New Directions in Psychiatry

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Preface

Despite efforts spent on caring for psychiatric patients and treating mental disorders, there are still many unmet needs in several domains of major mental disorders, including affective unipolar and bipolar disorders, schizophrenia, and suicide risk. For example, misdiagnosis, treatment resistance, noncompliance, and adverse effects are some of the more frequently reported unmet needs in clinical practice. Moreover, psychiatric practice is undergoing major changes, following the recent advances in science, society, and medicine. Many of these changes are common to other medical disciplines, but many others are specific to psychiatry, and these are fully addressed in one of this book's chapters.

As regards the unmet needs, it has been repeatedly shown that the needs of patients, relatives, the community at large, and those of the governmental bodies only partially overlap. For instance, patients in their families are more concerned about the quality of life, treatment, autonomy, independent living, and so on, whereas governmental stakeholders are typically more concerned about relapse prevention and reduction of hospitalizations. Yet, a volume aimed at bridging the gap between theoretical notions and practical understanding of patients' untreated aspects of their psychiatric disorders is much needed. Far from focusing on the traditional description of psychopathology and diagnostic criteria, the volume will guide the reader to the core problems for each topic.

This book is unique as it focuses on hot issues in modern psychiatry by providing an in-depth analysis of both met and unmet needs in the management of several psychiatric disorders. It is organized to guide the reader through the common problems faced by clinicians in their everyday practice and possible solutions, bridging the gap between evidence and experience.

This volume also focuses on new approaches in the classification of mental disorders as proposed by DSM-5 and ICD-11, but taking into account also modern proposals which bring together the knowledge coming from genetics, neuroimaging, and clinical trials.

Moreover, the book also points to much-debated controversial problems, such as the assessment and treatment of psychomotor agitation and the management of suicidal patients and support to survivors. These aspects, which are not proper mental disorders but are transversal to all mental health problems, are also covered in two specific chapters, which adopt a clinical and a preventive public health approach.

One chapter is dedicated to the management of patients at the beginning of their mental disorder, focusing on the need to reconsider the paradigm of early intervention services for psychoses toward a more general approach on youth mental health.

Although patient management, in every branch of medicine, encounters the problem of nonadherence to treatment, its impact in psychiatric practice assumes significant proportions, especially considering the burden of mental disorders—as in the case of major depressive disorder and bipolar disorder. The former is often related to treatment resistance, while the latter to relapses and partial adherence.

Moreover, the present volume also provides coverage of the more frequently reported problems faced by residents during the years of the residency training programs.

We are grateful to the authors of this book, who are all well-known experts in their respective field and who provided their chapters on time, despite their busy schedules.

We believe that this book will be useful not only for psychiatrists but also for psychologists, other mental health professionals, and physicians from other disciplines, who want to stay updated on modern approaches to patients with mental disorders or mental health problems.

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Unmet Needs in Modern Psychiatric Practice

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Gaia Sampogna, Mario Luciano, Valeria Del Vecchio, Vincenzo Giallonardo, Benedetta Pocai, Maurizio Pompili, and Andrea Fiorillo

1.1 Background

The social, economic and scientific changes occurred in the last years have had, and are still having, a significant impact on psychiatric practice [1] and on the clinical presentation of many mental disorders; in fact, while some traditional syndromes seem to be disappeared, new forms of mental health problems are coming to psychiatric consultation. The psychosocial distress caused by the economic crisis on the well-being of the general population, or the maladaptive use of the new technologies among the younger generation, are some good examples of psychosocial factors causing new mental health problems [2–4]. Psychiatrists and mental health professionals are not yet well-equipped for managing these, which represent major unmet needs in modern clinical practice [5].

Other changes are related to the introduction of new pharmacological and psychosocial treatment strategies, which are increasing the possibility to treat or even prevent the onset of full-blown mental disorders. However, despite these significant changes, psychiatry as a profession still bases its education, research and clinical practice on a knowledge formed over the last two centuries [6]. Some of the most significant changes that are modifying the role of psychiatrists and of mental health professionals in the modern society are summarized in Table 1.1 and will be discussed in this chapter.

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Table 1.1 Main changes affecting psychiatric practice worldwide

• Changes occurred at social level (e.g., globalization; migration; family structure; stigma and discrimination)
• Changes occurred at clinical level (new presentation of mental health problems; comorbidity; physical health care and mortality rates)
• Changes occurred at treatment level (pharmacological interventions; biological non-pharmacological interventions; psychosocial interventions)

1.2 Changes Occurred at Social Level

1.2.1 Globalization

The process of globalization started in the economic field and has widespread to everyday life [7]. Everywhere in the world, people are experiencing a reformulation of boundaries and a transformation of communication, which have an impact on the perception of times and space [8]. Moreover, individualism and personal autonomy has increased, with a loss of social cohesion and cultural identity [9]. Due to globalization, cultural differences among different regions of the world are disappearing.

Internet and social media have a central role in the globalization, facilitating exchange of information and communication. Social relationships are changing, and more relevance is attributed to virtual life, in terms of number of *likes*, *followers* and visualizations compared to face-to-face interactions. It has been highlighted that the use of Internet impacts on attentional capacities, memory processes and social cognition, with relevant neurophysiological changes in the brain [10].

1.2.2 Migration

The phenomenon of mass migration, due to different causes such as natural disasters, war or economic crises, is changing the modern society, modifying cultural boundaries across population and consequently the presentation of mental health problems and mental disorders. Moreover, the migration itself has been recognized as a stressful event acting as a possible precipitating factor for the onset of several mental disorders, such as psychosis, anxiety disorders or post-traumatic stress disorder (PTSD) [11, 12]. Furthermore, the recent massive migration has underlined the need for psychiatrists to be trained according to a transcultural perspective. According to this perspective, the role of cultural factors in understanding the development of mental disorders should be routinely evaluated. The migration process—impacting on local and regional cultures, with the integration of different cultural aspects, communication skills, religious beliefs, traditions, family and gender issues—is also modifying the presentation of some mental disorders. The socio-cultural factors should always be carefully considered when making a diagnosis of a given mental disorder; as witnessed by a specific chapter and a dedicated interview included in the DSM-5 for accommodating the diagnoses of mental disorders according to cultural factors.

1.2.3 Family Structure

Another relevant change occurred in recent years is the rise of new forms of family structure, such as single-parent families or same-sex families. Moreover, the traditional nuclear family model, with "vertical" relationships (e.g., grandparents, parents, children), is going to be replaced by a "horizontal" family network, with support provided mainly by peers and friends rather than by parents [13]. Changes in family patterns, with multiple generations of families no longer living in the same house or in the same town due to working reasons, is modifying the role of elderly people in the community and the way they are cared for. The increased demands for caregiving by younger family members for the older generations is less likely to be served when those younger generations live far away.

1.2.4 Stigma and Discrimination

Persons with mental disorders represent the only category of people significantly discriminated and excluded from social activities due to their condition [14]. Social exclusion and discrimination are due to the presence of stigma towards people with mental disorders. Due to stigma, people with severe mental disorders are excluded from civil society, are at increased risk of being in contact with the criminal justice system, are at higher risk of poverty and homelessness.

Mental disorders pose a massive burden on affected people, their families and the society at a large, but stigmatizing attitudes towards mental illness, mentally ill people and psychiatrists make it relatively difficult to obtain funding and help-seeking. Moreover, stigmatization has also an impact on patients' physical health, which is too often neglected due to lack of integration between psychiatry and general medicine.

Thornicroft [15] has conceptualized the phenomenon of stigma as a problem of stereotypes, attitudes and behaviours. In particular, stereotypes are beliefs concerning the habits, behaviours and characteristics that are associated with people with mental illness. Prejudice is the automatic emotional response to the stereotype (e.g., "people with schizophrenia are dangerous and I am afraid of them!"). Attitude leads to behaviour adopted to protect from possible consequences that might arise from the stereotype (e.g., "they are dangerous and should be excluded from the community").

The consequences of stigmatization against people with mental illness are dramatic and are often considered to be as important as the illness itself. Stigma can undermine many life goals of people with severe mental illness through reduced participation in higher education, employment and relationships, and lower levels of well-being and empowerment.

Several strategies have been described for overcoming stigma, namely protest, education and contact [16]. Protest aims to eliminate negative stereotypes in public statements, media reports or advertisements. Education aims to provide balanced and unbiased information about mental disorders or by showing how stereotypes (e.g.

dangerousness and unpredictability of people with schizophrenia) are frequent in the general population. It has been found that educational interventions are more effective when target population has already had a contact with a person with mental disorders. The contact-based strategy includes intervention involving a "testimonial", a person with a mental disorder sharing his/her experience about the disorder and his/her pathway towards recovery. Contact-based strategies have been recognized as one of the most effective interventions for fighting stigma, being effective in modifying the stigmatizing behaviours towards people with severe mental disorders.

Several anti-stigma interventions are still ongoing worldwide, including long-term programmes, such as the "Like Minds, Like Mine" campaign carried out in the New Zealand from 1990s [17], or the most recent ones such the Time to Change campaign in the United Kingdom [18] and the One of Us campaign running in Denmark [19]. The main differences among these interventions are related to the target population, to the inclusion of testimonials and to the use of social media channels of communication.

The changes occurred in communication technologies may help in fighting stigma. The Internet and all other technological tools offer new strategies of communication and can be helpful to reduce discrimination and social exclusion of people with severe mental disorders [20]. In particular, the Time To Change campaign has included a specific social marketing campaign, based on the use of Facebook, Instagram and Twitter, which has been found to be effective in the long term in improving attitudes and behaviours of the general population towards people with severe mental disorders [21]. It is likely that in the next future the appropriate use of new communication technology will help to overcome stigma in an effective and cost-saving approach.

Stigmatization affects also psychiatrists and mental health professionals. In fact, the "public" image of psychiatry and psychiatrists is still negative and not attractive: the efficacy of pharmacological drugs or psychotherapeutic interventions in improving patients' outcome is often underestimated not only by the general public, but also by other medical professionals [22, 23]. People should be aware that psychotropic drugs are among the most effective interventions available in the whole medicine, and that antipsychotic or antidepressant medications have a higher efficacy compared with medications used in general medicine; nonetheless, the general perception is that these drugs are not effective and even harmful [24]. Also mental health services and facilities are neglected by policy makers at global level, often resulting in poor resources and support.

1.3 Changes Occurred at Clinical Level

1.3.1 New Mental Health Problems

Mental health has been traditionally defined as the absence of mental diseases but, more recently, mental health has been defined as a state of the organism which allows the full performance of all its functions, or as a state of balance within oneself and

between oneself and one's physical and social environment [25]. Therefore, mental disorders and mental well-being can be considered as lying on a continuum, being based at the opposite ends of a spectrum of conditions. On this continuum, other conditions can be identified and defined as "mental health problems", which are not proper mental disorders, but conditions associated with reduced function and personal impairment, requiring the management by mental health professionals.

The terms "mental health issues" or "mental health problems" are being increasingly used, highlighting the recently occurred shift in the target of psychiatry. In particular, some "traditional" mental disorders, such as hebephrenia, catatonia or hysteria, seem to be disappeared (at least in Western countries), whereas other forms of mental health problems are coming to attention, such as videogames addiction, vigorexia, orthorexia or cyberbullying. The World Health Organization has included the "gaming disorder" in the chapter of behavioural addictions of the new version of the International Classification of Diseases (ICD-11). Young people are considered "digital natives" and they can access an enormous amount of information, without any limit or control. Even if this represents one of the big achievements of modern society, it carries on several risks for young people, such as cyberbullying, cybersuicide, pro-ana and pro-mia websites [26, 27].

Psychiatrists and mental health professionals have reported that they are trained to manage these mental health problems. It is clear that these paradigmatic changes represent a challenge in a modern psychiatric practice [28].

1.3.2 Comorbidity and Mortality

A phenomenon observed in the modern society is that the life expectancy has globally increased with a subsequent rise in the number of years of life lived suffering from more than one disorders, and higher rates of impairment and disability [29]. Moreover, the growth of the elderly population has the direct consequence of a further increase in age-related diseases and in comorbid diseases [30].

People suffering from comorbid diseases represent a challenge for mental health professionals in terms of complexity of the clinical presentations and implications for their optimal management [31]. The most frequent comorbidity is with cardiovascular and metabolic disorders, and patients very often do not receive an adequate treatment due to stigma, discrimination and fragmentation of health services. All these factors contribute to increase the mortality gap between people with severe mental disorders and the general population [32].

Moreover, the increased rate of comorbid diseases negatively impacts on the quality of life of patients with severe mental disorders, such as schizophrenia or bipolar disorders. In fact, the levels of care they receive for their physical health is much lower than those received by the general population, further contributing to the mortality gap. Patients with severe mental disorders usually adopt unhealthy lifestyle behaviours and report a reduced life expectancy of at least 20 years compared to the general population [33]. Therefore, the promotion of physical health

in their patients and the management of the comorbid illnesses represent a clinical challenge and an ethical priority for all health professionals. It is necessary to promote research into comorbidity and rethink the organization of health care in order to facilitate detection, treatment and recovery of people affected by comorbid mental and physical disorders.

1.4 Changes Occurred at Treatment Level

1.4.1 Pharmacological Interventions

Since the discovery of chlorpromazine, iproniazid and chlordiazepoxide, several pharmacological compounds have been developed, mainly differing according to their pharmacodynamic targets and tolerability profiles. As pointed out by Leucht et al. [24], psychotropic drugs are the most effective drugs available in the whole medicine, even considering contextual factors, such as disease's severity, natural course of the disorder, duration and outcomes. However, pharmacological treatments have been found to be effective in controlled conditions, such as those of randomized controlled trails, defining the so-called efficacy. On the other hand, there is the need to promote real-world studies in order to test the "effectiveness" of such pharmacological interventions in routine conditions, evaluating the impact of several mediator and moderator factors (such as age, gender, presence of comorbidities, etc.) [33, 34].

Moreover, it is important to disseminate well-balanced, unambiguous and unconditioned information about psychotropic drugs and to reduce the psychological and cultural barriers which limit the use of psychotropic drugs [1]. A modern pharmacological strategy recently launched is represented by the new long-acting injectable formulation for antipsychotics (LAI), which can be useful for the long-term management of patients with schizophrenia. However, several barriers still persist in the prescription and routine use of LAI medications, although their efficacy, safety and tolerability have been clearly demonstrated. Patients still have concerns about the use of LAIs in terms of perception of being coerced, fear of needle or of side effects [35]. The adoption of a shared decision-making approach in proposing LAI treatments and other evidence-based treatments represents an important innovation in clinical practice and it is quite often adopted by the young generation of psychiatrists.

1.4.2 Biological Non-Pharmacological Interventions

Several biological non-pharmacological interventions have been developed in the last decades using neurostimulation or neuromodulation approaches. Neurostimulation treatments use electrical or magnetic stimulation targeting specific brain regions with non-invasive techniques, such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy

(ECT) and magnetic seizure therapy (MST), as well as invasive surgical techniques, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Most of these neurostimulation treatments have been studied and are currently used in patients with treatment-resistant depression or severe obsessive-compulsive disorder (OCD) who have failed to respond to standard treatments [36, 37].

In particular, the use of ECT in major depression is associated with a response rate of 64.4% and remission rate of 52.9% [38].

Moreover, the DBS and the rTMS have also been found to be promising for the management of addictions [39]. According to the consensus paper by Ekhtiari et al. [40], non-invasive brain stimulation techniques—mainly rTMS and transcranial-electrical stimulation (tES)—represent a novel treatment option for patients with substance-use disorders, targeting the underlying neuronal pathways of addictive behaviours. Nevertheless, available studies are very heterogeneous in the adopted methodology and in the outcome measures considered, and shared research protocols are needed with large samples of patients and with an adequate statistical power.

The level of acceptability and tolerability reported by patients treated with non-invasive brain stimulation procedures is quite good, considering that no significant differences have been found in terms of drop-out rates compared to patients receiving pharmacological treatments [41]. However, these neuromodulation approaches need some refinement, e.g. the daily administration schedule over several weeks can be a barrier limiting their routine care feasibility.

1.4.3 Psychosocial Interventions

The rapidly expanding use of electronic communication in the digital world has led to revolutionary changes in the provision of psychosocial interventions for people with severe mental disorders. Online psychotherapies and psychosocial interventions for promoting healthy lifestyle behaviours, which have been found to be effective in several RCTs [42], have the great advantage of being cost-saving and being accessible also from a distance.

A novel treatment approach, still in its infancy, is represented by the AVATAR therapy for the treatment of auditory verbal hallucinations in patients with psychosis [43]. The pioneer studies carried out so far have shown that the AVATAR therapy is very effective since it allows a face-to-face interaction with a digital representation (avatar), whose speech is very similar to that of auditory hallucinations. The therapist facilitates a dialogue in which the voice-hearer gradually gains increased control over the voice [44]. Another promising non-pharmacological approach is represented by the virtual reality treatments for patients suffering from anxiety disorders, phobias, PTSD or addictions [45]. In particular, virtual reality exposure therapy represents a new way for conducting exposure therapy using a computer-generated virtual environment in order to expose the patient to the feared situations. The virtual reality therapy aims to overcome the limitations of traditional therapy in terms of patient's engagement with the treatment.

The dissemination on a large scale of psychosocial interventions is still far from being achieved. It will require a change in professionals' attitudes and the evaluation of the role of non-specific factors in mental health practice, such as communication styles and therapeutic alliance, considering the widespread of Internet as modality for treatment delivery [46, 47]. Moreover, many psychotherapeutic and psychosocial interventions will be delivered through Internet, which will give the possibility to treat many patients who would not be reached otherwise (e.g. patients with social phobia, patients living in distant areas, etc.). Finally, these approaches will have to be provided according to an individualized therapeutic plan and possibly integrated with pharmacological interventions. Ideally, these integrated approach should be provided in modern, non-stigmatizing settings [48, 49].

1.5 The Role of Psychiatrists in the Modern Society

The role of psychiatrists has changed over time. As a profession, psychiatry has a role in regulating itself and deciding on acceptable practice, but it is also subjected to strong societal pressures and controlled by legislation [30] (Table 1.2).

In this context of historical changes, the relationship of psychiatry with the other branches of medicine has changed, as well as the role attributed to psychiatrists by the society [26]. Psychiatrists in their routine care deal with different clinical conditions, from addiction disorders to severe mental disorders, such as schizophrenia and bipolar disorder. In the modern society, the role of psychiatrists includes also the need to promote mental health in the general population and to prevent mental disorders. The discrepancy between the requirements of society and the modernization of medicine has generated a profound debate about contemporary psychiatric practice [50]. Although we are living in a transitioning period, this should be considered as a possibility of growth for our discipline [34]. The achievements of psychiatry obtained in the last 30 years, such as the spread of mental health services worldwide, the affirmation of the community-based model of care, the multidisciplinary approach, the patient centrality in the process of care, the consolidation of the stress-vulnerability model in the pathogenesis of mental disorders, the need for integrated treatments and the integration of biological, psychological and social components of mental disorders, must be highlighted and defended without ideological prejudices [34, 51].

In order to defend their own identity, psychiatrists will have to address important challenges, such as the need to identify the causal pathways underlying severe mental disorders and to develop new pharmacological compounds based on those underlying brain dysfunctions. Psychiatrists will also have to preserve the specific skills of the discipline, i.e. dealing not only with the brain, but with human suffering

Table 1.2 The new agenda for psychiatrists

• Contract with society
• Identification of casual pathways underlying severe mental disorders
• Person-centred and recovery-oriented approach
• Collaboration with all stakeholders

as well. In order to do so, they will have to continuously update their knowledge on the basis of the new discoveries and evidence-based findings. Moreover, neurobiological, social and behavioural aspects of mental disorders will have to be integrated in a modern unitary perspective of psychiatry, having a global vision of the patient and of his/her disorder, avoiding useless and dangerous reductionistic approaches. Such an approach will help to avoid uncritical practices and scientific homologations, focusing on the patient as a person and to establish a truly therapeutic relationship. Therefore, post-graduate training curricula will need to be updated taking into account the biological, psychological and social factors involved in the development and treatment of mental disorders.

Psychiatry is now taking a person-centred approach with a focus on recovery from mental disorders and empowerment of mentally ill persons. In order to achieve this aim, collaboration of psychiatrists with other health professionals, including nurses, psychologists, occupational therapists and social workers, should be reinforced in order to provide an integrated and multimodal package of care to patients [52]. Furthermore, patients and caregivers will have to be involved as much as possible in their treatment plans in order to fulfil patients' clinical, functional and personal priorities [53, 54].

All stakeholders involved in mental health, including professionals, policy makers, users and carers, the media, can have different expectations regarding the role of psychiatry and psychiatrists in the next decades. In any case, whatever competencies and roles are considered, the main responsibility of psychiatrists worldwide is to ensure that patients get the best possible consideration and the best available treatments they need and deserve.

Psychiatrists as leaders need not only to engage with the public, but also to educate them. At the same time, psychiatrists have a key responsibility in providing clinical leadership in the development, quality assurance, efficiency and protection of mental health services, which must be available to all citizens.

1.6 Conclusions

In recent years, many social, economic and scientific changes have had a significant impact on the clinical presentation of many mental disorders, giving rise of new mental disorders and mental health problems.

It seems that the majority of mental health professionals are not adequately trained and equipped for managing these new mental health problems. These represent some of the most frequently reported unmet needs in clinical practice, research and education, underlining the need for setting a new agenda for mental health professionals. The items of the new agenda will have to include the contract between psychiatry and society, the refinement of the psychiatric model of care according to a person-centred and recovery-oriented approach, the identification of the causal pathways underlying mental disorders. Many other items could be identified and added to the agenda in the next years, on the basis of the evolving target of psychiatry.

References

1. Maj M. Technical and non-technical aspects of psychiatric care: the need for a balanced view. World Psychiatry. 2014;13(3):209–10.
2. Torous J, Andersson G, Bertagnoli A, Christensen H, Cuijpers P, Firth J, Haim A, Hsin H, Hollis C, Lewis S, Mohr DC, Pratap A, Roux S, Sherrill J, Arean PA. Towards a consensus around standards for smartphone apps and digital mental health. World Psychiatry. 2019;18(1):97–8.
3. Catani C. Mental health of children living in war zones: a risk and protection perspective. World Psychiatry. 2018;17(1):104–5.
4. Arseneault L. The long-term impact of bullying victimization on mental health. World Psychiatry. 2017;16(1):27–8.
5. Fiorillo A, Malik A, Luciano M, Del Vecchio V, Sampogna G, Del Gaudio L, Rojnic Kuzman M, Jovanovic N, Nawka A, Volpe U. Challenges for trainees in psychiatry and early career psychiatrists. Int Rev Psychiatry. 2013;25(4):431–7.
6. Sartorius N. Lezioni di psichiatria per il nuovo millennio. Il Pensiero Scientifico Editore: Roma; 2010.
7. Robertson R. Globalization: social theory and global culture. London: SAGE; 1992.
8. Bhavsar V, Zhang S, Bhugra D. Conceptualizing globalization for mental health research. Int J Soc Psychiatry. 2019;65(2):87–91.
9. Ventriglio A, Torales J, Bhugra D. Psychiatry's future. Int J Soc Psychiatry. 2016;62(7):599–600.
10. Firth J, Torous J, Stubbs B, Firth JA, Steiner GZ, Smith L, Alvarez-Jimenez M, Gleeson J, Vancampfort D, Armitage CJ, Sarris J. The "online brain": how the Internet may be changing our cognition. World Psychiatry. 2019;18(2):119–29.
11. Kirkbride JB. Migration and psychosis: our smoking lung? World Psychiatry. 2017;16(2):119–20.
12. Fiorillo A. The complexity of vulnerability to psychosis. Epidemiol Psychiatr Sci. 2019;28(2):138–9.
13. Luciano M, Sampogna G, Del Vecchio V, Giacco D, Mulè A, De Rosa C, Fiorillo A, Maj M. The family in Italy: cultural changes and implications for treatment. Int Rev Psychiatry. 2012;24(2):149–56.
14. Thornicroft G, Bakolis I, Evans-Lacko S, Gronholm PC, Henderson C, Kohrt BA, Koschorke M, Milenova M, Semrau M, Votruba N, Sartorius N. Key lessons learned from the INDIGO global network on mental health related stigma and discrimination. World Psychiatry. 2019;18(2):229–30.
15. Thornicroft G. Shunned: discrimination against people with mental illness. Oxford: Oxford University Press; 2006.
16. Corrigan PW, River LP, Lundin RK, Penn DL, Uphoff-Wasowski K, Campion J, Mathisen J, Gagnon C, Bergman M, Goldstein H, Kubiak MA. Three strategies for changing attributions about severe mental illness. Schizophr Bull. 2001;27(2):187–95.
17. Cunningham R, Peterson D, Collings S. Like Minds, Like Mine: seventeen years of countering stigma and discrimination against people with experience of mental distress in New Zealand. In: The stigma for mental illness. The end of the story? Berlin: Springer; 2017. p. 263–87.
18. Henderson C, Evans-Lacko S, Thornicroft G. The Time To Change programme to reduce stigma and discrimination in England and its wider context. In: The stigma for mental illness. The end of the story? Berlin: Springer; 2017. p. 339–56.
19. Bratbo J, Kare Vedelsby A. ONE OF US: the national campaign for anti-stigma in Denmark. In: The stigma for mental illness. The end of the story? Berlin: Springer; 2017. p. 317–38.
20. Link BG, Stuart H. On revisiting some origins of the stigma concept as it applies to mental illnesses. In: The stigma of mental illness. The end of the story? Berlin: Springer; 2017. p. 3–28.
21. Sampogna G, Bakolis I, Evans-Lacko S, Robinson E, Thornicroft G, Henderson C. The impact of social marketing campaigns on reducing mental health stigma: results from the 2009-2014 Time To Change programme. Eur Psychiatry. 2017;40:116–22.

22. Beezhold J, Gaebel W, Galderisi S, Gorwood P, Martin-Carrasco M, Wasserman D, EPA Board Members. EPA position paper: improving the image of psychiatry and psychiatrists. Eur Psychiatry. 2017;42:24–6.
23. Bhugra D, Sartorius N, Fiorillo A, Evans-Lacko S, Ventriglio A, Hermans MH, Vallon P, Dales J, Racetovic G, Samochowiec J, Roca Bennemar M, Becker T, Kurimay T, Gaebel W. EPA guidance on how to improve the image of psychiatry and of the psychiatrist. Eur Psychiatry. 2015;30:423–30.
24. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry. 2012;200(2):97–106.
25. Galderisi S, Heinz A, Kastrup M, Beezhold J, Sartorius N. Toward a new definition of mental health. World Psychiatry. 2015;14(2):231–3.
26. Starcevic V, Aboujaoude E. Cyberchondria, cyberbullying, cybersuicide, cybersex: "new" psychopathologies for the 21st century? World Psychiatry. 2015;14(1):97–100.
27. Kato TA, Kanba S, Teo AR. Hikikomori: experience in Japan and international relevance. World Psychiatry. 2018;17(1):105–6.
28. Fiorillo A, Dell'Osso B, Maina G, Fagiolini A. The role of psychopathology in modern psychiatry. J Psychopathology. 2018;24:111–2.
29. Sartorius N. Comorbidity of mental and physical disorders: a key problem for medicine in the 21st century. Acta Psychiatr Scand. 2018;137(5):369–70.
30. Bhugra D, Tasman A, Pathare S, Priebe S, Smith S, Torous J, Arbuckle MR, Langford A, Alarcón RD, Chiu HFK, First MB, Kay J, Sunkel C, Thapar A, Udomratn P, Baingana FK, Kestel D, Ng RMK, Patel A, Picker L, McKenzie KJ, Moussaoui D, Muijen M, Bartlett P, Davison S, Exworthy T, Loza N, Rose D, Torales J, Brown M, Christensen H, Firth J, Keshavan M, Li A, Onnela JP, Wykes T, Elkholy H, Kalra G, Lovett KF, Travis MJ, Ventriglio A. The WPA-lancet psychiatry commission on the future of psychiatry. Lancet Psychiatry. 2017;4(10):775–818.
31. Fiorillo A, Luciano M, Pompili M, Sartorius N. Editorial: reducing the mortality gap in people with severe mental disorders: the role of lifestyle psychosocial interventions. Front Psych. 2019;10:434.
32. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiat. 2015;72(4):334–41.
33. Fiorillo A, Luciano M, Sampogna G. Being influential or being misleading? Citation bias in psychiatric research and practice. Epidemiol Psychiatr Sci. 2018;27:242–3.
34. Fiorillo A, Maj M. The role of psychiatry in modern medicine. Int Rev Psychiatry. 2018;30(2):169–75.
35. Potkin S, Bera R, Zubek D, Lau G. Patient and prescriber perspectives on long-acting injectable (LAI) antipsychotics and analysis of in-office discussion regarding LAI treatment for schizophrenia. BMC Psychiatry. 2013;13:261.
36. Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, Modirrousta M, Patry S, Vila-Rodriguez F, Lam RW, MacQueen GM, Parikh SV, Ravindran AV, CANMAT Depression Work Group. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can J Psychiatr. 2016;61(9):561–75.
37. Bilge MT, Gosai AK, Widge AS. Deep brain stimulation in psychiatry: mechanisms, models, and next-generation therapies. Psychiatr Clin North Am. 2018;41(3):373–83.
38. Ren J, Li H, Palaniyappan L, Liu H, Wang J, Li C, Rossini PM. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2014;51:181–9.
39. Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, Croarkin PE. Accelerated TMS for depression: a systematic review and meta-analysis. Psychiatry Res. 2019;273:770–81.

40. Ekhtiari H, Tavakoli H, Addolorato G, Baeken C, Bonci A, Campanella S, Castelo-Branco L, Challet-Bouju G, Clark VP, Claus E, Dannon PN, Del Felice A, den Uyl T, Diana M, di Giannantonio M, Fedota JR, Fitzgerald P, Gallimberti L, Grall-Bronnec M, Herremans SC, Herrmann MJ, Jamil A, Khedr E, Kouimtsidis C, Kozak K, Krupitsky E, Lamm C, Lechner WV, Madeo G, Malmir N, Martinotti G, McDonald W, Montemitro C, Nakamura-Palacios EM, Nasehi M, Noël X, Nosratabadi M, Paulus M, Pettorruso M, Pradhan B, Praharaj SK, Rafferty H, Sahlem G, Jo Salmeron B, Sauvaget A, Schluter RS, Sergiou C, Shahbabaie A, Sheffer C, Spagnolo PA, Steele VR, Yuan TF, van Dongen J, Van Waes V, Venkatasubramanian G, Verdejo-García A, Verveer I, Welsh J, Wesley MJ, Witkiewitz K, Yavari F, Zarrindast MR, Zawertailo L, Zhang X, Cha YH, George TP, Frohlich F, Goudriaan AE, Fecteau S, Daughters SB, Stein EA, Fregni F, Nitsche MA, Zangen A, Bikson M, Hanlon CA. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: a consensus paper on the present state of the science and the road ahead. Neurosci Biobehav Rev. 2019;104:118.
41. Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic review and meta-analysis of randomised sham-controlled trials. Neurosci Biobehav Rev. 2018;92:291–303.
42. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. Cogn Behav Ther. 2018;47(1):1–18.
43. Craig TK, Rus-Calafell M, Ward T, Leff JP, Huckvale M, Howarth E, Emsley R, Garety PA. AVATAR therapy for auditory verbal hallucinations in people with psychosis: a single-blind, randomised controlled trial. Lancet Psychiatry. 2018;5(1):31–40.
44. Craig TKJ. AVATAR therapy: a promising new approach for persistent distressing voices. World Psychiatry. 2019;18(1):98–9.
45. Mishkind MC, Norr AM, Katz AC, Reger GM. Review of virtual reality treatment in psychiatry: evidence versus current diffusion and use. Curr Psychiatry Rep. 2017;19(11):80.
46. Ritterband LM, Thorndike FP, Ingersoll KS, Lord HR, Gonder-Frederick L, Frederick C, Quigg MS, Cohn WF, Morin CM. Effect of a web-based cognitive behavior therapy for insomnia intervention with 1-year follow-up: a randomized clinical trial. JAMA Psychiat. 2017;74(1):68–75.
47. Naslund JA, Aschbrenner KA, Scherer EA, McHugo GJ, Marsch LA, Bartels SJ. Wearable devices and mobile technologies for supporting behavioral weight loss among people with serious mental illness. Psychiatry Res. 2016;244:139–44.
48. Alda M. Personalized psychiatry: many questions, fewer answers. J Psychiatry Neurosci. 2013;38(6):363–5.
49. Jovanović N, Campbell J, Priebe S. How to design psychiatric facilities to foster positive social interaction - a systematic review. Eur Psychiatry. 2019;60:49–62.
50. Fiorillo A, Volpe U, Bhugra D. Role and responsibilities of psychiatrists. In: Psychiatry in practice. Oxford: Oxford University Press; 2016.
51. De Rosa C, Sampogna G, Luciano M, Del Vecchio V, Fabrazzo M, Fiorillo A. Social versus biological psychiatry: it's time for integration! Int J Soc Psychiatry. 2018;64(7):617–21.
52. Pingani L, Fiorillo A, Luciano M, Catellani S, Vinci V, Ferrari S, Rigatelli M. Who cares for it? How to provide psychosocial interventions in the community. Int J Soc Psychiatry. 2013;59(7):701–5.
53. Fiorillo A, Luciano M, Del Vecchio V, Sampogna G, Obradors-Tarragó C, Maj M, ROAMER Consortium. Priorities for mental health research in Europe: a survey among national stakeholders' associations within the ROAMER project. World Psychiatry. 2013;12(2):165–70.

54. Wykes T, Haro JM, Belli SR, Obradors-Tarragó C, Arango C, Ayuso-Mateos JL, Bitter I, Brunn M, Chevreul K, Demotes-Mainard J, Elfeddali I, Evans-Lacko S, Fiorillo A, Forsman AK, Hazo JB, Kuepper R, Knappe S, Leboyer M, Lewis SW, Linszen D, Luciano M, Maj M, McDaid D, Miret M, Papp S, Park AL, Schumann G, Thornicroft G, van der Feltz-Cornelis C, van Os J, Wahlbeck K, Walker-Tilley T, Wittchen HU, ROAMER Consortium. Mental health research priorities for Europe. Lancet Psychiatry. 2015;2(11):1036–42.

Unmet Needs in Patients with Schizophrenia

2

Herbert Y. Meltzer

2.1 Introduction

The unmet needs of patients with schizophrenia are many, complex, and diverse. Addressing them will require the combined efforts of both basic and clinical researchers, clinical and social service providers, family members, and society at large, to meet these needs. This article will address those which are of the highest priority and possibly even attainable within a decade or less with technologies that are available or highly likely. What is less clear is the willingness and ability of society to support the effort in light of many competing needs for health care, the stigma associated with schizophrenia, and the recent retreat from schizophrenia research by some leading pharma companies. There is disagreement as to whether schizophrenia is a discrete disorder or part of a psychotic spectrum which includes bipolar disorder and psychotic depression, all of which share psychotic features, cognitive impairment and negative symptoms/depression. The US National Institute of Mental Health now rejects the idea of schzophrenia as a legitimate target for clinical treatment trials.

The brighter side of the ledger for meeting the needs of patients with schizophrenia is the vastly increased knowledge of the genetic architecture of schizophrenia and the relation to that of other neuropsychiatric disorders [1] and the many advances in the treatment of schizophrenia which have been made in the last 30 years, or on the cusp of approval, e.g., TAAR1 agonists [2], likely to be effective antipsychotic without causing extrapyramidal side effects(EPS),and possibly a dopamine (DA) D1 partial agonist, which is likely to be highly

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effective to improve working memory and other types of cognitive impairment, but not be antipsychotic as well [3].

2.2 The Importance of Optimal Use of the Atypical APDs

Atypical antipsychotic drugs (APDs) such as clozapine, risperidone, lurasidone, and olanzapine rely on potent serotonin (5-HT)2A receptor blockade and weak dopamine (DA) D2 receptor blockade plus other pharmacologic features, e.g. 5-HT1A partial agonism, 5-HT7 antagonism, in some of these drugs, to achieve their beneficial effects of the three major components of the schizophrenia syndrome. Their multitargeted pharmacology enables them to avoid moderate to severe extrapyramidal symptoms and tardive dyskinesia in most patients. This intern enhances compliance [4]. The failure to develop more effective treatments for the cognitive impairment associated with schizophrenia (CIAS) during this period is lamentable. This is compounded by lack of recognition that the atypical APDs provide clinically significant cognitive benefit for many individuals with schizophrenia, even if many receive no apparent benefit other than avoiding the detrimental effects of unopposed D2 receptor blockade [5]. Addressing this issue, especially with biomarkers to identify the likelihood of improvement in cognition by switching to a drug which is likely to be beneficial for cognition in the absence of other reasons for a switch would at least partially address this need. The use of clozapine to improve working memory, based, in part, on the indirect muscarinic agonist properties of its metabolite, N-desmethylclozapine, and effects on GABAergic transmission in the prefrontal cortex (PFC) and hippocampus, is an example of this [6] and will be discussed in more detail subsequently.

The development of a number of atypical APDs which share the main pharmacologic profile of clozapine, e.g., lurasidone, olanzapine, quetiapine, risperidone, and ziprasidone, and the partially novel atypical APDs, aripiprazole, brexpiprazole, and cariprazine, have contributed much to the well-being of millions of patients with schizophrenia, as have improvements in adherence to treatment resulting from long acting formulations. Beyond drug treatment, improved methods of administering electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS),more available psychosocial treatments, larger disability payments enabling community living rather than chronic hospitalization, have reduced symptoms and improved quality of life for many patients. However, the outcome for many patients with schizophrenia leaves much to be desired, especially with regard to cognitive impairment and overall function.

Despite the absence of a biological test to establish the diagnosis or monitor the success of efforts for prevention and treatment, and that not all patients manifest all of the major types of psychopathology, at a given time, or rarely anytime, and that none of these symptoms are unique to schizophrenia, it has been possible for clinicians to make the diagnosis of schizophrenia and differentiate patients from those with closely related disorders, e.g., bipolar disorder, autism spectrum disorder, and Huntington's disease. The discovery and utilization of APDs such as

chlorpromazine, which are highly effective in many patients with schizophrenia to treat for positive symptoms but had little impact on negative symptoms or CIAS, identified the development of better treatments for CIAS as the major unmet need. While some believe that no effective treatments for the cognitive impairment have been developed, there is much evidence to argue against this, as we and others have discussed elsewhere [5, 7, 8]. What is needed are more effective treatments for CIAS and negative symptoms, for those patients who experience little or no improvement in cognition, even when their positive symptoms are controlled by APDs or other somatic treatments.

2.3 The Need for a Wide Range of Treatments Based on the Heterogeneity of Schizophrenia

It is well established that schizophrenia is a syndrome with multiple causes which can be characterized as genetic and environmental and that both are multifactorial. The ultimate goal is identify which of the causal factors, e.g., a subset of the greater 150 risk genes of small effect [9] and more penetrant, bur rarer copy number variations and chromosomal abnormalities, that have been identified, and are pleiomorphic, causing various types of psychopathology in individual patients. This would guide developing and applying treatments which address the particular subset of causal factors that are etiologic for that individual should produce better outcome. The majority of the loci in the risk genes are intronic, indicating that factors regulating gene expression are especially relevant. Epigenetic processes which regulate gene expression, are, therefore, likely targets for novel therapies. The risk genesare enriched in those which regulate neurodevelopment and synaptic plasticity [10]. When the disease process involves combinations of genes which are rare, unique treatments may be needed to ameliorate the syndrome. Table 2.1 provides a list of the specific types of additional treatments which would be expected to meet the major unmet and partially met needs of patients with schizophrenia.

2.4 Improving Utilization of Current Treatments

There is a great need to improve utilization of current treatments known to be effective in schizophrenia. The use of APDs as first line treatments increased greatly following the publication of the NIMH-supported CATIE study [11] and the UK national Health service – supported CUtLASS study [12]. These studies in chronic outpatients found that typical and atypical drugs were comparable in terms of time to relapse and positive and negative symptom control with the exception of clozapine which has been established as an effective treatment of ~two thirds of patients with schizophrenia whose psychosis does not respond to two or more typical APDs. Critique of the conclusions of the CATIE and CUtLASS study may be found elsewhere [13, 14].

Table 2.1 Pharmacotherapy and other somatic treatments unmet or met partially for schizophrenia

1. Development of drugs or other somatic treatments for cognitive impairment unresponsive to current APDs with emphasis on avoidance of D2 receptor blockade
2. Development of drugs or other somatic treatments for delusions, hallucinations, and thought disorder unresponsive to current APDs with emphasis on avoidance of D2 receptor blockade
3. Development of drugs or other somatic treatments for negative symptoms unresponsive to current APDs with emphasis on avoidance of D2 receptor blockade
4. Development of drugs or other somatic treatment with rapid onset of action for one or more of the three main types of psychopathology noted in 1–3
5. Drugs effective for psychopathology of schizophrenia which rarely, if ever, produce extrapyramidal side effects, including tardive dyskinesia, weight gain, drowsiness, adverse endocrine effects, e.g., prolactin elevations
6. Development of or wider use of drugs and other therapies to reduce the side effects of current treatments, e.g., weight gain
7. Enable wider use of clozapine, especially for suicide risk mitigation, but also for treatment resistant psychopathology
8. Validation of genetic and other biomarkers for suicide in schizophrenia patients
9. Development of drugs other than clozapine for suicide risk reduction
10. Institution of precision medicine approach based on biomarker prediction of clinical response to permit optimal choice of drug treatment
11. Validation of cognitive remediation protocols which facilitate somatic treatments for cognitive impairment

Typical APDs are capable of controlling positive symptoms in about 70% of schizophrenia patients but do so through blockade of DA D2 receptors in the dorsal or ventral striatum. Effects on D2 receptors in other brain regions, and other pharmacologic effects of some typical APDs, e.g., alpha 1 adrenergic receptor blockade [15], may also contribute to the efficacy for treating positive symptoms or improving cognition. However, EPS, including tardive dyskinesia and neuroleptic malignant syndrome, are mechanism-based side effects, which make these drugs much less desirable than atypical APDs, which can control the positive symptoms with markedly fewer EPS and a lesser incidence of tardive dyskinesia.EPS contribute to lack of compliance with APD treatment for many reasons, including sedation, weight gain, sexual dysfunction, muscle rigidity, and loss of motoric flexibility. Long acting injectable forms typical APDs, e.g., fluphenazine decanoate and haloperidol decanoate, are preferred over oral typical APDs, if one of these agents is to be used. There is no reliable evidence that there are significant differences in efficacy between typicals APDs for control of positive symptoms, indicating multiple trials of different typical APDs will not improve outcome. Moreover, the use of anticholinergic drugs to treat the EPS of typical APDs will further worsen cognitive function in many patients. Thus, it is strongly recommended to avoid using these drugs to treat schizophrenia.

There is some evidence with clozapine, lurasidone, olanzapine, melperone, and risperidone that these drugs may required as much as 6 months before response is noted [16–18]. These trial should are best with monotherapy with any of these atypical APDs; concomitant use of typical APD could compromise the efficacy of the

atypical APDs. The basis for this recommendation for monotherapy is that the pharmacology which enables atypical APDs to be effective at low D2 receptor occupancy is heavily dependent upon their direct or indirect effects on a variety of 5-HT receptors, especially 5-HT2A and 5-HT1Areceptors,other5-HT6, 5-HT7, and 5-HT2C receptors [19] and a variety of other mechanisms [20]. The relative amount of D2 receptor blockade, the 5-HT2/D2 receptor ratio, is an important determinant of their efficacy. Additional D2 receptor blockade, even from a second atypical APD, has been shown to adversely affect the response to clozapine [21]. The atypicals also are indirect DA and ACh receptor agonists because of their ability to enhance the release of DA and ACh in the cortex, hippocampus, striatum, and other regions. The DA release will affect D1 and D4 receptor stimulation while the ACh release will affect muscarinic and nicotinic receptors. They also enhance glutamate, glycine, and serine release and modulate GABAerigc function. The value of these indirect effects on various DA and glutamate receptors have been identified in our laboratory in studies of mice which received the NMDAR antagonist, PCP, to induce deficits in various cognitive functions and social interaction, a model of negative symptoms. For example, the ability of the atypical APD, lurasidone, to enhance the ability of subeffective dose of the D4 agonists to improve novel object recognition in scPCP-treated mice [22]. However, the core issue of choice of type APD is their ability to improve cognition and to decrease the likelihood of improvement with an atypical APD should tardive dyskinesia develop [23]. There is some suggestion that clozapine is more effective than other atypical APDs for non-treatment resistant patients based on a meta-analysis [24]. However, the side effect of clozapine, including weight gain and sedation, coupled with the need for weekly blood drawing, does not favor the use of clozapine as a first line treatment for non-treatment resistant patients. The choice among the other atypical APDs should be based on their side effect profile, e.g., less weight gain, sedation, and prolactin elevations.Aripiprazole and lurasidone are favored in these regards. Cariprazine is a recently introduced atypical APD with pharmacology that is distinct from clozapine, lurasidone, olanzapine, etc., in that it is a DA D3 and D2 receptor partial agonist. It is like the other atypical APDs in having some 5-HT2A inverse agonism and 5-Ht1A partial agonism. However, it did notacetylcholine release in the prefrontal cortex or hippocampus [25]. As the effect of other atypical APDs to improve cognition in the subchronic PCP rodent model has been partially attributed to cortical and hippocampal ACh efflux, it will be of interest to study the effect of cariprazine in that model and patients with schizophrenia.

