their systematic review and meta-analyses examining the effectiveness of family interventions in early psychosis and offered similar positive findings to those extensively reported in longer term psychosis populations (e.g. Pharoah et al. 2010). Drawing on patient data from three published trials of family interventions ($N = 288$), Bird and colleagues concluded that when used alone, family intervention significantly reduced relapse and hospital admission rates compared to standard care in early psychosis populations (Bird et al. 2010).

13.2.3 Carer Outcomes in FI

Interestingly, despite the extensive evidence base documenting the negative impact of caregiving on carer functioning and well-being, there is a paucity of data recording the impact of family interventions on carer-specific outcomes (Lobban et al. 2013). However, we do know that family interventions can have a positive impact on caregiver outcomes (Lobban et al. 2013; Pharoah et al. 2010) including reducing carer burden (Cuijpers 1999; Tomas et al. 2011; Giron et al. 2010), improving positive caregiving appraisals including those made about the patient (Gleeson et al. 2010), and increasing readiness of carers to continue providing care (Berglund et al. 2003; Giron et al. 2010).

13.2.4 Areas of Development in FI Evidence Base

There are some notable gaps in the FI literature base, for example, identifying the key mediators and mechanisms of positive change. Thus, there are limited data on what specific component(s) within the family-based intervention gives rise to the positive outcomes observed in reduced relapse and readmission rates. Further, given their numbers and unique needs, there is a paucity of data on FI with different carer subgroups for example, younger carers, siblings (Sin et al. 2013), and black and minority ethnic groups (NICE 2009). In the UK, for example, there are significantly higher incidence rates of schizophrenia and psychoses in Black African and Black Caribbean groups (Fearon et al. 2006; Cantor-Graae and Selten 2005). Both groups also tend to experience more negative forms of care including greater user of legal statutes to enforce care and treatment (Cochrane and Sashidharan 1996). In recent years there has been increasing attention on the impact of ethnic membership and culture on family functioning and outcomes, with some

findings indicating that impact of care (burden) and links between high EE and poor patient outcomes may not be uniform across all ethnic groups (Rosenfarb et al. 2006; Singh et al. 2013; Lopez et al. 2004). Research recommendations from the NICE schizophrenia treatment recommendations included a call for further studies to assess the impact of FI on minority ethnic groups. To date, worldwide, there have been a small number of studies that have examined applications of FI models with samples based in the Far East (e.g. Chien and Chan 2004), Latin American populations living in the USA (e.g. Weisman et al. 2006; Telles et al. 1995), and some European and Middle East countries (e.g. Tomas et al. 2011). Although far more investigations are required, data from some of the earlier studies suggest that FI can be successfully delivered but may require some revision for particular groups (Onwumere et al. 2009; Telles et al. 1995).

13.2.5 Models of Family Interventions

There are only a small handful of FI treatment manuals that are evidence based rather than commentary (Addington and Burnett 2004; Kuipers et al. 2002; Barrowclough and Tarrier 1992; Falloon et al. 1984). The treatment manuals vary in the emphasis given to the exact session format and location, how and whether the patient is included in the sessions, and if families are seen individually or as part of a large group of other families. However, the evidence-based manuals also share some key areas including explicit recognition of schizophrenia spectrum diagnoses as an illness and a stress-vulnerability model of its development and practitioners adopting a non-blaming and positive attitude towards families, a focus on current 'here and now' problems, and an overarching aim of reducing a patient's risk of relapse and the negative impact on family functioning.

In the Kuipers et al. (2002) treatment manual, family interventions are designed to promote cognitive and behavioural change via facilitating positive family communication; information sharing (psychoeducation); and negotiated problem-solving skills. They also include emotional processing of common affective responses linked to caregiving such as grief, loss, and anger. The interventions are provided by two therapists and will usually be offered in the family home.