The ability of genetic variation to predict the improvement in total psychopathology and positive symptoms in acutely psychotic schizophrenia patients was predicted by a group of genes which are crucial for synaptic plasticity, including genes affecting synaptic adhesion (PTPRD, LRRC4C, NRXN1, ILIRAPL1, SLITRK1) and protein scaffolding (MAGI1, MAGI2, NBEA) which are essential for synaptic function; also synaptic plasticity-related genes (NRG1/3 and KALRN). The neuron-specific RNA alternative splicing regulator, RBFOX1, and ion channel genes, e.g., KCNA10, KCNAB1, KCNK9 and CACNA2D3 [26]. A meta-analysis largely confirmed these results [27]. There were no cognitive measures in these studies. Further

studies with other atypical APDs are needed to determine if synaptic related genes also are predictive of their ability to improve positive symptoms and, more importantly, cognition. If so, this would enable the development of biomarkers to predict choice of APDs. It is also of interest to determine if genes related to synaptic plasticity predict response in patients with chronic symptoms.

The core pharmacology of most atypical APDs is 5-HT2A inverse agonism, combined with weaker D2 receptor antagonism. The selective 5-HT2A inverse agonist, pimavanserin, combined with a subeffective dose of the atypical APD risperidone produced a more rapid antipsychotic response in chronic schizophrenic patients experiencing an acute exacerbation [28]. The more rapid response (2 vs 62 weeks on average) was accompanied by less weight gain, EPS, and prolactin elevations. Animal studies suggest this strategy would produce similar advantages with drugs such as olanzapine and clozapine which at typical doses produce excessive weight gain and sedation.

2.5 Is Remission Possible?

The goal to achieve "remission" in schizophrenia has received much attention since it was operationalized by Andreasen et al. [29]. Those criteria do not sufficiently consider the presence of cognitive impairment or a decline in function which can be inferred from comparison with siblings or the general population and allow for the presence of significant psychopathology and functional impairment. The standard applied in other areas of medicine, e.g., cancer treatment, to identify patients for whom treatment removes all biological evidence of any active disease process, has not and cannot be applied to schizophrenia, since the disease processes themselves are only partially understood and are so diverse.

We have described in detail a single patient with a psychotic spectrum disorder that included a near decade of severe treatment resistant schizophrenia was present prior to remission [18]. We will not repeat the justification for considering this remission here. What was most noteworthy was how rapidly her cognitive impairment ended when the process which led to remission began. Marked improvement occurred within weeks, was complete within 6 months, and has persisted for over 8 years to date. MRI scans within the 6 months period captured a significant increase in the grey matter of the anterior cingulate cortex and perhaps the subthalamic nucleus. This response occurred while she was receiving risperidone decanoate 100 mg biweekly. She had previously failed to respond to oral risperidone, a trial of clozapine and other atypical APDs. Noteworthy is that her illness began with a period of bipolar symptoms, followed by nearly two decades of psychotic depression, before the schizophrenia phase. Each of the prior periods of psychopathology also ceased but were replaced by other psychopathology. We are engaged in further study of this exceptional patient who may have some unique genetic makeup. A master gene like RBFOX which can produce many phenotypes through diverse downstream pathways is a possible candidate for such an exceptional course [1].

Monitoring the extent of inflammation present in patients with schizophrenia is an example of a biological measure which might indicate remission. There is extensive evidence of various types, including the risk gene,C4, in the major histocompatibility regions, for inflammation as part of the pathogenesis of schizophrenia, including cognitive impairment [10, 30, 31] as well as in some laboratory models of schizophrenia, e.g., subchronic treatment with the NMDAR antagonist, phencyclidine (PCP; [32]). In both cases, atypical APDs have been shown to reduce the evidence of inflammation in terms of cytokine levels [33]. Cellular evidence of inflammation in the brains of PCP treated rodents is well documented as is the ability of atypical APDs to reduce the inflammation [32]. Clinical trials with anti-inflammatory drugs suggest that inflammation is not a sufficient cause of the major components of the syndrome to remit in most patients, but anti-inflammatory agents, including anti-inflammatory nutraceuticals such as curcumin, may be helpful adjunctive treatments for some patients [34].

2.6 Increased Utilization of Clozapine for Suicide

Completed suicide occurs in about 5% of patients with schizophrenia, making it a major challenge. Clozapine is underutilized as a means to reduce the suicide rate in schizophrenia because of the risk of agranulocytosis and required white blood cell monitoring [35]. This is particularly unfortunate because of its well-validated advantage to reduce the risk for suicide in schizophrenia [36, 37], while the risk of mortality from agranulocytosis with clozapine is very slight.

2.7 Developing Novel APDS for Schizophrenia and Other Disorders Within the Psychotic Spectrum

Clozapine is not unique for efficacy in patients whose positive symptoms do not respond to typical APDs. Similar response rates have been found with other atypical APDs, including melperone, olanzapine, and risperidone [16]. Enormous progress has been made in the last decade to understand the biological basis of schizophrenia without yielding the means to definitively make the diagnosis or to establish sharp boundaries between the schizophrenia syndrome and schizoaffective disorder, bipolar disorder or major depression with psychotic features, the psychiatric disorders with which clinicians most often find themselves struggling to exclude before making the diagnosis of schizophrenia. These disorder share many symptoms, co-occur in the same families, risk genes, response to treatment, and clinical trajectory. A recent study from the Psychiatric Genomics Consortium (PGC) based on a genome wide association study of 232,964 cases and 494,182 controls, used genome-wide data from patients with clinical diagnoses of schizophrenia, bipolar disorder, major depression, autism spectrum disorder, Tourette syndrome, attention deficit/hyperactivity disorder, and anorexia nervosa to demonstrate crucial shared genetic architecture. Three groups emerged on which one was schizophrenia, clustered with bipolar

disorder and major depression, with shared genetic architectures, mood and psychotic symptoms (Cross-Disorder Group of the Psychiatric Genomic Consortium). The top locus linking all eight disorders mapped within *DCC*, a gene fundamental to dearly development of white matter connections in the brain and affective midline tract development in the brain. Of particular interest, the second strongest locus was RBFOX1, a master regulator of alternative splicing in the brain, which as mentioned above was atop predictor or of response to lurasidone. This study supports the conclusion that that schizophrenia, schizoaffective disorder, bipolar disorder, and major depression with psychotic features, sometime referred to as the Psychotic Spectrum Disorder, constitute a continuum [38]. Thus, finding biomarkers which allows the diagnosis of schizophrenia to be made with certainty will be very challenging.

2.8 Meeting the Need for Better Treatment for CIAS

Enhancement of the improvement in CIAS is perhaps at the top of the list of goals for improving outcome in schizophrenia. As noted above, atypical APDs are able to control positive symptoms in almost all patients with schizophrenia when used for sufficient time, at adequate doses, and with attention to possible negative effects of polypharmacy. While the atypical APDs are able to help many patients with schizophrenia, they do not help all. We have called attention to the remarkable data from the CATIE study that the atypical APDs were unable to improve cognition in patients with schizophrenia who had tardive dyskinesia [16, 23]. The N-desmethylclozapine-clozapine ratio in plasma has been shown to predict improvement in working memory in a subgroup of schizophrenia patients [6, 39, 40]. Neither NDMC or clozapine levels alone had predictive value. It has been suggested that this is due to the M1 agonism of NDMC, partially negated by the M1 agonism of clozapine. More than M1 agonism contributed to the cognitive enhancing effects of NDMC. Both NDMC and clozapine depress inhibitory synaptic transmission, leading to increased excitatory transmission in hippocampal cultured neurons [41]. It was suggested that was due to inhibition of post-synaptic GABA A receptors, although action on calcium–related mechanism of synaptic function may also be involved. We have recently found evidence for a reversion of GABAA to an excitatory rather than inhibitory influence on cortical excitatory neurons in several mouse models of CIAS [42].

2.9 Conclusions

The major conclusions of this study is that better utilization of available treatments, especially the atypical APDs, can contribute to meeting some of the needs of patients with schizophrenia, including improved cognition and reducing the risk for suicide. We lack systematic evidence that various atypical APDs, of diverse pharmacology,

given for prolonged periods, without adverse polypharmacy, might produce better outcome in many more patients. The development of biomarkers for predicting response to specific drugs is a real possibility that has been not adequately studied. But optimal use of available drugs alone will be insufficient for many patients because of the heterogeneity of the pathogenesis of the illness, and the possibility that some drug treatments, especially typical APDs, may limit or prevent the efficacy of atypical APDs.

The use of subeffective doses of atypical APDs with adjunctive 5-HT2A inverse agonism or D1 positive allosteric modulators might lead to better outcome.

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References

1. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic relationships, novel loci, and pleiotropic mechanism across eight psychiatric disorders. Cell. 2019;179:1466–82.
2. Krogmann A, Peters L, von Hardenberg L, Bödeker K, Nöhles VB, Correll CU. Keeping up with the therapeutic advances in schizophrenia: a review of novel and emerging pharmacological entities. CNS Spectr. 2019;24(S1):38–69.
3. Meltzer HY, Rajagopal L, Matrisciano F, Hao J, Svensson KA, Huang M. The allosteric dopamine D1 receptor potentiator, DETQ, ameliorates subchronic phencyclidine-induced object recognition memory deficits and enhances cortical acetylcholine efflux in male humanized D1 receptor knock-in mice. Behav Brain Res. 2019;361:139–15.
4. Meltzer HY, Roth BL. Lorcaserin and pimavanserin: emerging selectivity of serotonin receptor subtype-targeted drugs. J Clin Invest. 2013;123(12):4986–91.
5. Meltzer HY. Pharmacotherapy of cognition in schizophrenia. Curr Opin Behav Sci. 2015;4:115–21.
6. Meltzer HY. Attention must be paid: the association of plasma clozapine/NDMC ratio with working memory. Am J Psychiatry. 2015;172(6):502–4.
7. Désaméricq G, Schurhoff F, Meary A, Szöke A, Macquin-Mavier I, Bachoud-Lévi AC, Maison P. Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. Eur J Clin Pharmacol. 2014;70(2):127–34.
8. Malhotra AK, Burdick KE, Razi K, Bates JA, Sanders M, Kane JM. Ziprasidone-induced cognitive enhancement in schizophrenia: specificity or pseudospecificity? Schizophr Res. 2006;87(1–3):181–4.
9. Avramopoulos D. Recent advances in the genetics of schizophrenia. Mol Neuropsychiatry. 2018;4(1):35–51.
10. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, Tooley K, Presumey J, Baum M, Van Doren V, Genovese G, Rose SA, Handsaker RE, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Daly MJ, Carroll MC, Stevens B, McCarroll SA. Schizophrenia risk from complex variation of complement component 4. Nature. 2016;530(7589):177–83.
11. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353(12):1209–23.

12. Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). Arch Gen Psychiatry. 2006;63(10):1079–87.
13. Kraemer HC, Glick ID, Klein DF. Clinical trials design lessons from the CATIE study. Am J Psychiatry. 2009;166(11):1222–8.
14. Meltzer HY, Bobo WV. Interpreting the efficacy findings in the CATIE study: what clinicians should know. CNS Spectr. 2006;11(7 Suppl 7):14–24.
15. Svensson TH. Dysfunctional brain dopamine systems induced by psychotomimetic NMDA-receptor antagonists and the effects of antipsychotic drugs. Brain Res Brain Res Rev. 2000;31:320–9.
16. Meltzer HY. New trends in the treatment of schizophrenia. CNS Neurol Disord Drug Targets. 2017;16(8):900–6.
17. Meltzer HY, Lindenmayer JP, Kwentus J, Share DB, Johnson R, Jayathilake K. A six month randomized controlled trial of long acting injectable risperidone 50 and 100mg in treatment resistant schizophrenia. Schizophr Res. 2014;154(1–3):14–22.
18. Meltzer HY, Sim MY, Anderson A, Cannistraci C, Jayathilake K, Share DB, Lee M. A within-subject consideration of the psychotic spectrum disorder concept in a patient in remission associated with cortical gray matter recovery. CNS Neurosci Ther. 2018;24(7):641–51.
19. Roth BL, Sheffler DJ, Kroeze WK. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat Rev Drug Discov. 2004;3:353–9.
20. Kondej M, Stępnicki P, Kaczor AA. Multi-target approach for drug discovery against schizophrenia. Int J Mol Sci. 2018;19(10):3105.
21. Anil Yağcioğlu AE, Kivircik Akdede BB, Turgut TI, Tümüklü M, Yazici MK, Alptekin K, Ertuğrul A, Jayathilake K, Göğüş A, Tunca Z, Meltzer HY. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. J Clin Psychiatry. 2005;66(1):63–72.
22. Miyauchi M, Neugebauer NM, Meltzer HY. Dopamine D4 receptor stimulation contributes to novel object recognition: Relevance to cognitive impairment in schizophrenia. J Psychopharmacol. 2017;31(4):442–52.
23. Caroff SN, Davis VG, Miller DD, Davis SM, Rosenheck RA, McEvoy JP, Campbell EC, Saltz BL, Riggio S, Chakos MH, Swartz MS, Keefe RS, Stroup TS, Lieberman JA, CATIE Investigators. Treatment outcomes of patients with tardive dyskinesia and chronic schizophrenia. J Clin Psychiatry. 2011;72(3):295–303.
24. MasudaT, MisawaF, TakaseM, KaneJM, CorrellCU. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: a systematic review and meta-analysis of cohort studies. JAMA Psychiat. 2019. https://doi.org/10.1001/jamapsychiatry.2019.1702. [Epub ahead of print].
25. Huang M, He W, Kiss B, Farkas B, Adham N, Meltzer HY. The role of dopamine D_3 receptor partial agonism in cariprazine-induced neurotransmitter efflux in rat hippocampus and nucleus accumbens. J Pharmacol Exp Ther. 2019;371(2):517–25.
26. Li J, Yoshikawa A, Brennan MD, Ramsey TL, Meltzer HY. Genetic predictors of antipsychotic response to lurasidone identified in a genome wide association study and by schizophrenia risk genes. Schizophr Res. 2018;192:194–204.
27. Li J, Loebel A, Meltzer HY. Identifying the genetic risk factors for treatment response to lurasidone by genome-wide association study: a meta-analysis of samples from three independent clinical trials. Schizophr Res. 2018;199:203–13.
28. Meltzer HY, Elkis H, Vanover K, Weiner DM, van Kammen DP, Peters P, Hacksell U. Pimavanserin, a selective serotonin (5-HT)2A-inverse agonist, enhances the efficacy and safety of risperidone, 2mg/day, but does not enhance efficacy of haloperidol, 2mg/day: comparison with reference dose risperidone, 6mg/day. Schizophr Res. 2012;141(2–3):144–52.

29. Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry. 2005;162(3):441–9.
30. KoganS, OspinaLH, MittalVA, KimhyD. The impact of inflammation on neurocognition and risk for psychosis: a critical review. Eur Arch Psychiatry Clin Neurosci. 2019. https://doi.org/10.1007/s00406-019-01073-2. [Epub ahead of print].
31. Müller N. Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. Schizophr Bull. 2018;44(5):973–82.
32. Zhu S, Wang H, Shi R, Zhang R, Wang J, Kong L, Sun Y, He J, Kong J, Wang JF, Li XM. Chronic phencyclidine induces inflammatory responses and activates GSK3β in mice. Neurochem Res. 2014;39(12):2385–93.
33. Tourjman V, Kouassi É, Koué MÈ, Rocchetti M, Fortin-Fournier S, Fusar-Poli P. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. Schizophr Res. 2013;151(1–3):43–7.
34. Miodownik C, Lerner V, Kudkaeva N, Lerner PP, Pashinian A, Bersudsky Y, Eliyahu R, Kreinin A, Bergman J. Curcumin as add-on to antipsychotic treatment in patients with chronic schizophrenia: a randomized, double-blind, placebo-controlled study. Clin Neuropharmacol. 2019;42(4):117–22.
35. Horvitz-Lennon M, Donohue JM, Domino ME, Normand SL. Improving quality and diffusing best practices: the case of schizophrenia. Health Aff. 2009;28:701–12.
36. Meltzer HY. Clozapine: balancing safety with superior antipsychotic efficacy. Clin Schizophr Relat Psychoses. 2012;6:134–44.
37. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer JP, Potkin S, International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry. 2003;60(1):82–91.
38. YamadaY, MatsumotoM, IijimaK, SumiyoshiT. Specificity and continuity of schizophrenia and bipolar disorder: relation to biomarkers. Curr Pharm Des. 2019. https://doi.org/10.2174/1381612825666191216153508. [Epub ahead of print].
39. Weiner DM, Meltzer HY, Veinbergs I, Donohue EM, Spalding TA, Smith TT, Mohell N, Harvey SC, Lameh J, Nash N, Vanover KE, Olsson R, Jayathilake K, Lee M, Levey AI, Hacksell U, Burstein ES, Davis RE, Brann MR. The role of M1 muscarinic receptor agonism of N-desmethylclozapine in the unique clinical effects of clozapine. Psychopharmacology. 2004;177:207–16.
40. Molins C, Carceller-Sindreu M, Navarro H, Carmona C, Piñeiro M, Martínez E, Álvarez E, Portella MJ. Plasma ratio of clozapine to N-desmethylclozapine can predict cognitive performance in treatment-resistant psychotic patients. Psychiatry Res. 2017;258:153–7.
41. Ohno-Shosaku T, Sugawara Y, Muranishi C, Nagasawa K, Kubono K, Aoki N, Taguchi M, Echigo R, Sugimoto N, Kikuchi Y, Watanabe R, Yoneda M. Effects of clozapine and N-desmethylclozapine on synaptic transmission at hippocampal inhibitory and excitatory synapses. Brain Res. 2011;1421:66–77.
42. Kim Ss, Rajagopal L, Meltzer HY, Martina M. Increased NKCCI expression in mPFC pyramidal cells of the subchronic phencyclidine (scPCP) mouse model of schizophrenia causes a depolarizing shift of GABAA current reversal potential and mediates cognitive impairment. Program No. 610.21. 2019: Society for Neuroscience; 2019 [online].

The Unmet Needs for Major Depressive Disorder

3

Roger McIntyre and Hartej Gill

Major depressive disorder (MDD) is one of the leading causes of morbidity and mortality around the world [1]. Approximately 264 million people worldwide reported being depressed [2]. Moreover, it is estimated that one in five US adults report symptoms of depression in their lifetime and the prevalence of MDD can be as high as 16% [3, 4]. By 2030, MDD is expected to be the leading cause of disease burden around the world [5]. While the direct death toll numbers are low for brain-based mental illnesses, MDD is highly comorbid with a number of mortality risk factors such as suicide and cardiovascular disease (CVD) [6, 7]. Depression contributes to both the development, as well as the progression of CVD [8, 9] and CVD is the number one cause of mortality in MDD populations [3, 8, 10].

Moreover, MDD is the leading cause of disability with reported cognitive, affective, and physical symptoms [3]. It is characterized by a chronic clinical course of illness with over 50% of individuals reporting recurrent depressive episodes [11]. Currently, the underlying etiology and pathophysiology of MDD is largely unclear. However, over the last few decades, there have been significant

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advancements in new psychopharmacological, image guided neurostimulation, and psychotherapeutic approaches (i.e., cognitive behavioral therapy, mindfulness training). For example, new pharmacological treatments aim to go beyond targeting the monoamine system. Trials with glutamate targets such as ketamine offer promising results for a novel MDD treatment intervention [12]. Notwithstanding the novel developments in MDD treatment, there remains significant unmet needs for MDD treatment and management. Meeting these needs can reduce healthcare costs and improve patient outcomes by avoiding functional decline, and decreasing emergency room and hospital visits [13]. This chapter will review the greatest unmet needs for MDD: (1) the need for personalized and precision medicine (treatment response); (2) anti-suicide treatments and premature mortality; (3) treatments that are not harmful to physical health; (4) preventative treatments and rapidly attenuating interventions for MDD; (5) disease modification for MDD; (6) achieving patient and provider desired outcomes (PROs) and domain based outcomes.

3.1 Improving Patient Outcomes with Personalized and Precision Interventions

Currently, antidepressant medications are the most common treatment for depressive episodes and thus, they are one of the most commonly prescribed drugs worldwide [12, 14]. The selection of antidepressants is largely based on clinician preference, treatment availability, acquisition cost, and patient preference and tolerability [15]. The response rate for initial antidepressant treatment is reportedly between 50% and 75% [16]. While antidepressant efficacy can vary, drug-placebo differences in antidepressant response has been associated with the severity of baseline depressive symptoms. Individuals with higher baseline depression severity also respond poorly to psychotherapy as the primary treatment option [15]. Therefore, this can lead to multiple trials, poor treatment response, and patient frustration in response to the prolongation of MDD symptoms. Advances in personalized medicine can help to improve patient outcomes by identifying a priori which groups will best respond to different therapeutic approaches.

The current therapeutic framework for MDD symptomatology is not predictive of response to antidepressants and other therapeutic approaches. Current depression treatment guidelines recommend antidepressants as a first-line treatment option [17]. Approximately 25% of individuals that take antidepressants have been taking the medication for more than a decade. Overall, antidepressant use has increased 5% over the course of the last decade [18]. Moreover, the economic burden of depression has drastically increased over the course of the last two decades. Between 2005 and 2010, the health care costs for MDD has increased by approximately 22% to $210.5 billion in the USA [19]. However, due to the lack of validated biomarkers, clinicians are unable to predict the tolerability profile and treatment response for antidepressants. Current literature is inconclusive regarding the efficacy of antidepressant co-treatment compared to antidepressant monotherapy [16]. Further research is needed to accurately evaluate the effectiveness of antidepressant co-treatment in patient populations. Directing treatment to

appropriate individuals will help reduce the economic and social burden associated with MDD.

New pharmacogenetic approaches offer the possibility of incorporating an individual's genetic architecture when selecting treatment options. Pharmacogenomic studies show that specific genes can have moderating effects for antidepressant response. For example, single nucleotide polymorphisms (SNPs) including FK506-binding protein-5 (FKBP5), glutamate receptor ionotropic kainate-1 (GRIK1), and 4 (GRIK4) were shown to be associated with treatment response to citalopram [20]. Furthermore, a recent study looking at common genes associated with antidepressant response found that glucocorticoid receptor (GR) regulated genes are enriched in antidepressant response genes. [21]. Moreover, genome-wide association studies (GWAS) have attempted to identify polymorphisms that predict antidepressant response. A meta-analysis of Genome-Based Therapeutic Drugs for Depression (GENDEP) and Sequenced Treatment Alternatives to Relieve Depression (STAR∗D) studies used rare variant analysis to assess antidepressant response. After 12 weeks of antidepressant treatment, SNPs rs116692768 and rs76191705 (both involved in regulatory processes) were significantly associated with symptom improvement using citalopram/escitalopram [22]. At the gene level, findings were inconsistent but the OR4K2 gene was associated with depressive symptom improvement. Meanwhile, individuals carrying rare alleles (i.e., rs199718838 A, rs116972349 A, rs151057533 C, and rs147651981 T) showed lower symptom improvement. With STAR∗D, the opposite trend was observed. Participants with rare alleles had a mean improvement of 70.3% versus common allele carriers that showed a mean improvement of 59.78% [22]. Overall, there were no consistent effects observed at the gene level. Further testing is required to validate the biological meaningfulness of rare genetic variants in antidepressant response.

Notwithstanding the novel developments in pharmacogenetic testing, recent clinical trials have not shown improved efficacy and health outcomes to warrant regular testing in MDD patients [23]. A recent blinded randomized control trial testing the efficacy of pharmacogenomics in MDD patients found negative effects [23]. Therefore, current results do not justify the inclusion of pharmacogenetic testing into regular testing and intervention for MDD [24]. Current pharmacogenetic testing may be better utilized for informing tolerability profiles and adverse health outcomes associated with antidepressants [24]. Future research should aim to address concerns with cost-effectiveness and treatment efficacy for current pharmacogenetic testing in order to improve health outcomes for MDD.

3.2 Anti-Suicide Treatments and Premature Mortality Prevention

Suicide literature shows a differential risk for suicidal ideation, suicide attempts, self-harm, and completed suicide in individuals with a mental health disorder. Up to 90% of reported deaths by suicide involve a brain-based disorder [25] and the risk of a future suicide attempt increases with the number of comorbid mental disorders [26]. Individual risk for suicide is approximately 20 times greater in MDD

populations [2] and two-thirds of suicide cases involve a diagnosis of depression [7]. Individuals with a previous history of suicide are at an elevated risk for future attempts and the risk of suicide is significantly higher in individuals with a family history of psychiatric illness [7]. However, the risk factors for suicide in depressed populations are similar to the suicide risk factors in the general population [7]. Very few studies examine suicide in primary care settings and subsequently, the meaningfulness of findings is often inconclusive. Approximately one in four individuals experiencing suicidal ideation will progress to active planning and attempts within the first year of ideation onset [27]. Consequently, there is an important need for treatments with anti-suicide effects.

There is a need for a pathoetiological model of suicide. Currently, there is no pharmacological treatment shown to reduce the risk of suicide. Recent antidepressant clinical trials show improved measures of suicidality over the course of the last 17 years. However, a similar effect is also observed in placebo-drug trials. Therefore, it is unlikely that improvements in suicidality are due to enhanced treatment efficacy of antidepressants [28]. Moreover, psychosocial support and psychotherapy are used in an effort to improve health outcomes and resiliency of MDD patients. Trials with cognitive behavioral therapy (CBT) have been shown to reduce depressive symptomatology and prevalence of suicidality [27]. However, current trials only exist in a clinical framework. The therapeutic efficacy of CBT needs to be assessed in a primary care setting. Furthermore, new developments have been made with machine learning, artificial intelligence, GWAS studies, and internet cognitive behavioral therapy (iCBT) for reducing suicidality in MDD populations [27, 29, 30]. For example, a GWAS study on suicide attempts revealed higher polygenic risk scores in MDD patients [31]. As a result, there may be a genetic component for the elevated risk of suicide in depressed patients. Moreover, a six lesson iCBT course resulted in significant reductions in suicidal ideation, offering the possibility for internet-based MDD therapies to have anti-suicide effects. Electronic administration of treatments can also improve cost-effectiveness, availability, and tolerability [32]. However, suicidal ideation does not directly inform us about the risk for suicide attempts. Rather, there appears to be an association between suicide attempt risk and the number of comorbid disorder [33]. Consequently, the anti-suicide effects of the aforementioned treatments will need to be unequivocally proven.

3.3 Treatments that Are Not Harmful for Physical Health and Help from Physical Comorbidities

Clinical, genetic, and environmental factors work together to shape individual response to antidepressant therapy [34]. Although SSRIs and SNRIs have fewer adverse effects compared to monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), the tolerability of the antidepressants may vary and patients report adverse effects such as headaches, gastrointestinal issues, insomnia, fatigue, and initial anxiety [34]. Also, SNRIs may cause restlessness and sexual dysfunction, and induce more nausea, insomnia, dry mouth, and sometimes high blood pressure than do SSRIs [34]. For example, the Food and Drug Administration (FDA) claims

that in patients testing positive for the HLA-B∗1502 allele, administration of carbamazepine may cause life-threatening skin reactions [35]. Through short-term pharmacogenetics/pharmacogenomics testing, adverse effects associated with antidepressant therapy may be predicted [24]. The pharmacological properties of antidepressants may help predict tolerability profiles [12]. Further research on treatments that are not harmful to physical health can help avoid the unwanted adverse effects present with first- and second-line antidepressants.

Obesity metastasizes the brain and is one of the most common physical comorbidities of MDD, with an estimated 350–500 million individuals affected by both disorders worldwide [36]. Several cross-sectional research trials have indicated a reciprocal link between obesity and depression [37]. That is, obese individuals are at an elevated risk to be depressed and depressed individuals are at an elevated risk for obesity. Notwithstanding the known association between obesity and MDD, mechanisms responsible for this effect remain unclear. Dysregulation of inflammatory pathways, changes in the hypothalamic pituitary adrenal (HPA)-axis, insulin resistance, and psychological distress resulting from obesity may all be factors that contribute to the association between obesity and depression (De Zwaan et al. 2011). However, a biological pathway that mediates the link between depression and obesity remains unclear [37]. Economically, the cost of treatment of both depression and obesity is an additional complication that often limits the effectiveness of treatment [38]. Thus, treatment methods simultaneously targeting both obesity and depression may help improve physical and mental health outcomes.

Stress, fatigue, physical inactivity, and a sedentary lifestyle can advance obesity and subsequently, contribute to a number of mental disorders [39]. Exercise has been shown to increase neurogenesis and plasticity in the hippocampus, which plays a major role in the pathophysiology of depressive disorders [40]. There is a positive dose-effect relationship between the amount of exercise and the resulting therapeutic benefits, where exercise at the recommended level can reduce the risk for future mental disorders. In an epidemiological study looking at the childhood activity of randomly selected men and women, it was shown that individuals that reported low levels of exercise in childhood had 35% higher prevalence of depression compared to individuals that reported high or moderate levels of childhood exercise [41]. A meta-analysis of randomized control trials examining exercise interventions in depressed individuals suggests that a large and significant effect of exercise on depression exists [42]. The largest effects existed for MDD, and within MDD, moderate intensity aerobic exercises showed the greatest success. Overall, current research supports exercise as an evidence-based treatment for MDD [42].

3.4 Preventative Treatments and Rapidly Attenuating Interventions for MDD

The increasing prevalence of depression among adolescents underscores the need for early preventative treatments. MDD is the leading cause of morbidity in adolescents. Approximately 60–80% depressed adolescents do not receive sufficient

treatment [43]. Reducing the disease burden of MDD will begin with improving remission and preventing new cases. Preventative interventions can lower depression incidence by 21% [44]. However, more effective preventative treatments (both pharmacological and non-pharmacological) are necessary to improve patient outcomes and reduce early mortality in MDD populations.

For treatment resistant MDD, intravenous racemic ketamine and intranasal esketamine provide rapid onset effects that reduce depression symptomatology within 24 h following administration [45–48].

In a randomized clinical trial with 67 adult patients, response to intranasally administered esketamine persisted for more than 2 months, and higher doses (56 mg or 84 mg) were associated with greater efficacy [49]. Subsequently, intranasally administered esketamine trials offer significant and clinically meaningful improvements compared to placebo trials [49]. However, these findings have not been replicated with the oral administration of ketamine [50]. While initial trials for ketamine are very promising, clinicians will need to account for the potential adverse effects associated with ketamine treatment. During the initial 4 h following intravenous ketamine administration in 97 MDD patients, drowsiness, dizziness, poor coordination, blurred vision, and feelings of strangeness/unrealness were the most commonly reported adverse effects [51]. A dose-response trend existed for dizziness and nausea in some patients [49]. Small, but significant psychotomimetic effects, were also observed in some patients but they did not persist [51]. However, the potential benefits of ketamine treatment outweigh reported adverse effects. Recent trials have shown promise for ketamine to have anti-suicide effects, as well as reduce inflammation and pro-apoptotic molecules in MDD patients [52, 53].

Additionally, diagnostic heterogeneity makes the diagnosis of depression difficult and MDD often receives a single label. Neuroimaging biomarkers can help diagnose and differentiate subtypes of depression. Resting state functional magnetic resonance imaging (rsfMRI) is able to predict four subtypes of depression by categorizing abnormal connectivity in the frontostriatal and limbic brain networks of depressed individuals [54]. For all four subtypes, abnormal connectivity in the frontostriatal and limbic network was correlated with severity scores on the mood, fatigue, and anhedonia components of the Hamilton Depression Rating Scale (HAM-D) [54]. Connectivity biomarkers were also able to accurately predict responsiveness to rTMS with greater accuracy than clinical features alone. MDD is associated with hypoconnectivity between the amygdala and cognitive control regions. Longitudinal functional principal components analysis (LFPCA) on the functional connectivity of the bilateral amygdala with the fronto-parietal network showed increases in connectivity following CBT in unmedicated patients [55].

3.5 Disease Modification

Changing the course of illness and altering the disease state of MDD are important next steps for improving patient outcomes. Currently, 25% of individuals treated with antidepressant medication continue to rely on the medication for a decade or more [18]. Notwithstanding the advances in antidepressants and other non-invasive

interventions (i.e., CBT, rTMS), the need for treatments with long-lasting effects is of great importance. The lack of validated biomarkers makes predicting patient outcomes difficult. The current understanding of biomarkers for MDD remains rudimentary. Differential responsiveness of a treatment can be tested using biomarkers [20]

Literature shows that only 50% of MDD patients respond to the first line of treatment [56]. Between 10% and 20% report permanent disability due to MDD [57]. To expedite the introduction of subsequent treatment plans, or to improve remission time, it is important to identify patients unlikely to respond to the initial treatment [56]. It has been suggested that a predictor of positive response to antidepressant therapy may be increased pretreatment activity in the pregenual anterior cingulate cortex in response to subliminal emotional information (i.e., brief, masked presentations of happy, and sad facial expressions) [56]. However, there are likely many causal mechanisms for predicting treatment response and it is unlikely for a single biomarker with enough sensitivity and specificity to guide treatment. A combination of many biomarkers can help guide treatment. This is known as the biopanel approach. Moreover, there are two types of widely recognized biomarkers. We can either have a diagnostic biomarker (presence or absence of a disease) or treatment biomarker that helps determine treatment response. Also, treatment moderators indicate under what conditions treatment works. They can also be useful for remodeling therapeutic approaches and treatment decision making [20].

Increasing evidence suggests that dysregulation of growth factors and pro-inflammatory processes may help guide the discovery of treatment biomarkers [20]. Pro-inflammatory cytokines seem to aggregate further in MDD patients compared to the general population [58]. A meta-analysis of 51 studies illustrated elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6) in individuals with MDD [59]. Additionally, damage in the cerebral vasculature is a distinct feature in MDD further suggests the presence of strong pro-inflammatory effects [9]. A high degree of prefrontal cortical dendritic spine instability and diminished brain derived neurotrophic factor (BDNF) mRNA expression due to increased stress hormone exposure also negatively impacts cortical structure. BDNF is a protein that stabilizes cortical neural structure and decline in BDNF is associated with vulnerability to depression symptomatology [60]. Furthermore, alterations in glucocorticoid receptors leads to chronic stress activation, HPA-dysfunction, and increased cortical awakening response in MDD patients [61]. Further research exploring these potential treatment moderators may help develop a biopanel of treatment indicators and moderators that guide treatment response, improve patient reported outcomes (PROs), and reduce the economic burden associated with MDD.

3.6 Domain Based and Patient Reported Outcomes in MDD

Despite significant advances in available MDD treatment, the majority of patients still fail to achieve societal and patient expected therapeutic outcomes [62]. Less than 50% of individuals report being depression-free following treatment [63].

Also, individuals that do achieve remission fail to gain complete functional recovery [64, 65]. All symptoms as part of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V are weighted equally. A combination of 681 symptoms meet the DSM criteria for depression [11]. This allows for many unique combinations of mood, appetite, sleep, energy, cognition, and motor activity [54]. However, literature suggests that the DSM reported depressive symptoms should not be considered equal in context to their contribution to patient outcomes. For example, it is shown that some depressive symptoms, such as hopelessness, have a stronger association with suicidal outcomes [25]. New treatment approaches should integrate multi-dimensional symptom relief for MDD; this includes targeting dimensions of anhedonia, motivation, and apathy. These are often associated with poor patient outcomes following treatment.

There are better overall health outcomes and PROs associated with improvements in cognition and/or anhedonia. MDD presents clinically significant deficits in cognition. However, 50% of MDD patients receive no assessment for cognitive deficits [66]. Residual cognitive symptoms impair functioning, contribute to workplace absenteeism, and lead to poor quality of life [67–69]. Approximately 15% of MDD patients attribute their unemployment to their cognitive symptoms [68]. Population level studies show that improvements in cognition are associated with better health outcomes [70]. Therefore, cognitive deficits may be used as a prognostic marker for identifying at-risk populations and help monitor disease onset and progression [71]. Similarly, anhedonic features are associated with decreased pleasure, poor quality of life, and negative mood [72]. At least one-third of MDD patients report clinically significant anhedonic features [73]. Improvements in mood are often the number one patient outcome expectations [74, 75]. However, restoration of positive mood is often not met and standard antidepressants may worsen mood [74]. For this reason, selected treatments should improve anhedonic and cognitive features in MDD.

3.7 Conclusion

Major depressive disorder is one of the leading causes of disability worldwide with a lifetime prevalence of one in six among adults [76]. Currently, no distinct mechanism exists to describe the various aspects of the disease and approximately 30% of patients fail to remit even after numerous treatment attempts [76]. This contributes to the economic burden of MDD. However, novel advancements in pharmacogenetics may provide clinicians with the opportunity to predict treatment outcome prior to administration, making therapeutic approaches more personalized to individual patients. Non-pharmacological treatments with minimal adverse physical effects, such as CBT, offer benefits to current pharmacological treatments may lack. Developments in preventative treatments as well as treatments that rapidly attenuate MDD symptomatology are also important in reducing the disease burden of MDD. The ability to identify mechanisms and biomarkers that rapidly attenuate

depressive symptoms, target secondary comorbidities such as cognition, anhedonia, and CVD, elicit anti-suicide effects, and limit the number of adverse health effects are of important clinical and public health relevance.

References

1. Depression. n.d. https://www.who.int/en/news-room/fact-sheets/detail/depression. Accessed 15 Aug 2019.
2. Ritchie H, Roser M. Mental health. Our world in data. 2018. https://ourworldindata.org/mental-health.
3. Halaris A. Inflammation-associated co-morbidity between depression and cardiovascular disease. Curr Top Behav Neurosci. 2017;31:45–70.
4. Weinberger AH, Gbedemah M, Martinez AM, Nash D, Galea S, Goodwin RD. Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. Psychol Med. 2018;48(8):1308–15.
5. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):e442.
6. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J. 2014;35(21):1365–72.
7. Hawton K, Casañas I, Comabella C, Haw C, Saunders K. Risk factors for suicide in individuals with depression: a systematic review. J Affect Disord. 2013;147(1–3):17–28.
8. Gathright EC, Goldstein CM, Josephson RA, Hughes JW. Depression increases the risk of mortality in patients with heart failure: a meta-analysis. J Psychosom Res. 2017;94:82–9.
9. Penninx BWJH. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. Neurosci Biobehav Rev. 2017;74(Pt B):277–86.
10. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med. 2004;66(6):802–13.
11. Akil H, Gordon J, Hen R, Javitch J, Mayberg H, McEwen B, et al. Treatment resistant depression: a multi-scale, systems biology approach. Neurosci Biobehav Rev. 2018;84:272–88.
12. Dale E, Bang-Andersen B, Sánchez C. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. Biochem Pharmacol. 2015;95(2):81–97.
13. Xiang X, An R, Heinemann A. Depression and unmet needs for assistance with daily activities among community-dwelling older adults. The Gerontologist. 2018;58(3):428–37.
14. Lopez JP, Fiori LM, Cruceanu C, Lin R, Labonte B, Cates HM, et al. MicroRNAs 146a/b-5 and 425-3p and 24-3p are markers of antidepressant response and regulate MAPK/Wnt-system genes. Nat Commun. 2017;8:15497.
15. McIntyre RS, Suppes T, Tandon R, Ostacher M. Florida best practice psychotherapeutic medication guidelines for adults with major depressive disorder. J Clin Psychiatry. 2017;78(6):703–13.
16. Galling B, Ferrer AC, Daou MAZ, Sangroula D, Hagi K, Correll CU. Safety and tolerability of antidepressant co-treatment in acute major depressive disorder: results from a systematic review and exploratory meta-analysis. Expert Opin Drug Saf. 2015;14:1587–608. https://doi.org/10.1517/14740338.2015.1085970.
17. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can J Psychiatry. 2016;61(9):540–60.
18. Pratt LA, Brody DJ, Gu Q. Antidepressant use among persons aged 12 and over: United States, 2011-2014. NCHS Data Brief. Number 283. National Center for Health Statistics. 2017. https://eric.ed.gov/?id=ED575709.

19. Greenberg PE, Fournier A-A, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry. 2015;76(2):155–62.
20. Schmidt HD, Shelton RC, Duman RS. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology. 2011;36(12):2375–94.
21. Carrillo-Roa T, Labermaier C, Weber P, Herzog DP, Lareau C, Santarelli S, et al. Common genes associated with antidepressant response in mouse and man identify key role of glucocorticoid receptor sensitivity. PLoS Biol. 2017;15(12):e2002690.
22. Fabbri C, Tansey KE, Perlis RH, Hauser J, Henigsberg N, Maier W, et al. New insights into the pharmacogenomics of antidepressant response from the GENDEP and STAR∗D studies: rare variant analysis and high-density imputation. Pharmacogenomics J. 2018;18:413–21. https://doi.org/10.1038/tpj.2017.44.
23. Rosenblat JD, Lee Y, McIntyre RS. The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: a meta-analysis. J Affect Disord. 2018;241:484–91.
24. Zeier Z, Carpenter LL, Kalin NH, Rodriguez CI, McDonald WM, Widge AS, Nemeroff CB. Clinical implementation of pharmacogenetic decision support tools for antidepressant drug prescribing. Am J Psychiatry. 2018;175(9):873–86.
25. Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15(8):868–76.
26. Wunderlich U, Bronisch T, Wittchen HU. Comorbidity patterns in adolescents and young adults with suicide attempts. Eur Arch Psychiatry Clin Neurosci. 1998;248(2):87–95.
27. Watts S, Newby JM, Mewton L, Andrews G. A clinical audit of changes in suicide ideas with internet treatment for depression. BMJ Open. 2012;2(5):e001558. https://doi.org/10.1136/bmjopen-2012-001558.
28. Khan A, Fahl Mar K, Gokul S, Brown WA. Decreased suicide rates in recent antidepressant clinical trials. Psychopharmacology. 2018;235(5):1455–62.
29. Mullins N, Bigdeli TB, Børglum AD, Coleman JRI, Demontis D, Mehta D, et al. GWAS of suicide attempt in psychiatric disorders and association with major depression polygenic risk scores. Am J Psychiatry. 2019;176(8):651–60.
30. Simon GE, Johnson E, Lawrence JM, Rossom RC, Ahmedani B, Lynch FL, et al. Predicting suicide attempts and suicide deaths following outpatient visits using electronic health records. Am J Psychiatry. 2018;175(10):951–60.
31. Mullins N, Bigdeli TB, Børglum AD, Coleman JRI, Demontis D, Fanous AH, et al. Genome-wide association study of suicide attempt in psychiatric disorders identifies association with major depression polygenic risk scores. bioRxiv. 2018:416008. https://doi.org/10.1101/416008.
32. Andrews G, Basu A, Cuijpers P, Craske MG, McEvoy P, English CL, Newby JM. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: an updated meta-analysis. J Anxiety Disord. 2018;55:70–8. https://doi.org/10.1016/j.janxdis.2018.01.001.
33. Nock MK, Hwang I, Sampson N, Kessler RC, Angermeyer M, Beautrais A, et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO World Mental Health Surveys. PLoS Medicine. 2009;6(8):e1000123.
34. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. Drugs Context. 2015;4:1.
35. Ferrell PB, McLeod HL. Carbamazepine, HLA-B∗1502 and risk of Stevens–Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008;9(10):1543–6.
36. García-Toro M, Vicens-Pons E, Gili M, Roca M, Serrano-Ripoll MJ, Vives M, et al. Obesity, metabolic syndrome and Mediterranean diet: impact on depression outcome. J Affect Disord. 2016;194:105–8.

37. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, Zitman FG. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010;67(3):220–9.
38. Krogh J, Speyer H, Gluud C, Nordentoft M. Exercise for patients with major depression: a protocol for a systematic review with meta-analysis and trial sequential analysis. Syst Rev. 2015;4:40.
39. Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M. Lifestyle medicine for depression. BMC Psychiatry. 2014;14:107.
40. Liu W, Ge T, Leng Y, Pan Z, Fan J, Yang W, Cui R. The role of neural plasticity in depression: from hippocampus to prefrontal cortex. Neural Plast. 2017;2017:6871089.
41. Jacka FN, Kremer PJ, Berk M, de Silva-Sanigorski AM, Moodie M, Leslie ER, et al. A prospective study of diet quality and mental health in adolescents. PLoS One. 2011;6(9):e24805.
42. Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB, Stubbs B. Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. J Psychiatr Res. 2016;77:42–51.
43. Rohde P, Brière FN, Stice E. Major depression prevention effects for a cognitive-behavioral adolescent indicated prevention group intervention across four trials. Behav Res Ther. 2018;100:1–6.
44. van Zoonen K, Buntrock C, Ebert DD, Smit F, Reynolds CF 3rd, Beekman ATF, Cuijpers P. Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. Int J Epidemiol. 2014;43(2):318–29.
45. Singh I, Morgan C, Curran V, Nutt D, Schlag A, McShane R. Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. The Lancet Psychiatry 2017;4(5):419–26.
46. Singh JB, Fedgchin M, Daly EJ, De Boer P, Cooper K, Lim P, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am J Psychiatry. 2017;173(8):816–26.
47. Mathew SJ, Zarate CA, Jr. (Eds.). Ketamine for Treatment-Resistant Depression: The First Decade of Progress. Adis, Cham. 2016.
48. de Zwaan M, Enderle J, Wagner S, Mühlhans B, Ditzen B, Gefeller O, et al. Anxiety and depression in bariatric surgery patients: a prospective, follow-up study using structured clinical interviews. J Affect Disord. 2011;133(1-2):61–8
49. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiat. 2018;75(2):139–48.
50. Rosenblat JD, Carvalho AF, Li M, Lee Y, Subramanieapillai M, McIntyre RS. Oral ketamine for depression: a systematic review. J Clin Psychiatry. 2019;80(3):18r12475. https://doi.org/10.4088/JCP.18r12475.
51. Wan L-B, Levitch CF, Perez AM, Brallier JW, Iosifescu DV, Chang LC, et al. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. J Clin Psychiatry. 2015;76(3):247–52.
52. Liang SH-Y, Yang Y-H, Kuo T-Y, Liao Y-T, Lin T-C, Lee Y, et al. Suicide risk reduction in youths with attention-deficit/hyperactivity disorder prescribed methylphenidate: a Taiwan nationwide population-based cohort study. Res Dev Disabil. 2018;72:96–105.
53. Zhang W, Sun Q, Jia L, Li M. Ketamine exerts a protective role in a cell-based model of major depressive disorder via the inhibition of apoptosis and inflammation and activation of the Krebs cycle. Bosn J Basic Med Sci. 2019. https://doi.org/10.17305/bjbms.2019.4222.
54. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2017;23(1):28–38.
55. Shou H, Yang Z, Satterthwaite TD, Cook PA, Bruce SE, Shinohara RT, et al. Cognitive behavioral therapy increases amygdala connectivity with the cognitive control network in both MDD and PTSD. NeuroImage: Clinical. 2017;14:464–70.

56. Godlewska BR, Browning M, Norbury R, Igoumenou A, Cowen PJ, Harmer CJ. Predicting treatment response in depression: the role of anterior cingulate cortex. Int J Neuropsychopharmacol. 2018;21(11):988–96.
57. Jaeger J, Berns S, Loftus S, Gonzalez C, Czobor P. Neurocognitive test performance predicts functional recovery from acute exacerbation leading to hospitalization in bipolar disorder. Bipolar Disord. 2007;9(1–2):93–102.
58. Lakhan SE, Vieira K, Hamlat E. Biomarkers in psychiatry: drawbacks and potential for misuse. Int Arch Med. 2010;3:1.
59. Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimäki M. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. Brain Behav Immun. 2015;49:206–15.
60. Gourley SL, Swanson AM, Koleske AJ. Corticosteroid-induced neural remodeling predicts behavioral vulnerability and resilience. J Neurosci Off J Soc Neurosci. 2013;33(7):3107–12.
61. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med. 2011;73(2):114–26.
62. McIntyre RS, Lee Y, Mansur RB. Treating to target in major depressive disorder: response to remission to functional recovery. CNS Spectr. 2015;20(Suppl 1):20–30; quiz 31.
63. Rush AJ. STAR∗D: what have we learned? Am J Psychiatry. 2007;164(2):201–4.
64. Cuijpers P, de Graaf R, van Dorsselaer S. Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. J Affect Disord. 2004;79(1–3):71–9.
65. Lee Y, Rosenblat JD, Lee J, Carmona NE, Subramaniapillai M, Shekotikhina M, et al. Efficacy of antidepressants on measures of workplace functioning in major depressive disorder: a systematic review. J Affect Disord. 2018;227:406–15.
66. Baune BT, Harmer C. Cognitive dimensions of major depressive disorder. Oxford: Oxford University Press; 2019.
67. Baune BT, Miller R, McAfoose J, Johnson M, Quirk F, Mitchell D. The role of cognitive impairment in general functioning in major depression. Psychiatry Res. 2010;176(2–3):183–9.
68. Druss BG, Schlesinger M, Allen HM Jr. Depressive symptoms, satisfaction with health care, and 2-year work outcomes in an employed population. Am J Psychiatry. 2001;158(5):731–4.
69. Lawrence C, Roy A, Harikrishnan V, Yu S, Dabbous O. Association between severity of depression and self-perceived cognitive difficulties among full-time employees. Prim Care Companion CNS Disord. 2013;15(3):PCC.12m01469. https://doi.org/10.4088/PCC.12m01469.
70. Beddington J, Cooper CL, Field J, Goswami U, Huppert FA, Jenkins R, et al. The mental wealth of nations. Nature. 2008;455(7216):1057–60.
71. Zuckerman H, Pan Z, Park C, Brietzke E, Musial N, Shariq AS, et al. Recognition and treatment of cognitive dysfunction in major depressive disorder. Front Psychiatry. 2018;9:655.
72. Black DW, Grant JE. DSM-5 guidebook: the essential companion to the diagnostic and statistical manual of mental disorders. 5th ed. Washington: American Psychiatric Publishing; 2014.
73. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? Ann General Psychiatry. 2009;8:22.
74. Craske MG, Meuret AE, Ritz T, Treanor M, Dour H, Rosenfield D. Positive affect treatment for depression and anxiety: a randomized clinical trial for a core feature of anhedonia. J Consult Clin Psychol. 2019;87(5):457–71.
75. Demyttenaere K, Donneau A-F, Albert A, Ansseau M, Constant E, van Heeringen K. What is important in being cured from depression? Discordance between physicians and patients (1). J Affect Disord. 2015;174:390–6.
76. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. Nat Rev Dis Primers. 2016;2:16065.

Unmet Needs in Psychiatry: Bipolar Depression

4

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4.1 Introduction and Overview of Bipolar Depression

4.1.1 History of the Bipolar Disorder Concept

Bipolar disorder (BD) is both one of the oldest and youngest of major psychiatric syndromes. Elements of the disorder, including melancholic depression and irrational excitement (by Hippocratic authors), as well as the occurrence of melancholia and excitement in the same persons at different times (by Aretaeus of Cappadocia) were described in ancient times [1]. However, co-occurrence of elements of both depression and mania at the same time ("mixed states") was described by Weygandt in 1895 [2]. The mixed-state concept may have encouraged Kraepelin to propose his broad concept of *manic-depressive illness* (MDI), which included a range of abnormal states of thought and behavior as well as of affect, usually considered as mood disorders [3]. Debate concerning the possibly excessively broadly inclusive concept of MDI

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continued to 1980 with publication of the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual* (DSM-III). It provided a first formal separation of a distinct *bipolar disorder* (BD) with mania from nonbipolar major depressive disorder (MDD). This separation was followed in 1994 by acknowledgment in DSM-IV of a type II BD (BD-II) marked by recurrent depression and episodes of hypomania, as well as of mixed manic-depressive states, and by later replacement of mixed states which were essentially manic with "mixed features" of opposite affective polarity in both mania and depression in DSM-5 in 2013. Parallel diagnostic categorizations appeared in the World Health Organization's *International Classification of Diseases* (ICD-10 of 1990 and reiterated in following revisions, and ICD-11 of 2018).

The century-long tension between lumping mood syndromes in MDI and separation of depressive and bipolar disorders or of unipolar and bipolar forms of depression, as well as consideration of a "spectrum" of mood disorders ranging from more or less pure major depression to archetypical BD continues to this day [4–7]. Additional challenges for the BD concept include how to categorize and clinically address relatively milder forms of mood-changes, as in *cyclothymic disorder* and in *cyclothymic or hyperthymic* temperaments [8–10]. This background indicates that one very basic need for BD is resolution of diagnostic ambiguities that remain regarding subtypes, as well as clarifying anticipated clinical implications of particular diagnostic formulations, especially of syndromes with mixed features, notably including their optimal treatment [11].

4.1.2 Characteristics of Bipolar Depression

Aside from such fundamental diagnostic-conceptual uncertainties, currently accepted forms of BD present some noteworthy needs. Adequate understanding, timely diagnosis, and effective short- and long-term treatment of depressive episodes in BD patients are critically important but insufficiently resolved needs [12]. The clinical significance of "bipolar depression" is underscored by its strong association with overall morbidity, other co-occurring psychiatric conditions (notably anxiety and substance-abuse disorders), disability, and excess mortality owing largely to early suicide in young patients, and increased morbidity and mortality associated with intercurrent medical illness, especially in older patients [12–19]. Additional clinical challenges include the difficult and often long-delayed diagnostic differentiation of depression as an initial presentation of BD or a manifestation of nonbipolar MDD [20–22].

Diagnoses of type I BD when patients present early in mania are straightforward, and they are among the most stable diagnoses of major psychiatric disorders over time [23, 24]. In contrast, diagnosis of BD presenting initially as a depressive episode, dysthymia, or dysphoria is much more challenging and requires ascertaining a history or awaiting an episode of mania (for type I BD), or hypomania only (for type II BD) [22]. However, hypomania and depression with mixed features are often overlooked or not recognized [25]. Depression as a manifestation of BD is initially considered as the expression of unipolar MDD in perhaps 10–40% of patients later considered to have BD [26–29]. Diagnosis of MDD instead of BD is especially

likely as depression is the most prevalent initial presenting polarity in BD, sometimes years before a first-lifetime episode of mania or hypomania, and it represents, by far, the highest proportion of total time ill in BD, even with apparently adequate treatment, in part owing to the typically longer duration of depressive than manic episodes [6, 7, 12, 30].

BD patients commonly fear, seek to avoid, and are especially likely to report and seek help for depressive phases of the illness. In contrast, they may not recognize moderate increases of mood, energy, activity, or libido as hypomanic symptoms or as abnormal, and may even prefer such states ("me at my best"). Misdiagnosis is especially likely early in the illness-course and if corroborating information from a family member or close friend is lacking [6, 12, 22, 31]. In perhaps 12–17% of cases, BD is not recognized until a depressed patient experiences a mood "switch" into hypomania or mania, either spontaneously or in association with exposure to a mood-elevating substance such as an antidepressant, stimulant, or corticosteroid [32–36]. Additional clues that suggest a diagnosis of BD rather than MDD include: (a) family history of mania, psychosis, "nervous breakdown," or psychiatric hospitalization; (b) onset of illness in adolescence or early 20s; (c) cyclothymic temperament; (d) multiple recurrences within relatively brief exposure times (such as ≥4 depressive episodes within 10 years); (e) depression with prominent agitation, anger, insomnia, psychotic features, or elements of hypomania (mixed features); (f) clinical "worsening" especially with agitation, anger, or insomnia when treated with antidepressants; (g) suicidal acts; (h) substance abuse; and possibly [i] male sex [6, 11, 22, 37–40].

The proportion of time spent in depressive, dysthymic, and dysphoric morbidity in BD over many years is much greater than time in mania or hypomania ("[hypo]mania") [6, 30, 41, 42]. Overall morbidity has been surprisingly high in BD despite ongoing treatment by community standards, typically 33–51%, but as high as 79%, and averaging 45% of time in follow-up [30, 41–43]. On average, depressive morbidity accounted for 3.7-fold more time than in [hypo]mania (9.5%) during long-term follow-up, across 15 studies [30], corresponding to more than three-quarters of total time ill (35.4%/44.9%), 70% in BD-I, and over 80% in BD-II patients (Table 4.1).

In addition, of particular note, future depressive morbidity in BD was strongly predicted from the nature of first-lifetime episodes, as was future morbidity based

Table 4.1 Depressive morbidity in clinically treated bipolar disorder subjects

Measure	Bipolar I	Bipolar II	All bipolar
Studies	12	8	15
Subjects	2760	822	3936
Exposure (years)	7.78 [3.53–12.0]	8.28 [2.18–14.4]	7.27 [4.43–10.1]
%-time depressed	30.6 [23.9–37.3]	35.9 [23.1–48.7]	35.4 [28.5–42.3]
Total %-time ill	43.7 [37.5–49.4]	43.2 [35.2–51.1]	44.9 [40.1–49.7]
%-of illness depressed	69.6 [60.4–78.9]	81.2 [71.3–91.0]	76.4 [69.4–83.3]

Data adapted from Forte et al. [30], based on systematic review of studies involving adult patients treated by community standards. Data are means with 95% confidence intervals. Depression includes major episodes plus dysthymia

Table 4.2 Long-term morbidity vs. type of first-episodes of bipolar disorder

Initial polarity	Proportion (%)	%-Time ill [95% CI]		D/M ratio
		Depression-like (D)	Mania-like (M)	
Anxiety	7.59 [6.07–9.33]	15.3 [10.6–20.1]	3.22 [1.86–4.58]	4.77
Depression	58.9 [55.9–61.9]	27.9 [24.8–30.9]	8.53 [6.91–10.1]	3.27
Mixed	5.46 [4.18–6.98]	28.6 [16.6–40.6]	20.6 [17.1–24.1]	1.39
[Hypo]mania	20.1 [17.7–22.6]	22.2 [17.7–36.6]	29.6 [10.9–48.2]	0.75
Psychosis	7.96 [6.41–9.73]	19.4 [10.3–28.4]	27.9 [15.2–40.5]	0.69

Data adapted from Baldessarini et al. [44] Data are means with 95% CI for 1081 adult bipolar disorder subjects followed for 15.7 [14.9–16.5] years. Mixed episodes are based on DSM-IV criteria. Data are ranked by ratio (D/M) of long-term proportion of time in depression or dysthymia (D) vs. [hypo]mania (M)

on sampling earlier morbidity, indicating considerable within-subject stability of the illness-course over time [44, 45]. Types of first-lifetime episodes among 1081 BD patients ranked: depression (58.9%) > [hypo]mania (20.1%) > apparently nonaffective psychosis (7.96%) ≥ anxiety (7.59%) ≥ DSM-IV mixed states (5.46%) [44]. In subjects with mixed features, subsequent time in depressive-dysphoric illness during 16 years of follow-up was nearly 5-times more likely than in [hypo]mania after a first episode of anxiety, 3.3-times more likely following initial depression, and 39% more following an initial DSM-IV mixed episode (Table 4.2). Not surprisingly, the nature of initial episodes can also predict the predominant morbidity-type (defined as ≥ twofold more time in depressive or mania-like illness) during long-term follow-up. That is, initial depression or anxiety was 7.2-times more likely to be followed by predominant depressive than mania-like morbidity, and 47-times more following an initial DSM-IV mixed episode, whereas initial [hypo]mania or psychosis was 6.0-times more likely to be followed by predominant mania-like morbidity [46]. In addition to the predictability of future illness in BD, these findings suggest an association of anxiety and of mixed states with prominent depressive morbidity in BD.

4.2 Morbidity and Disability with Bipolar Depression

4.2.1 Dysfunction in Bipolar Disorder

Given the high proportion of time in depressive states among BD patients, it is likely that depressive morbidity would be associated with dysfunction and disability, including limited academic achievement and decreased employment success. A great majority of BD patients, perhaps 80%, experience some work-loss, and 30–40% of BD-I or BD-II patients experience prolonged unemployment during adult working years [47, 48]. A strong association of bipolar depression with prolonged unemployment has been documented in several [45, 47–49] but not all studies [50]. Additional risk factors for unemployment (some of which are associated with bipolar depression) include depressive first-episodes, male sex, older age, anxiety, co-occurring personality disorders, and alcohol abuse [47, 48]. Dysfunction

is certainly associated with the number of manic episodes, which often require hospitalization [50], as well as cognitive impairment, which can persist even during euthymic periods in BD patients [49, 51]. A striking association with depressive versus manic phases of BD-I is a reported 4.75-fold excess risk of homicides [52].

4.2.2 Psychiatric Disorders Co-Occurring with Bipolar Disorder

As the dominant type of morbidity in BD, an association of bipolar depression with other medical and psychiatric disorders that often co-occur with BD also might be expected. However, their specific relationship to the proportion of time or severity of depressive morbidity in BD is not adequately evaluated. Commonly associated psychiatric conditions include substance-abuse and anxiety disorders, in addition to a variety of personality disorders and temperament types [6, 7, 53–60]. Whether these phenomena should be considered separate, "co-morbid" conditions or expressions of the range of psychopathology of BD itself remains unresolved [7, 17, 19]. This question is of more than academic interest as multiple diagnoses can contribute to complexity and potential incoherence of treatment choices and lack of adequately integrated clinical care, especially when comorbidity includes substance abuse and dependence [7, 17, 19].

Anxiety syndromes including panic and generalized anxiety are especially common in BD patients, at rates reported to be more than three-times greater than in the general population, and involving perhaps 45% of BD cases [17, 19, 56]. Risks of generalized anxiety, alone, may be as high as 15%, particularly prior to full clinical expression of BD [57]. Substance abuse also is prevalent in BD patients, notably including alcohol, cannabis, and stimulants, as well as with cigarette-smoking, with lifetime prevalence between 40% and 50% [53, 55, 59]. Alcohol abuse occurs at rates nearly six-times higher than in the general population, greater than in MDD, and in association with current mood-states, including both depression (as a means of self-medication) and [hypo]mania (as expression of excessive behavior) [54, 55, 58]. Risk factors for substance abuse in BD patients include male sex, general morbidity, and anxiety, but not diagnostic type (I or II), presence of psychotic features, or history of psychiatric hospitalization [58, 59]. Substance abuse in BD is also associated with suicide, accidents, and other violent behavior [59], and its presence is associated with a doubling of risk of early mortality, which is elevated even without substance abuse [61]. Attention deficit-hyperactivity disorder (ADHD) also is prevalent in association with BD [62]. Personality disorders of various types also have been associated with BD at rates of 25–50%, and diagnostic criteria for DSM personality disorders are especially likely to be met in BD depressive states [60].

4.2.3 General-Medical Morbidity with Bipolar Disorder

BD patients are at increased risk of many general-medical disorders; particularly notable are cardiovascular and cerebrovascular conditions, leading to increased morbidity, disability, and shortened longevity [63, 64]. In addition to cardiovascular

disorders, obesity, diabetes, migraine, and some infectious diseases all are more prevalent in BD patients [65–67]. Risk of myocardial infarction alone was 37% greater among BD patients overall than in the general population, and 88% higher among women with BD [68]; risk of stroke was elevated by 60%, and congestive heart failure by 2.3-fold [64] (Table 4.3). In one study, 80% of BD patients with cardiovascular disease had died within 10 years of follow-up, at an average age of only 47 years [69]. Risk factors for cardiovascular and cerebrovascular disease include elements of the metabolic syndrome (especially glucose intolerance and dyslipidemia) and being sedentary [70]. In addition, a growing number of studies have drawn attention to increased production in BD patients of metabolic signals associated with inflammatory responses, including circulating C-reactive protein, cytokines (including TNF-α, interleukins, and others), evidence of endothelial dysfunction and lipid indices of an elevated atherogenic index, as well as increased output of stress hormones and increased sympathetic tone [71–76]. All of these factors can contribute to cardiovascular risks. Of particular note in the present context, there is some evidence that inflammatory responses and obesity are particularly associated with depressive states [73, 76].

A specific and especially noteworthy form of morbidity which arises more among BD patients than in the general population is metabolic syndrome, including at least three of the following: development of abnormal glucose and insulin metabolism, dyslipidemia glucose and insulin metabolism, dyslipidemia (high triglyceride and low HDL cholesterol level), and hypertension, usually with obesity [77]. The syndrome is prevalent in the general populations of most developed cultures, commonly at rates of approximately 20–30% [77–79]. In contrast, the syndrome occurs with BD at rates as high as 48% [77], nearly twice that in matched general populations, and at higher prevalence than in MDD patients [80–82]. Even more BD patients show components of the syndrome, especially central abdominal obesity and elevated blood glucose [81, 83]. Fully half of BD patients (twice the rate in the local general population) were considered clinically obese (typically, with body-mass index [BMI] $\geq$30 kg/m^2) within 20 years of their first psychiatric hospitalization [84]. Not surprisingly, measures of insulin resistance have been strikingly abnormal among BD patients compared to healthy controls. Examples include 2.8-fold increases in fasting serum insulin concentrations, and 2.7-fold greater risks of standard measures of insulin resistance [83]. Identified risk factors for developing metabolic syndrome in BD patients include adverse effects during exposure to antipsychotic drugs [77,

Table 4.3 Risk of cardiovascular diseases in bipolar disorder patients vs. general population

Outcome	Studies	Subjects	HR [95% CI]	*p*-value
Congestive heart failure	1	1397	2.27 [1.49–3.45]	<0.0001
Cardiovascular mortality	3	179,651	1.65 [1.10–2.47]	0.02
Cerebrovascular disease	4	6,673,266	1.60 [0.99–2.57]	0.05
Any cardiovascular disease	10	7,058,912	1.57 [1.28–1.93]	<0.0001
Coronary artery disease	4	6,808,812	1.16 [0.76–1.78]	0.49

Based on longitudinal studies with 8.4 (range: 1.8–30) years of follow-up. Hazard ratio (HR) is adjusted for six potential confounders; ranked by HR. Data adapted from Correll et al. [63]

Table 4.4 Possible contributors to risk of metabolic syndrome in bipolar disorder

Metabolic factors
Altered immunological responses
Hypothalamic-pituitary-adrenal axis dysfunction
Altered function of the melanocortin-leptin system
Possible alterations in the microbiome
Lifestyle factors
Physical inactivity, sedentary lifestyle
Smoking (tobacco and cannabis)
Excessive use of alcohol and other substances
Poor sleep hygiene
Unhealthy diet
Clinical factors
Sedating and metabolic effects of psychotropic medicines
Erratic adherence to psychiatric treatment
More severe psychiatric morbidity
Inadequate general-medical assessment and clinical management
Poverty, disability, and limited access to healthcare

Modified from proposals by Pennix and Lange [78] that may be broadly applicable to major mental illnesses

85]. More broadly, possible contributors to risk of metabolic syndrome and associated with BD include intrinsic metabolic characteristics, effects of lifestyle choices and diet, as well as adverse effects of treatment (Table 4.4).

4.2.4 Increased Nonsuicide Mortality with Bipolar Disorder

Evidence is increasingly strong that, in addition to psychiatric morbidity and disability, BD patients have a shortened life-expectancy and high risks of unfavorable clinical outcomes of many general-medical disorders [18, 65, 86]. Mortality rates for particular ages or exposure times are reported to range from 2- to 15-times higher in BD than in the general population, to be somewhat higher among men than women with BD, and even greater than among schizophrenia patients [86, 87]. A particularly ominous finding is that, as mortality rates in Sweden unrelated to suicide have declined in the general population (increased life-expectancy) by approximately 17% in recent decades, they have *increased* steadily among BD patients by 30% [87] (Table 4.5). Similarly, all-cause mortality rates in Sweden have declined 3.3-times less among BD patients than in the general population since the 1980s [18]. Moreover, over the same period, rates of fatal strokes declined nearly 15-times *less* among BD patients than in the general population [18]. Strikingly, too, mortality rates for Australian BD patients were significantly elevated, by an average of 48% across a wide spectrum of medical conditions, ranging from alcohol abuse to cardiovascular disease (Table 4.6) [66, 67]. In the UK and in Denmark in recent years all-cause mortality rates have been increasing among BD patients at 3–14%

Table 4.5 Changes in age- and sex-adjusted mortality rates: bipolar disorder versus the general population

Measure	Change in mortality rate		
	General population (%)	Bipolar disorder (%)	Difference (%)
Change in all-cause mortality	–25	–15	10
Change in suicide	–37	–21	16
Change in nonsuicide mortality	–17	+30	47

Data derived from Swedish national health records, 1987–2010 for 42,964 relatively young BD patients of ages up to an average of 47.5 years. Relative decreases in mortality rates in general population vs. BD all disfavor BD subjects. Overall, mortality was 15-times higher in BD patients than in the general population. Adapted from Hällgren et al. [87]

Table 4.6 Relative mortality risks in elderly men with bipolar disorder

Cause of death	Mortality OR [95%CI]
Alcohol abuse	4.14 [2.72–6.30]
Pneumonia	3.75 [1.59–8.81]
Accident	3.49 [1.48–8.19]
Diabetes	1.79 [1.14–2.80]
Chronic lung disease	1.74 [1.26–2.40]
Cancer	1.57 [1.00–2.47]
Cardiovascular	1.37 [1.01–1.84]
Overall	1.48 [1.24–1.76]

Based on Australian study of men aged 65–85 years followed for 12.8 years, with (n = 250) vs. without (n = 37,923) BD starting at age ≤ 60 years. OR for suicide = 15.4 [5.40–43.7]. HR for dementia (at intake) = 9.84 [5.33–18.2]; for new cases of dementia, HR = 2.30 [1.80–2.94]. Data are adapted from Almeida et al. [66, 67] ranked by OR

per year, to become nearly 80% higher than in the general population [88, 89]. Of note, standardized mortality ratios (SMRs) comparing BD patients to the general population averaged 8.2 among relatively young BD patients aged 15–29 years to as low as 2.2 at ages 60–64 years, indicating a strong adverse impact of ill general-health even among young BD patients, who are also at relatively greater risk of substance abuse [89]. It also follows that life-expectancy among BD patients has been found to be reduced by an average of 12–15 years [90, 91].

Various factors have been associated with increased mortality rates or decreased longevity in BD patients. These include, notably, co-occurring substance abuse and smoking, as well as being overweight, unmarried, and having limited access to quality medical care—all of which are more likely with BD [91–93]. It is not clear whether adverse general-medical outcomes and increased mortality are selectively associated with depressive illness in BD patients, as opposed to overall morbidity. Nevertheless, depression is the major component of morbidity [30], and a specific association with antidepressant drug treatment (presumably for depression) and mortality in BD has been noted [93]. In addition, there are associations with exposure to mood-altering or stabilizing medicines in general, possibly in association

with weight-gain and development of metabolic syndrome, which is more likely with antipsychotic drug treatment, complex regimens ("polytherapy"), and higher average doses [85].

4.3 Bipolar Depression and Suicide

The worldwide annual rate of reported suicide averages approximately 15.4/100,000 (0.015% per year) [94]. There is wide variation among and even within regions, with relatively low reported rates in the Middle East and high rates in Eastern Europe. Average suicide rates in the general population of most regions are consistently much higher for men than women (by an average of 3.7-fold), very low in prepubertal children, and relatively high among elderly men [94, 95]. The marked differences in reported regional or national rates probably reflect actual genetic differences [96–98], limited access to healthcare services [99], and variance in case identification and reporting procedures [100, 101].

Suicide rates generally have decreased in the last 50 years, particularly in northern Europe and North America [94, 102], probably in association with improved diagnosis and treatment of mood disorder patients [86, 95, 101–106]. However, in some other world regions, reported suicide rates have increased, probably reflecting improvements in case-finding and reporting [95].

Women have been more than twice as likely as men to attempt suicide (34% vs. 16%), as well as more likely to be diagnosed with a psychiatric disorder (62% vs. 40%) and to seek and receive treatment for it (50% vs. 27%), itself perhaps contributing to their lower rate of suicide than in men [95]. In contrast, men are 3–4-times more likely than women to commit suicide [95, 107]. It may be that women attempt suicide with less lethal methods than men and so are more likely to survive.

The nomenclature of suicide ideation and behavior has received much attention recently. The broad, nonspecific, and potentially misleading term *suicidality* can include suicide, attempts, preparatory actions, or suicidal ideation. These behaviors and ideation are to be distinguished from other self-injurious acts or apparent accidents without identifiable suicidal intent, although intent often is not known [108, 109]. In both clinical practice and research, definitions and prevalence of nonfatal suicide-related behaviors and suicidal ideation are less reliable than for suicides and certainly are underreported, as are highly variable suicidal intent and the potential lethality of methods involved, though even the ascertainment of suicide can sometimes also be uncertain [110, 111].

It is generally accepted that 60–98% of suicides occur in persons with at least one clinically diagnosable psychiatric disorder [95, 112, 113], nearly half of which (48.5%) are mood disorders [95, 101]. People with major mood disorders (BD or MDD) have the highest prevalence of suicide and the highest standardized mortality ratio (SMR about 20 for BD and MDD severe enough as to require hospitalization) compared to the general population. By diagnosis, risks of suicide rank: bipolar disorders (BD-I $\geq$ BD-II) $\geq$ severe major depressive disorder with

hospitalization > moderate depression among outpatients [87, 95, 101, 112, 114]. The risk is approximately three-times greater among ever-hospitalized unipolar MDD patients, or those with severe current symptoms, compared to those treated only as outpatients [95, 115]. A time of particularly high risk for suicide and attempts is in the weeks following discharge from psychiatric hospitalization, probably in association with the quality and timeliness of aftercare; risk declines thereafter over several months [116–118].

In patients with mood disorders, depressive and dysphoric states are more associated with suicide than other phases of illness, especially if accompanied by mixed (hypomanic) features in either BD or MDD patients [11], or if complicated by co-occurring abuse of alcohol or illicit drugs [111, 119–122]. In addition, risk of suicide is highest among those who have attempted suicide previously. Risk also is elevated among young, impulsive-aggressive men and older, unmarried, or socially isolated men in the general population [101, 104], although such factors can be confounded by the presence of a psychiatric disorder or substance abuse. According to federal statistics, 42% of Americans considered to have committed suicide in 2010 were currently depressed, 45% had at least one diagnosable psychiatric disorder, and 33% abused alcohol or drugs, though only 32% were receiving any treatment [122].

We found a high risk of suicide and attempts in a review of the medical records of nearly 3000 outpatients diagnosed with a major mood disorder, and the risk was greater among those diagnosed with BD than with MDD [121]. In particular, among 843 Sardinian BD patients, suicide risk averaged 150/100,000 per year, or about 25-times greater than comparable regional rates in the general population (at 6/100,000 per year), and three-times greater than among 1983 outpatients with MDD (most, never hospitalized), with little difference between those diagnosed as BD-I or BD-II. These observations also accord with international findings in over 100,000 subjects that suicide attempts were more likely in association with diagnoses of BD than of MDD or dysthymia [121], and based on a systematic review of rates of suicide attempts in BD patients [15].

In contrast, rates of suicide *attempts* in the general population average 0.2–0.6% per year, or approximately 36 times the average international suicide rate [111, 113, 123–125]. Moreover, suicidal *ideation*, which may or may not be followed by suicidal acts, is 20-times more frequent (in approximately 6% of the general population, or 6000/100,000) than suicide attempts (approximately 300/100,000), which are about 20 times more frequent than suicides (15/100,000, or about 400-times less prevalent than suicidal ideation) [111].

The ratio of suicide attempts to suicides (A/S) is proposed as an index of lethality (reflecting severity of intent, violent or otherwise lethal method) of suicidal behaviors in that a lower A/S ratio implies a higher risk of suicide [14]. In the general population the A/S ratio is approximately 30–50 [111]. With BD and MDD, the A/S ratio is as low as 5–10, implying greater lethality of suicide attempts than in the general population [106, 121]. For example, we found an A/S ratio of 8.6 in patients with BD and 9.6 with MDD, about half as great in men as in women [106, 110], consistent with greater lethality of suicide attempts in men [103, 121]. This ratio is also influenced by age, and is somewhat lower among men than women over age 35.

Overall, the lethality of suicide attempts ranked: younger men ≥ older men ≥ older women > younger women [103, 106, 110, 121].

Among BD patients of either type I or II, risk of suicidal behavior is among the highest of all psychiatric disorders despite the growing variety of treatments with putative mood-altering or -stabilizing effects. This disparity almost certainly reflects the great difficulty of treating depressive and mixed manic-depressive states in BD [12, 121, 126, 127]. Indeed, as noted above, of the surprisingly high proportion (40–50%), of weeks ill during follow-up with treatment by community clinical standards, even from illness onset, approximately three-quarters of unresolved morbidity in BD is depressive or dysphoric [30, 42, 128, 129].

The preceding findings indicate that relationships among levels of suicidal risk (thoughts, acts, deaths) involve very different rates and that suicidal ideation has only a distant relationship to suicide, even among psychiatric patients at relatively high risk. Nevertheless, suicidal ideation is the first step toward a potential suicidal act and, appropriately, ideation is carefully considered in clinical and research assessments of suicidal risk, particularly in patients diagnosed with a major mood disorder.

4.3.1 Effects of Treatments on Suicidal Risks

Suicide cannot be "treated" but only prevented. Research on treatments aimed at suicide prevention, not surprisingly, is very limited because of clinical and ethical problems arising when an inactive or ineffective treatment, such as a placebo condition, would be compared to an experimental intervention, and death is a potential outcome. In addition, it is virtually impossible to know when a suicide has been prevented, whereas attempts and suicides can be counted. For research, the rarity of suicide, even among psychiatrically ill persons, encourages reliance on more prevalent surrogate outcome measures related to suicide, however remotely, including suicidal ideation, threats, self-injurious acts, or emergency interventions. The typically distant relationship of such measures to suicide can lead to misleading impressions and not prove therapeutic effects on suicide itself. Suicidal behaviors, including attempts, and the need for urgent clinical interventions to prevent progression from ideation to a suicide attempt have been employed in the research assessment of treatments aimed at reducing risk of suicide, including comparisons before vs. during an intervention or between two plausible interventions [106, 130, 131].

Although many BD and other psychiatric patients at risk for suicide receive various treatments with the implied aim of limiting suicidal risk, effects of very few treatments on suicidal behavior have been tested scientifically and their potential benefits or risks remain uncertain. Moreover, the relationship of psychiatric treatment to suicide is such that, at best, only about half of persons committing suicide were given any clinical care in the months preceding their deaths, and its adequacy and acceptance often were inadequate, suggesting that identification, enrollment, or retention in treatment programs as a means of preventing suicide has had limited success [61, 101, 132–134]. To reiterate, an additional limitation for assessment of

therapeutic interventions is that clinicians know when they fail, but not when they succeed in preventing a suicidal act. The following sections consider knowledge of effects on suicidal risks of various classes of psychotropic drugs (antidepressants, sedative-anxiolytics, lithium, anticonvulsants, antipsychotics), as well as of psychotherapies and miscellaneous interventions.

4.3.2 Antidepressants

The very frequent association of suicide behavior or acts with depression in BD patients has encouraged expectation that short- and long-term treatment with antidepressants might reduce suicidal risk [126]. However, most studies of antidepressant treatment have yielded inconsistent evidence concerning effects on suicides or attempts. They include a variety of experimental designs, including randomized, placebo-controlled trials, clinical cohort studies, data recovered from clinical records or health-maintenance organization or insurance programs, and epidemiological-ecological studies that compare suicide rates by regions or years with concurrent rates of prescriptions for antidepressant drugs (usually not in the same persons) [102, 135–138]. Many such studies were not designed to test for suicidal behavior as an explicit outcome measure and relied on post-hoc findings to test for possible differences in suicidal risks with vs. without antidepressants or in comparison to other treatments [14, 110, 139].

Such research efforts have encountered several noteworthy limitations: (a) suicidal ideation or behavior, even defined by objective standards, usually are not an explicit, predefined, outcome measure; (b) interpretation of findings from studies on the use of antidepressants is severely compromised by the possible confounding by morbidity or by indication (i.e., medical treatments including antidepressants are more likely to be given to, and taken by relatively severely ill patients at higher presumed risk of suicide, and so acting against finding a benefit of treatment); and (c) randomized controlled trials (RCTs), although being the best source of data on effects of antidepressant treatment on suicidal risk, are unlikely to include enough patients for sufficiently long times as to identify rare suicidal acts, and even rarer suicides. RCTs very rarely have defined suicidal behaviors as an explicit, a priori, outcome measure ascertained with well-validated assessment methods. In addition, even with efforts to exclude suicidal subjects from controlled trials, rates of suicidal behaviors may be at least as high in controlled trials as in clinical samples of depressive-disorder patients [140]. Moreover, rates of suicidal behaviors found in controlled treatment trials for depression often are exaggerated by *annualizing* observed rates based on relatively brief exposure times (typically 6–12 weeks). For instance, occurrence of an act during 12 vs. 52 weeks-at-risk will result in apparent rates of 4 per year vs. 1 per year.

Robust associations of effective treatment for depression with reduced suicidal risk have been expected to arise from analyses of data pooled from antidepressant RCTs so as to increase statistical power to detect infrequent events, but have remained elusive. A further potential limitation to this approach is that some

patients may *worsen* clinically when given an antidepressant drug. Such responses are particularly likely to arise with bipolar depression, which can shift to agitation, dysphoria, restlessness, irritability, anger, and insomnia, as well as a degree of behavioral disinhibition, which is even more likely when associated with substance abuse. Such responses increase risk of aggressive behaviors including impulsive suicidal acts [11, 101, 120, 141–144].

Several meta-analyses considered below have found only minor differences in rates of suicidal behaviors between depressed patients randomized to treatment with an antidepressant vs. a placebo. Other findings have included increased risks in juveniles and young adults but decreased risks in older adults, usually based on suicidal ideation as an unreliable surrogate outcome measure [127, 135, 136, 138]. Moreover, no such study has been based on explicit and validated, predefined outcome measures pertinent to suicide. Instead, indications of suicide ideation or behavior usually have emerged among "adverse events," almost always ascertained passively and incidentally rather than by direct inquiry and adequate, critical assessment.

One of the largest studies based on post-hoc meta-analysis reviewed 295 placebo-controlled trials submitted to the US Food and Drug Administration (FDA) for drug-licensing purposes. It analyzed 11 modern antidepressants in nearly 77,000 depressed or anxious adult subjects to compare the antidepressant drugs vs. inactive placebos for "suicidal risks" in trials lasting an average of 8 weeks. Reported risk was 0.010% for suicides and averaged 0.17% for suicide attempts—both similar to rates for the general population [123]. There was no overall difference in risk of suicidal acts (suicides were rare) between antidepressant treatments (76/39,729 = 0.19% [CI: 0.15–0.24]) and placebo controls (46/27,164 = 0.17% [0.12–0.23]), based on meta-analytic pooling of data. However, secondary post-hoc analyses, based on stratifying by age groups, suggested increased risk of broadly defined "suicidality" (again, mainly ideation) with modern antidepressants vs. placebo at ages below 25 years but apparent beneficial effects in older adults, and no overall difference. A meta-analytic review of large cohort and case–control studies of modern antidepressants found closely similar results as the FDA analyses, in that younger patients experienced increased risk of suicides or attempts, whereas older adults had lower risks associated with treatment with a modern antidepressant [137].

Contrary to these meta-analyses of data from RCTs or cohort studies, many placebo-controlled antidepressant trials in depressed adults have found substantial reductions in ratings of suicidal ideation with antidepressants compared to placebo, usually based on suicide-related items of standard depression symptom-rating scales [145–147]. However, these findings are subjective and based on post-hoc assessments of individual items on standard depression symptom-rating scales, which may be influenced by impressions of overall clinical improvement.

In our experience, emergence of new suicidal behaviors among adults treated with sustained antidepressant treatment in clinical settings is very uncommon, involving perhaps 5/1000 patients within a year, excluding patients whose treatment was altered earlier due to emerging suicidal tendencies [115]. Findings of selective worsening of suicidal risks in some young, antidepressant-treated patients

suggest clinically important differences among age groups. Such adverse reactions are especially likely to arise among depressed juveniles previously not recognized as having BD, who can worsen clinically when given an antidepressant, as well as others with particular behavioral sensitivities to mood-elevating agents that can lead to increased agitation, irritability, and insomnia. Such responses might contribute to the reported excess of suicidal ideation [136] and suicide attempts [148] in young patients treated with modern antidepressants. Nevertheless, such risks as well as the possibility that an acute depressive episode is the start of BD should be monitored at and following initiation of antidepressant treatment at any age.

4.3.3 Anxiolytics and Sedatives

Some studies have found elevated suicide rates among persons diagnosed with anxiety disorders [112, 149, 150], including in controlled trials, possibly reflecting their frequent co-occurrence with mood and substance-use disorders. Treatments aimed at reducing symptoms of anxiety can have unpredictable effects on suicidal behavior. Notably, behavioral disinhibition associated with benzodiazepine use can increase impulsive and aggressive behaviors, especially when combined with alcohol, and in personality-disordered patients [151]. On the contrary, a meta-analysis found little evidence of different risks of suicides or attempts among patients diagnosed with anxiety disorders who were randomized to receive a placebo or a variety of antianxiety medicines [149]. In general, there is little evidence that treatments effective for anxiety disorders reduce suicidal risk [152]. In contrast, discontinuing benzodiazepine treatment, especially rapidly, is a stressor that has been associated with increased suicidal risk [151].

4.3.4 Lithium

An association of reduced risk of suicides and attempts during long-term treatment with lithium in BD patients is supported consistently by many [14, 153–159], but not all studies [160, 161]. Support for this association includes meta-analyses and reviews, as well as results from several randomized, placebo-controlled efficacy trials not specifically designed to test for effects on suicide risk [106, 153, 162–165]. In meta-analyses of data from nearly three dozen trials (including 10 randomized, with placebo or active-alternative treatments as controls) involving more than 110,000 person-years of risk, we found five- to sixfold lower risks of suicides and attempts during treatment with lithium among patients with recurrent major mood disorders or BD [106, 155, 166]. Notably, in one of these studies, rates of suicidal acts increased by twentyfold within several months after discontinuing lithium maintenance treatment and were twice greater with abrupt or rapid versus gradual (over $\geq$2 weeks) discontinuation, later returning to levels encountered before lithium treatment had started [166]. In addition, in data meta-analytically pooled from eight studies of patients diagnosed with recurrent unipolar MDD (at risk a total of

2434 patient-years), we found evidence of a substantial (fourfold) reduction of risk of suicide and attempts with lithium versus alternatives that included anticonvulsants [167].

A rare RCT [164] found a substantial but statistically nonsignificant difference in rates of suicidal acts between patients treated for 12 months with lithium compared to others randomized to placebo (adjusted HR: 0.52; 95% CI: 0.18–1.43, favoring lithium); of note, the three suicides encountered in this study were associated with placebo treatment. In another randomized comparison of lithium vs. placebo added to treatment with the SRI antidepressant citalopram for 4 weeks, no suicides or attempts occurred in either group but suicidal rating scale scores decreased significantly more when lithium was part of the treatment regimen [165]. Based on all of these studies, several expert reports have recommended the use of long-term lithium treatment to reduce risk of suicidal behavior in BD patients [168–170].

Despite these several findings, a direct role of lithium treatment in decreasing suicide risk is not securely demonstrated. As for studies with other agents, the major limitation is that support for lower suicidal risk during long-term treatment with lithium derives almost entirely from incidental findings (of adverse effects) in studies designed for other therapeutic purposes but not addressing suicidal behavior as an explicit outcome measure. An additional potential limitation to studies of lithium—and, indeed, of all studies of therapeutic effects—is that patients who accept, tolerate, and sustain long-term treatment with particular treatments may well be self-selected and not adequately representative of the full spectrum of clinically encountered patients. Such factors can confound interpretation of observed effects of lithium without randomization to active treatment vs. a comparison condition (placebo is rarely an ethical option), with suicide-relevant measures as explicit outcomes. On the other hand, in testing for long-term effects of any treatment, only patients who accept and tolerate it can be considered for analysis.

The apparent effectiveness of lithium treatment in reducing risks of suicide and attempts is likely to be associated with reduction of risk or severity of recurrences of depression or dysphoric-agitated, mixed states in BD or MDD and probably also with reduced impulsivity and aggressiveness in various mood disorders that may be mediated by enhancing the function of the central serotonin system [171–174]. Alternatively, some experts have proposed that lithium may have specific effects against suicide independent of its mood-stabilizing actions, based on reductions of suicidal risk even among patients whose primary mood symptoms had not responded well to lithium [173]. It has also been suggested that in long-term treatment with lithium, as well as with clozapine [130], their requirement for unusually close clinical monitoring might facilitate identification of emerging symptoms associated with suicidal behavior, including suicidal ideation and early agitation, dysphoria, anger, or impulsivity. Nevertheless, additional clinical contact and close supervision may not be critical, given the results of the InterSePT trial of clozapine vs. olanzapine for schizophrenia patients at high suicidal risk, in which clinician contact time was very similar between treatment options [130].

A consideration in the use of lithium treatment for potentially suicidal patients is that it can be highly neurotoxic and lethal with acute overdoses, especially if they

are not detected early and provided emergency supportive treatment and hemodialysis [175]. Detailed reviews of research on lithium in suicide prevention are provided in recent book chapters [14, 176].

4.3.5 Anticonvulsants

There is limited research to directly compare suicidal risks during treatment with proved or putative mood-stabilizers other than lithium [161, 177], but at least two studies found nearly threefold lower average risks of suicide with lithium than with carbamazepine or valproate among bipolar or schizoaffective disorder patients [178, 179]. Moreover, FDA has expressed concerns that anticonvulsants may increase suicidal risks, at least among some epileptic disorder patients [180]. Other evidence did not indicate increased risk among psychiatric patients, specifically with BD, treated with anticonvulsants, but instead suggested that this class of drugs may have beneficial effects on suicidal behavior associated with the mood-stabilizing actions of some anticonvulsants [181–183]. In a meta-analysis we compared protective effects against suicidal behavior of lithium vs. several mood-stabilizing anticonvulsants (mainly valproate and some use of carbamazepine or lamotrigine) in six direct comparisons including more than 30,000 patients. We found a nearly threefold superiority of lithium over the few tested anticonvulsants [184].

4.3.6 Antipsychotics

Older antipsychotic-neuroleptic agents are little studied for effects on suicidal behavior compared to modern, atypical, or second-generation antipsychotic agents (SGAs) [101]. However, a study based on more than 10,000 psychotic patients found no statistical difference in relatively short-term risk of suicides and attempts during treatment with modern or older antipsychotics vs. placebo [185].

A lack of significant difference also was reported in a study on short-term mortality, including suicide, in several diagnostic groups (more than 108,000 subjects) treated with SGAs [186]. Instead, a large study found that mortality, including due to suicide, was more prevalent among untreated psychotic-disorder patients [187].