13.2.5.1 Facilitating Communication

Communication styles that are constructive, in terms of achieving a good balance of talking and listening skills and being able to elicit the perspective of the other, have been linked to improved social functioning in patients (O'Brien et al. 2009). Facilitating optimal communication styles between family members will often provide the foundation for all the other FI therapeutic activities (e.g. problem-solving, psychoeducation) and can minimise the difficulties linked to their implementation (Kuipers et al. 2002; Onwumere and Kuipers 2009). In FI sessions, there are three main communication strategies highlighted. First, all family members are asked to talk directly to each other instead of about one another. This method can

help to reduce the negative exchanges between family members and will often encourage the speaker to apply greater thought and sensitivity to what they say and how they say it and, thus, immediately promote behavioural change within the session. We know that far less effort is required when you make a negative statement about a person: compared to when you have to speak directly to them. Greater thought and sensitivity are also given to the content and the tone in which the statement is delivered when you are encouraged to talk directly. Auditory hallucinations are common symptoms in psychosis and thus likely to be experienced by many patients attending family sessions. Encouraging the use of direct speech can also be helpful for patients, since referring to a patient in the second or third person, particularly when making negative comments, can run the risk of mirroring their own negative experience of auditory verbal hallucinations, particularly where they may have felt isolated, victimised, or humiliated (e.g. Birchwood et al. 2000). Second, family members are asked to talk one person at a time. This simply ensures that the therapists and family members are able to hear what is being said. It also minimises the risk of important information, including expressions of warmth and positivity between family members, being lost, and models good listening skills. Third, as part of a strategy to ensure that all family members are involved with the intervention and have a key role to play in the outcome, therapists ensure that equal talking time is given to all family members. This rather simple yet effective technique serves to reduce the risk of an individual's mental disengagement from the session, which may be a particular concern for some service users especially those with more negative symptoms. Here, the therapists take an active and lead role in facilitating positive communication styles, but always with a view to family members, themselves, monitoring and revising their own behaviour independent of therapists' prompts (Kuipers et al. 2002). In line with the Kuipers et al. (2002) treatment manual, the overview of the communication styles, which can sometimes be described as 'ground rules' in the literature (e.g. Gamble et al. 2012), are always discussed in the initial session to make the process of the sessions transparent. Our clinical experience confirms that promoting and prompting optimal communication styles will often extend over the course of the intervention.

13.2.5.2 Information Sharing (Psychoeducation)

Carers with more optimistic beliefs about how much control patients and themselves have over the illness have tended to report more positive caregiving experiences (Onwumere et al. 2008). Moreover, carer and patient functioning are linked to the appraisals they report about the illness (Watson et al. 2006; Barrowclough et al. 2001) and discrepant illness beliefs (Lobban et al. 2006; Kuipers et al. 2007). Lobban et al. (2006) found that high EE relationships were more common where carers and patients report dissimilar illness beliefs about areas such as the illness impact and consequences. Kuipers et al. (2007) reported that discrepant illness beliefs between patients and carers had a mutual impact on mood.

Psychoeducation can play a significant role in dispelling some of the myths and factual errors that often surround psychosis and impact negatively on family

functioning. In family sessions, psychoeducation will seek to facilitate the families' cognitive reappraisal of patient symptoms and difficulties with the goal of promoting less person blaming appraisals and encourage more adaptive coping behaviours and affective responses from family members. For example, if we look at the appraisal of: '*my son is lazy since he does not like to get up in the morning, and I know he is taking advantage of my good will and generosity*', psychoeducation will be used to help the parents conceptualise their son's behaviour and difficulties getting up in the morning as part of his negative symptoms. Using feedback from the son, directly within a family session, the carer will be supported in improving their understanding of negative symptoms and the unique way in which it affects their son, including difficulties with motivation and initiation plans.

In the Kuipers et al. (2002) model, a comprehensive information leaflet purposively designed for use with carers and service users together is utilised as part of the psychoeducation. The leaflet covers several key areas on understanding psychosis including diagnosis, incidence/prevalence, symptoms, causes, treatments, and impact on families. In sessions, the patient is always recognised as the expert in their experiences and supported in using their unique lived experience and knowledge to shape conversations with family members. In psychoeducation sessions, the family will be supported to systematically work through different areas of the information leaflet and have guided and facilitated discussions around relevant areas. All family members are encouraged to offer their own perspective and to both listen to and comment on the material offered by fellow family members and the therapists. The psychoeducation sessions are not designed to be didactic or inflexible teaching sessions. On the contrary, the process is interactive and is at its best and most effective when the views of all family members are sought; when patients can be supported to discuss distressing experiences directly with their family, often for the first time, and then discuss how the whole family can begin to cope with this.

13.2.5.3 Problem-Solving

Evidence suggests a positive relationship between carer and patient problem-solving skills; good problem-solving in patients is linked to improved social functioning in patients and carer expressions of warmth towards patients (O'Brien et al. 2009). Kuipers et al. (2002) identifies an important role for structured and focused problem-solving within FI sessions. Given the negative impact that psychosis can exert on service users and their families, it is often important to help families to focus on one problem at any one time; to specify in exact terms the nature of the problem to be solved, and to help the family to negotiate solutions. Families are encouraged to implement (practise) cognitive and behavioural changes as part of their between session homework. This is in order to facilitate emotional processing and to promote more successful coping. In turn, the between session work can provide more immediate feedback of positive experiences, which can encourage feelings of optimism amongst all family members. At all stages, the therapists remain focused on reinforcing any attempts to implement change, however small.

13.2.5.4 Emotional Processing

As reported earlier, carers can experience and report experiencing a broad range of emotional responses as part of their role including high levels of grief and loss over 'what could have been' and equivalent to levels observed in a bereavement (Patterson et al. 2005). These emotions can often arise at different times within a session. As part of the tested approach to supporting carers to process these emotions and their impact, therapists will spend time normalising carer feelings in the context of what is readily known about the impact of psychosis on families. Carers are also actively encouraged to attend carer-only support groups that are designed to offer support and to help carers cope with the negative emotional sequelae.

13.3 Case Illustration

The following case of Janet and Lily[1] briefly illustrates some of the aforementioned FI in psychosis therapeutic activities. In FI, different aspects of the work can often overlap within session. For example, facilitating communication and emotional processing can also occur in the context of working on psychoeducation.

13.3.1 Janet and Lily

Janet is 25-year-old woman with a 6-year history of psychosis and is currently seen by her local community mental health team. The onset of her mental health difficulties occurred not long after she started her first job in a publishing office, after leaving college at 18 years. During the last four years, Janet has had three inpatient admissions, two of which involved her being detained under a section of the Mental Health Act (1983, 2007). The admissions were prompted by increasing concerns raised by her family, of Janet's suspicious and paranoid behaviour, poor levels of self-care and social isolation, and increased levels of voice-related distress.

Janet experiences auditory hallucinations and often hears several voices at once. The content of the voices is predominately negative and tends to oscillate between making derogatory comments about her physical appearance, commenting on her behaviour, and issuing threats. She has poor levels of social functioning and participates in few activities during the day apart from visiting the post office once a week. Janet can generally be found in her bedroom sometimes sleeping and at other times she can be found simply lying down on her bed staring up at her ceiling listening to her voices. Janet lives with her mother, Lily (aged 54 years), and younger half brother, Adam (aged 13 years). Janet's biological father lives abroad and they have limited telephone contact. Lily works in a part-time domestic role in

[1] This is a composite case using pseudonyms and where all identifiable details have been disguised.

the local primary school and has a childminding job for a couple of hours each week. Lily spends a lot of time driving her son to his various after-school clubs and sporting activities. In recent months, her relationship with her daughter has become strained; Lily has found her daughter's lack of motivation and inactivity (which she perceives as her 'laziness') an increasing source of annoyance and a focus of ill-tempered exchanges between both of them. In addition, she has found it difficult to cope with her daughter's minimal contribution to keeping the house going.