The first US FDA-approved treatment of any kind with an antisuicide indication was clozapine for schizophrenia patients, based largely on the remarkable InterSePT study comparing clozapine with olanzapine in suicide-prone patients [130]. This pivotal trial found fewer and greater time to interventions for emerging suicidal risk and reduced rates of suicide attempt favoring clozapine. Not surprisingly for a single study, there were too few suicides to evaluate their association with the treatments given. The beneficial effect of clozapine in suicidal schizophrenia patients has been supported by other studies, including its clinical comparison with risperidone or quetiapine, as well as olanzapine [131, 188–191]. Some emerging evidence suggests that effects of clozapine on suicidal risk in schizophrenia patients may not differ appreciably from other antipsychotics [192], although increased suicidal risk was reported to follow discontinuation of clozapine in schizophrenia patients

[193]. It is not known whether clozapine can exert antisuicidal effects in BD or other major psychiatric disorders, though it appears to have antimanic and mood-stabilizing effects in BD [194].

4.3.7 Psychosocial Interventions

Scientifically adequate research trials of psychotherapy or other psychosocial interventions for suicidal patients are rare, and case reports on the topic are more likely to describe positive outcomes; both factors contribute to a deficiency of balanced and critical assessments. In addition, data on psychotherapies to prevent suicide are difficult to collect and, again, are limited by the rarity of suicidal events as well as other major methodological pitfalls [195]. This impression is supported by a meta-analytic review based on 20 RCTs involving 2460 acutely suicidal subjects exposed to 10 different treatment conditions [196]. It found that only dialectic behavior therapy (DBT) appeared to be superior to standard clinical care in reducing repetitions of self-injurious behavior (by 56%; $p = 0.03$) among subjects diagnosed with borderline disorder, but based on a single, small trial. Other psychosocial treatments did not differ significantly from their control conditions, including problem-solving vs. standard clinical care, behavior therapy vs. insight-oriented psychotherapy in hospital, and long-term vs. brief psychotherapy. Similar conclusions about the lack of adequate research in this area are supported by a more recent, systematic review, in which outcome measures ranged from suicidal ideation to suicide [131].

With modifications specific for suicidal patients, cognitive-behavioral therapy (CBT), aimed at improving cognitive understanding, coping strategies, problem solving, and behavioral skills, may be helpful to limit suicidal risk in clinical crises and perhaps longer term [101, 197]. A recent review of 18 studies of CBT-based psychotherapy included a total of 2433 subjects (mean age 30 years; 63% women) found a significant reduction of recurrences of self-harm in subjects although they were also receiving standard pharmacological treatments [198].

Linehan's DBT—a combination of cognitive therapy and Buddhism-like, meditative acceptance-based strategies, tested mainly in persons diagnosed with borderline syndrome—may be an effective treatment for suicidal patients, perhaps including those with BD [199, 200].

Interpersonal psychotherapy (IPT) in 16 weekly sessions also was found effective in suicidal subjects older than 60 years, as reflected in reduced symptoms of depression and suicidal ideation [200]. Another study found a significantly greater reduction of suicide attempts among subjects randomized to IPT compared to intensive clinical management, both with use of mood-stabilizing drugs [201]. A rare, randomized study of acutely suicidal patients recruited in an emergency service found that 6 months of IPT—based on four home visits vs. a treatment-as-usual control condition—was more effective against suicidal ideation [202].

The preceding research indicates that beneficial effects of psychotherapy on suicidal ideation, self-harm, or suicide attempts compared to controls were found with CBT, DBT, IPT, and day-care with psychodynamic psychotherapy [203]. Nevertheless, other work leaves some doubt about the specific value of particular

forms of psychotherapy. For example, one study involving 218 patients with a variety of psychiatric disorders and a recent suicide attempt were randomized to follow-up treatments for 12 months after an index hospitalization [204]. In this study, outcomes with routine clinical care that included suicide specialists did not differ significantly from brief outpatient psychotherapy. This conclusion is congruent with other reviewed findings [196]. In addition, some recent reviews have been skeptical about the efficacy of psychotherapeutic interventions to prevent suicide, although they found evidence of reduced hopelessness [200, 205]. Moreover, most of the findings reviewed involved clinical improvement, particularly in depressive symptoms, which may itself reduce suicidal ideation and perhaps suicidal behavior. Nevertheless, despite lack of consistent and compelling evidence of specific effectiveness of some psychotherapeutic interventions in BD patients, prudent clinical practice usually includes providing patients psychological support, addressing their suicidal thinking directly, and maintaining contact with other clinicians involved as well as family members [104].

4.3.8 Miscellaneous and Experimental Treatments

A potential, experimental, antisuicidal treatment is the glutamate NMDA-receptor antagonist ketamine, which is considered below for treatment of BD depression. It has been associated with rapid, short-term reduction of suicidal ideation (not behavior) along with rapid reduction of symptoms of depression in recent studies [206, 207].

Additional options for clinical management of suicidal patients are usually empirical and lack formal testing but are often based on decades of accumulated clinical experience, though largely limited to brief interventions for acute suicidal risk. A good example is the use of ECT, which often appears to be lifesaving in suicidal emergencies but lacks evidence of *sustained* antisuicidal efficacy [208]. Other methods of external electrical or magnetic stimulation of the brain, vagal nerve stimulation, or deep-brain stimulation are being investigated or introduced for the treatment of otherwise treatment-resistant depression but remain to be tested for specific effects on suicidal behavior, particularly in BD.

Additional interventions include emergency hospitalization, which remains a prevalent indication for inpatient psychiatric care that almost surely has practical, short-term value but is less likely to have long-lasting effectiveness against future suicidal risk [131]. Indeed, the weeks and months following discharge from psychiatric hospitalization, for indications including suicidal behavior or risk, are associated with very high rates of suicide and attempts, particularly when aftercare is delayed or inadequate [117, 118, 209]. Some apparently widely employed techniques of clinical management, including “contracts for safety” as a means of encouraging suicidal patients to avoid self-harm and to seek help when in danger, are of unproved value and might even increase suicidal risk if clinical vigilance is reduced. A summary of proposed treatments aimed at reducing suicidal risk, including in bipolar depression is provided in Table 4.7.

Table 4.7 Treatments aimed at reducing suicidal risk in bipolar disorder patients

Intervention	Timing	Findings	Comments
Antidepressants	Short-term benefits are not clear; long-term effects are virtually untested	Research findings are inconclusive. Suicidal risk may increase with agitation, especially in youth but may be lower in older adults	Studies lack long-term randomization with suicidal acts as an explicit outcome measure
Antipsychotics	Short-term benefits are not adequately tested. Clozapine is probably beneficial long-term in schizophrenia (with FDA approval) but untested in BD	Except for clozapine, testing remains inadequate and inconclusive	Effects of clozapine rely mainly on a single randomized trial vs. olanzapine, without reduction of mortality
Anticonvulsants	Short-term effects are not established; long-term benefits have been proposed	Valproate most studied; anticonvulsants may be less effective than lithium	Studies lack suicidal acts as an explicit outcome
Anxiolytics/ sedatives	If there are benefits, they are probably short-term	Inconclusive research	Possible disinhibition of behavior, risk of abuse, and discontinuation associated with increased suicidal risk
Lithium	Very likely effective long-term	Consistent decrease of risk of suicide and attempts in controlled and uncontrolled studies; not clear if effect is via reducing risk of depression, impulsivity, or other antisuicidal action	Even randomized trials lack suicidal behavior as explicit outcome measure. Long-term acceptance and tolerance suggests some self-selection
Other pharmacological treatments	Only short-term effects have been tested	Ketamine can reduce suicidal ideation; effects on suicidal behavior are untested; other agents are untested	Ketamine has a short-term antidepressant effect in BD
Other somatic treatments	If there are benefits, they are probably short-term	ECT, magnetic, vagal nerve, or deep-brain stimulations can benefit depression	Inadequate testing vs. suicidal behavior specifically
Psychotherapies	Effects not established, but widely assumed to be helpful clinically	Cognitive-behavioral, dialectic and interpersonal methods best studied, but research results are inconclusive	Psychotherapy involves self-selection

References to studies of these methods are provided in the text

4.4 Treatment of Bipolar Depression

As reviewed above, depressive, dysthymic, and mixed (dysphoric-agitated) states are the major components of total illness-burden in BD, and are strongly associated with and predicted by depressive, mixed, or anxious first-lifetime episodes [6, 7, 30, 44, 210]. Remarkably, despite the high prevalence of bipolar depression and its major clinical, public-health, and economic significance, few treatments are proved to be highly and consistently effective in acute episodes, and there is even less evidence of effective and safe means of providing substantial long-term protection from recurrences of bipolar depression or of related, highly prevalent, dysthymic, or dysphoric states or symptoms in BD patients. In particular, there is continued controversy about the value and risks of antidepressant drugs in the treatment of bipolar depression [144, 211, 212]. In turn, lack of highly effective treatments encourages widespread empirical clinical trials of combinations of drugs ("polytherapy") and other off-label methods that remain largely untested for effectiveness and safety.

It seems likely that the relative paucity of experimental therapeutic studies for bipolar depression reflects an evidently broadly accepted view that "major depression" is similar in its clinical characteristics as well as its responses to treatment in BD as well as MDD [12, 126]. Instead, there is abundant evidence that depressive episodes in BD and MDD differ in many ways, including family history, sex-distribution, onset-age, long-term diagnostic stability, and especially in episode duration, recurrence rates, and responses to particular treatments [12, 129].

The preceding considerations indicate that bipolar depression remains a leading clinical problem—indeed, arguably, one of the most critical, unsolved challenges for contemporary psychiatric therapeutics [6, 7, 129, 213]. The current status of treatment of bipolar depression is summarized next, with an emphasis on pharmacological and other biomedical methods, relying in part on our recent systematic literature review [210].

4.4.1 Antidepressants for Bipolar Depression

The apparent ease and relative safety of treating major depressive episodes with widely employed modern, relatively safe, antidepressants, combined with the strong wish to minimize or avoid depression by BD patients and their clinicians, have made antidepressants the leading form of treatment provided to BD patients [12, 129, 210, 214]. Nevertheless, knowledge of the value and potential risks of antidepressants to treat bipolar depression, especially the risk of a manic switch, is greatly constrained by a striking paucity of therapeutic experimentation for bipolar depression and by inconsistent findings, despite more than a half-century of research and clinical use of antidepressant drugs to treat "depression" [144, 215–217]. Research is particularly limited regarding dysthymia and dysphoria, depression with mixed features, the prominent depression of BD-II, and long-term prophylaxis for bipolar depression [144, 218–223]. Many experts call for caution in the use of antidepressants, particularly for depression in BD-I (in which mood switches can be particularly dangerous), discouraging their use as a monotherapy, but if needed, only in

combination with mood-stabilizing agents or second-generation antipsychotics, or when patients are known to have responded favorably to an antidepressant previously [144, 170, 213].

4.4.2 Antidepressants in Acute Bipolar Depression

Well-designed, controlled, monotherapy trials focusing on efficacy of antidepressants for acute bipolar depression are surprisingly few, vary in size and quality, and have yielded inconsistent findings (Table 4.8) [170, 215–223, 230–232]. Two large trials are often cited as providing compelling support for lack of efficacy of antidepressant treatment in bipolar depression. One, not a monotherapy trial, found no additional achievement of sustained remission of depressive symptoms by adding an antidepressant (paroxetine or bupropion) to already more or less clinically optimized treatment of BD patients with mood-stabilizing or antipsychotic drugs [230]. The second randomized relatively few depressed BD subjects to paroxetine or placebo in an 8-week trial designed primarily to test the efficacy of quetiapine, and found little additional benefit with antidepressant added [219]. Two meta-analyses including these and the few other relevant trials supported possible efficacy of various antidepressants in bipolar depression [211, 215], but another did not [217]. Findings from reported RCTs of antidepressants for bipolar depression are summarized in Table 4.8 [211, 212, 219, 224–229, 233]. However, a naturalistic comparison

Table 4.8 Results of randomized, placebo-controlled trials of antidepressants for acute depression in bipolar disorder

	Duration (weeks)	Dropouts (%)	Dose [IMI-eq mg/day]	Responders/cases (n/N) (%)		Meta-analytic RR
				Antidepressant	Placebo	
Pooled/averages [95% CI] (12 trials)	8.2 [6.7–9.6]	31.1 [19.9–42.3]	172 [146–198]	393/803 (48.9%) [45.4–52.5]	419/1092 (38.4%) [35.5–41.3]	1.32 [1.07–1.62]

Data are pooled by random-effects meta-analysis or averaged across 12 trials, with 95% confidence intervals [CI]. Trials involved antidepressant alone or combined with mood-stabilizers (MSs), vs. placebo (PBO) alone or with MSs. Antidepressants tested vs. PBO include: agomelatine + MS; bupropion or paroxetine + MS; citalopram + MS; fluoxetine + lithium; fluoxetine + olanzapine alone; imipramine alone; imipramine + lithium (twice); phenelzine alone; paroxetine alone; and paroxetine + MS (twice). Of the 12 trials, 9 included both BD-I and BD-II subjects, 2 had BD-II, and 1 had BD-I cases. The pooled RR (1.32) indicated statistically significant overall superiority to PBO controls ($z = 2.65$, $p = 0.008$), but in only 3/12 individual trials was antidepressant significantly superior to PBO. The pooled number-needed-to-treat (NNT) was modest (7.5 [4.4–25.3]); overall heterogeneity of findings was substantial ($I^2 = 66.9\%$). Monotherapy trials yielded nonsignificantly greater efficacy than in those combining an antidepressant (or PBO) with a mood-stabilizer (MS): pooled RR = 1.64 [1.05–2.56] vs. 1.18 [0.96–1.46]. Crude weighted response rates favored antidepressants over PBO by 1.27-fold overall (48.9%/38.4%; $\chi^2 = 21.1$, $p < 0.0001$), and in monotherapy (55.4%/35.0% = 2.00-fold; $\chi^2 = 28.2$, $p < 0.0001$), but not polytherapy trials (45.8%/41.4% = 1.11-fold; $\chi^2 = 2.15$, $p = 0.14$). Findings are derived from 12 separate trials in 9 peer-reviewed reports [212, 219, 224–229], as detailed in previous reviews [210–212]. Drug dosage equivalence is addressed elsewhere [126]

of clinical responses in large samples of depressed patients with BD-I, BD-II, or recurrent unipolar MDD found only minor differences in rates of response or remission by diagnostic type, and low risk of mood-switching provided that subjects with evidence of agitation or even minor hypomanic features at baseline were excluded [232]. Such features are quite prevalent in episodes of bipolar depression [11, 234].

The impression that antidepressants are less effective in bipolar depression than in MDD may, to some extent, reflect adverse effects of antidepressant treatment, including worsening of agitation, anger, or dysphoria, which can be interpreted as failure of depression to respond [232]. A tentative overall conclusion arising from the available controlled trials is that antidepressant treatment has yielded a significant, 32% superiority over placebo in the treatment of acute bipolar depression, with moderately high heterogeneity of outcomes among trials (Table 4.8). Despite this inconsistent and thin body of research-based knowledge, it is evidently widely assumed clinically that antidepressants may be appropriate for some BD patients, and especially safe for BD-II depression [218, 220, 223, 235]. Selection of patients as candidates for a clinical trial of an antidepressant may be guided usefully by previous beneficial and tolerated responses to antidepressants, a relatively less severe or nonrapidly cycling illness-course, relatively few previous depressions, lack of depressive episodes followed by mania, and lack of current agitation or even minor hypomanic (mixed) features [144, 222, 232].

4.4.3 Antidepressants and Mood Switching

Concern about adverse outcomes of antidepressant treatment for bipolar depression often focuses on risk of switching of mood and behavior from depression into potentially dangerous, manic agitation. Accordingly, a diagnosis of BD-I, with a history of mania, is often a basis for avoiding antidepressants or other potentially mood-elevating agents (stimulants, steroids) [235]. BD patients with the predominant sequence pattern of depression followed by mania before a euthymic interval ("DMI" type) appear to be at higher risk of mood-switching [236]. In addition, BD-I patients appear to be more likely to experience excessive mood-elevation when treated with antidepressants than BD-II patients [237]. Nevertheless, available information about the epidemiology of mood-switching rates in BD patients is surprisingly limited. Reports of such studies usually do not include clear quantitative and qualitative distinctions between types I and II BD, and commonly lack exposure times, estimates of recurrences-per-time, or definition of the time-course of mood-shifts with vs. without antidepressant treatment. Lack of information about timing of mood switches in relation to antidepressant exposure makes it difficult to distinguish spontaneous from antidepressant-associated switching.

Although it is widely assumed that mood-stabilizing treatments and antipsychotic drugs can prevent mood-switching during antidepressant treatment of bipolar depression, randomized comparisons of switching rates with antidepressants given with vs. without such co-treatments are lacking [32, 210]. Data available on this point are based on comparing clinically chosen (non-randomized) treatment with an

antidepressant alone or with a mood-stabilizing or antipsychotic agent added, with a strong likelihood that patients given the stabilizing co-treatments have been prone to mania in the past [32]. It is therefore not surprising that differences in outcomes are minor or apparently even less favorable when a mood-stabilizing or antimanic treatment was given with an antidepressant [32].

One large study found that risk of mood-switching in BD patients was increased by 2.8-fold within 9 months of adding an antidepressant, but not if a mood-stabilizing agent also was given [238]. In a comprehensive review of switching risk, we found that risk of spontaneous mania *without* antidepressants itself was high (averaging 13.8%), but that adding an antidepressant increased the risk by only 1.5%, suggesting a "ceiling effect" on risk of mood-switching in depressed BD patients [32]. In addition, evidence from randomized trials indicates that types of antidepressants vary significantly in their association with mood switches. The risk appears to be especially high with tricyclic antidepressants (TCAs) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, but lower with serotonin reuptake inhibitors (SRIs), monoamine oxidase inhibitors (MAOIs), and bupropion [32].

There is an evident clinical consensus that antidepressants should be used in BD patients only cautiously, briefly, with short-acting agents given in moderate, slowly increased doses, and in association with an effective mood-stabilizing regimen, while monitoring closely for signs of emerging hypomania as an indication to reduce or discontinue the antidepressant. Despite insufficient research on the topic, it seems prudent that antidepressants, especially TCAs and SNRIs, be used very cautiously for BD depression, and perhaps avoided altogether if there is a history of mood-switching during antidepressant treatment, spontaneous rapid-cycling without antidepressant treatment, or with current agitation or hypomanic symptoms, and in BD-I patients [32, 144].

4.4.4 Long-Term Use of Antidepressants

Another matter of concern is that the potential value and risks of long-term use of antidepressants in both BD-I and BD-II patients with the intent of limiting future depressive recurrences remains extraordinarily poorly studied. Again, the lack of research-based information appears to have little impact on empirical use of such treatment in clinical practice, especially in combination with mood-stabilizing or antimanic agents [12, 144, 216, 239–241]. In particular, the value and safety of long-term antidepressant treatment beyond the initial months of recovery from an index depressive episode, in contrast to recurrent unipolar major depression [242], remain uncertain. Such trials have a high risk of being confounded by clinically adverse effects of treatment discontinuation as a stressor rather than a result of lack of treatment [243]. Nevertheless, relatively long-term use of antidepressants along with mood-stabilizers may be appropriate in response to depressive relapses after antidepressant discontinuation [144, 243].

At least three randomized controlled trials of continuation of modern antidepressants involve "enrichment" by including patients who have had a favorable

short-term response to the same treatments. Despite involving enriched samples, these trials suggest that a minority of patients may experience minor delay or reduced frequency of depressive recurrences when an antidepressant is added to their treatment, but with an even larger risk of mood-switching [217, 244, 245]. Moreover, rapidly cycling BD patients had far more recurrences with an antidepressant included in their treatment, suggesting cycle-acceleration of their illness [144, 216, 245]. Such an effect may be particularly likely in BD-II patients, who are more prone to rapid-cycling than BD-I [246].

4.4.5 Mood-Stabilizers

In recent decades, certain anticonvulsants have been used widely to treat BD patients, based on secure evidence of short-term antimanic effects (carbamazepine and valproate) or long-term reduction of risk of recurrences of BD depressive episodes (lamotrigine), but far less secure evidence of long-term, prophylactic effectiveness of other anticonvulsants [126, 247, 248]. Use of such anticonvulsants also has been encouraged by efforts to avoid the relative complexities of managing clinical treatment with lithium [126]. Despite widespread use of anticonvulsants to treat mania and efforts to afford long-term protective effects in BD patients, evidence concerning their value and risks for treatment of acute depression in BD is limited, and evidence concerning long-term effects is even less abundant [249].

Four small trials involving fewer than 100 total BD subjects suggest possible value of divalproex as a monotherapy for acute bipolar depression (Table 4.9) [250]. An impression that lamotrigine may have some effect in acute bipolar depression has arisen from pooling inconsistent data, even from individually failed trials against placebo (Table 4.9) [251]. Importantly, lamotrigine is approved by the US FDA only for long-term prophylaxis in BD, with demonstrated effectiveness against recurrences of bipolar depression but little efficacy against acute or recurrent mania [126, 252]. Moreover, the requirement for slow increases of doses of lamotrigine to avoid potentially serious dermatological reactions makes the drug somewhat impractical for off-label use in acute phases of bipolar depression. Evidence concerning carbamazepine for short- or long-term use for bipolar depression is very limited (Table 4.9), and controlled trials for other anticonvulsants in BD are lacking [241, 248].

Although there is remarkably little information concerning effects of lithium in acute bipolar depression, this drug has been considered a fundamental treatment for BD for more than six decades, and is still positioned as a first-line treatment in some expert guidelines [170, 213]. Use of lithium for bipolar depression is based on a single controlled trial in which it was included as a third-arm of a trial designed primarily to evaluate quetiapine, and its possible benefits were very modest (Table 4.9) [75, 210, 253]. Nevertheless, lithium appears to have some long-term effectiveness against recurrences of bipolar depression as well as its more prominent prophylactic

Table 4.9 Placebo-controlled trials for acute depression in bipolar disorder: lithium, anticonvulsants, and antipsychotics

Treatments [*n* trials and agents]	Subjects (n)	Dropouts drug/placebo	Responders/subjects [%]		RR [95%CI]
			Drug	Placebo	
Lithium [1 trial, 1 agent]	265	25.0%/27.8%	85/136 [62.5%]	72/129 [55.8%]	1.12 [0.92–1.37]
Anticonvulsants [10 trials, 3 agents]	1281	34.1%/40.5%	313/657 [47.6%]	181/624 [29.0%]	1.61 [1.39–1.87]
Antipsychotics [13 trials, 6 agents]	6044	36.6%/35.1%	2135/3859 [55.3%]	904/2185 [41.4%]	1.28 [1.09–1.51]
Pooled/totals [24 trials, 10 agents]	7590	35.7%/39.9%	2533/4652 [54.4%]	1157/2938 [39.4%]	1.34 [1.17–1.53]

Response usually involved ≥50% improvement in depression symptom-ratings. Of 24 individual RCTs, 14 (58.3%) did not find drug superior to placebo (PBO). By random-effects meta-analysis: overall RR (1.34) is statistically highly significant ($z = 4.31$, $p < 0.0001$), as is the difference in weighted-average response rate (54.4% with all drugs vs. 39.4% with PBO; χ^2=164, $p < 0.0001$), though the overall drug-PBO difference is modest by both measures (34%–38%). Treatments significantly superior to PBO were: *carbamazepine* ($p = 0.02$), *lamotrigine* ($p < 0.0001$), *valproate* ($p = 0.004$), *anticonvulsants* overall ($p = 0.001$); *lurasidone* ($p < 0.0001$), *olanzapine* ($p = 0.0002$), *quetiapine* ($p < 0.0001$), and *antipsychotics* overall ($p < 0.0001$); but not aripiprazole, cariprazine, lithium, or ziprasidone. Numbers-needed-to-treat (NNT) for effective agents ranked: *carbamazepine* (3.4 [CI: 1.9–19]), *valproate* (4.5 [2.7–13]), *lurasidone* (4.6 [3.3–7.8]), *quetiapine* (5.0 [4.1–6.3]), *anticonvulsants* overall (5.5 [4.3–7.7], *lamotrigine* (5.9 [4.4–8.9]), *antipsychotics* overall (8.8 [5.3–27]), and *olanzapine* alone (9.5 [6.2–20]). Overall heterogeneity was substantial ($I^2 = 79.4\%$). Data are adapted from recent systematic reviews which provide references for individual trials [75, 210]

effects against [hypo]mania [126, 170, 254]. Moreover, lithium appears to reduce risk of suicide substantially in BD patients, as was reviewed above [106, 162, 167, 176, 255, 256].

4.4.6 Second-Generation Antipsychotics

Modern or "second-generation" antipsychotic drugs (SGAs), including olanzapine combined with fluoxetine, as well as quetiapine and lurasidone, are currently the only medicines with FDA approval for short-term treatment of acute major depressive episodes in BD patients [126, 241]. Nevertheless, of these agents, only quetiapine has been found to outperform placebo consistently in multiple trials. In these trials, dose-dependent differences in efficacy (with 300 vs. 600 mg/day) were not found and only the lower dose is explicitly FDA-approved. The FDA-approved combination of olanzapine + fluoxetine has produced superior benefits to

placebo, whereas olanzapine alone was less effective than in combination with the SRI antidepressant [225]. Unsurprisingly, as both olanzapine and quetiapine have antimanic properties, they have yielded somewhat *lower* risks of mood-switching than with placebo [241]. Lurasidone, olanzapine, and quetiapine have yielded favorable estimated *number-needed-to-treat* (NNT) values below 10 in the treatment of acute bipolar depression (Table 4.9) [16, 221] as did the combination of olanzapine + fluoxetine (Table 4.8) [16, 221], and they were substantially more effective than lamotrigine [225, 241]. Nevertheless, all of these responses in acute bipolar depression have been modest (Table 4.9), and possible long-term protective effects require further study.

As only some modern antipsychotic agents appear to reduce symptoms of acute depression in BD patients, such responses are evidently not a class effect of all SGAs. Notably, ziprasidone and aripiprazole were ineffective in two trials for each [241]. Cariprazine remains to be evaluated adequately as only on a dose of 1.5 mg/day was found to be efficacious for the treatment of acute depression in BD-I subjects, whereas the response rate with a lower (0.75 mg/day) and higher (3 mg/day) dose was similar to that found with an inactive placebo [257].

In effective doses, antipsychotic drugs risk adverse effects that may not be well tolerated by some patients, particularly excessive sedation as well as distressing restlessness (akathisia) [258, 259]. Although risks of tardive dyskinesia (TD) with most modern antipsychotic drugs are far lower than with older, or first-generation antipsychotics (FGAs) [260, 261], the great increase in use and broadening indications for SGAs may risk increased numbers of cases of even uncommon adverse effects including TD [190]. Moreover, risks of weight-gain, type 2 diabetes mellitus, and other features of metabolic syndrome (hyperlipidemia, hypertension) are encountered with some SGAs (particularly olanzapine, risperidone and quetiapine), sometimes in less than 3 months [17, 126, 262]. These medically important adverse effects tend to limit the potential, but *unproved*, value of SGAs for prophylactic treatment against recurrences of bipolar depression [16, 221, 249]. In summary, quetiapine and lurasidone as well as olanzapine + fluoxetine, and cariprazine have evidence of efficacy in acute bipolar depression, although with some risks, and as yet without compelling evidence for long-term, prophylactic effects against bipolar depression, with the probable exception of quetiapine [263].

4.4.7 Innovative Pharmacological Treatments

Several novel pharmacological treatments are under investigation for bipolar depression. They include the NMDA-glutamate receptor antagonist ketamine and possibly better-tolerated agents that affect glutamate neurotransmission, as well perhaps as fatty acids, anti-inflammatory agents, and probiotics [75]. *R*,*S*-ketamine is a particularly promising innovative agent for major depression generally, especially for treatment-resistant depressions (TRD), with apparent short-term benefit against suicidal ideation [206, 207]. Typical antidepressant doses of ketamine are

0.10–0.50 mg/kg, usually infused slowly intravenously (IV) over 40–100 min to limit adverse effects, although doses of 0.5–1.0 mg/kg are more likely to be effective [264]. Such treatment is sometimes repeated daily for several days or 2–3-times a week for several weeks. Analgesic and dissociative effects of ketamine are achieved at 0.20–0.75 mg/kg, IV, overlapping the range for antidepressant effects, whereas anesthetic doses average 1.0–4.5 mg/kg, IV. Of note, usual doses for hallucinatory and recreational effects of ketamine ("Special K") are much higher, typically 60−250 mg by inhalation [265–267].

The first, small but controlled clinical trial of *R,S*-ketamine as an antidepressant was reported in 2000 [268], based on pharmacological theory and animal modeling [269]. Substantial clinical research has been reported on the use of ketamine for short-term treatment of acute major depressive episodes in MDD and less in bipolar depression, although much of it involves case reports and uncontrolled trials [75]. Some emerging reports also have found beneficial effects for acute depression or suicidal ideation in BD [75, 206, 207]. Most reports concerning ketamine, encouragingly, support rapidly achieved benefits, including in bipolar depression, within 1–2 days, often after failure of other treatments, but usually with gradual loss of benefits without further treatment over the following 1–2 weeks. Of note, the benefits in controlled trials have been only about half as great when the control treatment was with the potent sedative benzodiazepine midazolam compared to inert saline as a placebo [207]. In addition, possible implications of new evidence that the antidepressant effects (but not dissociative effects) of ketamine can selectively be prevented by treatment with the opioid antagonist naltrexone remain to be clarified [270]. Also remaining to be clarified are the long-term value and safety of this interesting innovation, as very little research has addressed prolonged use of ketamine to maintain antidepressant effects in either unipolar or bipolar depression, and such efforts may encounter difficulties in maintaining double-blind conditions [271].

Several innovative potential clinical treatments for depression are emerging, including drugs that act at NMDA receptor sites (e.g., the tetrapeptide rapastinel), or GABA-A receptors (e.g., SAGE-217), and others [272, 273]. Such novel agents remain to be established as safe and effective in unipolar major and treatment-resistant depressive episodes and have not been evaluated for BD depression.

4.4.8 Nonpharmacological Treatments

Acute bipolar depression is responsive to electroconvulsive treatment (ECT), possibly even more rapidly than in MDD [274], leaving uncertainty about optimal treatment following successful ECT [275, 276]. As noted above, ECT also may have short-term suicide-preventing effects in BD as well as MDD patients [277]. Additional non-pharmacological biological treatments also may be of value for treating bipolar depression. Intense light therapy and sleep deprivation are plausible candidate treatments but require adequate testing among BD patients [278–281]. Vagal nerve stimulation is FDA-approved for TRD without specification of MDD

or BD, but with evidence of efficacy in depression of both BD and MDD [282, 283], although it has been associated with emergence of mania [284]. Repeated transcranial magnetic stimulation and various forms of electrical stimulation of the brain from the surface or through stereotaxically placed deep-brain electrodes remain experimental [75, 285–293]. Many candidates for deep-brain stimulation are excluded, especially if they have not previously failed trials of ECT [288]. Moreover, optimal neuroanatomical targets for such treatment remain unclear, and the results of clinical trials have been inconsistent [291].

4.4.9 Psychotherapy for Bipolar Depression

Several manual-based, replicable forms of psychotherapy have been studied extensively and found to be effective in the treatment of MDD, including in combination with antidepressant medicines [170, 294]. Some of these methods have emerging research support for their feasibility and effectiveness in the treatment of patients with bipolar depression, often in combination with standard medicines and in groups so as to enhance their efficiency [170, 295]. Methods best studied for use in bipolar depression include *cognitive-behavioral therapy* (CBT) [295, 296], *interpersonal and social rhythm therapy* (IPT) [297], *family-focused psychoeducation* (FFT) [298], and *mindfulness-based cognitive therapy* (MBCT) [299, 300]. Other techniques, including *dialectical behavioral therapy* (DBT), that are established for treating MDD have had limited investigation for use in bipolar depression specifically [296]. More than one of these approaches have been used at the same time, or at different times to address particular problems. There are even emerging, tentative, suggestions that specific techniques may be especially helpful for particular prominent problems. These include use of CBT or MBCT with behavioral or cognitive dysfunction, FFT with high expressed emotion in patients' families, IPT for patients with prominent interpersonal problems, MBCT with residual dysthymic symptoms following remission of major depressive episodes, and perhaps DBT in the presence of emotional instability, comorbidities, or suicidal preoccupations [294].

4.5 Conclusions

Depression, dysthymia, and dysphoria in BD represent major, largely unsolved, clinical challenges (Table 4.10). As the main component of unresolved psychiatric morbidity in BD, even with standard treatment, bipolar depression is associated with excess morbidity and mortality from co-occurring general-medical disorders as well as very high suicide risk, with mortality rates that are several-times higher than in the general population and in most other psychiatric disorders, and suicide risk 20-times above general population rates and in strong association with mixed (agitated depressive), depressive, and dysphoric phases of BD. Clinically effective

Table 4.10 Current status of depression in bipolar disorder

• Depressive phases of bipolar disorder (BD) are the major residual psychiatric morbidity with available treatments, accounting for three-quarters of the 40%–50% of long-term time ill
• Unresolved morbidity, and especially depression, is associated with excess medical morbidity, including metabolic syndrome and cardiovascular disease, with increased mortality
• Suicide risk in BD is similar in types I and II BD, greater than in most other psychiatric disorders, ca. 20-times above general population rates, and strongly associated with depression, especially with agitation (mixed-dysphoric states), and in the weeks following hospital discharge
• Predicting suicide in BD clinically is limited in power and precision regarding individuals and timing
• Some treatments to prevent suicidal behavior in BD are promising but require further study (including lithium, clozapine, and possibly ketamine and psychotherapies)
• The therapeutics of bipolar depression is far less well developed than for nonbipolar major depression
• The value of antidepressant treatment for bipolar depression remains controversial, and it is best avoided with ongoing dysphoric agitation or mixed features
• For bipolar depression, some modern antipsychotics are effective short-term; lithium and lamotrigine have modest prophylactic value long-term but are virtually untested short-term; other anticonvulsant mood-stabilizers have very limited evidence of short- or long-term efficacy
• All available treatments for bipolar depression have risks of adverse metabolic or neurological effects; valproate and carbamazepine are also highly teratogenic

prediction of suicide risk is limited, and treatments proposed to reduce suicide risk, notably including lithium, are not securely proved effective. Treatment of bipolar depression is far less well investigated than for MDD, and the value and safety of standard antidepressants for depression in BD remain controversial. Evidence of efficacy of mood-stabilizing agents, including lithium and several anticonvulsants (except lamotrigine, long-term) remains limited, though benefits of some second-generation antipsychotics for short-term treatment of acute bipolar depression are emerging. All available pharmacological treatments used for bipolar depression present risks that include adverse metabolic and neurological effects. Overall, we strongly encourage renewed efforts to consider bipolar depression as distinct from depression in MDD and to seek more effective treatment especially for long-term prophylaxis and reduction of both morbidity and mortality.

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References

1. Baldessarini RJ, Pérez J, Salvatore P, Trede K, Maggini C. History of bipolar manic-depressive disorder. In: Yildiz A, Nemeroff C, Ruiz P, editors. The bipolar book: history, neurobiology, and treatment. New York: Oxford University Press; 2015. p. 3–20, chap. 1.
2. Salvatore P, Baldessarini RJ, Centorrino F, et al. Weygandt's, the manic-depressive mixed states: a translation and commentary on its significance in the evolution of the concept of bipolar manic-depressive disorder. Harv Rev Psychiatry. 2002;10(5):255–75.
3. Trede K, Salvatore P, Baethge C, Gerhard A, Maggini C, Baldessarini RJ. Manic-depressive illness: evolution in Kraepelin's textbook, 1883–1926. Harv Rev Psychiatry. 2005;13(3):155–78.
4. Cuellar AK, Johnson SL, Winters R. Distinctions between bipolar and unipolar depression. Clin Psychol Rev. 2005;25(3):307–39.
5. Akiskal HS. Emergence of the bipolar spectrum: validation along clinical-epidemiologic and familial-genetic lines. Psychopharmacol Bull. 2007;40(4):99–115.
6. Goodwin FK, Jamison KR. Manic-depressive illness. 2nd ed. New York: Oxford University Press; 2007.
7. Yildiz A, Nemeroff C, Ruiz P, editors. The bipolar book: history, neurobiology, and treatment. New York: Oxford University Press; 2015.
8. Rihmer Z, Akiskal KK, Rihmer A, Akiskal HS. Current research on affective temperaments. Curr Opin Psychiatry. 2010;23(1):12–8.
9. Baldessarini RJ, Vázquez G, Tondo L. Treatment of cyclothymic disorder. Psychother Psychosom. 2011;80(3):131–5.
10. Perugi G, Hantouche E, Vannucchi G. Diagnosis and treatment of cyclothymia: the "primacy" of temperament. Curr Neuropharmacol. 2017;15(3):372–9.
11. Tondo L, Vázquez GH, Pinna M, Vaccotto PA, Baldessarini RJ. Characteristics of depressive and bipolar patients with mixed features. Acta Psychiatr Scand. 2018;138(3):243–52.
12. Baldessarini RJ, Vieta E, Calabrese JR, Tohen M, Bowden C. Bipolar depression: overview and commentary. Harv Rev Psychiatry. 2010a;18(3):143–57.
13. Ösby U, Brandt L, Correia N, Ekbom A, Sparén P. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry. 2001;58(9):844–50.
14. Tondo L, Baldessarini RJ. Suicide in bipolar disorder. In: Yildiz A, Nemeroff C, Ruiz P, editors. The bipolar book: history, neurobiology, and treatment. New York: Oxford University Press; 2015. p. 509–28, chap. 37.
15. Tondo L, Pompili M, Forte A, Baldessarini RJ. Suicide attempts in bipolar disorders: comprehensive review of 101 reports. Acta Psychiatr Scand. 2016;133(3):174–86.
16. Vázquez GH, Holtzman J, Tondo L, Baldessarini RJ. Efficacy and tolerability of treatments for bipolar depression. J Affect Disord. 2015;183(9):258–62.
17. Vázquez GH, Forte A, Camino S, Tondo L, Baldessarini RJ. Psychiatric comorbidity in bipolar disorder: treatment implications: anxiety syndromes and substance abuse. In: Carvalho E, Vieta E, editors. The treatment of bipolar disorder: integrative treatment strategies and future directions. New York: Oxford University Press; 2017. p. 225–54, chap. 17.
18. Ösby U, Westman J, Hällgren J, Gissler M. Mortality trends in cardiovascular causes in schizophrenia, bipolar and unipolar mood disorder in Sweden 1987–2010. Eur J Pub Health. 2018;26(5):867–71.
19. Vázquez GH, Gonda X, Lolich M, Tondo L, Baldessarini RJ. Suicidal risk and affective temperaments evaluated with TEMPS-A. Harv Rev Psychiatry. 2018;26(1):8–18.
20. Baethge C, Tondo L, Bratti IM, et al. Prophylaxis latency and outcome in bipolar disorders. Can J Psychiatr. 2003;48(7):449–57.
21. Post RM, Leverich GS, Kupka RW, et al. Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. J Clin Psychiatry. 2010;71(7):864–72.
22. Vöhringer PA, Perlis RH. Discriminating between bipolar disorder and major depressive disorder. Psychiatr Clin N Am. 2016;39(1):1–10.

23. Salvatore P, Baldessarini RJ, Tohen M, et al. McLean-Harvard international first-episode project: two-year stability of DSM-IV diagnoses in 500 first-episode psychotic disorder patients. J Clin Psychiatry. 2009;70(4):458–66.
24. Salvatore P, Baldessarini RJ, Tohen M, et al. McLean-Harvard International First-Episode Project: two-year stability of ICD-10 diagnoses in 500 first-episode psychotic disorder patients. J Clin Psychiatry. 2011;72(2):183–93.
25. Bschor T, Angst J, Azorin JM, et al. Are bipolar disorders underdiagnosed in patients with depressive episodes? Results of the multicenter BRIDGE screening study in Germany. J Affect Disord. 2012;142(1–3):45–52.
26. Kiejna A, Rymaszewska J, Hadrys T, Suvalska A, Lojko D, Rybakowski J. Bipolar or unipolar: the question for clinicians and researchers. J Affect Disord. 2006;93(1–3):177–83.
27. Berk M, Dodd S, Callaly P, et al. History of illness prior to a diagnosis of bipolar disorder or schizoaffective disorder. J Affect Disord. 2007;103(1–3):181–6.
28. Stensland MD, Schultz JF, Frytak JR. Diagnosis of unipolar depression following initial identification of bipolar disorder: common and costly misdiagnosis. J Clin Psychiatry. 2008;69(5):749–58.
29. Shen H, Zhang L, Xu C, Zhu J, Chen M, Fang Y. Analysis of misdiagnosis of bipolar disorder in an outpatient setting. Shanghai Arch Psychiatry. 2018;30(2):93–101.
30. Forte A, Baldessarini RJ, Tondo L, Vázquez G, Pompili M, Girardi P. Long-term morbidity in bipolar-I, bipolar-II, and major depressive disorders. J Affect Disord. 2015;178(6):71–8.
31. Perlis RH. Misdiagnosis of bipolar disorder. Am J Manag Care. 2005;11(Suppl 9):271–4.
32. Tondo L, Vázquez GH, Baldessarini RJ. Mania associated with antidepressant-treatment: comprehensive meta-analytic review. Acta Psychiatr Scand. 2010;121(6):404–14.
33. Smith DJ, Griffiths E, Kelly M, Hood K, Craddock N, Simpson SA. Unrecognized bipolar disorder in primary care patients with depression. Br J Psychiatry. 2011;199(1):49–56.
34. Newport DJ, Baldessarini RJ, Knight BT, et al. Comparison of women with confirmed versus presumably misdiagnosed bipolar disorder. J Clin Psychiatry. 2012;73(2):242–6.
35. Baldessarini RJ, Faedda GL, Offidani E, et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder. J Affect Disord. 2013;148(1):129–35.
36. Barbuti M, Pacchiarotti I, Vieta E, et al. Antidepressant-induced hypomania/mania in patients with major depression: evidence from the BRIDGE-II-MIX study. J Affect Disord. 2017;219(9):187–92.
37. Hantouche EG, Akiskal HS. Bipolar II vs. unipolar depression: psychopathologic differentiation by dimensional measures. J Affect Disord. 2005;84(2–3):127–32.
38. Mendlowicz MV, Akiskal HS, Kelsoe JR, Rapaport MH, Jean-Louis G, Gillin JC. Temperament in the clinical differentiation of depressed bipolar and unipolar major depressive patients. J Affect Disord. 2005;84(2–3):219–23.
39. Tondo L, Visioli C, Preti A, Baldessarini RJ. Bipolar disorders following initial depression: modeling predictive clinical factors. J Affect Disord. 2014;167(10):44–9.
40. Serra G, Koukopolos A, De Chiara L, et al. Features preceding diagnosis of bipolar versus major depressive disorders. J Affect Disord. 2015;173(3):134–42.
41. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar Disord. 2007;9(5):531–325.
42. De Dios C, Ezquiaga E, Garcia A, Soler B, Vieta E. Time spent with symptoms in a cohort of bipolar disorder outpatients in Spain: prospective, 18-month follow-up study. J Affect Disord. 2010;125(1–3):74–81.
43. Brodaty H, Luscombe G, Peisah C, Anstey K, Andrews G. 25-year longitudinal, comparison study of the outcome of depression. Psychol Med. 2001;31(8):1347–59.
44. Baldessarini RJ, Tondo L, Visioli C. First-episode types in bipolar disorder: predictive associations with later illness. Acta Psychiatr Scand. 2014;129(5):383–92.
45. Uher R, Pallaskorpi S, Suominen K, Mantere O, Pavlova B, Isometsä E. Clinical course predicts long-term outcomes in bipolar disorder. Psychol Med. 2019;49(7):1109–17.