Following a pre-engagement session with Janet and Lily on their own, where both women were encouraged by Janet's mental health team key worker to consider family intervention sessions and given some written information about the intervention, they agreed to meet for family intervention sessions to discuss the recent difficulties in their relationship and ideas for making things a little easier for them both The sessions were scheduled for midday when Adam was at school, which was a timing that Janet had requested. There was a discussion with the therapists about reviewing the options, at a later date, of perhaps making time to schedule a meeting where her brother might be able to attend. Overall, the family were seen for 11 sessions over a 7-month period. Each session lasted for approximately 60 min.

Engaging with individual family members is a therapist behaviour that runs throughout the duration of the intervention and not just for the first few sessions. To facilitate Lily and Janet's engagement with the sessions, the therapists met the family at home. Further, given Lily and Janet's initial reluctance to attend the sessions, the therapists were mindful of the possibility of either party dropping out and thus agreed to focus on actively trying to engage both family members. For each session, one therapist would work on positively engaging Lily, while the other would engage Janet. To ensure the therapist roles were balanced and to reduce the risk of one family member only engaging with one therapist, the therapists swapped the focus of their engagement at every session. The therapists were able to engage the family through using standard techniques such as empathy and validation alongside active listening, for example, checking with each family member whether they had heard and understood what had been said.

From the very beginning of the intervention, facilitating positive communication styles was an important area for the therapists to focus on. At the start of the intervention, Janet often sat with her head lowered. She tended to speak with a low voice tone and the pace of her speech was slow. This presentation often meant that Lily, as part of a bid to move things along and ensure the therapists time was not 'wasted', would interrupt the therapist's question that was designed for her daughter or attempt to speak on her behalf. Thus, it was important for the therapists to establish a balance between Lily and Janet in the levels of listening and talking and encourage both family members to pay close attention to how they talked and listened to each other.

Lily was able to report that one of the main issues that she wanted to address in the sessions was her concern that Janet did not want to get better. She was upset with her daughter over her lack of progress since her discharge from her most recent admission, 7 months ago. Lily felt that if Janet showed greater motivation and effort, she would 'obviously' make far greater progress and could return to work

since she was always bright. She accepted that her daughter had some difficulties with her mental health, but was aware of other people with similar difficulties who were doing more with their time. Lily often referred to a young man who was a relative of a colleague at work who had similar difficulties to Janet but held down a job in the local supermarket. One of the main issues that Janet wanted to address in the session was feeling that no one cared for her or understood what it was like with her difficulties.

In line with their agreed agenda and forming part of the problem-solving strategies, Lily was encouraged to be specific about what aspect of Janet's behaviour she was referring to and in what way she would like the situation to be different. Although she struggled with this request in the initial session, through careful questioning and the therapists' support and modelling of non-vague (clear) communications, Lily was able to specify that she would like to see her daughter looking after laundry. In behavioural terms, this meant that she wanted her daughter to be able to sort the soiled clothes from the recently laundered clothes. This was helpful for Janet to hear since sorting the laundry into clean and soiled piles was something that she felt able to do. The family were encouraged to think about how Lily could support Janet with this task. Janet was able to communicate clearly that she did not need any help. However, Lily and Janet were both able to agree that Lily acknowledging the positive contribution Janet made to the household chores was important and impacted positively on Janet's beliefs about herself.

It was clear to the therapists that some of Lily's main issues reflected, in parts, her limited understanding of psychosis and its clinical expression. Although she knew of other people with psychosis, this did not necessarily facilitate her understanding or appraisal of her daughter's symptoms. Psychoeducation proved a very helpful way to address issues around her understanding of psychosis and relate this to Janet's lived experience. It also served as a perfect opportunity to begin to address Janet's goal for the therapy and thus for Janet to explain to her mother and help her to understand how things were for her. The sessions given over to psychoeducation extended over the course of the intervention and provided a helpful platform for discussion of areas that were bothersome to Lily and Janet, but hitherto had only been raised as part of a heated argument or indirectly. As part of the discussion on positive symptoms, Janet was able to talk directly to her mother about her voice hearing, which often kept her up at night-time and impacted negatively on being able to get up the following day. In addition, the negative content of the voices tended to heavily influence her ability and motivation to engage in activities and to be with other people.

Lily reported that she had not previously been aware of the extent of Janet's difficulties. She now wondered whether trying to do something together in the evening that was pleasant could benefit Janet in terms of her mood and 'perhaps' distract her. Both women generated a few activities that they added to their 'evening fun list' and set about completing an activity and feeding back at each session on how they found it. Lily and Janet negotiated with each other what item of the list they would follow. The items on the list were varied and included activities such as watching a popular situational comedy together and going for a short walk

in a nearby park, Janet accompanying her mother to watch Adam at one of his sports classes, shopping together in the local mini market, and sitting in their garden. As we approached the end of the intervention, Janet and Lily became more flexible about when they completed items from their list and occasionally swapped an evening activity for a daytime activity at the weekend. Feedback on what the family had been able to achieve outside of the appointments and a recap of what they were planning to do always provided an excellent start and end to the individual sessions.

In parallel to addressing issues of psychoeducation, the sessions were also used to facilitate emotional processing for Lily. The family discussions about causal explanations for psychosis and for Janet's difficulties, which included discussions on the initial onset and the months immediately preceding onset were emotive, particularly for Lily. Through questioning, the therapists learnt that Lily had never really spoken to anyone about how she felt at the time or the years that followed including coping with subsequent admissions. The therapists were able to enlist the help of Janet to make suggestions about what her mother could do to help Janet to feel a little better.

The therapists also encouraged Lily to attend a support group for the family members of people with psychosis. In parallel to the FI sessions, support groups for carers can often provide a valued source of support. They provide a safe setting where an individual can express and normalise their feelings about their role and the person they care for, for example, feelings of anger, guilt, and loss (Kuipers et al. 2002; Lowenstein et al. 2010). Initially Lily was unsure about attending the group because she did not think it would be of any help to her. She was also reluctant to attend due to the timing of the group; for example, she was concerned over whether she would have enough time to prepare an evening meal for Adam and Janet and be on time for the group. Lily and Janet were encouraged to problem-solve the issue and devised a plan where Janet would prepare a pasta-based meal for Adam and herself. The therapists learnt that Janet had always liked pasta, enjoyed cooking, and looked forward to doing something else around the house. Janet reported that it was important to feel that she was doing something useful.

The shared family discussions about psychosis alongside the facilitation of communication skills, emotional processing, and problem-solving slowly but gradually led to a much more positive interaction cycle that the family were able to build upon on. This was in contrast to the feelings of hopelessness, anger, and isolation that the family previously exhibited. For the therapists, there was evidence of increased warmth between Janet and Lily. In her reflection on her experience of the sessions, Janet was candid in her reports that she was initially doubtful about attending appointments. She reported that it was helpful to do things with her mother because it provided them with some nice things to talk about. Janet also found it helpful to have the psychoeducation material to discuss since it allowed her to feel less isolated, because she felt her mother understood her a little better. Attending her brother's weekly football practice became a regular fixture for Janet. The lead she took in preparing an evening meal for her brother and herself once every 3 weeks had gradually progressed to a weekend breakfast and a weekday

meal. She frequently expressed enjoying cooking and was in discussion with her key worker about attending a community-based cookery class.

Janet continued to be distressed by some of her voices, but subjectively reported that her distress levels and episodes of feeling overwhelmed by her experiences had reduced. This was evident in her improved social functioning. As part of a plan to address her ongoing difficulties with the voices, Janet was due to be seen by a clinical psychologist for individual cognitive behavioural therapy sessions soon after the FI sessions had ended and expressed an interest in attending a community-based coping with voices group at some point in the future. In her reflection about the FI sessions, Lily said that she liked the sessions because she felt she understood more about her daughter's experiences. She reported that the meetings had increased and improved the level of communication between Janet and herself. She was attending the carers' meetings regularly and had signed up for additional carer well-being days.