46. Baldessarini RJ, Undurraga J, Vazquez GH, et al. Predominant recurrence polarity among 928 adult international bipolar I disorder patients. Acta Psychiatr Scand. 2012;125(4):293–302.
47. Zimmerman M, Galione JN, Chelminski I, Young D, Dalrymple K, Ruggero CJ. Sustained unemployment in psychiatric outpatients with bipolar disorder: frequency and association with demographic variables and comorbid disorders. Bipolar Disord. 2010;12(7):720–6.
48. Arvilommi P, Suominen K, Mantere O, Valtonen H, Leppamaki S, Isometsa E. Predictors of long-term work disability among patients with type I and II bipolar disorder: prospective 18-month follow-up study. Bipolar Disord. 2015;17(8):821–35.
49. Godard J, Baruch P, Grondin S, Lafleur MF. Psychosocial and neurocognitive functioning in unipolar and bipolar depression: 12 month prospective study. Psychiatry Res. 2012;196(1):145–53.
50. Grande I, Goikolea JM, de Dios C, et al. Occupational disability in bipolar disorder: analysis of predictors of being on severe disablement benefit (PREBIS study data). Acta Psychiatr Scand. 2013;127(5):403–11.
51. Wingo AP, Harvey PD, Baldessarini RJ. Cognitive impairment in euthymic bipolar disorder patients: functional implications. Bipolar Disord. 2009;11(2):113–25.
52. Yoon JK, Kim SS, Choi SS, et al. Homicide and bipolar I disorder: 22-year study. Forensic Sci Int. 2012;217(1–3):113–8.
53. Baethge C, Baldessarini RJ, Khalsa HM, Hennen J, Salvatore P, Tohen M. Substance abuse in first-episode bipolar I disorder: indications for early intervention. Am J Psychiatry. 2005;162(5):1008–10.
54. Baethge C, Hennen J, Khalsa HM, Salvatore P, Tohen M, Baldessarini RJ. Sequencing of substance abuse and affective morbidity in 166 first-episode bipolar I disorder patients. Bipolar Disord. 2008;10(6):738–41.
55. Klimkiewicz A, Klimkiewicz J, Jokubczyk A, Kieres-Salomonski I, Wojnar M. Comorbidity of alcohol dependence with other psychiatric disorders: epidemiology of dual diagnosis. Psychiatr Pol. 2015;49(2):65–275.
56. Pavlova B, Perlis RH, Uher R. Lifetime prevalence of anxiety disorders in people with bipolar disorder: systematic review and meta-analysis. Lancet Psychiatry. 2015;2(8):710–7.
57. Preti A, Vrublevska J, Veroniki AA, Huedo-Medina TB, Fountoulakis KN. Prevalence, impact and treatment of generalized anxiety disorder in bipolar disorder: systematic review and meta-analysis. Evid Based Ment Health. 2016;19(3):73–81.
58. Messer T, Lammers G, Müller-Siecheneder F, Schmidt RF, Latifi S. Substance abuse in patients with bipolar disorder: systematic review and meta-analysis. Psychiatry Res. 2017;253(7):338–50.
59. Stokes PRA, Kalk NJ, Young AH. Bipolar disorder and addictions: the elephant in the room. Br J Psychiatry. 2017;211(3):132–4.
60. Post RM, Leverich GS, McElroy S, et al. Prevalence of axis-II comorbidities in bipolar disorder: relationship to mood-state. Bipolar Disord. 2018;20(4):303–12.
61. Hjorthøj AR, Madsen T, Agerbo E, Nordentoft M. Risk of suicide according to level of psychiatric treatment: nationwide nested case-control study. Soc Psychiatry Psychiatr Epidemiol. 2014;49(9):1357–65.
62. Pinna M, Visioli C, Rago CM, Manchia M, Tondo L, Baldessarini RJ. Attention deficit-hyperactivity disorder in adult bipolar disorder patients. J Affect Disord. 2019;243(1):391–6.
63. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale, meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry. 2017;16(2):163–80.
64. Fornaro M, Solmi M, Veronese N, et al. Burden of mood-disorder/cerebrovascular disease comorbidity: essential neurobiology, psychopharmacology, and physical activity interventions. Int Rev Psychiatry. 2017;29(5):425–35.
65. McIntyre RS, Soczynska JK, Beyer JL, et al. Medical comorbidity in bipolar disorder: reprioritizing unmet needs. Curr Opin Psychiatry. 2007;20(4):406–16.

66. Almeida OP, McCaul K, Hankey GJ, et al. Duration of diabetes and its association with depression in later life: Health In Men Study (HIMS). Maturitas. 2016;86(4):3–9.
67. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L. Older men with bipolar disorder: clinical associations with early and late illness. Int J Geriatr Psychiatry. 2018;33(12):1613–9.
68. Wu SI, Chen SC, Liu SI, et al. Relative risk of acute myocardial infarction in people with schizophrenia and bipolar disorder: population-based cohort study. PLoS One. 2015;10(8):e013463.
69. Tsai SY, Lee CH, Chen PH, et al. Risk factors for early cardiovascular mortality in patients with bipolar disorder. Psychiatry Clin Neurosci. 2017;71(10):716–24.
70. Vancampfort D, Firth J, Schuch FB, et al. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder; global systematic review and meta-analysis. World Psychiatry. 2017;16(3):308–15.
71. Fiedorowicz JG, Prossin AR, Johnson CP, Christensen GE, Magnotta VA, Wemmie JA. Peripheral inflammation during abnormal mood states in bipolar I disorder. J Affect Disord. 2015;187(11):172–8.
72. Rosenblat JD, McIntyre RS. Bipolar disorder and inflammation. Psychiatr Clin N Am. 2016;39(1):125–37.
73. Halaris A. Inflammation-associated co-morbidity between depression and cardiovascular disease. Curr Top Behav Neurosci. 2017;31(11):45–70.
74. Horsdal HT, Kohler-Forsberg O, Benros ME, Gasse C. C-reactive protein and white blood cell levels in schizophrenia, bipolar disorders and depression: associations with mortality and psychiatric outcomes, a population-based study. Eur Psychiatry. 2017;44(7):164–72.
75. Vázquez GH, Camino S, Tondo L, Baldessarini RJ. Potential novel treatments for bipolar depression: ketamine, fatty acids, anti-inflammatory agents, and probiotics. CNS Neurol Disord Drug Targets. 2017;16(8):858–69.
76. Kalelioğlu T, Ünalan P, Kök B, et al. Atherogenic index of plasma as a cardiovascular risk marker in manic, depressive, and euthymic stages of bipolar disorder. Turk Kardiyol Dern Ars. 2018;46(1):32–8.
77. Vancampfort D, Vansteelandt K, Correll CU, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: meta-analysis of prevalence rates and moderators. Am J Psychiatry. 2013;170(3):265–74.
78. Pennix BWJH, Lange SMM. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. Dialogues Clin Neurosci. 2018;20(1):63–73.
79. American Heart Association (AHA). Symptoms and diagnosis of metabolic syndrome. http://www.heart.org/en/health-topics/metabolic-syndrome/symptoms-and-diagnosis-of-metabolic-syndrome. Accessed 18 Nov 2018.
80. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of metabolic syndrome in the United States, 2003–2012. JAMA. 2015;313(19):1973–4.
81. Silarova B, Giltay EJ, Van Reedt-Dortland A, et al. Metabolic syndrome in patients with bipolar disorder: comparison with major depressive disorder and nonpsychiatric controls. J Psychosom Res. 2015;78(4):391–8.
82. Moreira FP, Jansen K, Cardoso TA, et al. Metabolic syndrome in subjects with bipolar disorder and major depressive disorder in a current depressive episode: population-based study. J Psychiatr Res. 2017;92(9):119–23.
83. Guha P, Bhowmick K, Mazumder P, Ghosal M, Chakraborty I, Burman P. Assessment of insulin resistance and metabolic syndrome in drug-naïve patients of bipolar disorder. Indian J Clin Biochem. 2014;29(1):51–6.
84. Strassnig M, Kotov R, Cornaccio D, Fochtmann L, Harvey PD, Bromet EJ. Twenty-year progression of body-mass index in a county-wide cohort of people with schizophrenia or bipolar disorder identified at their first episode of psychosis. Bipolar Disord. 2017;19(5):336–43.
85. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression, or bipolar disorder. World Psychiatry. 2015;14(20):119–36.

86. Høye A, Nesvåg R, Reichborn-Kiennerud T, Kacobsen BK. Sex differences in mortality among patients admitted with affective disorders in North Norway: 33-year prospective register study. Bipolar Disord. 2016;18(3):272–81.
87. Hällgren J, Ösby U, Westman J, Gissler M. Mortality trends in external causes of death in people with mental health disorders in Sweden, 1987-2010. Scand J Public Health. 2018;47(2):121–6.
88. Hayes JF, Marston L, Walters K, King MB, Osborn PJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000–2014. Br J Psychiatry. 2017;211(3):175–81.
89. Staudt-Hansen P, Frahm-Laursen M, Grøntved S, Puggard-Vogt-Straszek S, Licht RW, Nielsen RE. Increasing mortality gap for patients diagnosed with bipolar disorder: nationwide study with 20 years of follow-up. Bipolar Disord. 2019;21(3):270–5.
90. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: meta-review. World Psychiatry. 2014;13(2):153–60.
91. Brietzke E, Mansur RB, McIntyre RS. Impact of inequalities in healthcare on the mortality risk of individuals with severe mental illnesses. Braz J Psychiatry. 2017;39(3):193–4.
92. Hjorthøj C, Drivsholm-Østergaard ML, Eriksen-Benros M, et al. Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: nationwide, prospective, register-based study. Lancet Psychiatry. 2015;2(9):801–8.
93. Dickerson F, Origoni A, Schroeder J, et al. Natural cause mortality in persons with serious mental illness. Acta Psychiatr Scand. 2018;137(5):371–9.
94. World Health Organization (WHO). International suicide rates, 2018. http://www.who.int/gho/mental_health/suicide_rates_crude/en/. Accessed 3 Dec 2018.
95. Bachmann S. Epidemiology of suicide and the psychiatric perspective. Int J Environ Res Public Health. 2018;15(7):E1425–47.
96. Baldessarini RJ, Hennen J. Genetics of suicide: overview. Harv Rev Psychiatry. 2004;12(1):1–13.
97. Charlier P, Malaurie J, Wasserman D, et al. EPA guidance on suicide treatment and prevention needs to be adjusted to fight the epidemics of suicide at the North Pole area and other autochthonous communities. Eur Psychiatry. 2017;41(3):129–31.
98. Levey DF, Polimanti R, Cheng Z, et al. Genetic associations with suicide attempt severity and genetic overlap with major depression. Transl Psychiatry. 2019;9:22–4.
99. Tondo L, Albert M, Baldessarini RJ. Suicide rates in relation to health-care access in the United States. J Clin Psychiatry. 2006;67(4):517–23.
100. Diekstra RFW. Epidemiology of suicide and parasuicide. Acta Psychiatr Scand Suppl. 1993;371(Suppl):9–20.
101. Simon RI, Hales RE, editors. Textbook of suicide assessment and management. 2nd ed. Washington: American Psychiatric Press; 2012.
102. Baldessarini RJ, Tondo L, Strombom IM, et al. Analysis of ecological studies of relationships between antidepressant utilization and suicidal risk. Harv Rev Psychiatry. 2007;15(4):133–45.
103. Nordstrom P, Samuelsson M, Åsberg M. Survival analysis of suicide risk after attempted suicide. Acta Psychiatr Scand. 1995;91(5):336–40.
104. American Psychiatric Association (APA). Practice guideline for the assessment and treatment of patients with suicidal behaviors. Am J Psychiatry. 2003;160(11 Suppl):1–60.
105. Oquendo MA, Chaudhury SR, Mann JJ. Pharmacotherapy of suicidal behavior in bipolar disorder. Arch Suicide Res. 2005;9(3):237–50.
106. Baldessarini RJ, Tondo L, Davis P, et al. Decreased risk of suicides and attempts during long-term lithium treatment: meta-analytic review. Bipolar Disord. 2006;8(5):625–39.
107. Lenz B, Röther M, Bouna-Pyrrou P, Mühle C, Tektas OY, Kornhuber J. Androgen model of suicide completion. Prog Neurobiol. 2019;172(1):84–103.
108. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035–43.

109. Sheehan DV, Giddens JM. Suicidality: roadmap for assessment and treatment. Tampa: Harm Research Press; 2015.
110. Tondo L, Isacsson G, Baldessarini RJ. Suicide in bipolar disorder: risk and prevention. CNS Drugs. 2003;17(7):491–511.
111. Kessler RC, Berglund P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the US, 1990–1992 to 2001–2003. JAMA. 2005;293(20):2487–95.
112. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry. 1998;173(7):11–53.
113. Goldsmith SK, Pellmar TC, Kleinman AM, Bunney WE Jr, editors. Reducing suicide. Washington: Institute of Medicine of the US National Academies of Science; 2002.
114. Plans L, Barrot C, Nieto E, et al. Association between completed suicide and bipolar disorder: systematic review. J Affect Disord. 2019;242(1):111–22.
115. Tondo L, Lepri B, Baldessarini RJ. Suicidal status during antidepressant treatment in 789 Sardinian patients with major affective disorder. Acta Psychiatr Scand. 2008;118(2):106–15.
116. Large M, Swaraj S. Suicide, substance use and natural causes are respectively the most important causes of mortality in the first year post discharge from psychiatric hospitals. Evid Based Ment Health. 2018;21(2):e8–9.
117. Walter F, Carr MJ, Mok PLH, et al. Suicide methods and specific types of accidental death and fatal poisoning among discharged psychiatric patients: national cohort study. J Clin Psychiatry. 2018;79(6):17m11809–26.
118. Forte A, Buscaioni A, Fiorillo A, Pompili M, Baldessarini RJ. Suicidal risk following hospital discharge: review. Harv Rev Psychiatry. 2019;27(4):209–16.
119. Isometsä ET, Henriksson MM, Aro HM, Heikkinen ME, Kuoppasalmi KI, Lönnqvist JK. Suicide in major depression. Am J Psychiatry. 1994;151(4):530–6.
120. Tondo L, Baldessarini RJ, Hennen J, et al. Suicide attempts in major affective disorder patients with comorbid substance use disorders. J Clin Psychiatry. 1999;60(2):63–9.
121. Tondo L, Lepri B, Baldessarini RJ. Risks of suicidal ideation, attempts and suicides among 2826 men and women with types I and II bipolar, and recurrent major depressive disorders. Acta Psychiatr Scand. 2007;116(6):419–28.
122. Murphy SL, Xu J, Kochanek KD. Deaths: preliminary data for 2010. Nat Vital Stat Rep. 2012;60(4):1–51. http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_04.pdf. Accessed 20 Dec 2018.
123. Laughren TP. In Proceedings of a meeting of the Psychopharmacology Drug Advisory Committee (PDAC) concerning suicidal risk in trials of antidepressant drugs in juvenile and adult patients; 2006. http://www.fda.gov/ohrms/dockets/ac/06/briefing//2006-4272b1-01-fda.pdf. Accessed 22 Dec 2018.
124. Nock MK, Borges G, Bromet EJ, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. Br J Psychiatry. 2008;192(2):98–105.
125. Nock MK, Hwang I, Sampson N, et al. Cross-national analysis of associations among mental disorders and suicidal behavior: findings from WHO world mental health surveys. PLoS Med. 2009;6(8):e1000123–40.
126. Baldessarini RJ. Chemotherapy in psychiatry. 3rd ed. New York: Springer Press; 2013.
127. Saunders KE, Hawton K. Clinical assessment and crisis intervention for the suicidal bipolar disorder patient. Bipolar Disord. 2013;15(5):575–83.
128. Judd LL, Akiskal HS, Schettler PJ, et al. Long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002;59(6):530–7.
129. Baldessarini RJ, Salvatore P, Khalsa HM, et al. Morbidity in 303 first-episode bipolar I disorder patients. Bipolar Disord. 2010b;12(3):264–70.
130. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry. 2003;60(1):82–91.
131. Zalsman G, Hawton K, Wasserman D, et al. Suicide prevention strategies revisited: 10-year systematic review. Lancet Psychiatry. 2016;3(7):646–59.
132. Isometsä ET. Suicide in bipolar I disorder in Finland: psychological autopsy findings from the National Suicide Prevention Project in Finland. Arch Suicide Res. 2005;9(3):251–60.

133. Ernst CL, Bird SA, Goldberg JF, Ghaemi SN. Prescription of psychotropic medications for patients discharged from a psychiatric emergency service. J Clin Psychiatry. 2006;67(5):720–6.
134. Ahmedani BK, Simon GE, Stewart C, et al. Healthcare contacts in the year before suicide death. J Gen Intern Med. 2014;29(6):870–7.
135. Hammad TA, Laughren TP, Racoosin JA. Suicide rates in short-term randomized controlled trials of newer antidepressants. J Clin Psychopharmacol. 2006;26(2):203–7.
136. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: meta-analysis of randomized controlled trials. JAMA. 2007;297(15):1683–96.
137. Barbui C, Esposito E, Cipriani A. Selective serotonin reuptake inhibitors and risk of suicide: systematic review of observational studies. CMAJ. 2009;180(3):291–7.
138. Braun C, Bschor T, Franklin J, Baethge C. Suicides and suicide attempts during long-term treatment with antidepressants: meta-analysis of 29 placebo-controlled studies including 6934 patients with major depressive disorder. Psychother Psychosom. 2016;85(3):171–9.
139. Möller HJ. Is there evidence for negative effects of antidepressants on suicidality in depressive patients? Systematic review. Eur Arch Psychiatry Clin Neurosci. 2006;256(8):476–96.
140. Baldessarini RJ, Lau WK, Sim J, Sum MY, Sim K. Suicidal risks in reports of long-term treatment trials for major depressive disorder. Int J Neuropsychopharmacol. 2016;19(3):1–2.
141. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. Psychiatr Clin N Am. 1999;22(3):547–64.
142. Akiskal HS, Benazzi F, Perugi G, Rimher Z. Agitated "unipolar" depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. J Affect Disord. 2005;85(3):245–58.
143. Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L. Agitated "unipolar" major depression: prevalence, phenomenology and outcome. J Clin Psychiatry. 2006;67(5):712–9.
144. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. International Society for Bipolar Disorders (ISBD) Task-Force report on antidepressant use in bipolar disorders. Am J Psychiatry. 2013;170(11):1249–62.
145. Beasley CM Jr, Dornseif BE, Bosomworth JC, et al. Fluoxetine and suicide: meta-analysis of controlled trials of treatment for depression. BMJ. 1991;303(3804):685–92.
146. Tollefson GD, Rampey AH Jr, Beasley CM Jr, Enas GG, Potvin JH. Absence of a relationship between adverse events and suicidality during pharmacotherapy for depression. J Clin Psychopharmacol. 1994;14(3):163–9.
147. Acharya N, Rosen AS, Polzer JP, et al. Duloxetine: meta-analyses of suicidal behaviors and ideation in clinical trials for major depressive disorder. J Clin Psychopharmacol. 2006;26(6):587–94.
148. Plöderl M, Hengartner MP. Antidepressant prescription rates and suicide attempt rates from 2004 and 2016 in a nationally representative sample of adolescents in the USA. Epidemiol Psychiatr Sci. 2019;28:589.
149. Khan A, Leventhal RM, Khan S, Brown WA. Suicide risk in patients with anxiety disorders: meta-analysis of the FDA database. J Affect Disord. 2002;68(2–3):183–90.
150. Diefenbach GJ, Woolley SB, Goethe JW. Association between self-reported anxiety symptoms and suicidality. J Nerv Ment Dis. 2009;197(2):92–7.
151. Gaertner I, Gilot C, Heidrich P, Gaertner HJ. Case control study on psychopharmacotherapy before suicide committed by 61 psychiatric inpatients. Pharmacopsychiatry. 2002;35(2):37–43.
152. Yerevanian BI, Choi YM. Impact of psychotropic drugs on suicide and suicidal behaviors. Bipolar Disord. 2013;315(5):594–621.
153. Angst J, Angst F, Gerber-Werder R, Gamma A. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch Suicide Res. 2005;9(3):279–300.
154. Müller-Oerlinghausen B, Ahrens B, Felber W. Suicide-preventive and mortality-reducing effect of lithium. In: Bauer M, Grof P, Müller-Oerlinghausen B, editors. Lithium in neuropsychiatry. London: Informa Healthcare; 2006. p. 79–192.

155. Baldessarini RJ, Tondo L. Lithium and suicidal risk. Bipolar Disord. 2008;10(1):114–5.
156. Roberts E, Cipriani A, Geddes JR, Nierenberg AA, Young AH. Evidence for lithium in suicide prevention. Br J Psychiatry. 2017;211(6):396–7.
157. Felber W, Bauer M, Lewitzka U, Müller-Oerlinghausen B. Lithium clinics in Berlin and Dresden: 50-year experience. Pharmacopsychiatry. 2018;51(5):166–71.
158. Malhi GS. Lithium: global perspective. Pharmacopsychiatry. 2018;51(5):220–1.
159. Tondo L, Baldessarini RJ. Antisuicidal effects in mood disorders: are they unique to lithium? Pharmacopsychiatry. 2018;51(5):177–88.
160. Marangell LB, Dennehy EB, Wisniewski SR, et al. Case-control analyses of the impact of pharmacotherapy on prospectively observed suicide attempts and completed suicides in bipolar disorder. J Clin Psychiatry. 2008;69(6):916–22.
161. Oquendo MA, Galfalvy HC, Currier D, et al. Treatment of suicide attempters with bipolar disorder: randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior. Am J Psychiatry. 2011;168(10):1050–6.
162. Tondo L, Hennen J, Baldessarini RJ. Reduced suicide risk with long-term lithium treatment in major affective illness: meta-analysis. Acta Psychiatr Scand. 2001;104(3):163–72.
163. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: systematic review of randomized trials. Am J Psychiatry. 2005;162(10):1805–19.
164. Lauterbach E, Felber W, Müller-Oerlinghausen B, et al. Adjunctive lithium treatment in the prevention of suicidal behavior in depressive disorders: randomized, placebo-controlled, one-year trial. Acta Psychiatr Scand. 2008;118(6):469–79.
165. Khan A, Khan SR, Hobus J, et al. Differential pattern of response in mood symptoms and suicide risk measures in severely ill depressed patients assigned to citalopram with placebo or citalopram combined with lithium: role of lithium levels. J Psychiatr Res. 2011;45(11):1489–96.
166. Tondo L, Baldessarini RJ, Hennen J, Floris G, Silvetti F, Tohen M. Lithium treatment and risk of suicidal behavior in bipolar disorder patients. J Clin Psychiatry. 1998;59(8):405–14.
167. Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry. 2007;68(3):380–3.
168. Wasserman D, Rihmer Z, Rujescu D, et al. European Psychiatric Association (EPA) guidance on suicide treatment and prevention. Eur Psychiatry. 2012;27(2):129–41.
169. Lewitzka U, Bauer M, Felber W, Müller-Oerlinghausen B. Antisuicidal effect of lithium: current state of research and its clinical implications for the long-term treatment of affective disorders. Nervenarzt. 2013;84(3):294–306.
170. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97–170.
171. Bschor T, Bauer M. Efficacy and mechanisms of action of lithium augmentation in refractory major depression. Curr Pharm Des. 2006;12(23):2985–92.
172. Kovacsics CE, Gottesman II, Gould T. Lithium's antisuicidal efficacy: elucidation of neurobiological targets using endophenotype strategies. Annu Rev Pharmacol Toxicol. 2009;49(12):175–98.
173. Müller-Oerlinghausen B, Lewitzka U. Lithium reduces pathological aggression and suicidality: mini-review. Neuropsychobiology. 2010;62(1):43–9.
174. Manchia M, Hajek T, O'Donovan C, et al. Genetic risk of suicidal behavior in bipolar spectrum disorder: analysis of 737 pedigrees. Bipolar Disord. 2013;15(5):496–506.
175. Nelson JC, Spyker DA. Morbidity and mortality associated with medications used in the treatment of depression: analysis of cases reported to US poison control centers, 2000–2014. Am J Psychiatry. 2017;174(5):438–50.
176. Tondo L, Baldessarini RJ. Reduction of suicidal behavior in bipolar disorder patients during long-term treatment with lithium. In: Koslow SH, Ruiz P, Nemeroff CB, editors. Concise guide to understanding suicide: epidemiology pathophysiology and prevention. Cambridge: Cambridge University Press; 2014. p. 217–28.

177. Søndergård L, Lopez AG, Andersen PK, Kessing LV. Mood-stabilizing pharmacological treatment in bipolar disorders and risk of suicide. Bipolar Disord. 2008;10(1):87–94.
178. Thies-Flechtner K, Müller-Oerlinghausen B, Seibert W, Walther A, Greil W. Effect of prophylactic treatment on suicide risk in patients with major affective disorders: data from a randomized prospective trial. Pharmacopsychiatry. 1996;29(3):103–7.
179. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA. 2003;290(11):1467–73.
180. Food and Drug Administration (US FDA). Antiepileptic drugs and suicidality 2008. Anticon. https://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm192556.pdf. Accessed 22 Dec 2018.
181. Yerevanian BI, Koek RJ, Mintz J. Bipolar pharmacotherapy and suicidal behavior: lithium, divalproex and carbamazepine. J Affect Disord. 2007;103(1–3):23–8.
182. Gibbons RD, Hur K, Brown CH, Mann JJ. Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. Arch Gen Psychiatry. 2009;66(12):1354–60.
183. Smith EG, Søndergård L, Lopez AG, Andersen PK, Kessing LV. Association between consistent purchase of anticonvulsants or lithium and suicide risk: longitudinal cohort study from Denmark, 1995–2001. J Affect Disord. 2009;117(3):162–7.
184. Baldessarini RJ, Tondo L. Suicidal risks during treatment of bipolar disorder patients with lithium versus anticonvulsants. Pharmacopsychiatry. 2009;42(2):72–5.
185. Khan A, Khan SR, Leventhal RM, Brown WA. Symptom reduction and suicide risk among patients treated with placebo in antipsychotic clinical trials: analysis of the FDA database. Am J Psychiatry. 2001;158(9):1449–54.
186. Schneider-Thoma J, Efthimiou O, Huhn M, et al. Second-generation antipsychotic drugs and short-term mortality: systematic review and meta-analysis of randomized placebo-controlled trials. Lancet Psychiatry. 2018;5(8):653–63.
187. Tiihonen J, Wahlbeck K, Lönnqvist J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalization due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ. 2006;333(7561):224–9.
188. Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: meta-analysis. Schizophr Res. 2005;73(2–3):139–45.
189. Haukka J, Tiihonen J, Härkänen T, Lönnqvist J. Association between medication and risk of suicide, attempted suicide and death in nationwide cohort of suicidal patients with schizophrenia. Pharmacoepidemiol Drug Saf. 2008;17(7):686–96.
190. Pompili M, Baldessarini RJ, Forte A, et al. Do atypical antipsychotics have antisuicidal effects? A hypothesis-generating overview. Int J Mol Sci. 2016;17(10):E1700–13.
191. Wimberley T, MacCabe JH, Laursen TM, et al. Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia. Am J Psychiatry. 2017;174(10):990–8.
192. Vermeulen JM, van Rooihen G, van de Kerkhof MPJ, Sutterland AL, Correll CU, de Haan L. Clozapine and long-term mortality risk in patients with schizophrenia: systematic review and meta-analysis of studies lasting 1.1–12.5 years. Schizophr Bull. 2019;45(2):315–29.
193. Patchan KM, Richardson C, Vyas G, Kelly DL. Risk of suicide after clozapine discontinuation: cause for concern. Ann Clin Psychiatry. 2015;27(4):253–6.
194. Li XB, Tang YL, Wang CY, de Leon J. Clozapine for treatment-resistant bipolar disorder: systematic review. Bipolar Disord. 2015;17(3):235–47.
195. Arensman E, Townsend E, Hawton K, et al. Psychosocial and pharmacological treatment of patients following deliberate self-harm: methodological issues involved in evaluating effectiveness. Suicide Life Threat Behav. 2001;31(2):169–80.
196. Hawton K, Arensman E, Townsend E, et al. Deliberate self-harm: systematic review of efficacy of psychosocial and pharmacological treatments in preventing repetition. BMJ. 1998;317(7156):441–7.
197. Brown GK, Ten Have T, Henriques GR, Xie SX, Hollander JE, Beck AT. Cognitive therapy for the prevention of suicide attempts: randomized controlled trial. JAMA. 2005;294(5):563–70.

198. Witt K, de Moraes DP, Salisbury TT, et al. Treatment as usual (TAU) as a control condition in trials of cognitive behavioral-based psychotherapy for self-harm: impact of content and quality on outcomes in a systematic review. J Affect Disord. 2018;235(8):434–47.
199. Linehan MM, Armstrong HE, Suarez A, Allmon D, Heard HL. Cognitive-behavioral treatment of chronically parasuicidal borderline patients. Arch Gen Psychiatry. 1991;48(12):1060–4.
200. Chesin M, Stanley B. Risk assessment and psychosocial interventions for suicidal patients. Bipolar Disord. 2013;15(5):584–93.
201. Rucci P, Frank E, Kostelnik B, et al. Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy. Am J Psychiatry. 2002;159(7):1160–4.
202. Guthrie E, Kapur NE, Mackway-Jones K, et al. Predictors of outcome following brief psychodynamic-interpersonal therapy for deliberate self-poisoning. Aust N Z J Psychiatry. 2003;37(5):532–6.
203. Mehlum L, Dieserud G, Ekeberg Ø, et al. Prevention of suicide: psychotherapy, drug treatment and electroconvulsive treatment. Kunnskapssenteret report 24-2006. Oslo: Norwegian Knowledge Centre for the Health Services; 2006.
204. Möller HJ. Attempted suicide: efficacy of different aftercare strategies. Int Clin Psychopharmacol. 1992;6(6):58–69.
205. Cuijpers P, de Beurs DP, van Spijker BA, Berking M, Andersson G, Kerkhof AJ. Effects of psychotherapy for adult depression on suicidality and hopelessness: systematic review and meta-analysis. J Affect Disord. 2013;144(3):183–90.
206. Parsaik AK, Singh B, Khosh-Chashm D, Mascarenhas SS. Efficacy of ketamine in bipolar depression: systematic review and meta-analysis. J Psychiatr Pract. 2015;21(6):427–35.
207. Wilkinson ST, Ballard ED, Bloch MH, et al. Effect of a single dose of intravenous ketamine on suicidal ideation: systematic review and individual participant data meta-analysis. Am J Psychiatry. 2018;175(2):150–8.
208. Fink M, Kellner CH, McCall WV. Role of ECT in suicide prevention. J ECT. 2014;30(1):5–9.
209. Chung DT, Ryan CJ, Hadzi-Pavlovic D, Singh SP, Stanton C, Large MM. Suicide rates after discharge from psychiatric facilities. JAMA Psychiat. 2017;74(7):694–702.
210. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. Mol Psychiatry. 2019;24(2):198–217.
211. Vázquez GH, Tondo L, Undurraga J, Baldessarini RJ. Overview of antidepressant treatment of bipolar depression. Int J Neuropsychopharmacol. 2013;16(7):1673–85.
212. McGirr A, Vöhringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second generation antidepressant therapy with a mood-stabilizer or an atypical antipsychotic in acute bipolar depression: systematic review and meta-analysis of randomized placebo-controlled trials. Lancet Psychiatry. 2016;3(12):1138–46.. [and eAppendix; accessible at doi.org/10.1016/S2215-0366(16)30264-4].
213. Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016;30(6):495–553.
214. Baldessarini RJ, Henk H, Sklar A, Chang J, Leahy L. Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. Psychiatr Serv. 2008;59(10):1175–83.
215. Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: systematic review of randomized, controlled trials. Am J Psychiatry. 2004;161(9):1537–47.
216. Ghaemi SN, Wingo AF, Filkowski MA, Baldessarini RJ. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. Acta Psychiatr Scand. 2008;118(5):347–56.
217. Sidor MM, MacQueen GM. Update on antidepressant use in bipolar depression. Curr Psychiatry Rep. 2012;14(6):696–704.

218. Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine vs. lithium monotherapy of bipolar II disorder: randomized, double-blind, placebo-substitution study. Am J Psychiatry. 2010;167(7):792–800.
219. McElroy SL, Weisler RH, Chan W, et al. Double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry. 2010;71(2):163–74.
220. Altshuler LL, Sugar CA, McElroy SL, et al. Switch rates during acute treatment for bipolar II depression with lithium, sertraline, or the two combined: randomized, double-blind comparison. Am J Psychiatry. 2017;174(3):266–76.
221. Fountoulakis KN, Vieta E, Young A, et al. Unmet needs in the treatment of bipolar disorder and recommendations for future research. Int J Neuropsychopharmacol. 2017;20(2):196–205.
222. Liu B, Zhang Y, Fang H, et al. Efficacy and safety of long-term antidepressant treatment for bipolar disorders: meta-analysis of randomized controlled trials. J Affect Disord. 2017;223(12):41–8.
223. Gitlin MJ. Antidepressants in bipolar depression: an enduring controversy. Int J Bipolar Disord. 2018;6(1):25–31.
224. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry. 2001;158:906–12.
225. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry. 2003;60(11):1079–88.
226. Shelton RC, Stahl SM. Risperidone and paroxetine given singly and in combination for bipolar depression. J Clin Psychiatry. 2004;65:1715–9.
227. Agosti V, Stewart JW. Hypomania with and without dysphoria: comparison of comorbidity and clinical characteristics of respondents from a national community sample. J Affect Disord. 2008;108(1–2):177–82.
228. Ghaemi SN. Antidepressants in bipolar depression: an update. In Proceedings of the 168th annual meeting of the American Psychiatric Association; Toronto, Ontario, Canada; 16–20 May 2015.
229. Yatham LN, Vieta E, Goodwin GM, et al. Agomelatine or placebo as adjunctive therapy to a mood-stabilizer in bipolar I depression: randomized double-blind placebo-controlled trial. Br J Psychiatry. 2016;208(1):78–86.
230. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med. 2007;356(17):1711–22.
231. Vázquez GH, Tondo L, Baldessarini RJ. Comparison of antidepressant responses in patients with bipolar vs. unipolar depression: meta-analytic review. Pharmacopsychiatry. 2011;44(1):21–6.
232. Tondo L, Baldessarini RJ, Vázquez GH, Lepri B, Visioli C. Clinical responses to antidepressants among 1036 acutely depressed patients with bipolar or unipolar major affective disorders. Acta Psychiatr Scand. 2013;127(5):355–64.
233. Cohn JB, Collins G, Ashbrook E, Wernicke JF. Combination of fluoxetine, imipramine, and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol. 1989;4:313–22.
234. Fountoulakis KN, Kasper S, Andreassen O, et al. Efficacy of pharmacotherapy in bipolar disorder: report by the WPA section on pharmacopsychiatry. Eur Arch Psychiatry Clin Neurosci. 2012;262(1):1–48.
235. Undurraga J, Baldessarini RJ, Valenti M, et al. Bipolar depression: clinical correlates of receiving antidepressants. J Affect Disord. 2012;139(1):89–93.
236. Koukopoulos A, Reginaldi D, Tondo L, Visioli C, Baldessarini RJ. Course sequences in bipolar disorder: depressions preceding or following manias or hypomanias. J Affect Disord. 2013;151(1):105–10.
237. Bond DJ, Noronha MM, Kauer-Sant'Anna M, Lam RW, Yatham LN. Antidepressant-associated mood elevations in bipolar II disorder compared with bipolar I disorder and

major depressive disorder: systematic review and meta-analysis. J Clin Psychiatry. 2008;69(10):1589–601.
238. Viktorin A, Lichtenstein P, Thase ME, et al. Risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry. 2014;171(10):1067–673.
239. Grande I, De Arce R, Jimenez-Arrieto MA, et al. Patterns of pharmacological maintenance treatment in a community mental health services bipolar disorder cohort study (SIN-DERES). Int J Neuropsychopharmacol. 2013;16(3):513–23.
240. Miura T, Noma H, Furukawa TA, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):351–9.. [and eAppendix; accessible at doi.org/10.1016/S2215-0366(14)70314-1].
241. Selle V, Schalkwijk S, Vázquez GH, Baldessarini RJ. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium, and second-generation antipsychotics. Pharmacopsychiatry. 2014;47(2):43–52.
242. Sim K, Lau KL, Sim J, Sum MY, Baldessarini RJ. Prevention of relapse and recurrence in adults with major depressive disorder: systematic review and meta-analyses of controlled trials. Int J Neuropsychopharmacol. 2015;19(2):1–13.
243. Baldessarini RJ, Tondo L, Ghiani C, Lepri B. Illness risk following rapid vs. gradual discontinuation of antidepressants. Am J Psychiatry. 2010;167(8):934–41.
244. Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry. 2006;163(2):232–329.
245. Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. Antidepressant discontinuation in bipolar depression: randomized clinical trial of long-term effectiveness and safety. J Clin Psychiatry. 2010;71(4):372–80.
246. Erol A, Winham SJ, McElrory SL, et al. Sex differences in the risk of rapid cycling and other indicators of adverse illness course in patients with bipolar I and II disorder. Bipolar Disord. 2015;17(6):670–6.
247. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet. 2013;381(9878):1672–82.
248. Reinares M, Rosa AR, Franco C, et al. Systematic review on the role of anticonvulsants in the treatment of acute bipolar depression. Int J Neuropsychopharmacol. 2013;16(2):485–96.
249. Vázquez GH, Tondo L, Undurraga J, Zaratiegui R, Selle V, Baldessarini RJ. Pharmacological treatment of bipolar depression. Adv Psychiatr Treat. 2014;20(1):193–201.
250. Muzina DJ, Gao K, Kemp DE, et al. Acute efficacy of divalproex sodium versus placebo in mood stabilizer-naive bipolar I or II depression: double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2011;72(6):813–9.
251. Solmi M, Veronese N, Zaninoto L, et al. Lamotrigine compared to placebo and other agents with antidepressant activity in patients with unipolar and bipolar depression: comprehensive meta-analysis of efficacy and safety outcomes in short-term trials. CNS Spectr. 2016;21(5):403–18.
252. Frye MA, Ha K, Kanba S, et al. International consensus group on depression prevention in bipolar disorder. J Clin Psychiatry. 2011;72(10):1295–310.
253. Young AH, McElroy SL, Bauer M, et al. Double-blind, placebo-controlled study (EMBOLDEN I) of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression. J Clin Psychiatry. 2010;71(2):150–62.
254. Bschor T. Lithium in the treatment of major depressive disorder. Drugs. 2014;74(8):855–62.
255. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ. 2013;346(6):f3646–59.
256. Song J, Sjolander A, Joas E, et al. Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. Am J Psychiatry. 2017;174(8):795–802.

257. Durgam S, Earley W, Lipschitz A, et al. Eight-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar-I depression. Am J Psychiatry. 2016;173(3):271–81.
258. Brown EB, McElroy SL, Keck PE Jr, et al. Seven-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. J Clin Psychiatry. 2006;67(7):1025–33.
259. Tamayo JM, Zarate CA Jr, Vieta E, Vázquez GH, Tohen M. Level of response and safety of pharmacological monotherapy in the treatment of acute bipolar I disorder phases: systematic review and meta-analysis. Int J Neuropsychopharmacol. 2010;13(6):813–32.
260. Tarsy D, Lungu C, Baldessarini RJ. Epidemiology of tardive dyskinesia before and during the era of modern antipsychotic drugs. In: Weiner WJ, Tolosa E, editors. Hyperkinetic movement disorders. In: Aminoff MJ, Boller F, Swaab DF (series editors). Handbook of clinical neurology. Edinburgh: Elsevier Press; 2010, pp. 601–16.
261. Carbon M, Hsieh C-H, Kane JM, Correll CU. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use, meta-analysis. J Clin Psychiatry. 2017;78(3):e264–78.
262. Centorrino F, Masters GA, Talamo A, Baldessarini RJ, Öngür D. Metabolic syndrome in psychiatrically hospitalized patients treated with antipsychotics and other psychotropics. Hum Psychopharmacol. 2012;27(5):521–6.
263. Lindström L, Lindström E, Nilsson M, Höistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder – systematic review and meta-analysis. J Affect Disord. 2017;213(12):138–50.
264. Fava M, Freeman MP, Flynn M, et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry. 2018; https://doi.org/10.1038/s41380-018-0256-5; [Epub ahead of print 3 Oct].
265. Aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry. 2010;67(2):139–45.
266. Rasmussen KG, Lineberry TW, Galardy CW, Kung S, Lapid MI, Palmer BA, Ritter MJ, Schak KM, Sola CL, Hanson AJ, Frye MA. Serial infusions of low-dose ketamine for major depression. J Psychopharmacol. 2013;27(5):444–50.
267. Muller J, Pentyala S, Dilger J, Pentyala S. Ketamine enantiomers in rapid and sustained antidepressant effects. Ther Adv Psychopharmacol. 2016;6(3):185–92.
268. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47(4):351–4.
269. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-dependent antidepressant actions of ketamine metabolites. Nature. 2016;533(7604):481–2.
270. Williams NR, Heifets BD, Blasey C, et al. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. Am J Psychiatry. 2018;175(12):1205–15.
271. Van de Voort JL, Morgan RJ, Kung S, et al. Continuation phase intravenous ketamine in adults with treatment-resistant depression. J Affect Disord. 2016;206(12):300–4.
272. Dhir A. Investigational drugs for treating major depressive disorder. Expert Opin Investig Drugs. 2017;26(1):9–24.
273. Garay RP, Zarate CA Jr, Charpeaud T, et al. Investigational drugs in recent clinical trials for treatment-resistant depression. Expert Rev Neurother. 2017;17(6):593–609.
274. Bahji A, Hawken ER, Sepehry AA, Cabrera CA, Vázquez GH. ECT beyond unipolar major depression: systematic review and meta-analysis of electroconvulsive therapy in bipolar depression. Acta Psychiatr Scand. 2019;139(3):214–26.
275. Itagaki K, Takebayashi M, Shibasaki C, et al. Factors associated with relapse after a response to electroconvulsive therapy in unipolar versus bipolar depression. J Affect Disord. 2017;208(1):113–9.
276. Perugi G, Medda P, Toni C, et al. Role of electroconvulsive therapy (ECT) in bipolar disorder: effectiveness in 522 patients with bipolar depression, mixed-state, mania and catatonic features. Curr Neuropharmacol. 2017;15(3):359–71.

277. Liang CS, Chung CH, Ho PS, Tsai CK, Chien WC. Superior antisuicidal effects of electroconvulsive therapy in unipolar disorder and bipolar depression. Bipolar Disord. 2018;41(3):341–53.
278. Tseng PT, Chen YW, Tu KY, et al. Light therapy in the treatment of patients with bipolar depression: meta-analytic study. Eur Neuropsychopharmacol. 2016;26(6):1037–47.
279. Kurczewska E, Ferensztajn-Rochowiak E, Jasińska-Mikołajczyk A, Chłopocka-Woźniak M, Rybakowski JK. Augmentation of pharmacotherapy by sleep deprivation with sleep phase advance in treatment-resistant depression. Pharmacopsychiatry. 2019;52(4):186–92.
280. Sit DK, McGowan J, Wiltrout C, et al. Adjunctive bright light therapy for bipolar depression: randomized double-blind placebo-controlled trial. Am J Psychiatry. 2018;175(2):131–9.
281. Suzuki M, Dallaspezia S, Locatelli C, Uchiyama M, Colombo C, Benedetti F. Does early response predict subsequent remission in bipolar depression treated with repeated sleep deprivation combined with light therapy and lithium? J Affect Disord. 2018;229(3):371–6.
282. Cimpianu CL, Strube W, Falkai P, Palm U, Hasan A. Vagus nerve stimulation in psychiatry: systematic review of the available evidence. J Neural Transm. 2017;124(1):145–58.
283. Conway CR, Kumar A, Xiong W, Bunker M, Aaronson ST, Rush AJ. Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression. J Clin Psychiatry. 2018;79(5):52–9.
284. Salloum NC, Walker MC, Gangwani S, Conway CR. Emergence of mania in two middle-aged patients with a history of unipolar, treatment-refractory depression receiving vagus nerve stimulation. Bipolar Disord. 2017;19(1):60–4.
285. Nierenberg AA, Alpert JE, Gardner-Schuster EE, Seay S, Mischoulon D. Vagus nerve stimulation: 2-year outcomes for bipolar versus unipolar treatment-resistant depression. Biol Psychiatry. 2008;64(6):455–60.
286. Mayberg HS. Targeted electrode-based modulation of neural circuits for depression. J Clin Invest. 2009;119(4):717–25.
287. Loo C, Katalinic N, Mitchell PB, Greenberg B. Physical treatments for bipolar disorder: review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. J Affect Disord. 2011;32(1–2):1–13.
288. Filkowski MM, Mayberg HS, Holtzheimer PE. Considering eligibility for studies of deep brain stimulation for treatment-resistant depression: insights from a clinical trial in unipolar and bipolar depression. J ECT. 2016;32(2):122–6.
289. Oldani L, Altamura AC, Abdelghani M, Young AH. Brain stimulation treatments in bipolar disorder: review of the current literature. World J Biol Psychiatry. 2016;17(7):482–94.
290. Dondé C, Amad A, Nieto I, et al. Transcranial direct-current stimulation (tDCS) for bipolar depression: systematic review and meta-analysis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2017;78(8):123–31.
291. Widge AS, Malone DA Jr, Dougherty DD. Closing the loop on deep brain stimulation for treatment-resistant depression. Front Neurosci. 2018;12(3):1–9.
292. Fitzgerald PB, Hoy KE, Elliot D, McQueen S, Wambeek LE, Daskalakis ZJ. Negative double-blind controlled trial of sequential bilateral rTMS in the treatment of bipolar depression. J Affect Disord. 2016;198(7):158–62.
293. Kazemi R, Rostami R, Khomami D, et al. Electrophysiological correlates of bilateral and unilateral repetitive transcranial magnetic stimulation in patients with bipolar depression. Psychiatry Res. 2015;240(6):364–75.
294. McMahon K, Herr NR, Zerubavel N, Hoertel N, Neacsiu AD. Psychotherapeutic treatment of bipolar depression. Psychiatr Clin N Am. 2016;39(1):35–56.
295. Costa RT, Cheniaux E, Range BP, Versiani M, Nardi AE. Group cognitive behavior therapy for bipolar disorder can improve the quality of life. Braz J Med Biol Res. 2012;45:862–8.
296. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: one-year randomized trial from the systematic treatment enhancement program. Arch Gen Psychiatry. 2007;64:419–26.

297. Bouwkamp CG, de Kruiff ME, van Troost TM, et al. Interpersonal and social rhythm group therapy for patients with bipolar disorder. Int J Group Psychother. 2013;63:97–115.
298. Miklowitz DJ, George EL, Richards JA, Simoneau TL, Sudduth RL. Randomized study of family focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry. 2003;60:904–12.
299. Lovas DA, Schuman-Olivier Z. Mindfulness-based cognitive therapy for bipolar disorder: systematic review. J Affect Disord. 2018;240:247–61.
300. Deckersbach T, Hölzel B, Eisner L, Lazar SW, Nierenberg AA. Mindfulness-based cognitive therapy for bipolar disorder. New York: Guilford Press; 2014.

Unmet Needs in Mixed States

5

Terence A. Ketter

5.1 Introduction

Over 100 years ago, mixed states were defined by Dr. Emil Kraepelin as manic-depressive illness (later known as Bipolar Disorder (BD)) core features, in which opposite polarity (contropolar) symptom coexistence was explained by lack of synchrony between change patterns for three parameters, namely mood, activity (volition), and thought [1, 2] (Table 5.1). Along with pure (orthodox) mania (with euphoria, hyperactivity, and racing thoughts) and pure (orthodox) depression (with sadness, hypoactivity, and poverty of thoughts), Dr. Kraepelin, in the 1913 eighth edition of his textbook, identified two depressive mixed states, one of which appeared particularly noteworthy and a source of ongoing controversy, specifically: *agitated (excited) depression*, with hyperactivity replacing the hypoactivity of pure depression. The other depressive mixed state was depression with flight of ideas, with racing thoughts replacing the poverty of thoughts of pure depression. Thus, bipolar depressive states could be considered to include: *pure (anergic) depression*, *agitated (excited) depression,* and *depression with flight of ideas*. In this Chapter, we will focus primarily on agitated (excited) depression versus pure (anergic) depression.

Of interest, sadness itself was not sufficient in Kraepelin's view to stipulate depression, as the combination of sadness, hyperactivity, and flight of ideas was called depressive (anxious) mania [1] (Table 5.1). Some (primarily) Europeans viewed agitated bipolar depression to substantially overlap mixed bipolar depression [3–12] and thus merit particularly careful consideration.

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Table 5.1 Kraepelin's pure (orthodox) and mixed states of manic-depressive illness

	Mood	Activity	Thought
Mania (mostly ≥ 2↑'s)			
– Pure (orthodox) mania	↑	↑	↑
– Mania with poverty of thought	↑	↑	↓
– Inhibited mania	↑	↓	↑
– Depressive (anxious) mania	↓	↑	↑
– *Manic stupor (exception to ≥ 2↑'s)*	↑	↓	↓
Depression (≥ 2 ↓'s)			
– Pure (orthodox) depression	↓	↓	↓
– Agitated (excited) depression	↓	↑	↓
– Depression with flight of ideas	↓	↓	↑

Adapted from Kraepelin E. Manic-Depressive Insanity and Paranoia. E. & S. Livingstone, Edinburgh, Scotland, 1921

5.2 DSM-IV Mixed Manic Episodes

The American Psychiatric Association's fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) took a rather (viewed by many as overly) exclusive approach, defining mixed (manic) episodes in patients with BD as the concurrent occurrence of syndromal (full, threshold-level) DSM-IV manic and depressive episode symptoms for at least 1 week [13], but *NOT* defining what were viewed by most as more common states with concurrent occurrences of syndromal manic [14, 15] or hypomanic [14] episodes and subsyndromal depressive symptoms (e.g., dysphoric mania/hypomania), as well as concurrent occurrences of syndromal depressive episodes and subsyndromal manic symptoms (i.e., mixed depression) [9].

Indeed, subsyndromal DSM-IV mood elevation symptoms very commonly appear in Bipolar Depression, and thus were present in most Systematic Treatment Enhancement Program for BD (STEP-BD) patients with baseline Bipolar Depressive episodes [16]. Moreover, it has been established that even modest baseline mood elevation (e.g., mean Young Mania Rating Scale (YMRS) [17] total score during depression = 3.7) has been associated with clinically important phenomena in BD, such as antidepressant treatment-emergent mania [18]. In view of the over-exclusivity problem with the DSM-IV approach, Dr. Susan McElroy defined definite (non-DSM) dysphoric mania/hypomania as a concurrent DSM-IV manic/hypomanic episode plus 3 depressive symptoms [14], whereas Dr. Alan Swann defined (non-DSM) dysphoric mania as a concurrent DSM-IV manic episode plus ≥2 Schedule for Affective Disorders and Schizophrenia (SADS) depressive symptoms [15, 19].

Hence, the differential diagnosis of DSM-IV mixed states included: (1) (DSM-5) mixed depression (as described below); (2) (Non-DSM) severe delirious (Stage III) mania; (3) (Non-DSM) ultrarapid cycling and ultradian cycling bipolar disorder; and (4) (DSM-IV) affective instability of personality disorder [4, 14, 20–24].

It has commonly been challenging to distinguish ultrarapid cycling (i.e., a non-DSM term, reflecting mood polarity shifting over days to weeks), and especially ultradian cycling (i.e., another non-DSM term, reflecting mood polarity shifting within a day), from single mixed episodes [23, 25, 26]. According to DSM-IV, mixed manic episodes required criteria be met for both manic and major depressive episodes, nearly every day during at least a 1-week period. Also, in DSM-IV and its Text Revision (DSM-IV-TR [27]), but not in DSM-5, the narrative text specified that *"the individual experiences rapidly alternating moods (sadness, irritability, and euphoria) accompanied by symptoms of a manic episode and a major depressive episode."* Prof. Mario Maj thus contended that the latter statement which was in the text of DSM-IV and DSM-IV-TR (but not in the text of DSM-5) stipulated DSM-IV or DSM-IV-TR mixed manic episodes (but not DSM-5 episodes with mixed features) encompassed ultradian cycling [23].

In spite of being widely considered overly exclusive, DSM-IV mixed manic episodes have been reported in up to 1/3 of patients with bipolar disorders (commonly related to subject selection) [28, 29], with female predominance [14], and with neurological abnormalities (e.g., EEG abnormalities, seizures, developmental delay, migraine headaches, and head injury) [30]. It has been contended that DSM-IV mixed manic episodes or (non-DSM-IV) dysphoric manic episodes compared to (pure) manic episodes indicated more severe illness, commonly with treatment resistance [15, 31].

For example, among 184 bipolar I disorder (BDI) inpatients, all of whom had received lithium, carbamazepine, or divalproex for dysphoric/mixed ($N = 107$) versus pure ($N = 77$) manic episodes, 36.7% versus 8.2% ($p < 0.0001$) had at least one suicide attempt, 57.9% versus 1.3% had current suicidal ideation or attempt ($p < 0.0001$), with remission probability declining 49% for every prior suicide attempt [31]. In addition, mixed manic episodes may be related to rapid cycling (≥4 mood episodes per year) [23], a DSM-IV (and DSM-5) bipolar disorder course modifier associated with poor outcome [32, 33], and unfavorable clinical correlates that overlap DSM-IV mixed mania, including treatment resistance to agents such as lithium [32, 33]. Thus, examples of poorer DSM-IV mixed versus pure mania outcomes have included delayed mood episode recovery (e.g., mean 17 weeks versus 6 weeks [34], i.e., acute mood episode treatment resistance) [31, 34–37] and hastened mood episode recurrence [38] (e.g., lithium maintenance treatment resistance [38]).

Indeed, DSM-IV mixed versus (pure) manic episodes may yield differential medication outcomes. For example, in a registration study of the efficacy and safety of divalproex Delayed Release (DR) in DSM-IV acute pure manic episodes, in which patients with DSM-IV acute mixed manic episodes were excluded [39], 62% of patients had (non-DSM-IV) classic (pure) mania (with <2 SADS depressive symptoms), whereas 38% of patients had (non-DSM-IV) dysphoric mania (with ≥2 SADS depressive symptoms) [15], and it was considered important to identify and monitor such depressive symptoms in mania, as they indicated poorer illness course and acute treatment resistance with lithium, but better responses with divalproex DR) [15]. Moreover, concerns have been raised that antidepressants could exacerbate DSM-IV mixed mania (as well as rapid cycling) [40–45]. For the treatment

of DSM-IV mixed manic episodes, although the United States Food and Drug Administration (US FDA) *has not* approved antidepressants, lithium, divalproex DR, carbamazepine tablets, lamotrigine, chlorpromazine, haloperidol, or quetiapine immediate release (IR), it *has* approved carbamazepine Extended Release Capsule (ERC), divalproex Extended Release (ER), olanzapine, risperidone, ziprasidone, aripiprazole, quetiapine eXtended Release (XR), asenapine, and cariprazine for this indication [46].

In summary, despite being widely considered overly exclusive, DSM-IV mixed manic episodes were reported in as many as over approximately 1/3 of bipolar disorder patients (commonly related to subject selection) [28, 29], with female predominance [14], were seen along with neurological abnormalities (e.g., EEG abnormalities, seizures, developmental delay, migraine headaches, and head injury) [30], and compared to pure manic episodes were associated with multiple unfavorable illness characteristics, including earlier bipolar disorder onset [14], more suicidality (suicidal ideation and attempts) [14, 31, 47–49], more comorbid alcohol and substance use disorders [13, 14, 28, 50], poorer lithium and antidepressant, but somewhat better anticonvulsant mood stabilizer and atypical antipsychotic responses, and poorer outcomes [14, 28, 29, 34]. Indeed, as noted above, nine agents have US FDA-approval for the treatment of DSM-IV mixed mania [46].

5.3 DSM-5 Episodes with Mixed Features

The American Psychiatric Association's fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) took a somewhat more inclusive approach to "mixity". It defines manic episode with mixed features (analogous to DSM-IV mixed mania), if accompanied by a syndromal major depressive episode, but new (and more inclusive) if only accompanied by subsyndromal major depressive symptoms) and (new and more inclusive) Hypomanic Episode with mixed features (Mixed Hypomania), as well as (new and more inclusive) Depressive Episode with mixed features (Mixed Depression) if opposite pole (contropolar) symptoms were subsyndromal [51]. Nevertheless, DSM-5 remained relatively exclusive versus the European Mixed Depression approach (referred to as depression mixed state (DMX), i.e., a major depressive episode accompanied by at least three mood elevation symptoms, including distractibility, irritability, and psychomotor agitation). Specifically, DSM-5 required "with mixed features" to include ≥3 "non-overlapping" mood elevation symptoms (NOMES) i.e., not counting *d*istractibility, *i*rritability, and *p*sychomotor agitation (the so-called *dip* symptoms [52]) towards mixed depression, stating that such symptoms lacked polar specificity as they could be seen in both mood elevation and depression) [51]. Multiple investigators, primarily outside of the USA, have challenged this relatively exclusive approach of not counting "*dip*" symptoms [11, 12, 52, 53]. In particular, of concern to some investigators, DSM-5 did not consider (non-DSM) agitated depression (i.e., major depressive episode with prominent psychomotor agitation) to be included in mixed depression [11, 54].

DSM-5 stipulated that manic episodes superseded major depressive episodes, as manic episodes were considered generally more severe than major depressive episodes. If a patient met criteria for both manic and major depressive episodes (i.e., had DSM-IV mixed mania), in DSM-5 the patient would be considered to have a "manic episode with mixed features," rather than a "major depressive episode with mixed features." In contrast, DSM-5 was silent regarding how to characterize concurrent hypomanic and major depressive episodes, leaving it up to clinicians to choose between "hypomanic episode with mixed features" and "major depressive episode with mixed features," depending on which pole was more clinically prominent (although this was not specifically stated in the DSM-5). Finally, Maj claimed that the (then proposed, later finalized) DSM-5 mixity characterization, unlike with the DSM-IV and DSM-IV-TR versions, had failed to encompass ultradian cycling [23].

Thus, DSM-5 episodes entailed: (1) syndromal (full criteria) manic, hypomanic, *or* major depressive episodes; (2) psychosis, hospitalization, or marked functional impairment (manic episode criteria only, and not major depressive or hypomanic episode criteria); (3) being not due to a substance or general medical condition; and a (4) "with mixed features" episode specifier, provided there were $\geq$ 3 non-overlapping opposite pole symptoms nearly every day for $\geq$1 week.

There remain substantial unmet needs related to ongoing controversies regarding DSM-5 (and DSM-IV) mixed states. For example, it remains undetermined the degree to which DSM-5 (and DSM-IV) mixed states are: (1) dimensionally similar versus categorically different from "pure" states; (2) transitional states between depression and mania; (3) related to bipolar subtype (i.e., type I versus II); and (4) the clinical implications of gradations of subsyndromal depression in hypo/mania (which are now answerable as mixed/dysphoric hypo/mania was "finally" included in DSM-5 as manic or hypomanic episodes with mixed features); as well as (5) the clinical implications of gradations of subsyndromal hypo/mania in depression (which are now answerable as mixed depression was "finally" included in DSM-5 as major depressive episode with mixed features) [4, 13, 14, 20, 22, 51].

5.4 DSM-5 Mixed Depression

DSM-5 was published in 2013 [51], and strove to better harmonize with the eleventh edition of the International Classification of Diseases (ICD-11) [23, 55]. DSM-5 major depressive episodes with mixed features (mixed depression) have attracted more attention than DSM-5 manic or hypomanic episodes with mixed features (mixed mania or mixed hypomania). This could be related to mixed mania and mixed hypomania having already (as discussed above) received considerable attention earlier on, during the DSM-IV era, before mixed depression was included in the DSM [14, 15].

Although DSM-5 Mixed Depression has had prevalence reported as high as more than approximately 1/3 (commonly related to subject selection) [56, 57], it has still been considered by some as overly exclusive [52, 53, 58, 59], as distractibility, irritability, and psychomotor agitation do not count towards this diagnosis [52, 53, 58]. DSM-5 Mixed versus Pure Depression has been associated with unfavorable illness characteristics, such as comorbid alcohol and substance use disorders in BD (but not in unipolar Major Depressive Disorder (MDD) [56]. Using less exclusive mixed depression definitions, mixed vs. pure depression was associated with comorbid borderline personality [60], more lifetime anxiety disorder comorbidity and current irritability, and less current antidepressant use [59], more antidepressant resistance [61], more suicidality [57], and more aggressiveness [62], and in BDII versus unipolar Major Depressive Disorder (MDD) Mixed Depression, younger age at onset, more Major Depressive Episode recurrence, more atypical features, and more BDII family history [63].

An important unmet need for DSM-5 mixed depression is determining how inclusive this construct ought to be. Limited data indicate that DSM-5 mixed depression may have been defined exclusively [11, 12, 58, 59]. Study assessed the strengths and limitations of using a BD Mixed Depression definition made more inclusive than that of DSM-5 by counting rather than "non-overlapping" mood elevation symptoms (NOMES, which *excluded* counting distractibility, irritability, and psychomotor agitation) towards Mixed Depression, as in DSM-5, but instead included counting "overlapping" mood elevation symptoms (OMES, which *included* counting distractibility, irritability, and psychomotor agitation) towards Mixed Depression, which was more inclusive than DSM-5 [59], and overlapped the European DMX3 construct [8, 63–66]. In this study, among 153 depressed BD outpatients assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation, using the more inclusive ($\geq$ 3 OMES) versus the less inclusive DSM-5 ($\geq$ 3 NOMES) definition of BD Mixed Depression yielded a three-fold higher mixed depression rate (22.9% vs. 7.2%). Differential clinical correlates for mixed versus pure depression such as more lifetime anxiety disorder comorbidity, more current irritability, and less current antidepressant use were found, which were not significant using the more exclusive DSM-5 threshold [59].

In another study [56], 26% ($N = 149$) and 34% ($N = 65$) of patients met criteria for mixed depression during a major depressive episode index as part of unipolar major depressive disorder (MDD) or bipolar disorder (BD). Patients with DSM-5 mixed versus pure depression as part of BD or unipolar MDD had a more severe depressive phenotype ($p \leq 0.0002$), and a higher rate of alcohol/substance use disorder in BD ($p = 0.002$), but not in unipolar MDD.

Thus, important unmet needs for DSM-5 mood disorders include answering questions regarding the optimal definitions of "mixed" or "dysphoric" mania and mixed depression, the clinical correlates and treatment implications of subsyndromal mixed symptoms, and the roles of psychomotor agitation [11] and anxiety [67] in DSM mixed mania and mixed depression.

5.5 Treatment for DSM-5 Mixed Depression

Patients with a DSM-5 mixed versus pure depression are expected to have better outcomes with antipsychotic treatments than antidepressants drugs. A relevant unmet need for DSM-5 mixed depression is the lack of definitive establishment of optimal treatments. However, individual *post hoc* and a priori analyses of randomized, placebo-controlled trials indicated that effective treatment might include certain atypical antipsychotics (e.g., olanzapine [68], ziprasidone [69], and lurasidone [61, 70]), rather than antidepressants [11].

In a post hoc analysis of two pooled similar randomized, placebo-controlled olanzapine monotherapy trials ($N = 1214$) in DSM-IV-TR bipolar I disorder depression, olanzapine was at least numerically superior to placebo, independent of level of "mixity" [68]. At baseline, patients with mixed versus pure depression had younger age of onset, and more often had rapid cycling course and concurrent psychotic features.

MADRS depression response rates for olanzapine versus placebo were: 52.6% versus 39.8% (NNT = 8, $p < 0.05$, among 154 OLZ (olanzapine), and 108 placebo (PBO) patients) with none mixed symptom (i.e., pure depression); 50.3% versus 40.0% (NNT = 10, $p < 0.05$, in 332 OLZ versus 250 PBO patients) with 1–2 mixed symptoms (less mixed depression); and 42.2% versus 33.7% (NNT = 12, p = not significant, in 204 OLZ versus 166 PBO patients) with ≥3 mixed symptoms (more mixed depression) (Fig. 5.1).

As there was no significant interaction between number of mixed features and treatment for MADRS response rate, the authors stated that there was no significant statistical interaction between mixed features and treatment, and thus concluded that olanzapine worked similarly for bipolar depression irrespective of the presence of concurrent manic symptoms. However, the olanzapine versus placebo NNT for MADRS response analysis was consistent with at least a non-significant relationship between more mixed symptoms and higher NNT (NNT = 8 with 0 mixed symptom, NNT = 10 with 1–2 mixed symptoms, and NNT = 12 with ≥3 mixed symptoms) (Fig. 5.1). The authors admitted that in a prior study [71], olanzapine monotherapy had progressively lower response rates as the number of mood elevation symptoms increased, with numerically higher response rates than placebo. However, the Benazzi 2009 study used data only from one of the two studies used by Tohen in 2014, and the Benazzi 2009 study's mixed features criteria (co-occurrence of major depressive episode and ≥ 2 manic/hypomanic symptoms, i.e., ≥ 2 YMRS items scoring ≥2) differed from those used by Tohen in 2014.

McIntyre and associates, reported a post hoc analysis of a randomized, placebo-controlled study of lurasidone monotherapy in 485 patients with DSM-IV-TR bipolar I disorder depression [70], defining patients to have mixed (YMRS ≥4, $N = 272$, 56.1%) and pure (YMRS <4, $N = 213$, 43.9%) depression. Thus, at baseline, patients with mixed versus pure depression were more female (60.7% versus

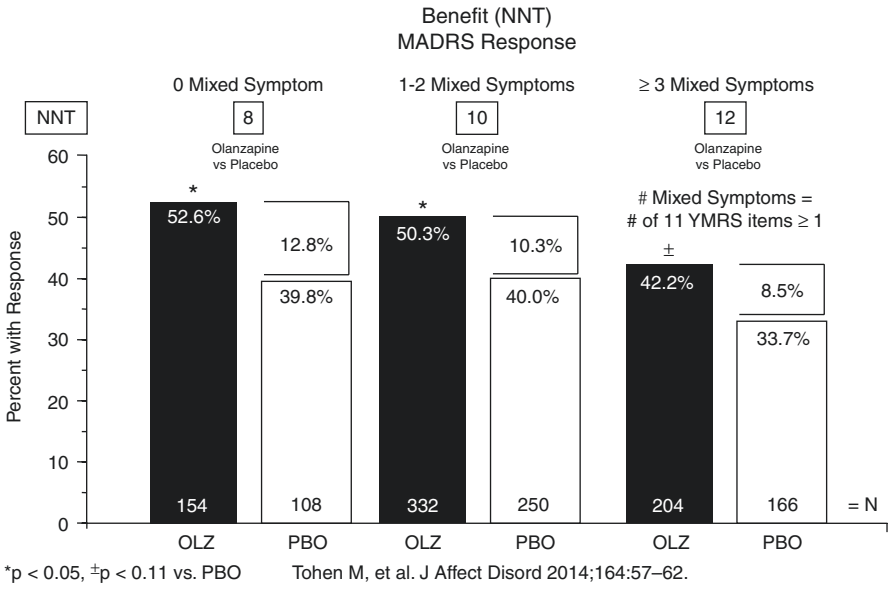

Fig. 5.1 Olanzapine versus placebo monotherapy in bipolar I disorder mixed depression (*post hoc* analysis of two DSM-IV-TR bipolar I disorder depression trials) numbers needed to treat and response rates, stratified by number of mixed symptoms

52.1%; $p = 0.0065$) and Caucasian (71.3% versus 59.2%; $p = 0.002$), with an earlier age at onset of bipolar illness (26.6 years versus 29.0 years; $p = 0.020$), and more often had a history of rapid cycling (9.2% versus 2.8%; $p = 0.005$), as well as higher anxiety levels (mean Hamilton Anxiety Rating Scale score, 17.2 versus 14.5; $p < 0.001$).

Among the 272 patients with post-hoc mixed depression, lurasidone was superior to placebo, with a lurasidone versus placebo MADRS Response NNT = 6 [70]. Thus, lurasidone was nearly twice as likely to yield benefit versus harm, as the lurasidone versus placebo NNH for akathisia in these mixed depression patients was 11 (Fig. 5.2). Finally, in patients with mixed depression, the NNH for lurasidone versus placebo Treatment Emergent Affective Switch was non-significant.

Similarly, among the 213 patients with such post-hoc pure depression, lurasidone was also superior to placebo, with a lurasidone versus placebo MADRS Response NNT = 4 [70]. Thus, lurasidone was nine times as likely to yield benefit versus harm, as the lurasidone versus placebo NNH for Akathisia in Pure Depression patients was 36 (Fig. 5.3). Also, in patients with pure depression, the NNH for lurasidone versus placebo Treatment Emergent Affective Switch was non-significant at 29.

Finally, lurasidone versus placebo in mixed versus pure depression had no significant difference in lurasidone versus placebo MADRS Response Rates (Fig. 5.2); and lurasidone. Lurasidone versus placebo advantage in Mixed versus Pure Depression did not differ significantly (18.9% versus 25.4%), $p = 0.51$) (Fig. 5.3).

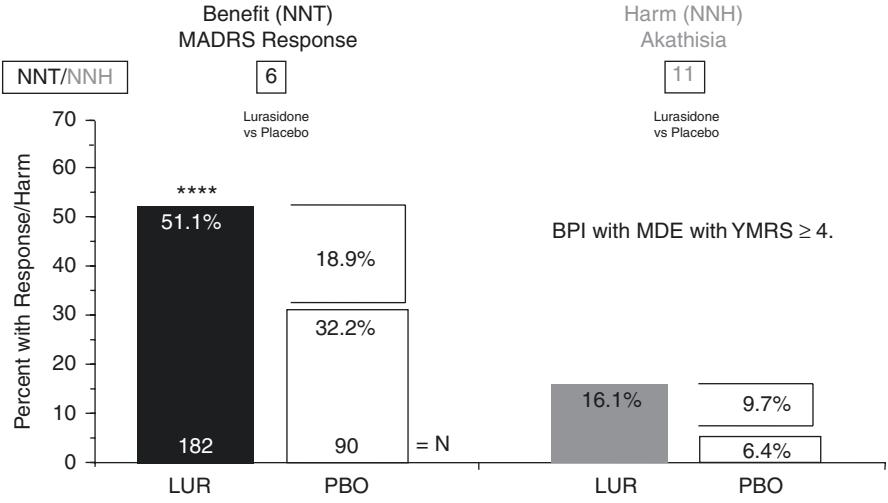

Fig. 5.2 Lurasidone monotherapy in bipolar I disorder mixed depression (*post hoc* analysis of one DSM-IV-TR bipolar I disorder depression trial) numbers needed to treat and harm, response and akathisia rates

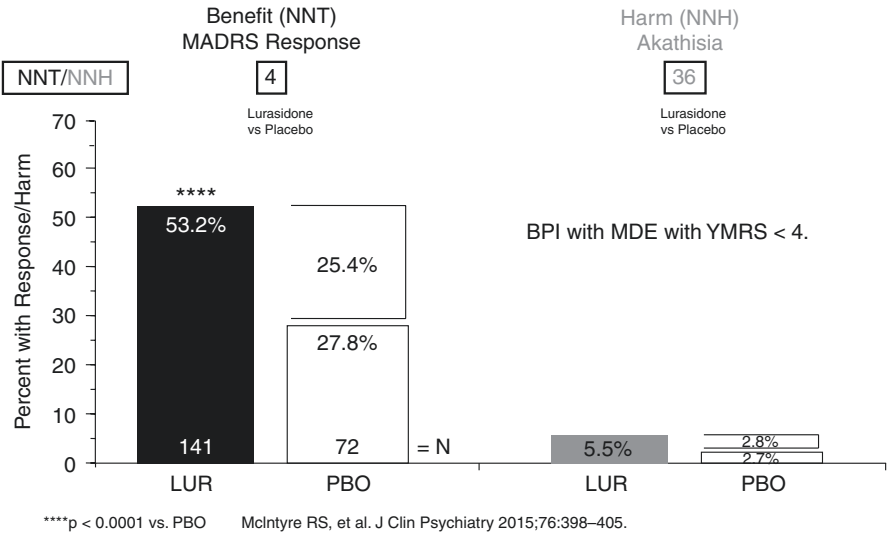

Fig. 5.3 Lurasidone monotherapy in bipolar I disorder pure depression (*post hoc* analysis of one DSM-IV-TR bipolar I disorder depression trial) numbers needed to treat and harm, response and akathisia rates

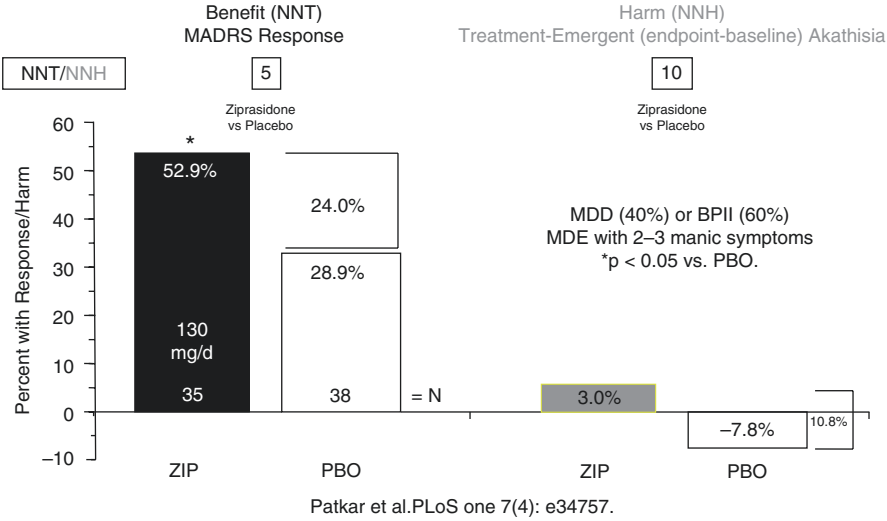

Fig. 5.4 Ziprasidone adjunctive-/mono-therapy in bipolar II disorder or unipolar major depressive disorder mixed depression (a priori analysis) numbers needed to treat and harm, response and treatment-emergent akathisia rates

Moreover, in a small (N = 73) a priori analysis of a randomized, placebo-controlled study of ziprasidone adjunctive-/mono-therapy in mixed (2–3 overlapping mood elevation symptoms) depression in bipolar II disorder or unipolar major depressive disorder, ziprasidone (mean dose 130 mg/day) had efficacy superior to placebo, with a ziprasidone versus placebo MADRS Response NNT = 5, and hence was approximately twice as likely to yield benefit versus harm, with a ziprasidone versus placebo Akathisia Number Needed to Harm (NNH) = 10 (Fig. 5.4) [69].

Finally, in a priori analysis of a randomized, placebo-controlled study of lurasidone adjunctive therapy in Mixed (≥ 2 NOMES) Depression in patients with unipolar Major Depressive Disorder (N = 208), lurasidone (mean dose 36.2 mg/day) was superior to placebo, with a lurasidone versus placebo MADRS Response NNT = 3, and was approximately seven times as likely to yield benefit versus harm, with a lurasidone versus placebo Somnolence NNH = 22 [61] (Fig. 5.5).

In summary, for the treatment of mood episodes with mixed features, there are only scant treatment data [61, 68–70], and the United States Food and Drug Administration (US FDA) has *NOT* approved any treatment for these indications. However, as noted above, preliminary data suggest that certain second-generation antipsychotics, such as olanzapine [68], ziprasidone [69], and lurasidone [61, 70] may ultimately be determined effective in mixed depression.

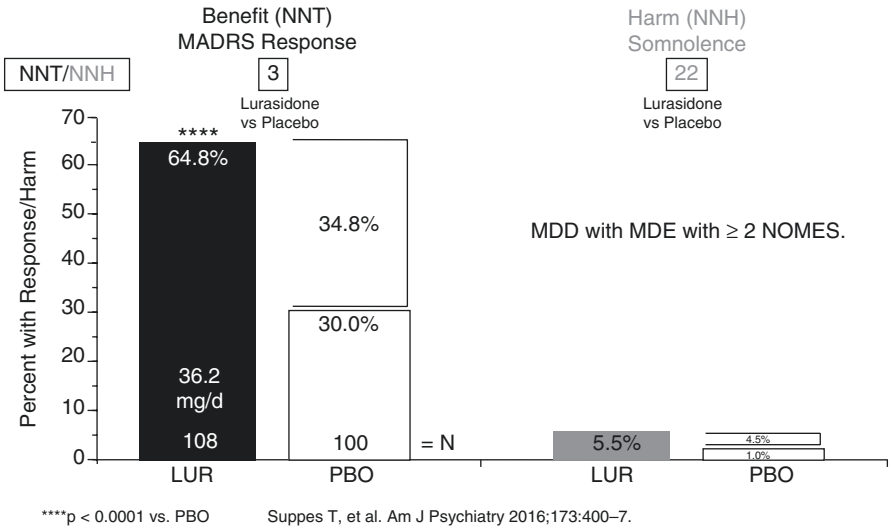

Fig. 5.5 Lurasidone adjunctive therapy in mixed unipolar depression (a priori analysis) numbers needed to treat and harm, response and nausea rates

5.6 Case: Ms. A—Bipolar I Disorder, Depressed, with Mixed Features and Rapid Cycling Course

Presenting (First Outpatient Visit) Background

Ms. A was a 35-year-old, recently separated, female, Chinese-American bank teller, who complained of current irritability, impulsivity, and depression, and only minimal improvement in her depression as well as emergence of subthreshold anxiety since starting bupropion 1 month ago. She reported having been hospitalized for mania at age 18, as well as she reported one hypomanic and three depressive episodes in the prior year, but denied any history of syndromal anxiety/substance use disorder or suicide attempt.

She reported declining individual and couples psychotherapy in the past, due to "lack of time."

Prior pharmacotherapy had included the mood stabilizing anticonvulsant lamotrigine up to 200 mg/day, which had yielded benign rash; but *NOT* carbamazepine (which the patient reported refusing, due to serious rash risk, as the patient also reported being positive for the HLA-B∗1502 haplotype), and *NOT* divalproex (which the patient reported refusing due to polycystic ovary syndrome (PCOS) exacerbation risk), but included the atypical antipsychotic aripiprazole, up to 15 mg/day (which had been ineffective for depression, and caused 10 lb. weight gain) and the antidepressant paroxetine (which had been ineffective for depression, as well as yielding psychomotor agitation, irritability, and sexual dysfunction).

Current psychopharmacotherapy included bupropion 300 mg/day (maximum tolerated dose for one month, due to anxiety/activation/irritability), and lithium 900 mg/day, which yielded a serum concentration 0.8 mEq/L (maximum tolerated dose for two years, due to sedation).

Her medical history was remarkable for PCOS, which had attenuated with her current hormonal contraceptive (which by her report had lacked any substantive mood effect), and a history of obesity, with a current Body Mass Index (BMI) of 29.5 kg/m^2.

Her family history was remarkable for a mother with bipolar I disorder with psychotic manias, and obesity, who had been non-adherent with psychiatric medications, and had experienced a poor psychiatric course; as well as a sister with bipolar I disorder with psychotic mania, who improved somewhat, but had sedation and weight gain of 20 lbs with quetiapine (max dose 300 mg/day, due to sedation).

Her social history was remarkable for two weeks ago separating from her husband of four years (due in part to patient infidelity and irritability), and considering moving in with married male co-worker, but she admitted reconsidering this plan due to recent tension in this new relationship.

Next Outpatient Visit

At her next outpatient visit (three days later), her history was confirmed, and her current depressive symptoms remained largely unchanged, and thus included anhedonia, poor self-esteem and concentration; insomnia; and passive suicidal ideation, without intent, preparation, or plans. Her current mood elevation symptoms included (for the past 2 weeks) decreased need for sleep (with 3 h per night being sufficient by her report); increased goal directed activity (working 60 h/week); impulsivity (uncharacteristic new affair with a married co-worker); and prominent irritability and psychomotor agitation (although the latter two symptoms did not count towards the DSM-5 "with mixed features" specifier). She admitted to current subsyndromal anxiety (limiting bupropion dose), but denied current syndromal anxiety symptoms. Her current attitude towards treatment included asking for medication for irritability and depression that did not yield side effects of anxiety, sedation, weight gain, or sexual dysfunction.

Question 1: Current Advisability of Antidepressants?

1. Worth considering
2. Avoid

Answer 1: Current Advisability of Antidepressants

Worth considering (probably not)

There appeared little to support this position—although the patient's current age was over 25 years (older than the age at which antidepressants tended to yield poorer outcomes), and she was already taking lithium (which in theory could have

antimanic counterbalance, as it permitted her Pure Major Depression to worsen to Mixed Depression after adding bupropion to lithium).

Avoid (probably)

This patient's rapid cycling course, current antidepressant-induced worsening (converting from pure to mixed depression with addition of bupropion to lithium), history of problems with another antidepressant (paroxetine), and having two first relatives with psychotic mania increased her risk of poor outcome with antidepressants. Moreover, the potential utility of other agents (specifically, the antipsychotics lurasidone and quetiapine) made non-antidepressant approaches such as these atypical antipsychotics worth considering.

Question 2: Current Advisability of Mood Stabilizers vs. Antipsychotics

1. Certain mood stabilizers
2. Certain second-generation antipsychotics

Answer 2: Current Advisability of Mood Stabilizers vs. Antipsychotics

- *Certain mood stabilizers (probably not)*

  Lithium had already proved ineffective in preventing depression, and in preventing switching from pure to mixed depression with addition of bupropion. Lamotrigine had not been tolerated, due to benign rash. This patient had already refused carbamazepine, due to the risk of serious rash. Indeed, it was confirmed that this patient was positive for the HLA-B∗1502 haplotype, a marker for increased risk of serious rash with carbamazepine. This patient had already refused divalproex, due to the risk of exacerbation of her PCOS. These considerations outweighed the general tendency of mood stabilizers to be better tolerated than atypical antipsychotics when selecting treatment.
- **Certain second-generation antipsychotics (probably)**

  Olanzapine plus fluoxetine, quetiapine, and lurasidone have all been US FDA-approved for the treatment of DSM-IV acute bipolar depression. Although the risks of serious weight gain and even diabetes mellitus with olanzapine plus fluoxetine supported avoiding this combination at this time, the atypical antipsychotics quetiapine and lurasidone have had fewer and milder weight and metabolic problem associations.

Question 3: Choice of Antipsychotic

1. Olanzapine (with fluoxetine)
2. Quetiapine
3. Ziprasidone
4. Aripiprazole
5. Lurasidone

Answer 3: Choice of Antipsychotic

Olanzapine with fluoxetine (probably not)

The risks of serious weight gain and even diabetes mellitus with olanzapine plus fluoxetine support avoiding this combination at this time, despite the documented efficacy of this combination in acute bipolar depression.

Quetiapine (possibly)

Although compared to olanzapine plus fluoxetine, the atypical antipsychotic quetiapine has fewer and milder weight and metabolic problems, this agent's problems with sedation/somnolence and the patient's sister's 20 lb weight gain with quetiapine may limit its utility, despite the documented efficacy of this agent in acute bipolar depression.

Ziprasidone (probably not)

*The risks of inefficacy for acute bipolar depression (*e.g.*, no FDA indication for acute bipolar depression) and akathisia supported avoiding this agent at this time, despite it being the most weight-neutral* versus *the other atypical antipsychotics listed.*

Aripiprazole (probably not)

*The risks of inefficacy for bipolar depression (*e.g.*, no FDA indication for acute bipolar depression, and it had already failed in this patient for this problem) and akathisia supported avoiding this agent at this time, despite it being more weight-neutral than some other atypical antipsychotics, and having adjunctive utility in unipolar major depressive disorder.*

Lurasidone (probably)

Compared to the olanzapine plus fluoxetine combination and quetiapine, lurasidone has had fewer and milder weight/metabolic and sedation/somnolence problems, respectively. Although this agent's problems with akathisia and nausea may limit its utility, it has documented efficacy (and a US FDA indication) in acute bipolar depression, making it an attractive option for this patient at this time.

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References

1. Kraepelin E. Manic-depressive insanity and paranoia. Edinburgh: E. & S. Livingstone; 1921.
2. Akiskal HS, Benazzi F. Validating Kraepelin's two types of depressive mixed states: "depression with flight of ideas" and "excited depression". World J Biol Psychiatry. 2004;5(2):107–13.
3. Benazzi F. Mixed depression: a clinical marker of bipolar-II disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2005;29(2):267–74.
4. Benazzi F. The continuum/spectrum concept of mood disorders: is mixed depression the basic link? Eur Arch Psychiatry Clin Neurosci. 2006;256(8):512–5.
5. Benazzi F. Bipolar disorder—focus on bipolar II disorder and mixed depression. Lancet. 2007;369(9565):935–45.

6. Benazzi F. Challenging the unipolar-bipolar division: does mixed depression bridge the gap? Prog Neuro-Psychopharmacol Biol Psychiatry. 2007;31(1):97–103.
7. Benazzi F. Irritability in depression can be a symptom of mixed depression. Acta Psychiatr Scand. 2010;121(1):80; author reply.
8. Benazzi F, Akiskal HS. Delineating bipolar II mixed states in the Ravenna-San Diego collaborative study: the relative prevalence and diagnostic significance of hypomanic features during major depressive episodes. J Affect Disord. 2001;67(1–3):115–22.
9. Koukopoulos A, Albert MJ, Sani G, Koukopoulos AE, Girardi P. Mixed depressive states: nosologic and therapeutic issues. Int Rev Psychiatry. 2005;17(1):21–37.
10. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. Psychiatr Clin North Am. 1999;22(3):547–64.
11. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. Acta Psychiatr Scand. 2014;129(1):4–16.
12. Koukopoulos A, Sani G, Ghaemi SN. Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV). Br J Psychiatry. 2013;203(1):3–5.
13. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV). Washington: American Psychiatric Association; 1994.
14. McElroy SL, Keck PE Jr, Pope HG Jr, Hudson JI, Faedda GL, Swann AC. Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. Am J Psychiatry. 1992;149(12):1633–44.
15. Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, et al. Depression during mania. Treatment response to lithium or divalproex. Arch Gen Psychiatry. 1997;54(1):37–42.
16. Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. Am J Psychiatry. 2009;166(2):173–81.
17. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429–35.
18. Frye MA, Helleman G, McElroy SL, Altshuler LL, Black DO, Keck PE Jr, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am J Psychiatry. 2009;166(2):164–72.
19. Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry. 1978;35(7):837–44.
20. Benazzi F. Symptoms of depression as possible markers of bipolar II disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2006;30(3):471–7.
21. Carlson GA, Goodwin FK. The stages of mania. A longitudinal analysis of the manic episode. Arch Gen Psychiatry. 1973;28(2):221–8.
22. Frye MA. Diagnostic dilemmas and clinical correlates of mixed states in bipolar disorder. J Clin Psychiatry. 2008;69(5):e13.
23. Maj M. Mixed states and rapid cycling: conceptual issues and options for ICD-11. World Psychiatry. 2012;11(Suppl):65–8.
24. Hantouche EG, Akiskal HS, Azorin JM, Chatenet-Duchene L, Lancrenon S. Clinical and psychometric characterization of depression in mixed mania: a report from the French National Cohort of 1090 manic patients. J Affect Disord. 2006;96(3):225–32.
25. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry. 2003;60(3):261–9.
26. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002;59(6):530–7.
27. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR). Washington: American Psychiatric Association; 2000.
28. Himmelhoch JM, Mulla D, Neil JF, Detre TP, Kupfer DJ. Incidence and significance of mixed affective states in a bipolar population. Arch Gen Psychiatry. 1976;33(9):1062–6.

29. Kruger S, Trevor Young L, Braunig P. Pharmacotherapy of bipolar mixed states. Bipolar Disord. 2005;7(3):205–15.
30. Himmelhoch JM, Garfinkel ME. Sources of lithium resistance in mixed mania. Psychopharmacol Bull. 1986;22(3):613–20.
31. Goldberg JF, Garno JL, Leon AC, Kocsis JH, Portera L. Association of recurrent suicidal ideation with nonremission from acute mixed mania. Am J Psychiatry. 1998;155(12):1753–5.
32. Ananth J, Wohl M, Ranganath V, Beshay M. Rapid cycling patients: conceptual and etiological factors. Neuropsychobiology. 1993;27(4):193–8.
33. Dunner DL, Fieve RR. Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry. 1974;30(2):229–33.
34. Keller MB, Lavori PW, Coryell W, Endicott J, Mueller TI. Bipolar I: a five-year prospective follow-up. J Nerv Ment Dis. 1993;181(4):238–45.
35. Keller MB. The course of manic-depressive illness. J Clin Psychiatry. 1988;49(11 Suppl):4–7.
36. Dilsaver SC, Swann AC, Shoaib AM, Bowers TC, Halle MT. Depressive mania associated with nonresponse to antimanic agents. Am J Psychiatry. 1993;150(10):1548–51.
37. Kupfer DJ, Frank E, Grochocinski VJ, Luther JF, Houck PR, Swartz HA, et al. Stabilization in the treatment of mania, depression and mixed states. Acta Neuropsychiatr. 2000;12(3):110–4.
38. Prien RF, Himmelhoch JM, Kupfer DJ. Treatment of mixed mania. J Affect Disord. 1988;15(1):9–15.
39. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. JAMA. 1994;271(12):918–24.
40. Fornaro M, Martino M, De Pasquale C, Moussaoui D. The argument of antidepressant drugs in the treatment of bipolar depression: mixed evidence or mixed states? Expert Opin Pharmacother. 2012;13(14):2037–51.
41. Lee HJ, Son GH, Geum D. Circadian rhythm hypotheses of mixed features, antidepressant treatment resistance, and manic switching in bipolar disorder. Psychiatry Investig. 2013;10(3):225–32.
42. Sani G, Napoletano F, Vohringer PA, Sullivan M, Simonetti A, Koukopoulos A, et al. Mixed depression: clinical features and predictors of its onset associated with antidepressant use. Psychother Psychosom. 2014;83(4):213–21.
43. Sussman M, Friedman M, Korn JR, Hassan M, Kim J, Menzin J. The relationship between use of antidepressants and resource utilization among patients with manic or mixed bipolar disorder episodes: findings from a managed care setting. J Affect Disord. 2012;138(3):425–32.
44. Valenti M, Pacchiarotti I, Rosa AR, Bonnin CM, Popovic D, Nivoli AM, et al. Bipolar mixed episodes and antidepressants: a cohort study of bipolar I disorder patients. Bipolar Disord. 2011;13(2):145–54.
45. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry. 2013;170(11):1249–62.
46. Ketter TA. Advances in the treatment of bipolar disorder. Washington: American Psychiatric Publishing; 2015.
47. Balazs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS. The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. J Affect Disord. 2006;91(2–3):133–8.
48. Strakowski SM, McElroy SL, Keck PE Jr, West SA. Suicidality among patients with mixed and manic bipolar disorder. Am J Psychiatry. 1996;153(5):674–6.
49. Dilsaver SC, Chen YW, Swann AC, Shoaib AM, Krajewski KJ. Suicidality in patients with pure and depressive mania. Am J Psychiatry. 1994;151(9):1312–5.
50. Tohen M, Greenfield SF, Weiss RD, Zarate CA Jr, Vagge LM. The effect of comorbid substance use disorders on the course of bipolar disorder: a review. Harv Rev Psychiatry. 1998;6(3):133–41.
51. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). Washington: American Psychiatric Association; 2013.