13.4 Summary and Future Developments

The negative impact of psychosis on patients and their families is widely recognised in the literature. The family environment, including interpersonal exchanges, has an important role to play in patient and carer outcomes in psychosis. Since the early 2000s, family interventions have been recommended treatments for schizophrenia spectrum disorders in the UK (NICE 2003, 2009) and the USA (PORT 2004, 2010). The interventions are cost-effective, acceptable to patients and carers (Gregory et al. 2009), and underpinned by a strong evidence base particularly for their role in reducing relapse and readmission rates (Pharoah et al. 2010) even at first episode (Bird et al. 2010).

The costs of psychosis to the individual, their family, and the wider society remain high. Each relapse and readmission is associated with increased risks of further disability and social exclusion. The raison d'être of evidence-based family interventions in psychosis continues to be the reduction of the patient's vulnerability to and risk of relapse. Through its key therapeutic activities, which include facilitating positive communication, psychoeducation, problem-solving, and emotional processing, family members are encouraged and supported to engage in cognitive and behavioural changes. These are designed to lead to optimal outcomes, including improved family relations, adaptive coping, and more time in recovery.

Despite the strong evidence base underpinning family interventions, their proven application in routine clinical settings, and the publication of treatment guidance advocating their provision, the numbers of families actually receiving the intensive family interventions in clinical services are low (Glynn 2012; The Schizophrenia Commission 2012; Dixon et al. 2001; Berry and Haddock 2008). Anderson and Adams (1996) described FIs as effective but underused treatments. Sadly, it remains common that contact between professionals and carers can remain limited to telephone calls and only during crisis periods (Kim and Salyers 2008). Several factors have been identified as playing a role in the limited access to and provision

of evidence-based family interventions (Kuipers 2010, 2011). To date, these have included a lack of understanding from clinical staff about family interventions and its role in treatment outcomes; organisational barriers which are not conducive to staff offering such interventions to meet the specific needs of families (e.g. high caseloads; financial cutbacks; no out of hours provision; lack of time); workforce issues that include a lack of specialist training and supervision opportunities for practitioners; engagement difficulties from carers and patients; and poor translation from research settings to routine services (Onwumere et al. 2013; Prytys et al. 2011; Fadden, 2006; Kim and Salyers 2008; Berry and Haddock 2008). Thus, patients may decline an offer to engage in the intervention or refuse to have their carers involved despite having high levels of contact with their carer and carers being negatively affected by their role.

In the UK, it is typically not the job of any one professional to provide a service to families of people with psychosis. Consequently, families can often lose out and feel neglected by services that are caring for their relative (Kuipers 2010). However, it is important to note that not all families require or need intensive help (Cohen et al. 2008; Gamble 2004). Some families may not agree that help is required at a particular time point or fail to perceive the relevance for family meetings. However, most families at some point during the illness course are likely to benefit from some additional professional help. Future developments in family interventions in psychosis have begun to focus on offering the least intensive interventions necessary to reduce family distress (Cohen et al. 2008). There is some early work evaluating service models designed to offer triaged interventions that cater for those in need of full family interventions but also for those who require brief, focused interventions. The latter interventions can be delivered to carers alone or carers and patients, together, for a few sessions and are more likely to be delivered by larger sections of front-line mental health staff (Cohen et al. 2008).

Data are also emerging on the impact of utilising more novel methods for supporting families. For example, recent developments in the online provision of family interventions have yielded promising results for service users and carers in their understanding of psychosis (Rotondi et al. 2010). (Dixon et al. 2011) also offered some encouraging findings, in terms of impact on carer coping, from a randomised 12-week intervention that was delivered by family members of service users with mental health problems who had themselves undergone training.

Conclusion

As the UK Schizophrenia Commission ('The Abandoned Illness' 2012) commented, 'Families who are carers save the public purse £1.24 billion per year but are not receiving support and are not treated as partners'. There is a range of targeted psychological interventions that have good evidence for improving outcomes for both carers and patients of those with psychosis, of which FI has the largest evidence base. There is a continuing need to offer this kind of support to those with psychosis and their families. Although such therapy can be difficult to prioritise in our currently stretched mental health services,

where they can be incorporated, such as in early intervention services (Bird et al. 2010), the benefits are clear as reflected by the evidence base.

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