52. Malhi GS, Fritz K, Allwang C, Burston N, Cocks C, Devlin J, et al. Are manic symptoms that 'dip' into depression the essence of mixed features? J Affect Disord. 2016;192:104–8.
53. Malhi GS, Irwin L, Hamilton A, Morris G, Boyce P, Mulder R, et al. Modelling mood disorders: an ACE solution? Bipolar Disord. 2018;20(Suppl 2):4–16.
54. Parker G. The DSM-5 classification of mood disorders: some fallacies and fault lines [editorial]. Acta Psychiatr Scand. 2014;129(6):404–9.
55. de Dios C, Goikolea JM, Colom F, Moreno C, Vieta E. Bipolar disorders in the new DSM-5 and ICD-11 classifications. Rev Psiquiatr Salud Ment. 2014;7(4):179–85.
56. McIntyre RS, Soczynska JK, Cha DS, Woldeyohannes HO, Dale RS, Alsuwaidan MT, et al. The prevalence and illness characteristics of DSM-5-defined "mixed feature specifier" in adults with major depressive disorder and bipolar disorder: results from the International Mood Disorders Collaborative Project. J Affect Disord. 2015;172:259–64.
57. Judd LL, Schettler PJ, Akiskal H, Coryell W, Fawcett J, Fiedorowicz JG, et al. Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. J Affect Disord. 2012;138(3):440–8.
58. Malhi GS, Byrow Y, Outhred T, Fritz K. Exclusion of overlapping symptoms in DSM-5 mixed features specifier: heuristic diagnostic and treatment implications. CNS Spectr. 2017;22(2):126–33.
59. Kim H, Kim W, Citrome L, Akiskal HS, Goffin KC, Miller S, et al. More inclusive bipolar mixed depression definition by permitting overlapping and non-overlapping mood elevation symptoms. Acta Psychiatr Scand. 2016;134(3):199–206.
60. Perugi G, Angst J, Azorin JM, Bowden CL, Caciagli A, Mosolov S, et al. Relationships between mixed features and borderline personality disorder in 2811 patients with major depressive episode. Acta Psychiatr Scand. 2016;133(2):133–43.
61. Suppes T, Silva R, Cucchiaro J, Mao Y, Targum S, Streicher C, et al. Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 2016;173(4):400–7.
62. Verdolini N, Perugi G, Samalin L, Murru A, Angst J, Azorin JM, et al. Aggressiveness in depression: a neglected symptom possibly associated with bipolarity and mixed features. Acta Psychiatr Scand. 2017;136(4):362–72.
63. Akiskal HS, Benazzi F. Family history validation of the bipolar nature of depressive mixed states. J Affect Disord. 2003;73(1–2):113–22.
64. Benazzi F. Sensitivity and specificity of clinical markers for the diagnosis of bipolar II disorder. Compr Psychiatry. 2001;42(6):461–5.
65. Benazzi F. Depressive mixed state: testing different definitions. Psychiatry Clin Neurosci. 2001;55(6):647–52.
66. Benazzi F. Clinical differences between bipolar II depression and unipolar major depressive disorder: lack of an effect of age. J Affect Disord. 2003;75(2):191–5.
67. Cassidy F. Anxiety as a symptom of mixed mania: implications for DSM-5. Bipolar Disord. 2010;12(4):437–9.
68. Tohen M, Kanba S, McIntyre RS, Fujikoshi S, Katagiri H. Efficacy of olanzapine monotherapy in the treatment of bipolar depression with mixed features. J Affect Disord. 2014;164:57–62.
69. Patkar A, Gilmer W, Pae CU, Vöhringer PA, Ziffra M, Pirok E, et al. A 6 week randomized double-blind placebo-controlled trial of ziprasidone for the acute depressive mixed state. PLoS One. 2012;7(4):e34757.
70. McIntyre RS, Cucchiaro J, Pikalov A, Kroger H, Loebel A. Lurasidone in the treatment of bipolar depression with mixed (subsyndromal hypomanic) features: post hoc analysis of a randomized placebo-controlled trial. J Clin Psychiatry. 2015;76(4):398–405.
71. Benazzi F, Berk M, Frye MA, Wang W, Barraco A, Tohen M. Olanzapine/fluoxetine combination for the treatment of mixed depression in bipolar I disorder: a post hoc analysis. J Clin Psychiatry. 2009;70(10):1424–31.

Unmet Needs in the Treatment of Personality Disorders

6

Joel Paris

6.1 Failure to Recognize Personality Disorders

Personality disorder is a diagnostic construct that describes complex conditions that are not episodes of symptomatic illness, but lifelong dysfunctional patterns affecting work and relationships [1, 2]. Thus, PDs can only be understood in the context of life histories. Problems begin early, usually in adolescence, or at the latest in early adulthood. PDs negatively affect functioning over many years. Patients may not be able to launch a career or attain stable interpersonal attachments.

The classification of PDs has long been controversial. DSM-5, Section II [1], like earlier editions of this manual, describes a set of categories, only a few of which are well researched. Of these categories, borderline personality disorder (BPD) has generated the most empirical data [3]. There is also a large literature on antisocial personality disorder [4] and the narrower construct of psychopathy [5], but these studies are mostly found in forensic journals.

An alternative system was added in DSM-5, Section III [1], in which 6 of the original ten categories are constructed on the basis of trait profiles that can be scored dimensionally. While this system was not well researched at the time of publication of the 5th edition of DSM, it has generated many more studies since [6].

ICD-11 [2] goes a step further, allowing only a single category of PD, which is further described by trait profiles and by severity ratings. The result is that we now have three different systems, not one. If the Research Domain Criteria [7] are included, we may even have four. Perhaps this confusing situation may only reflect the complexity of the PD construct.

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Borderline Personality Disorder (BPD) has attracted the most research, and is one of the most common conditions seen in clinical psychiatry. It has a community prevalence of 1–2% [8, 9], and a clinical prevalence of 9% [9].

BPD is primarily characterized by emotion dysregulation, mood that shows high intensity and rapid shifts that last for hours rather than days [10]. These phenomena can be distinguished from the affective instability seen in bipolar disorder, in which abnormal mood lasts for weeks at a time [11]. BPD is also associated with a wide range of other symptoms, including impulsive behaviors, particularly suicide attempts, self-harm, and substance abuse; unstable interpersonal relationships; with rapid attachments followed by severe conflict; as well as micro-psychotic symptoms, such as depersonalization, paranoid trends, and auditory hallucinations [3]. All these features lead BPD patients to seek treatment. When all are present, clinicians can easily diagnose the disorder.

The ICD-11, following its goal of avoiding categories, had aimed for the elimination of the BPD diagnosis but ended up compromising with members of the personality disorder research community, represented by investigators who have spent decades studying BPD [12]. The result is that ICD-11 diagnosis [2] of PDs allows for a "borderline pattern" on top of a trait profile, based on a description that uses much the same criteria as those found in DSM, Section II.

Given the fact that BPD is the most clinically important PD, and has been examined in several thousand empirical studies, this chapter will focus on this borderline pattern.

The most important unmet need for BPD is related to a failure of recognition. Clinicians can find the diagnosis of any PD challenging, preferring to focus on "comorbid" symptoms, such as depression, anxiety, or substance abuse, and focusing their efforts on managing these problems. About half of the patients in a large clinical cohort who met formal criteria for BPD remained undiagnosed in practice [13]. Moreover, one cannot simply treat "comorbidity" as if a patient with a PD will respond in the same way to interventions as those who do not have any PD. A large literature supports the principle when patients have a PD, they do not respond to standard treatments, especially medications for major depression [14]. This is why neither the NICE guidelines [15] nor the Cochrane reports [16] recommend the routine use of antidepressants in patients with BPD. Even so, these prescriptions are often written, putatively targeting "comorbid" depression.

Paradoxically, one of the reasons why BPD often goes unrecognized is that the most evidence-based treatment is specialized and empirically supported psychotherapy, methods that are not always understood by clinicians. Psychiatrists are much less likely than they used to be to offer psychotherapy, as the practice of the specialty has come to focus almost exclusively on psychopharmacology [17, 18].

Finally, patients with BPD have a reputation for being difficult, and many psychiatrists dislike and avoid them [19]. These views may be especially common among clinicians who only see this population of patients in emergency rooms, when they are at their worst, or in short-term in-patient settings, where there is often no active treatment of the disorder. Diagnosis can be driven by this perception of untreatability. This is probably the main reason why patients receive diagnoses that

are assumed to be manageable with drug prescriptions. Moreover, every clinician will see PD patients who have had years of psychotherapy with little benefit. Only in recent years has the word gotten out that evidence-based psychological treatment for these patients is usually helpful [20]. This having been said, it is fair to say that these therapies are expensive and generally inaccessible. If they were more readily available, it is likely that PD diagnoses would be more frequent.

6.2 Ineffective Pharmacological Treatment

There is a large literature on the treatment of BPD with pharmacological agents [15, 16]. However, all of the drugs that have been studied were originally designed for other mental disorders. It is therefore not surprising that the evidence for any of these agents in BPD is weak [15, 16]. There are times when patients need to be medicated, particularly when severe insomnia is a problem. However pharmacological interventions never produce a remission of a PD, as they can in the disorders for which they were originally developed.

Thus, one sees only weak effects for antidepressants in BPD [16]. Mood stabilizers developed for bipolar disorder are also ineffective for BPD, with a recent large-scale study finding no value whatsoever for lamotrigine [21]. Benzodiazepines have not been well researched in BPD, and they carry a risk for addiction. The one drug group that can sometimes be useful are antipsychotics [22]. However, in view of their side effects, these agents should be used short-term and in low doses.

In spite of these empirical findings, it is common to find that BPD patients are on multiple medications, leading to a polypharmacy regime [23]. The explanation lies in the fact that BPD patients often have either a temporary placebo-based response to drugs or no response at all. But instead of making referrals for psychotherapy, many psychiatrists see this problem as treatment resistant depression [24] and follow algorithms that add additional drugs to the regime with the aim of "augmentation." Thus, when the course is chronic, more and more drugs are added, and few are subtracted. The result is often a poor response but a high load of side effects.

It is possible that sometime in the future, we will have drugs that target more specifically the traits that underlie BPD, particularly affective instability (also called emotion dysregulation) and impulsivity. If so, we would be able to treat this population more effectively. But as it stands, specialized psychotherapies are the most evidence-based treatments.

6.3 Lack of Access to Evidence-Based Psychotherapies

We now know that most patients with BPD get better with time [25], and that specialized psychotherapies can produce a more rapid recovery. There is evidence for several forms of therapy, with the most researched being Marsha Linehan's dialectical behavior therapy (DBT [26]). This innovative treatment is based on the theory that BPD patients suffer from a temperamentally based emotion dysregulation,

amplified by experiences of invalidation by family members, has become a standard therapy. And where DBT is available, BPD diagnoses tend to be readily made. There are also a number of alternatives on the market [27], including mentalization-based treatment (MBT), transference-focused psychotherapy (TFP), schema-focused psychotherapy (SFT), systems training for emotional predictability and problem solving (STEPPS), and general psychiatric management (GPM). All of these, while somewhat different in theory, have notable similarities in practice.

The problem is that evidence-based treatments for BPD are not readily available. In the US mental health system, psychotherapy of all kinds is poorly insured, and most plans only cover a few sessions. In the UK, Canada and Australia, medical care is insured in principle by government, but the human resources required to carry out DBT or other psychotherapies are very limited. The situation in continental Europe is variable, with access being best in the generous health care systems of Germany and Scandinavia, but worse in less affluent countries.

Access to care is a problem that needs to be dealt with by shortening therapy. Zanarini [28, p. 376] stated that: "less intensive and less costly forms of treatment need to be developed." McMain and Pos [29, p. 649] recommend that: "given the lack of availability of effective treatments for borderline personality disorder, research is needed on the effectiveness of less-intensive models of care in order to help inform decisions about the allocation of scarce health care resources."

The most efficient way to meet demand is to shorten treatment. And patients need not suffer from not getting insufficiently lengthy therapy. Most patients with BPD improve symptomatically after only 12 weeks of treatment [30]. Moreover, the majority who are seen briefly do not necessarily return asking for longer interventions. Shortening therapy means there is room to treat more people, without asking highly impulsive patients to remain on a long wait list. While there always be patients who need more treatment, brief therapy is usually effective. It prevents blockages in emergency rooms, out-patient clinics, and in-patient wards. To address this problem one can offer *stepped care* [31], in which most patients are offered briefer therapy, with extensive courses of treatment reserved for those who fail this first step (or have failed many other treatments).

6.4 Failure to Develop Integrative Treatment for Borderline Personality Disorder

Psychotherapy as a treatment for mental disorders has suffered from being fragmented into a large number of methods, each associated with an acronym. This is also the case in the treatment of BPD, where the treatments are all described by acronyms. Most have three letters—easy to remember, but the six-letter acronym for STEPPS does not imply a better outcome.

Research does not support differences between well-planned and systematic psychotherapies of any kind for mental disorders. Head-to-head comparisons of psychodynamic and cognitive-behavioral approaches have failed to find differences in

efficacy [32]. These are among the most consistent findings in psychotherapy research. The results of comparative studies have been called a "dodo bird" verdict, after a scene from Lewis Carroll's "Alice in Wonderland," where the bird announces that after a race, "everyone has won and all shall have prizes."

This does not mean that any old therapy will do. In BPD, all the evidence-based methods are superior to treatment as usual (TAU), i.e., the somewhat messy way that patients are managed in non-specialized clinics. But comparisons between treatments have found only minor differences in outcome [27]. Each approach may have something valuable to offer, but there is no basis to have a strong preference for one over another.

These findings suggest that there should be one therapy for BPD, combining the best ideas from all these sources. Moreover, given that most of the existing approaches are lengthy (lasting at least a year), integrated therapy of this kind should also be made brief and accessible. The basic elements of DBT (emotional regulation, control of impulsivity, improvement of interpersonal relationships) probably need to be a crucial part of any treatment package.

6.5 Failure to Develop Therapies for Non-Borderline Disorders

There have been some attempts to use specific methods (parallel to those developed for BPD) in the treatment of other PDs [33]. However, one cannot conclude much from the small number of published studies. For example, while a few studies have supported the use of CBT methods in avoidant PD that are used for social anxiety, Cochrane found the evidence insufficient for a conclusion [34]. Similar problems with firm recommendations emerge from studies of antisocial PD, which is famous for being refractory to interventions of all kinds [35]. It would also be valuable to develop a method of treating narcissistic PD, but research in that area is essentially absent.

6.6 Lack of Knowledge Concerning Etiology

We badly need a better understanding of the origins of PDs. But these are complex biopsychosocial conditions with a multifactorial etiology. At this point we can identify statistically significant risk factors, but cannot predict whether a PD will develop in any individual. Sorting out these pathways could take many decades of further research.

Since these conditions often begin in childhood, we are in particular need of prospective research to study early identification and treatment of these conditions. A few studies have recently attempted to answer this question [36]. Thus far, the expense of such investigations, as well as the tendency of patients with PDs to be lost to follow-up, has stood in the way. But we need to know more to avoid providing inappropriate treatment.

6.7 Conclusions

PDs have been described as "the stepchildren of psychiatry" [37]. Yet these conditions are very common, both in the community and the clinic [9]. Fortunately, the last decades have seen the development of a personality disorder research community, with organizations that sponsor many international meetings, and with several journal that are devoted to research on PDs.

Translating this research effort into clinical practice will take longer. However, there has been real progress. First, we now know that the long-term outcome of BPD is much more benign than previously believed. Second, we have developed a number of specialized therapies that can treat patients successfully.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Publishing; 2013.
2. World Health Organization. International classification of diseases, 11th rev. Geneva: World Health Organization; 2018 www.who.int/classifications/icd/em.
3. Gunderson JG. Borderline personality disorder. N Engl J Med. 2011;364:2037–42.
4. DeBrito S, Hodgins S. Antisocial personality disorder. In: McMurran M, Howard R, editors. Personality, personality disorder, and violence: an evidence-based approach. London: Wiley; 2009. p. 133–55.
5. Kiehl KA. The psychopath whisperer: the science of those without conscience. New York: Crown; 2014.
6. Hopwood CJ, Kotov R, Krueger RF, Watson D, Widiger TA. The time has come for dimensional personality disorder diagnosis. Personal Ment Health. 2018;12:82–6.
7. Cuthbert N. Research domain criteria: toward future psychiatric nosologies. Dialogues Clin Neurosci. 2015;17:89–97.
8. Trull TJ, Jahng S, Tomko D, Wood PK, Sher KJ. Revised NESARC personality disorder diagnoses: gender, prevalence, and comorbidity with substance dependence disorders. J Personal Disord. 2010;24:412–26.
9. Ellison WD, Rosenstein LK, Morgan TA, Zimmerman M. Community and clinical epidemiology of borderline personality disorder. Psychiatr Clin North Am. 2018;41:561–73.
10. Koenigsberg H. Affective instability: toward an integration of neuroscience and psychological perspectives. J Personal Disord. 2010;24:60–82.
11. Paris J. Differentiating borderline personality disorder from bipolar-II disorder. In: Parker G, editor. Bipolar-II disorder. 2nd ed. Cambridge: Cambridge University Press; 2013. p. 81–8.
12. Herpertz SC, Huprich SK, Bohus M, Chanen A, Goodman M. The challenge of transforming the diagnostic system of personality disorders. J Pers Disord. 2017;31:577–89.
13. Zimmerman M, Mattia J. Differences between clinical and research practices in diagnosing borderline personality disorder. Am J Psychiatry. 1999;156:1570–4.
14. Newton-Howes G, Tyrer P, Johnson T. Personality disorder and the outcome of depression: meta-analysis of published studies. Br J Psychiatry. 2006;188:13–22.
15. Stoffers J, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. Cochrane Database Syst Rev. 2010;(6):CD005653. https://doi.org/10.1002/14651858.CD005653.pub2. Accessed 3 Dec 2018.
16. National Institute for Health and Care Excellence. Borderline personality disorder: recognition and management. NICE guidelines. 2009. https://www.nice.org.uk/guidance/CG78/. Accessed 3 Dec 2018.

17. Mojtabai R, Olfson M. National trends in psychotherapy by office-based psychiatrists. Arch Gen Psychiatry. 2008;65:962–70.
18. Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. Arch Gen Psychiatry. 2010;67:26–31.
19. Chartonas D, Kyratsous M, Dracass S, Lee T, Bhui K. Personality disorder: still the patients psychiatrists dislike? BJPsych Bull. 2017;41:12–7.
20. Stoffers-Winterling JM, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Psychological interventions for borderline personality disorder. Cochrane Database Syst Rev. 2012;(8):CD005652. https://doi.org/10.1002/14651858.CD005652.pub2.
21. Crawford M, Sanatinia R, Barrett BM, Cunningham G. The clinical effectiveness and cost-effectiveness of lamotrigine in borderline personality disorder: a randomized placebo-controlled trial. Am J Psychiatry. 2018;175:576–80.
22. Black DW, Zanarini MC, Ronine A, Shaw M, Allen J, Schulz SC. Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry. 2014;171:1174–82.
23. Zanarini MC, Frankenburg FR, Khera GS, Bleichmar J. Treatment histories of borderline inpatients. Compr Psychiatry. 2001;42:144–50.
24. Demyttenaera K, van Duppen Z. The impact of (the concept of) treatment-resistant depression: an opinion review. Int J Neuropsychopharmacol. 2019;22:85. https://doi.org/10.1093/ijnp/pyy052.
25. Temes CM, Zanarini MC. The longitudinal course of borderline personality disorder. Psychiatr Clin North Am. 2018;41:685–94.
26. Linehan MM. Cognitive behavior therapy for borderline personality disorder. New York: Guilford Press; 1993.
27. Paris J. Applying the principles of psychotherapy integration to the treatment of borderline personality disorder. J Psychother Integr. 2015;25:13–9.
28. Zanarini MC. Psychotherapy of borderline personality disorder. Acta Psychiatr Scand. 2009;120:373–7.
29. McMain S, Pos AE. Advances in psychotherapy of personality disorders: a research update. Curr Psychiatry Rep. 2007;9:46–52.
30. Laporte L, Paris J, Zelkowitz P, Cardin JF. Clinical outcomes of a stepped care program for the treatment of borderline personality disorder. Personal Ment Health. 2018;12:252–64.
31. Paris J. Stepped care for borderline personality disorder. New York: Academic Press; 2017.
32. Wampold BE. The great psychotherapy debate: models, methods, and findings. Mahwah: L. Erlbaum Associates; 2001.
33. Paris J. A concise guide to personality disorders. Washington, DC: American Psychological Association; 2015.
34. Ahmed U, Gibbon S, Jones H, Huband N, Ferriter M, Völlm BA, Stoffers JM, Lieb K, Dennis JA, Duggan C. Psychological interventions for avoidant personality disorder (protocol). Cochrane Database Syst Rev. 2012;(1):CD009549. https://doi.org/10.1002/14651858.CD00954935.
35. Gibbon S, Duggan C, Stoffers J, Huband N, Völlm BA, Ferriter M, Lieb K. Psychological interventions for antisocial personality disorder. Cochrane Database Syst Rev. 2010;(6):CD007668. https://doi.org/10.1002/14651858.CD007668.pub2s.
36. Stepp SD, Lazarus SA, Byrd AL. A systematic review of risk factors prospectively associated with borderline personality disorder: taking stock and moving forward. Personal Disord Theory Res Treat. 2016;7:316–23.
37. Gabbard GO. Personality disorders come of age. Am J Psychiatry. 2005;162:833–5.

Unmet Needs in the Assessment and Treatment of Psychomotor Agitation

7

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7.1 Overview

Agitation is a common concern in psychiatric and medical emergency settings and may be described as excessive motor (e.g., pacing, restlessness) or psychological activity, with a feeling of inner tension, accompanied by a cluster of related symptoms, such as irritability, aggression, excessive vocalization or shouting, anxiety [1–4].

Agitation may be associated with psychiatric conditions, drug or alcohol withdrawal or intoxication, or physical conditions such as dementia, trauma, delirium, endocrine abnormalities, sepsis or infection, stroke, and many other illnesses. We hereby describe the epidemiology, pathophysiology, assessment strategies and treatment of agitation.

7.2 Epidemiology and Risk Factors

The prevalence of agitation varies depending on several issues, such as the underlying cause, the environmental factors and the age range of affected individuals. For instance, agitation and aggressive behaviours are reported in up to 80% of

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institutionalized patients with dementia, 33% of community-dwelling patients and 70% of patients hospitalized due to a traumatic brain injury (TBI) [4, 5]. A cross-sectional, observational, multicenter study reporting the prevalence of cases in the psychiatric emergency room (ER) or Acute Inpatient Unit (AIU) of 27 participating centers in Europe, identified a total of 334 episodes of agitation out of 7295 emergencies in the psychiatric department. Bipolar disorder, personality disorder and schizophrenia were the most common psychiatric conditions associated with agitation. The study concluded that acute agitation is a common psychiatric symptom in the psychiatric AIU and ER [6]. Another multicentre observational study performed in newly admitted patients with schizophrenia in 14 hospitals in China concluded that overall agitation prevalence was 47.50% (665 of 1400) [7]. A study published in the *Indian Journal of Psychological Medicine* observed that the risk of suicide is higher in depressed patients with agitation [8]. In a prospective, single-centre cohort study evaluating the incidence of agitation in patients admitted to the ICU (Intensive Care Unit), a Richmond Agitation Sedation Scale score of ≥+2 was reported in 31.8% of the 113 participating patients. Not surprisingly, most individuals experienced agitation in the first 3 days of ICU admission. According to the multivariate analysis, smoking habits, severe or moderate pain, delirium and mechanical ventilation were the independent factors for agitation, while hyperlactatemia was associated with a lower risk of agitation [9]. Factors like the differences in the instruments that were used to measure agitation across the various studies as well as the differences in the definition of agitation, have likely contributed to the inconsistencies in the range of reported incidences of agitation, which nonetheless has resulted as very prevalent in the great majority of studies [10].

7.3 Pathophysiology

Animal studies have identified various regions of the brain, both excitatory and inhibitory, as involved in agitated and aggressive behaviours [11, 12]. Dysregulations of GABAergic (gamma-aminobutyric acid), dopaminergic, noradrenergic and serotonergic systems mediate the underlying pathophysiologic abnormalities of agitation and aggression. There are no distinct clinical features associated with these abnormalities, nor is there a unifying etiologic pathophysiology of agitation, even though there might be a final common pathway. Irrespective of the aetiology, agents that increase the GABAergic or serotonergic tone and/or reduce the noradrenergic or dopaminergic tone may reduce agitation [12].

After evaluating the effects of lithium for 3 months, Sheard and colleagues [13] concluded that lithium has a serotonin activity that might be clinically beneficial in reducing impulsive aggression unrelated to psychosis in inmate populations. Asberg and colleagues [14] observed that patients with low 5-HIAA (5-hydroxyindoleacetic acid) levels were more likely to commit suicide using violent means. These seminal trials lead to many similar studies, which consistently suggested a significant

association between low 5-HIAA (a breakdown product of serotonin) levels and violent behaviours [4].

Four experimental studies, in which tryptophan supplementation or depletion were performed to manipulate the 5HT levels in the brain, confirmed an inverse relationship between aggression and 5HT activity [4]. Interestingly, a serotonin transporter gene promoter polymorphism was correlated with aggressive behaviour in children, via a reduction in serotonin levels [11, 15]. Thus, polymorphism of tryptophan hydroxylase might also be a cause for aggression [11]. Animal studies have shown that an increased dopaminergic and noradrenergic activity may trigger or at least facilitate an aggressive behaviour in humans. Testosterone has also been hypothesized as a contributing factor to aggression [4]. However, high levels of aggression are not observed in hirsute females after increasing their androgen levels, nor are they observed in hypogonadal males receiving exogenous testosterone. Yet, Rasanen et al. found that aggressive individuals, in criminal and psychiatric populations, have higher plasma testosterone levels, as compared to the testosterone levels of non-aggressive schizophrenic prisoners. Vasopressin, cortisol and prolactin have also been postulated to cause aggression; however, conclusive results are missing [4].

7.4 Assessment and Evaluation

Agitation is not uniformly defined. For instance, the Agitation Definition Working Group (ADWG) of the International Psychogeriatric Association (IPA) identified several features of agitation in persons with cognitive disorders and evaluated those that were recognized by at least 50% of respondents, which were then established as the core features in agitation (Table 7.1).

Providing and accurate assessment, determining the aetiology (when possible) and establishing a diagnosis is key to a successful management agitation [11].

For instance, a clinician should assess whether the condition is due to a major mental illness, to the use of alcohol or substances of abuse (which often still qualifies as a mental illness), or to a medical condition, given that the treatment approach is different. Table 7.2 reports an example of conditions that are frequently associated with agitation.

Assessment of acutely agitated patients may represent a dramatic situation. Such situation may be very challenging in terms of determining the accurate diagnosis and establishing the most appropriate management strategy [11].

De-escalation represents the first-line procedure during the assessment of the aggressive patient, and when it fails, the least restrictive coercive measures have to be applied. De-escalation includes the effective use of verbal and non-verbal communication skills to help reducing agitation or aggressive behaviour and preventing further escalation of aggression and violence. Such procedure aims to reduce the level of anxiety, reduce the risk of injury to the patient and other persons as well as to the physical environment: also, de-escalation enables the appropriate therapeutic procedures that will lead to the elimination of aggressive behaviour [17].

Table 7.1 Common behaviours in people with agitation [16]

Item	Percentage of respondents who thought the item belonged to the definition of agitation
Pacing	68
Aimless wandering	52
Spitting at meals	29
Spitting at people	40
Cursing	42
Verbal aggression	71
Constant unwarranted requests for attention or help	53
Repetitive questions	35
Repetitive sentences	31
Hitting others	58
Hitting self	57
Grabbing people	48
Pushing people	54
Throwing things	56
General restlessness	80
Screaming	63
Biting	49
Scratching	48
Trying to get to a different place (e.g., out of the room or building)	48
Intentional falling	16
Complaining	20
Negativism	21
Resistiveness	54
Eating/drinking inappropriate substances	15
Hurting self	54
Hurting others	53
Handling things inappropriately	26
Hiding things	11
Hoarding things	12
Tearing things or destroying property	62
Performing repetitious mannerisms	45
Making verbal sexual advances	23
Making physical sexual advances	24
Making strange noises (weird laugher or crying)	38
Stubbornness	17
Shouting	62
Slamming doors intentionally	46
Kicking furniture	52

Table 7.2 Possible causes of agitation

Category	Diagnosis/cause
Neurodevelopmental disorders	Autism-spectrum disorder Hyperactivity disorder/attention-deficit Intellectual disability
Neurocognitive disorders	Aphasias Catatonia Delirium Dementia Frontal lobe syndrome Organic hallucinosis Organic mood disorder Seizure disorders
Psychotic or mood disorders	Brief reactive psychosis Delusional disorder Mood disorders (e.g., bipolar disorders, major depressive disorders) Other psychotic disorders Schizoaffective disorder Schizophrenia
Personality disorders	Antisocial Borderline Paranoid Schizotypal
Impulse control, disruptive and conduct disorders	Intermittent explosive disorder Kleptomania Pyromania
Medications and substances	Antibiotics Anticholinergics Isoniazid Procarbazine hydrochloride Steroids Substances of abuse (e.g., cocaine, amphetamines, other stimulants, opiates, etc.)
Medications and substances withdrawal	Clonidine Opiates Sedative-hypnotics (benzodiazepines and barbiturates)

According to Fishkind, there are 10 main domains in de-escalation:

1. Respecting personal space—in order to ensure the safety for both patient and health care professionals, it is recommended to keep the distance of at least two arms from the patient, without blocking the door of the room.
2. Avoid being provocative—in order to avoid a secondary (iatrogenic) escalation of aggression, it is important for health care providers to use appropriate body language that may have a calming effect to the patient. Facial expression should reflect calmness, but with avoidance of constant eye contact, which a patient might misinterpret as violent. Hands should be opened and knees moderately bend. The overall body expression should reflect verbal content, in order to ensure trust.

3. Establish verbal contact—in the situation of having an acutely aggressive patient, it is important to leave de-escalation to the first health care professional who has established the contact with such patient, or in lack of adequate training, to one who is capable to proceed. The contact with an aggressive patient should start with introducing themselves and assuring that the patient's safety will be obtained. Further, patient should be asked to introduce themselves and to say how he prefers to be addressed (by the first or the last name). Afterwards, it is necessary to orient patient about the place this conversation is taking place and about which the further steps will be.
4. Be concise—short sentences and use of simple vocabulary is the most effective way to achieve understanding by an agitated patient. Slow speech, with frequent repeating of messages enables agitated patient to process the information.
5. Identify wants and feelings—agitated patients should be asked about their expectations. Skilled health care professionals can recognize patient's wishes and feelings by perceiving both verbal and non-verbal patient's messages and reply accordingly.
6. Listen closely to what the patient is saying—there are techniques of active listening that should be used during the de-escalation of an agitated patient, such as reflection (repeat back of what a patient has said and ask for confirmation) or use of Miller's law (trying to assume that it is true what the other person is telling) to avoid being judgmental and to engage more effectively in the conversation.
7. Agree or agree to disagree—health care professional may agree with the patient in terms of the truth, the principle or the odds. In case of being asked by the patient to agree with something that is undoubtedly untrue, it is recommended to honestly disagree with the patient.
8. Lay down the law and set clear limits—it is important to set ground rules to the patient about boundaries in his behaviour (i.e., telling him about zero tolerance on violence and its consequences). It is also essential to let patient know about necessity to establish optimal working conditions by maintaining a bi-directional respect and the consequences of violating such environment. Once the mutual trust is obtained, it is important to guide the patient how to stay in the control and avoid further escalation of aggression.
9. Offer choices and optimism—by using the assertive techniques to stop the aggression and prevent potential violence, it is recommended to offer the patient alternatives to violence, along with offering him anything that might make him feel better (i.e., food or drink). Further, it is appropriate to discuss medication options with the patient, with explanation that the goal of such treatment is calming, not sedating and if possible, offering to decide between oral and parenteral route of administration. At the end, patient should be given realistic prediction of timeframe for overcoming the aggression episode.
10. Debrief the patient and staff—in case of involuntary intervention is needed, the health care professional has to explain to the patient why it is necessary to

undertake and to work with patient on preventing future aggression. In addition, the staff also has to be debriefed if coercive measures were needed to be used during the aggressive episode [18].

When de-escalation fails, it may be inevitable to use coercive measures, using strict protocols to avoid violation of human rights. Such measures include involuntary medication, isolation, seclusion, physical and chemical restraints. Even though they are used only as a final attempt to calm the agitated patient, in psychiatric hospitals in Europe, rates of coercive measures use varies between 21% and 59% [19].

In terms of the initial assessments, the following general guidelines should be followed:

- Any serious, possibly life-threatening, medical condition should be immediately detected or ruled out. If the patient has no previous history of psychiatric illness, agitation should be suspected as possibly related to a medical condition that is yet to be diagnosed [20].
- Patients with psychotic disorders or with severely aggressive behaviours should receive medications to allow a safe physical and mental examination. If the violent behaviour is anticipated to escalate, verbal de-escalation, environmental modification and medication treatment should be in place. The physical or medical contraindications (e.g., allergies) to the medications that are about to be administered should be established [11].
- The following steps should be followed to achieve accurate differential diagnosis:
  - Obtain vital signs of the psychiatric and medical history of the patient.
  - Conduct a visual examination by evaluating the patient's appearance, attentional deficits, level of awareness and cognitive skills [11].
  - Obtain additional information from medical records and collateral sources to identify previously diagnosed conditions and medications [17].
  - A mental status examination should be performed as soon as possible, as it will help establishing the probable cause of agitation and selecting the most appropriate intervention [17].
- If cognitive impairment is detected, a collateral history (interview with friends and families, medical records, interviews with outpatient care providers and other people who might be aware of the patient's history) is required to determine if the onset of the impairment is recent [17].
- The patient should be checked for intoxication or withdrawal. Recent drug use should be investigated to recognize clinical symptoms based on different substances of use [17].
- Routine examination, including blood glucose and oxygenation level, thyroid tests, pregnancy test in female patients of a childbearing age, electrolyte profile and renal function, should be performed as soon as possible [17].
- An accurate mental and psychiatric status evaluation should be conducted once an acute medical cause of agitation is ruled out [17].

7.5 The Interview

Before conducting the interview with an agitated patient, it is important to perform environmental adjustments that might minimize the risk of violence and its aggravation. Such measures should include removing all of dangerous objects from the examination room, including pens, phones and needles, which might be used as weapons. The clinician should pay attention for any signs of impending danger like signs of invasion of personal space, clenching of the jaw, verbal gestures or threats, and slamming doors or knocking off furniture. If the clinician fails at reducing the patient's agitation, tranquilization and emergency restraints might be required to ensure safety and regain control [11]. The distance from the door should be equal for the patient and health care professional (to avoid the sense of being cornered). Ideally, all examination rooms should be equipped with the alarm button [21] and escape routes visible only to security and staff members. Architectural and environment adjustments have been successfully tested in Sweden, with a significant decline in the use of coercive medication or restraint measures. Those adjustments include a reduction of crowding stress by enabling privacy to patients (single rooms with private bathrooms), a reduction of environmental stress (i.e., noise reduction, projection of natural views, provision of comfortable room temperature, etc.) [22]. The interview with an agitated patient should be performed once the patient is calm enough.

Stowell et al. [23] recommend to include the following assessments:

- Chief complaint (which might differ between the patient and persons who accompanied him to the psychiatric ward).
- History of present illness (symptoms onset and duration, potential stressors).
- Past medical history (including medical conditions, especially head injuries and previous surgeries).
- Past psychiatric history (including contacts with psychiatric care and determined diagnoses, suicide attempts, history of violence, etc.)
- Substance use history (use of nicotine, caffeine, alcohol, street drugs, etc.)
- Social history (educational background, family, marital status, employment status and history, military service, history of sexual/physical abuse, etc.)
- Family history (with emphasize on mental conditions and substance abuse in the family).

There is a number of assessment tools that have been developed to estimate the risk of violence in agitated patients. Examples of the scales that have been widely used include:

- Behavioural Activity Rating Scale (BARS)—a 3-area (physical aggression, non-physical aggression and verbal agitation), 10-item scale that is useful for rapid assessment of the level of aggression [24, 25].
- The Brøset Violence Checklist (BVC)—a 6-item assessment tool for prediction of imminent violent behaviour within the next 24 h [24, 25].

- Violence risk screening-10 (V-RISK-10)—useful for acute psychiatric settings [26].
- Agitation severity scale (ASS)—a 21-item scale that is useful for evaluation of behaviour involved in agitation in acute settings [20].

Several laboratory tests may be necessary while evaluating an agitated patient [27], including:

- *Comprehensive Metabolic Panel (CMP): Glucose, Calcium, Albumin, Total Protein, Electrolytes, CO_2, Chloride, BUN (blood urea nitrogen), Creatinine, ALP (alkaline phosphatase), ALT (alanine amino transferase, also called SGPT), AST (aspartate amino transferase, also called SGOT), Bilirubin.*
- *Complete Blood Count.*
- *Oxygen saturation (mostly* via *pulse oximetry, given that arterial blood gas test is often unfeasible).*
- *Thyroid Panel.*
- *Folate level.*
- *Toxicology of serum and urine.*
- *Serum chemistry panel.*
- *Vitamin B12 levels.*
- *Sexually Transmitted Diseases serologies.*
- *Pregnancy test, urine or serum β-human chorionic gonadotropin (women of childbearing age).*
- *Urine analysis.*
- *Calcium.*
- *Ammonia.*
- *Erythrocyte Sedimentation Rate.*
- Other diagnostic studies based on clinical suspicion may include:
- *Arterial blood gas.*
- *Chest X-ray.*
- *Electroencephalogram.*
- *Lumbar puncture: specialized markers, cell count, gram stain and opening pressure.*
- *Electrocardiogram.*
- *Blood or urine cultures.*
- *Paraneoplastic studies.*
- *Serum heavy metals.*

Neuroimaging tests may include:

- *X Rays.*
- *Computed tomography.*
- *Magnetic resonance imaging.*
- *Positron emission tomography.*

7.6 Pharmacological Management of Agitation

There are three main goals for the pharmacological treatment of acute agitation: (a) to calm the patient without oversedation, (b) to reduce aggressiveness and therefore create a safe environment, for both health care providers and the patient and (c) to enable health care providers to provide the management of any patient's primary disease. Treatment of acute agitation should be individualized, with special attention to those conditions that are specific to each case (i.e., taking into consideration patient's age, pregnancy, drug intoxication, liver or renal insufficiency) [28].

So far, there is no universal consensus about most preferable pharmacological agent to be administered to acute agitated patient. The most commonly used medications for agitated patients include benzodiazepines and typical (first-generation) or atypical (second-generation) antipsychotics, which may be administered orally (or fast-dissolving tablets), intramuscularly or intravenously [3].

The criteria for medication choice usually include: prompt tranquilization (avoiding oversedation, if possible), immediate efficacy, low possibility of adverse effects, non-interference with the diagnostic procedures [29].

Oral administration is usually safer and preferred; however, severely agitated patients might refuse swallowing the tablet. Intravenous (IV) route provides a prompt drug action, but—again—agitated patients may oppose to the insertion of an IV line. IM route is usually more convenient then IV, despite the longer time to response. However, the IM route is complicated by issues such as patient's fear of the needle and poor tolerance to pain, along with a substantial risk of needle stick injuries for healthcare workers [30]. Novel oral formulations, such as sublingual tablets, aerosols or rapidly dissolving oral tablets, might offer an alternative [20].

Benzodiazepines are first-line treatment for moderate to severe agitation. Drugs belonging to this group (e.g., lorazepam, diazepam) may be administered via the oral or parenteral (IM or IV) route [11]. Benzodiazepines are also a first-line treatment for alcohol withdrawal-induced agitation [31].

Benzodiazepines target the GABA receptors, by increasing the activity of gamma-aminobutyric acid, which is one of the main fast-acting inhibitory neurotransmitters of the central nervous system. There are three classes of GABA receptors—GABA-A, GABA-B and GABA-C—and benzodiazepines enhance the activity of GABA-A receptors. The advantages of benzodiazepines include an immediate anxiolytic and calming activity. Benzodiazepines (BDZ) have been a first choice treatment for agitation, for instance, in patients intoxicated with stimulants (BDZ have a low risk of arrhythmias), patients with alcohol withdrawal-induced violent behaviour or patients with agitation related to a mental disease, such as schizophrenia, bipolar disorder or personality disorders. However, clinicians should be careful with longer term benzodiazepines use in patients diagnosed with psychosis, given that BDZ usually have only a sedating, hypnotic and anxiolytic effect but are unable to target the core psychotic symptoms. Serious side effects of benzodiazepines include respiratory and cardiovascular depression in predisposed patients or in patients intoxicated with ethanol or other CNS depressant (i.e.,

opioids) [3]. If the respiratory rate decreases below 10/min or the oxygen saturation goes below 90%, it is necessary to promptly react, administer flumazenil and monitor the patient's respiration [29]. Patients whose agitation is related to amphetamines abuse should not take benzodiazepines as monotherapy, because of the possibility of psychotic symptoms; in those cases antipsychotics alone or in combination with benzodiazepines might be a treatment option [3], provided that the patient is not experiencing arrhythmias.

Lorazepam is one the most convenient benzodiazepines for the treatment of acute agitation. This agent may be associated with most of the available antipsychotics. Lorazepam can be administered orally or parenterally. One of the main advantages of this agent is the small risk of drug accumulation, due to its metabolism (it does not undergo oxidation via the cytochrome P450, it is eliminated after glucuronidation and does not have any active metabolite). However, despite its overall safety and tolerability, attention should be payed to side effects, including respiratory depression, ataxia or paradoxical disinhibition [32, 33].

Diazepam and alprazolam are less commonly used benzodiazepines in treatment of acute agitation, mainly because of tolerability issues. A frequent problem encountered with these drugs is due to their prolonged half-lives, their many active metabolites, and the possible oversedation, which is frequent in elderly patients, who are also at risk of paradoxical activation [11, 34].

Antipsychotics are also frequently used for the treatment of agitation. The common pharmacodynamics feature of these drugs is blockage of dopaminergic neurotransmission, even though some agents in this group affect serotonergic neurotransmission too. Antipsychotics have frequently been referred as antagonists at the dopamine 2 (D2) receptor. For D2 antagonist antipsychotics, a favourable effect on psychotic symptoms usually occurs when approximately 65% of the D2 receptor population is blocked [35].

There are two classes of antipsychotics:

- Typical or first-generation antipsychotics—introduced in the clinical practice of the 1950s: chlorpromazine, followed by fluphenazine, thioridazine, haloperidol, etc.
- Atypical or second-generation antipsychotics: olanzapine, risperidone, amisulpride, quetiapine, ziprasidone, asenapine, lurasidone, partial agonists (aripiprazole, brexpiprazole, cariprazine), etc.

First-generation antipsychotics (FGA) include low- and high-potency agents. Low-potency antipsychotics include phenothiazines (e.g., chlorpromazine). These agents do not have adequate safety profile and hence are not usually prescribed as a first-line treatment for acute agitation, mainly because of their increased risk of oversedation, hypotension or QT interval prolongation, as well as lowering of the seizure threshold. Haloperidol, a high-potency drug, is the most preferred FGA for the treatment of acute agitation. This drug can induce rapid tranquilization. Comparing to chlorpromazine, there usually is a lower possibility of side effects.

However, haloperidol can induce extrapyramidal symptoms, including acute dystonia or akathisia, and—especially if it is administered IV in high doses—prolonged QT interval and torsades de pointes (TdP), which is often followed by sudden cardiac arrest. Therefore, in some medical settings, an off-label protocol of IV administration at low doses (maximal dose of 5–10 mg/day), with continuous ECG monitoring is still followed. Nevertheless, haloperidol is mostly used orally or intramuscularly and remains one of the first-line agents for acutely agitated patients, for instance, those with acute ethanol intoxication [3, 11, 20, 21, 36].

Loxapine, a typical antipsychotic that may be administered by oral inhalation, has recently been approved and granted an indication for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. In clinical trials, the effect of loxapine was apparent at 10 min following dosing. However, the use of this medication is complicated by the possibility that acutely agitated patients refuse to inhale the medication. Also, although infrequently (2 patients out of 259 that received loxapine in the 3 short-term-24-h, placebo-controlled trials involving patients with agitation associated with schizophrenia or bipolar disorder), the medication can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest [37].

Second-generation antipsychotics (SGA) or atypical antipsychotics were introduced in the clinical practice in the last decade of the twentieth century. They can be divided into four groups according to the pharmacodynamics properties that result from their affinity for specific receptors: (A) highly selective for serotonin 5-HT2A and dopamine D2 receptors (as well as for alpha-1 adrenergic receptors)—risperidone, ziprasidone; (B) agents that show affinity for serotonin 5-HT2A and dopamine D2 receptors as well as for other systems (cholinergic, histamine)—olanzapine, quetiapine, (C) agents that predominantly block D2 and D3 receptors—amisulpride; (D) partial agonists of dopamine receptors—aripiprazole, brexpiprazole, cariprazine. One of the advantages of SGA, compared to their older counterparts, is their better safety profile. They can be used for rapid tranquilization of acute agitated patients, especially those who are antipsychotic naïve, with low risk of causing oversedation (which can lead to respiratory and cardiovascular depression) and extrapyramidal symptoms. Side effects of SGA are also significantly lower compared to the combined therapy of FGA (haloperidol) [3, 11, 20, 21, 32, 36].

Risperidone has usually been used via oral route in acute setting. It is manufactured as orally disintegrating tablet, with pharmacokinetic characteristics that are relatively similar to parenterally administered haloperidol. However, due to the possibility of orthostatic hypotension, clinicians should pay attention while using risperidone in rapid tranquilization, especially in elderly patients suffering from CVD, who have an increased risk of stroke.

Olanzapine can be administered both orally as disintegrated tablet and intramuscularly. In a study of 42 patients with agitation, orally disintegrating olanzapine tablets, intramuscular olanzapine and oral risperidone solution resulted as effective treatments as IM haloperidol. However, disintegrating olanzapine tablets and intramuscular olanzapine resulted more effective than IM haloperidol in the early phase of the intervention [38].

IM combination of olanzapine with IM or IV benzodiazepines, e.g., lorazepam, should be avoided. As for risperidone, there is an increased risk of stroke in elderly patients with CVD.

Ziprasidone is available as oral or intramuscular formulation. The IM formulation is characterized by a rapid onset, resulting in symptom improvement up within 30 min from the administration, and by a low risk of sedation. Therefore, IM ziprasidone can be used in acutely agitated patients who need rapid tranquilization without sedation. The most serious side effects of this agent include the possibility of prolonged QT interval and irregular cardiac rhythm, while extrapyramidal symptoms and oversedation are less likely to occur [3, 11, 20, 21, 36].

One of the most commonly prescribed combinations of medications for the management of acute agitation is haloperidol (high-potency typical antipsychotic) with lorazepam (benzodiazepine). This combination is considered as the first-line care for undifferentiated agitation worldwide. The incidence of side effects, including extrapyramidal syndrome, is usually low. The co-administration of anticholinergic agents, such as benztropine, further reduce the risk of extrapyramidal symptoms. The combination of haloperidol, lorazepam and benztropine is often administered to young muscular males who are at increased risk of dystonia. This "9-1-1 IM cocktail" (9 mg of haloperidol, 1 mg of lorazepam, 1 mg of benztropine) has long been used in the US medical settings. However, its popularity is primarily based on empirical evidence and a lower (5 mg) dose of IM haloperidol may be preferred. Clinical trials are needed to confirm the validity and safety of the combination. Other antihistaminic agents, e.g., diphenhydramine, have been added to the haloperidol and lorazepam combination. However, clinicians should be aware that each drug combination is accompanied with the risk of side effects, such as excessive sedation, interactions with other medications, increased risk of arrhythmia [3, 11, 33].

Special consideration should be taken in treatment of acutely agitated elderly persons, because of their increased susceptibility to adverse drug reaction. To opt for the most suitable agent in elderly patients, it is important to perform a thorough assessment to identify the underlying cause of agitation. Usually, it is recommended to start with small doses of a single agent. The choice of a drug to be administered should be made based on the physical status (i.e., CVD, liver failure). Each medication carries specific risks. For instance, anticholinergic agents—including antipsychotics that have higher anticholinergic properties (e.g., olanzapine, low potency FGA, quetiapine, clozapine, quetiapine, etc.)—may worsen existing cardiovascular problems, cognitive functions, constipation, urinary retention, etc. Anti-histamine or anti alpha-adrenergic agents may also increase the risk of falls, especially in late life patients. In such cases, agents such as ziprasidone or aripiprazole may be preferable. In patients with history of Chronic Obstructive Pulmonary Disease (COPD), benzodiazepines might enhance oversedation and increase the risk of respiratory depression [3, 20].

Long-term management of agitation should be aimed at the treatment of the underlying causes of this behavioural problem, including the psychological factors if they are present. In these cases, a combination of psychotherapy (e.g., behavioural, cognitive-behavioural, interpersonal, group or family therapy) and medication treatment may be necessary [11].

References

1. Agency for Healthcare Research and Quality. Non-pharmacologic interventions for agitation and aggression in dementia. 2014. https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/dementia-agitation-aggression_research-protocol.pdf. Accessed 21 May 2019.
2. Holloman GH Jr, Zeller SL. Overview of project BETA: best practices in evaluation and treatment of agitation. West J Emerg Med. 2012;13(1):1–2. https://doi.org/10.5811/westjem.2011.9.6865.
3. Wilson MP, Pepper D, Currier GW, Holloman GH Jr, Feifel D. The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry Project Beta Psychopharmacology Workgroup. West J Emerg Med. 2012;13(1):26–34. https://doi.org/10.5811/westjem.2011.9.6866.
4. Siddiqui W, Huecker MR. Agitation. In: StatPearls. Treasure Island: StatPearls Publishing; 2019. https://www.ncbi.nlm.nih.gov/books/NBK493153/. Accessed 21 May 2019.
5. McNett M, Sarver W, Wilczewski P. The prevalence, treatment and outcomes of agitation among patients with brain injury admitted to acute care units. Brain Inj. 2012;26(9):1155–62. https://doi.org/10.3109/02699052.2012.667587.
6. San L, Marksteiner J, Zwanzger P, Figuero MA, Romero FT, Kyropoulos G, et al. State of acute agitation at psychiatric emergencies in Europe: the STAGE study. Clin Pract Epidemiol Ment Health. 2016;12:75–86. https://doi.org/10.2174/1745017901612010075.
7. Mi W, Zhang S, Liu Q, Yang F, Wang Y, Li T, et al. Prevalence and risk factors of agitation in newly hospitalized schizophrenia patients in China: an observational survey. Psychiatry Res. 2017;253:401–6. https://doi.org/10.1016/j.psychres.2017.02.065.
8. Reddy MS. Suicide incidence and epidemiology. Indian J Psychol Med. 2010;32(2):77–82. https://doi.org/10.4103/0253-7176.78501.
9. Almeida TM, Azevedo LC, Nosé PM, Freitas FG, Machado FR. Risk factors for agitation in critically ill patients. Rev Bras Ter Intensiva. 2016;28(4):413–9. https://doi.org/10.5935/0103-507x.20160074.
10. Yudofsky SC, Kopecky HJ, Kunik M, Silver JM, Endicott J. The overt agitation severity scale for the objective rating of agitation. J Neuropsychiatry Clin Neurosci. 1997;9(4):541–8.
11. Gerken AT, Gross AF, Sanders KM. Aggression and violence. In: Stern TA, Fava M, Wilens TE, Rosenbaum JF, editors. Massachusetts general hospital comprehensive clinical psychiatry. 2nd ed. St. Louis: Elsevier; 2016. p. 709–17.
12. Lindenmayer JP. The pathophysiology of agitation. J Clin Psychiatry. 2000;61(14):5–10.
13. Sheard MH, Marini JL, Bridges CI, Wagner E. The effect of lithium on impulsive aggressive behavior in man. Am J Psychiatry. 1976;133(12):1409–13.
14. Asberg M, Träskman L, Thorén P. 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? Arch Gen Psychiatry. 1976;33(10):1193–7.
15. Beitchman JH, Baldassarra L, Mik H, De Luca V, King N, Bender D, et al. Serotonin transporter polymorphisms and persistent, pervasive childhood aggression. Am J Psychiatry. 2006;163(6):1103–5.
16. Cummings J, Mintzer J, Brodaty H, Sano M, Banerjee S, Devanand DP, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int Psychogeriatr. 2015;27(1):7–17. https://doi.org/10.1017/S1041610214001963.
17. Richmond JS, Berlin JS, Fishkind AB, Holloman GH Jr, Zeller SL, Wilson MP, et al. Verbal de-escalation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA De-escalation Workgroup. West J Emerg Med. 2012;13(1):17–25. https://doi.org/10.5811/westjem.2011.9.6864.
18. Fishkind A. Calming agitation with words, not drugs: 10 commandments for safety. Curr Psychol. 2002;1(4):32–9.
19. Baumgardt J, Jackel D, Helber-Bohlen H, Stiehm N, Morgenstern K, Voight A, et al. Preventing and reducing coercive measures—an evaluation of the implementation of the Safewards

model in two locked wards in Germany. Front Psych. 2019;10:340. https://doi.org/10.3389/fpsyt.2019.00340.
20. Garriga M, Pacchiarotti I, Kasper S, Zeller SL, Allen MH, Vázquez G, et al. Assessment and management of agitation in psychiatry: expert consensus. World J Biol Psychiatry. 2016;17(2):86–128. https://doi.org/10.3109/15622975.2015.1132007.
21. Mantovani C, Nobre Migon M, Valdozende Alheira F, Del-Ben CM. Managing agitated or aggressive patients. Rev Bras Psiquiatr. 2010;32(2):S96–S103.
22. Ulrich R, Bogren L, Gardiner SK, Lundin S. Psychiatric ward design can reduce aggressive behavior. J Environ Psychol. 2018;57:53–66. https://doi.org/10.1016/j.jenvp.2018.05.002.
23. Stowell KR, Florence P, Harman HJ, Glick RL. Psychiatric evaluation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project Beta Psychiatric Evaluation Workgroup. West J Emerg Med. 2012;13(1):11–6. https://doi.org/10.5811/westjem.2011.9.6868.
24. Nordstrom K, Zun LS, Wilson MP, Stiebel V, Ng AT, Bregman B, et al. Medical evaluation and triage of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project Beta Medical Evaluation Workgroup. West J Emerg Med. 2012;13(1):3–10. https://doi.org/10.5811/westjem.2011.9.6863.
25. Vieta E, Garriga M, Cardete L, Bernardo M, Lombraña M, Blanch J, et al. Protocol for the management of psychiatric patients with psychomotor agitation. BMC Psychiatry. 2017;17(1):328. https://doi.org/10.1186/s12888-017-1490-0.
26. Anderson KK, Jenson CE. Violence risk-assessment screening tools for acute care mental health settings: literature review. Arch Psychiatr Nurs. 2019;33(1):112–9. https://doi.org/10.1016/j.apnu.2018.08.012.
27. Smith FA, Hogan CH. Laboratory tests and diagnostic procedures. In: Stern TA, Fava M, Wilens TE, Rosenbaum JF, editors. Massachusetts general hospital comprehensive clinical psychiatry. 2nd ed. St. Louis: Elsevier; 2016. p. 20–38.
28. Baker SN. Management of acute agitation in the emergency department. Adv Emerg Nurs J. 2012;34(4):306–18. https://doi.org/10.1097/TME.0b013e31826f12d6.
29. Ng AT, Zeller SL, Rhoades RW. Clinical challenges in the pharmacologic management of agitation. Prim Psychiatry. 2010;17(8):46–52.
30. Pacciardi B, Mauri M, Cargioli C, Belli S, Cutugno B, Di Paolo L, et al. Issues in the management of acute agitation: how much current guidelines consider safety? Front Psych. 2013;4:26. https://doi.org/10.3389/fpsyt.2013.00026.
31. Kattimani S, Bharadwaj B. Clinical management of alcohol withdrawal: a systematic review. Ind Psychiatry J. 2013;22(2):100–8. https://doi.org/10.4103/0972-6748.132914.
32. Taylor DM, Barnes TRE, Young AH. The Maudsley prescribing guidelines in psychiatry. 13th ed. New Jersey: Wiley-Blackwell; 2018.
33. Battaglia J. Pharmacological management of acute agitation. Drugs. 2005;65(9):1207–22.
34. Jones KA, Nielsen S, Bruno R, Frei M, Lubman DI. Benzodiazepines - their role in aggression and why GPs should prescribe with caution. Aust Fam Physician. 2011;40(11):862–5.
35. Richards JR, Schneir AB. Droperidol in the emergency department: is it safe? J Emerg Med. 2003;24:441–7.
36. Ziaei M, Massoudifar A, Rajabpour-Sanati A, Pourbagher-Shahri AM, Abdolrazaghnejad A. Management of violence and aggression in emergency environment; a narrative review of 200 related articles. Adv J Emerg Med. 2018;3(1):e7. https://doi.org/10.22114/AJEM.v0i0.117.
37. ADASUVE™ (loxapine) inhalation powder [package insert]. Souderton: Galen US; 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022549s006lbl.pdf. Accessed 4 Aug 2019.
38. Hsu WY, Huang SS, Lee BS, Chiu NY. Comparison of intramuscular olanzapine, orally disintegrating olanzapine tablets, oral risperidone solution, and intramuscular haloperidol in the management of acute agitation in an acute care psychiatric ward in Taiwan. J Clin Psychopharmacol. 2010;30(3):230–4.

Unmet Needs in the Management of Suicide Risk

8

Maurizio Pompili

Although suicide is a major public health issue worldwide, both mental health professionals and lay-people struggle to cope with it. A part of the problem comes from the myths, obsolete paradigms, and stigma associated with suicide that results in anxiety and fear. However, most suicidal individuals want to live even when facing serious suicidal stress. Clinicians are, therefore, called upon to unlock the suicidal mind, relieve the suffering, and pay attention to the unmet needs of these individuals.

There are so many unmet needs in individuals at risk of suicide. Too often, the medical model is imposed as a treatment plan. Therapists are more likely to treat the psychiatric disorder and, therefore, assume that this treatment also reduces suicide risk. In this way, the "one fits for all" model precludes understanding the suicidal mind, with its unique characteristics for each subject.

Furthermore, there are still no agreed upon models for managing patients accessing the emergency room and, in addition, there are still no data on patient adherence to prevention programs at follow-up. The emergency department is often a crowded environment where the clinician engages in data collection and brief assessments suitable for understanding the current crisis. The clinician's need to collect preliminary information in a limited time often results in the patient's image of a therapist who is not empathic and available. The result is that the patients will not be motivated to return and will not have observed the clinician's skills for dealing with suicide risk.

One of the central elements of caring for people at risk of suicide lies in the ability to formulate the question, "What is like to be suicidal?" To answer this question,

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the therapist must necessarily leave his formal position and try to identify himself with the subject in crisis. It is an exercise that is not necessarily easy but for which you can train. Throughout this chapter, the reader is helped to understand the suicidal mind to facilitate this action.

The increasing number of articles on suicide facilitates a significant increase in our understanding of suicide, but the role of the therapist as a critical element in determining the outcome of therapy with a patient at risk of suicide has received only limited attention.

It is widely believed that patients at risk of suicide arouse anxiety in the therapist, and their treatment takes on the aspects of a therapeutic challenge in which therapists confront the ghosts of death with their professional skills. In certain moments of treatment, it is evident how much the patient's life is subordinated to the therapist protecting his career. Experiencing the loss of a patient from suicide affects the personal and professional balance of the therapist significantly [1]. Furthermore, even the fear that this event may take place has consequences for the patient and the therapist. Some psychiatrists fear that a patient may choose suicide sooner or later in the course of clinical practice. It is estimated that about half of all psychiatrists lose at least one patient from suicide during their career [2].

The emotional difficulties experienced after a suicide are greater than those experienced after other forms of death. The former is usually experienced as an offense to the therapist's ability to understand and help clients. He experiences the unpredictable, unknowable, and the uncontrollable. The experience of the therapist is, without doubt, of primary importance in the management of the patient at risk of suicide.

However, both young therapists and those with more experience react similarly to the risk of a patient's suicide, showing anxiety reactions and feelings of incapacity [3]. Also, those who have had themselves the thought of suicide are undoubtedly more vulnerable in the management of the risk of suicide, especially if the therapist shows behaviors such as avoidance in the face of strong feelings, defensiveness, and passivity.

In reading articles on the treatment of suicide risk, the frequency in which the word *assessment* or *evaluation* is used as a synonym for therapy is noteworthy. These articles are usually designed for guiding and helping the therapist treat the potentially suicidal person [4]. They contain a series of practical recommendations such as: "Do everything to eliminate firearms and drugs that are potentially lethal from the home of the suicidal patient"; "Check carefully the prescriptions of potentially lethal drugs"; "Alert family members"; and so on.

Such precautions or warnings may seem reasonable, but in reality, reflect a state of mind and a way of relating to patient suicides which often jeopardize successful treatment. As many suicidal patients are struggling with management and control of themselves, an excessive emphasis on precautions and on the evaluation, dictated by the therapist's apprehension, can facilitate one of the most lethal aspects of the suicidal person, that is, his tendency to make someone else responsible for keeping him alive.

Some patients have an approach to therapy in which they attempt manipulation. There is evidence in the literature in which therapy for the suicidal patient is based on the belief that the unbearable mental pain will eventually pass, that the crisis is

time-limited. This belief is based on the example of other patients who found themselves in similar situations but who improved. It is often stressed that the behavior of the suicidal patient can interfere with therapy. Since treatment cannot help the patient if he is dead, it is necessary to remind the patient of his feelings for the spouse, children, or pets. To encourage a suicidal patient to live for the sake of his family reinforces what many patients already feel, that is, that they are living just for the sake of others.

A therapist threatened by the fact that a patient may kill himself while he is in his care, cannot help that patient. Indeed, the emergency measures necessary to prevent suicide and make therapy possible often reflect the anxiety of the therapist and make treatment impossible.

Fear of responsibility when taking care of patients at risk of suicide, and the anxieties that this entails, serve as conscious motivation for therapists to avoid treating suicidal patients. Patients with suicidal tendencies are usually sensitive to the therapist's anxieties. Many suicidal patients (including those who eventually kill themselves) have learned to use the anxiety they can arouse in others by the threat of their death in a coercive or manipulative manner. If the therapist, in the face of death threats, responds to the unreasonable demands of the patient, there will be an escalation of requests from the patient accompanied by growing anger and dissatisfaction in both the patient and the therapist. Unless these attitudes and patient expectations are explored, the therapist may make himself the slave of the patient, with terrible therapeutic results.

Wheat [5] conducted a retrospective study of the therapeutic interaction of 30 patients who had died by suicide during or after admission. He reported three factors that partially explain these suicides: (1) the refusal of the therapist to tolerate the patient's childlike dependence [6]; (2) a discouraged attitude on the part of the therapist regarding treatment progress; and (3) an event or crisis of enormous importance for the patient that is not adequately recognized by the therapist.

Bloom [7], in a similar study on the treatment of suicidal patients conducted by training psychiatrists, recognized that some elements appeared to be precipitating factors. Specifically, the rejection of specific behaviors of the patient by the therapist with verbal and facial expressions of anger, premature abandonment of the patient, reduction in the frequency of psychotherapy sessions, and a lack of availability of the therapist himself.

Lesse [8] emphasized that the experience and competence of the therapist, as well as self-knowledge, are of vital importance in the treatment of suicidal patients. He stressed the need for constant and competent supervision of the beginning therapists in training as they deal with patients with suicidal tendencies. In these cases, the dominant idea felt by the therapist is that a suicide attempt is a form of rejection of the therapist. At a professional level, it is necessary to correctly evaluate the probability that the patient has acted impulsively and following his feelings of the moment. If the patient dies by suicide, the therapist might believe that he is not a good doctor. He may fear the disapproval of his colleagues, blame from the coroner, and bad publicity.

8.1 The Formulation of Suicide Risk

The so-called "suicide risk formulation" offers the clinician a valid method to assess the danger of suicide, which integrates the clinical presentation material, the history of the patient, his current illness, and the current mental state. There are five components in the formulation of suicide risk [9]:

1. evaluate the patient's responses to stress suffered in the past, especially resulting from losses;
2. assess the patient's vulnerability to adverse life events, loneliness, contempt of self and homicidal anger;
3. assess the nature of the resource available and external support;
4. evaluate the emergence and the emotional importance of fantasies of death; and,
5. evaluate the patient's capacity for analyzing reality.

8.2 Understanding the Suicidal Mind

Campaigns have been launched to make sense of what makes a specific individual suicidal. However, encountering a suicidal individual remains for the majority of professionals and common people, a challenging task. We know that suicidal individuals give definite warning signs, mostly derived from their ambivalence about ending their own lives. Among the constructs used to describe the wish to die, a simple but extraordinary model has proved, at least for its straightforwardness, to be useful in describing the suicidal mind. Edwin Shneidman [10] first posited that the suicidal individual experiences unbearable psychological pain (*psychache*) or suffering and that suicide might be, at least in part, an attempt to escape from this suffering. Shneidman [10] considered psychache to be the main ingredient of suicide. According to this model, suicide is an escape from intolerable suffering, emphasizing that suicide is not as a movement toward death but rather as an escape from intolerable emotion, unendurable or unacceptable anguish. Experiencing negative emotions, with an internal dialogue making the flow of consciousness painful and leading the individual to the ultimate conclusion, may be related to the fact that, if tormented individuals could somehow stop consciousness and still live, they would opt for that solution. Suicide occurs when the psychache is deemed by that individual to be unbearable [11].

For Shneidman [12], suicide is the result of an explosive mixture consisting of four basic ingredients. He listed such ingredients as follows: heightened inimicality (acting against the individual's best interest); exacerbation of perturbation (refers to how disturbed the individual is); increased constriction of intellectual focus; tunneling or narrowing of the mind's content (dichotomous thinking); and the idea of cessation: the insight that it is possible to stop consciousness and put an end to suffering

The concept of inimicality in this instance refers to those attitudes of the individual that lead him to act in a way that is not at all friendly to himself, to the point

of becoming his perverse enemy. In suicidal individuals, this state is present, and the individual is struggling with pressures of various kinds such as physical health, refusals, feelings of failure, pain, and other negative emotions. The individual fails to manage these issues with the resources he has available.

Shneidman believed that in suicide, "death" is not the keyword. The key word is "psychological pain" and, if the pain were relieved, then the individual would be willing to continue to live.

Two main concepts are relevant to this discussion: perturbation and lethality. Perturbation refers to how upset (disturbed, agitated, discomposed) the individual is, while lethality refers to the likelihood of an individual dying by suicide in the future.

The understanding of the suicidal mind requires knowledge of the perturbed state of the individual in crisis since this provides the motivations for the individual to contemplate suicide. Therefore, asking where the suffering comes from and how it has changed and become more acute is a method of intervention which, although simple and intuitive, is often forgotten by those who are responsible for managing the person in crisis. In the internal debate, essentially involving ambivalence, being able to tune into the suffering of the person makes it possible to stem such ruminations and bring the discussion back to a position of vitality and hope.

Perturbation supplies the motivation for suicide; lethality is the fatal trigger. Everyone who dies by suicide feel driven to it and feels that suicide is the only option left [13]. The concept of "constriction" is defined as tunnel vision or rather finding oneself with a reduced number of options to cope with the suffering. Suicidal individuals experience dichotomous thinking, that is, wishing either some specific (almost magical) total solution for their perturbation or for cessation, in other words, suicide. It seems that, although there may be effective supports from family and friends, the individual is unable to benefit from them. The pleasant memories and their history in relation to others are not helpful, and the individual focuses on intolerable emotions and how to escape from them.

The concept of cessation comes into play when the individual develops the idea that one can put an end to the drama that takes place in his mind through dying. The individual then realizes that with death, he will bring a solution to his experience by eliminating all the elements that torment him in life.

Suicide is the result of an interior dialogue during which the mind scans its options [13]. During the early phases of this process, suicide is considered as an option, but it may be rejected a number of times. Shneidman [14] reported an emblematic process referring to the word "therefore" "*almost every decision that a person makes (based on some unspoken reasoning in the mind): it is the logical bridge between almost every thought and every action (or deliberated inaction). Among all the . . .therefore, I. . .*" *sequences that are possible in the mind, one of the most important ones is contained in the words: I'. . .therefore, I must kill myself*."

Suicide planning is often a long and complex process. The person begins to think of a propitious moment; he must have time to prepare. During the weeks and days preceding the actual planning until the act is implemented, the individual continues to dialogue with himself or herself with a large number of thoughts. They can refer

to the fact of not being worth anything for themselves let alone for others, of not having been a success, of being a burden for oneself and one's loved ones, that no one will ever love them, or to be a coward so much that one cannot even die by suicide. After debating, to overcome the survival instinct, the person must have, at least just before the act, such impulsiveness and aggression as to make a gesture against nature. Thus begins an increasingly tight challenge in which a moment of excitement in the mood may also occur during which the person sees salvation in suicide, begins to glorify the act, and configures it as a plan to put into practice, avoiding any interference on the part of the others. One must think of an act that appears to the subject as something forbidden but which feels necessary to improve his state. Suicide is an act that, in many cases, is premeditated for a longer time than is believed. Only after this time does the act become an impulsive gesture. The individual has repeatedly thought about taking his own life, but this option, every time it occurred, although it was discarded, took on a greater value. It is at this juncture that the subject at risk of suicide begins to give signals in which he conveys the message of being tired of living, of thinking about death and of wanting to die. It is a problem of human life for which "emotional storms" occur, great movements of ambivalence, and at the same time changes in sleep habits, appetite, personal hygiene, and social relations. In this period of premeditation of the lethal act, the subject at risk also thinks of his loved ones, feeling regret and guilt for considering such a tragic solution. In some cases, there are also complex dynamics within the family, with the partner, or with friends, such that the suicidal individual almost reproaches them for not receiving adequate help from them.

Moreover, the subject at risk feels hopeless, and his mental pain feels unique, and he reaches this conclusion after experiencing the fact of not being able to communicate his suffering to the people assigned to help. The desire to die happens in each person with substantially unique motivations and thoughts, which makes him different from all other people at risk of suicide.

Shneidman [10] also considers that the main sources of psychological pain are shame, guilt, anger, loneliness, and despair originating in the frustrated and denied psychological needs. In the suicidal individual, it is the frustration of these needs and the pain that results from it, which is considered by him to be an unacceptable condition for which suicide is seen as the most appropriate remedy. There are psychological needs with which the individual lives and which define his personality and psychological needs which, when frustrated, induce the individual to choose to die. We could say that this is the frustration of vital needs. These psychological needs include the need to achieve some goals such as joining a friend or a group of people, gaining autonomy, opposing something, imposing on someone, and the need to be accepted and understood and receive comfort.

It is essential to monitor suicide risk at all times by taking into consideration warning signs for suicide, such as any change in habits, especially if insomnia is presented and any reference to the wish to die. People may feel trapped and may engage in maladaptive behavior, such as drinking alcohol and using psychoactive substances. Suicidal individuals also often put their affairs in order and give away

symbolic items, as if they wish another person will take care of a prized possession, regardless of their economic value.

Studying the content analysis of the pain narratives of suicidal patients, Orbach [15] refers to specific features of the suicidal mind: These include change in the self, experiences of self-estrangement accompanied by dissociative characteristics; a sense of worthlessness, emotional impoverishment, and loss of self-esteem. Furthermore, the mind is often characterized by the experience of loss, such as events of loss that lead to an interruption in one's sense of self-continuity together with loss in one's meaning of life. There are also oxymoronic experiences, extreme contradictions in feelings, thoughts, and desires—to live and die at the same time or grandiosity vs. humiliation. Besides, the language of pain points to the fact that ordinary words do not suffice to describe these idiosyncratic experiences.

8.3 Critical Appraisal of Psychiatric Disorders in the Context of the Suicidal Scenario

Unlike the decision to confine suicide risk to the realm of symptomatology of psychiatric disorders, nowadays new insights into the phenomenon of suicide have led to considering that psychiatric disorders do play a contributing role, but a more profound understanding of the suicidal mind is needed [16]. Rather than categorizing the suicidal individual under the diagnosis of psychiatric entities, clinicians need to be able to recognize the drama occurring in the mind of a unique individual who may also be depressed, bipolar or suffering from other disorders. Most psychiatric patients do not die by suicide. Psychiatric patients are suicidal only when negative emotions are so painful that suicide is the only option left, and when the suicidal mind is hosted in an individual's mentally disturbed brain. Suicide is not, therefore, a specific and narrow symptom of depression. Instead, it is a behavior "combining features of a declaration of war with a petition for bankruptcy" [17] as well as having profound social implications [18].

Considering suicide risk to be fully a symptom impairs the opportunity to investigate and understand suicide. Attempts to explain, predict, and control suicide requires an understanding of what suicidal thoughts and feelings mean to those who live it. Other than collecting a huge amount of data for research activities, efforts should also be directed to understanding first-person data of the subjective, lived experience. Such an approach is an essential complement to the objective, third-person data, and methods of traditional science. Understanding the unbearable mental pain means thinking phenomenologically and, therefore, the development of suicidal tendencies can be traced back to a state with similar characteristics as falling in love but flipped for affective valences. It is a pervasive condition with both psychological and somatic roots that incorporate the individual as a whole. An unpleasant sensation is often localized in the chest and hypochondrium. The mind tries each option to release the tension but never finds a safe haven and ends up convinced that nothing will bring relief.

Clinicians should distinguish suicidal contents from a psychiatric diagnosis, it is, therefore, necessary to think that the elements that support the desire to dying constitute a process in its own right, with a logic typical of the mind that suffers and that tries to devise a solution to reduce and resolve this suffering. Since the nature of suffering that results in suicide is due to the personality of the individual, to his frustrated psychological needs, and to the wounds of the ego (defeats, humiliation, shame, etc.), one can, therefore, differentiate that suffering from the typical suffering of depressive symptoms. Subjects at risk of suicide develop a thinking process called dichotomous thinking because they reason with only two options when confronting the suffering that has become unbearable: continue to suffer or obtaining immediate relief from pain by suicide [13].

This process derives from an inner dialogue that the individual has with himself to seek a solution to his drama in the mind. Independent of psychiatric disorder, clinicians are required to understand this complexity, without which the risk of suicide cannot be decoded. If this process is not interrupted by a change through, for example, help from someone, the individual approaches the final decision and, to quote Shneidman, *"The spark that ignites this potentially explosive mixture is the idea that one can put a stop to the pain. The idea of cessation provides the solution for the desperate person"* [12].

8.4 Communication of Suicidal Intentions

Among the myths often cited to describe idiosyncrasies in the phenomenon of suicidal behavior, classical suicidology, and current opinion state that people who talk about killing themselves rarely die by suicide. Whereas most people who die by suicide have given some verbal clue or warning of their intentions. Some studies show that as many as 2/3rds of suicide deaths share their intentions before dying by suicide. The study by Robins and colleagues [19] was probably the first attempt to address this issue through collecting data for a sample of suicides, and the study remains as one of the few contributions to the literature in this area. Despite the understanding of the communication of suicidal intent, no previous work has examined this fact through a meta-analytic investigation. A recent meta-analysis has shown how suicidal communications are key elements preceding suicides, confirming for this element for the first time [20].

8.5 Unlocking the Suicidal Mind by a Proper Understanding of the Subjective Experience

Unlocking the suicidal mind is the most challenging of all tasks. Many models describing suicide fail to provide a proper understanding of this multifaceted human condition. Stigmatization and fear often provide reasons for empathic disconnection. Furthermore, even when dedicated clinicians are willing to consider all of the patient's needs, we cannot imagine how much these patients suffer. In fact, in order

for empathy to occur, it is necessary that we should have, in our own experience and in our own minds, some points of reference that correspond to those of the patients' experience of states of intense suicidal arousal or excitement (Maltsberger, personal communication 1988) [21, 22].

I agree with Zoe Boden [23] in her view of the experience of suicidal individuals, "*Acknowledging the felt aspect of the experience is, I will argue, necessary for developing a fuller understanding. Recognizing that feelings do not exist solely within a person, but between people, intersubjectively, is also necessary to understand the experience of suicidality more deeply. However, because feelings are immediate and sensory, I will suggest that there are times when understanding is difficult, not because the experience or meaning is hard to discern, but because the visceral power of understanding can feel too much. Feeling overwhelmed is one of the ways that we respond at the edges of our understanding. In our suicide research, there were times when understanding, really understanding, was more problematic than I initially wanted to admit"*. The individual must be understood holistically and met in his or her experience as it is, rather than broken down into risk factors and behaviors.

I also support what suicidologist David Jobes [24], recently stated. "*First, the goal of the clinician is to develop a mutual understanding of an individual's suicidality with the respective patient. This goal differs from the medical model emphasis, which tends to emphasize immediate and overriding emphasis on clinical diagnosis. Second, clinicians must be cognizant of a suicidal person's potential anguish and total loss of self-respect. Many patients are likely to withdraw and express vulnerability when discussing their own suicidal thoughts and behaviors. Third, the clinician should express a nonjudgmental and supportive attitude toward the patient. Empathy is significant in strengthening the therapeutic alliance, and the patient should be validated as the expert of their own experiences. Fourth, suicidal crises are not simply about the present but also often about the past. In the exploration of the crisis/crises, the clinician should encourage the patient to tell their story in a narrative fashion. Fifth, new models are necessary to conceptualize suicidal behavior so that the clinician and patient share an understanding of the patient's suicidality. An objective of this guideline is to not view the patient just as someone with psychopathology, but as someone with logical reasons for being suicidal. Sixth, the ultimate goal in clinical work is to garner a therapeutic relationship with the patient, right from the initial assessment.*"

8.6 Conclusions

There are still many unmet needs for suicidal individuals, and too often, such needs are disregarded as unimportant or of secondary importance. Clinical experience and recent data point to the need for a broader understanding of the suicidal mind. Although many scholars emphasize the importance of risk factors for suicide, such factors are usually static and derived from studies of people not necessarily representative of suicidal individuals in the general population. Such cohorts are

sometimes small and belonging to narrow subpopulations, which impair proper generalization.

Each individual is unique, with a unique presentation of suicidal wishes. However, most individuals can refer their suffering to specific unmet needs, allowing categorization according to the nature of what is lacking in their lives.

Modern psychiatry now witnesses that which is conveyed in a paragraph of the introduction of DSM-5 [25] that is "*Diagnosis of a mental disorder should have clinical utility*" but "*the diagnosis of a mental disorder is not equivalent to a need for treatment. Need for treatment is a complex clinical decision that takes into consideration symptom severity, symptom salience (e.g., the presence of suicidal ideation), the patient's distress (mental pain)*" and "*Clinicians may thus encounter individuals whose symptoms do not meet full criteria for a mental disorder but who demonstrate a clear need for treatment or care. The fact that some individuals do not show all symptoms indicative of a diagnosis should not be used to justify limiting their access to appropriate care*" (p. 20).

Far from being an unexpected phenomenon, suicidal behavior is characterized by many warning signs that often allow key clinical decisions that save the lives of individuals in crisis. The challenge of suicide prevention is to painstakingly develop a culture both in clinical populations and the general population to take care of suicidal individuals starting from their basic frustrated psychological needs. The task is to adopt a phenomenological approach that directs the attention of helpers inside the human experience of mental pain. Although empathic understanding of the pain of suicidal individuals is not sufficient, it is the start of a process that might prevent the individual's suicide.

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References

1. Pompili M, Mancinelli I, Tatarelli R. Confrontarsi con il suicidio del paziente. Minerva Psichiatr. 2002;43:181–6.
2. Chemtob CM, Hamada RS, Bauer G, Kinney B, Torigoe RY. Patients' suicides: frequency and impact on psychiatrists. Am J Psychiatry. 1988;145(2):224–8.
3. Kirchberg TM, Neimeyer RA. Reactions of beginning counselors to situations involving death and dying. Death Stud. 1991;15(6):603–10.
4. Hendin H. Psychotherapy and suicide. Am J Psychother. 1981;35(4):469–80.
5. Wheat WD. Motivational aspects of suicide in patients during and after psychiatric treatment. South Med J. 1960;53:273–8.
6. Simon RI. Suicide risk assessment: what is the standard of care? J Am Acad Psychiatry Law. 2002;30(3):340–4.
7. Bloom V. An analysis of suicide at a training center. Am J Psychiatry. 1967;123(8):918–25.
8. Lesse S. The range of therapies in the treatment of severely depressed suicidal patients. Am J Psychother. 1975;29(3):308–26.
9. Maltsberger JT. Suicide danger: clinical estimation and decision. Suicide Life Threat Behav. 1988;18(1):47–54.

10. Shneidman ES. Suicide as psychache. J Nerv Ment Dis. 1993;181(3):145–7.
11. Pompili M. La prevenzione del suicidio. Bologna: Il Mulino; 2013.
12. Shneidman ES. A psychologic theory of suicide. Psychiatr Ann. 1976;6:51–66.
13. Shneidman ES. The suicidal mind. New York: Oxford University Press; 1996.
14. Shneidman ES. On "therefore I must kill myself". Suicide Life Threat Behav. 1982;12(1):52–5.
15. Orbach I. Taking an inside view: stories of pain. In: Michel K, Jobes DA, editors. Building a therapeutic alliance with the suicidal patient. Washington: American Psychological Association; 2011. p. 111–28.
16. Pompili M. The increase of suicide rates: the need for a paradigm shift. Lancet. 2018;392(10146):474–5.
17. Weisman AD. Is suicide a disease? Suicide Life Threat Behav. 1971;1:219–31.
18. Pompili M. Social network theory and rising suicide rates in the USA. Lancet. 2019a;393(10183):1801–2.
19. Robins E, Gassner S, Kayes J, Wilkinson RH Jr, Murphy GE. The communication of suicidal intent: a study of 134 consecutive cases of successful (completed) suicide. Am J Psychiatry. 1959;115(8):724–33.
20. Pompili M, Belvederi Murri M, Patti S, Innamorati M, Lester D, Girardi P, et al. The communication of suicidal intentions: a meta-analysis. Psychol Med. 2016;46(11):2239–53.
21. Pompili M. Our empathic brain and suicidal individuals. Crisis. 2015;36(4):227–30.
22. Pompili M. Critical appraisal of major depression with suicidal ideation. Ann General Psychiatry. 2019b;18:7.
23. Boden Z. Terror and horror: feelings, intersubjectivity and 'understanding at the edges' in an interview on a suicide attempt. In: Pompili M, editor. Phenomenology of suicide: unlocking the suicidal mind. Cham: Springer; 2017. p. 51–71.
24. Jobes D, Piehl B, Chalker S. A collaborative approach to working with the suicidal mind. In: Pompili M, editor. Phenomenology of suicide: unlocking the suicidal mind. Cham: Springer; 2017. p. 187–201.
25. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Arlington: American Psychiatric Association; 2013.

Unmet Needs in Psychiatry Training

9

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Within this chapter, we explore three major questions (why, what, and how) as a framework for considering unmet needs in psychiatry training (Fig. 9.1). Here we take a close look at three major challenges driving change in mental healthcare: ensuring access to care, providing affordable care, and delivering high-quality care. We discuss how addressing each of these challenges in psychiatry has led to emerging priorities for training in psychiatry. For example, in order to contain costs and expand access to care, new models of healthcare delivery are emerging, which in turn will require psychiatrists to expand skills across numerous domains, including measurement-based care, resource management, multi-disciplinary team leadership, continuous quality improvement, and the use of new technologies. Meeting all of these training demands will require innovative approaches to training. To address these needs, we highlight several evolving approaches to medical education. While much of the data presented is drawn from research in high-income countries, particularly the USA, we believe that most of these issues have broad implications across countries, including low- and middle-income settings.

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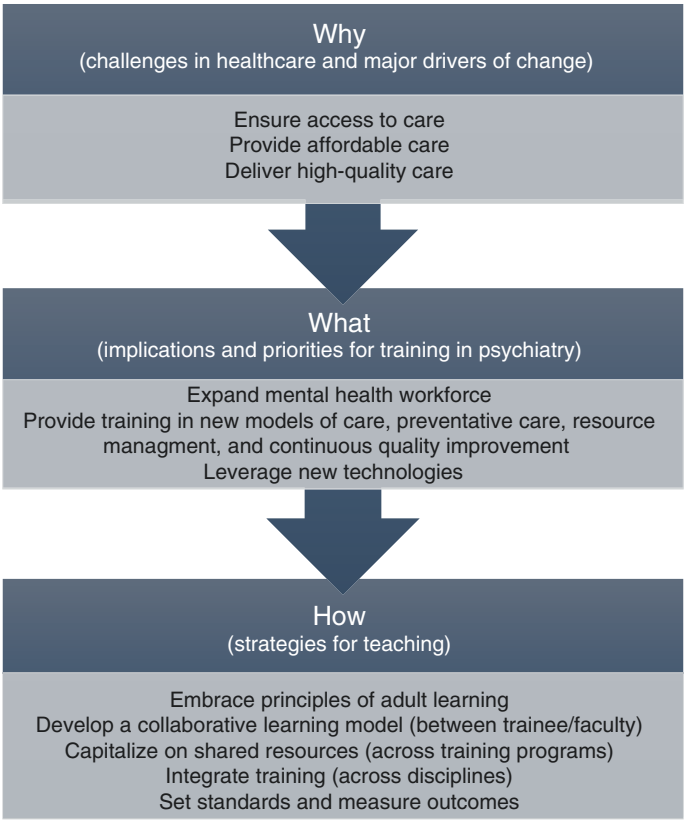

Fig. 9.1 Within psychiatry, unmet needs in training are driven predominately by three major challenges facing healthcare across disciplines. Each of these challenges (accessibility, affordability, and quality) has specific implications for training priorities. Addressing these priorities will require focusing on not only *what* to teach but also *how*

9.1 Priorities in Psychiatry Training

9.1.1 Ensuring Access to Care

One of the major challenges facing the field of psychiatry is the lack of access to care in the setting of enormous need. Mental disorders are the leading cause of years lived with disability with one in five adults reporting a common mental disorder each year. Nearly 30% of the general population will experience mood, anxiety, or substance use disorders over the course of their lifetime [1]. However, access to care is often hampered by stigma, limited resources, and the logistics of navigating a

complex and fragmented healthcare system. On average, there are only nine mental health providers for 100,000 individuals worldwide. The situation is even more dire in low- and middle-income countries, where over 75% of individuals with serious mental illness receive no care [2]. This mental health gap is particularly notable among children and adolescents who account for one quarter of disability-adjusted life years due to mental illness [3]. At the same time the field is not keeping pace with the needs of a growing geriatric population [4, 5] and an escalating addiction crisis with an estimated 16 million individuals worldwide with a current or past diagnosis of opioid use disorder [6].

Ensuring access to mental healthcare has numerous implications for training in psychiatry (Table 9.1). These include: expanding the psychiatrist workforce; aligning training priorities with population needs; and providing training in new models of healthcare to more effectively deploy scarce human resources. This also includes providing training in the use of new technologies such as telepsychiatry and online self-help applications, as well as training a new cohort of mental health providers.

Table 9.1 Approaches for increasing *access* to mental healthcare and associated implications for training in psychiatry

Challenge: ensuring access to care	
Solutions	Training implications
Expand psychiatrist workforce	• Increase exposure earlier in medical training • Provide mentorship for interested students • Address stigma towards a career in psychiatry • Increase compensation for psychiatrists • Include underrepresented minority groups • Increase the number of training programs in psychiatry • Enhance retention • Address physician burnout
Align training priorities with population needs	• Child and adolescent psychiatry • Geriatric psychiatry • Addiction psychiatry
Provide training in new models of care (such as stepped care, and integrated care)	• Work with and lead a multi-disciplinary team • Provide measurement-based care • Provide population-based care • Work with registries
Provide training in new technologies	• Train psychiatrists in the use of remote technologies (telepsychiatry) • Train psychiatrists to evaluate the quality of self-help approaches and online apps
Train additional mental health providers	• Provide training in mental health for a diverse set of learners (including lay professionals) • Expand training in psychiatry for all physicians

9.1.1.1 Expanding the Psychiatrist Workforce

One solution to addressing the mental health gap is to expand the number of physicians entering the field of psychiatry. As reviewed by Brenner and colleagues, strategies for enhancing recruitment to psychiatry include: (1) considering the pipeline at the level of undergraduate training; (2) actively mentoring those medical students who express an early interest in psychiatry; (3) enhancing training in psychiatry during medical school so that students have an opportunity to see the importance and effectiveness of psychiatric treatment; (4) actively addressing persistent stigma towards a career in psychiatry; and (5) revising medical school curricula so that mental health and psychosocial issues are seen as a valuable component of care [7].

An additional challenge for recruiting physicians into psychiatry is the relatively low financial compensation in comparison to other fields of medicine in certain countries [8]. In the setting of escalating debt (with a median debt level of $200,000 for USA medical schools), many graduates may feel compelled to enter more lucrative specialties [9, 10]. Low salaries in some countries may also contribute to the migration of psychiatrists, contributing to the loss of highly skilled professionals in some countries which may be already underserved [8]. Within the USA, some programs have offered loan repayment for students who commit up front to working in underserved areas after completion of their psychiatry training. These types of programs may help to recruit into psychiatry [7]. With a growing emphasis on mental health parity, salaries for psychiatrists may also increase, impacting recruitment [11].

Developing a psychiatrist workforce that reflects the diverse backgrounds, ideas, perspectives, and experiences of population will also require enhanced efforts to recruit those from underrepresented groups, including ethnic, sexual, and religious minorities. Recruiting underrepresented students is also important as physicians from underrepresented groups are more likely to care for minority patients and underserved populations [12].

In addition to providing additional clinical exposure to psychiatry earlier in training [13], recommendations for recruiting underrepresented students include maximizing medical student exposure to faculty and other trainees from underrepresented groups, improving outreach to underrepresented students in medical school and conveying enthusiasm for their interest in psychiatry, communicating a commitment to diversity as a departmental priority, and improving curricula in community psychiatry and cultural competence [12]. However, given the relatively low number of these students in medical school, it is clear that interventions must occur earlier, at the level of high school and undergraduate training [12, 14].

Although recruitment to psychiatry is important, increasing residency training slots would be another potential mechanism to expand the workforce. The World Psychiatric Association urges policy makers in each country to ensure that there are sufficient training posts available to meet the mental health needs of their population [15]. Securing funding for new programs will likely require psychiatrists joining together with professional organizations, major mental health employers, and patient advocacy groups to appeal to policy makers. Highlighting the economic impact of untreated mental illness may be one way to appeal to legislative bodies [7]. Developing new psychiatry training programs is likely to be critical, particularly in low- and middle-income countries where trainees leave their home country

for training due to limited psychiatry training opportunities. As trainees migrate for training, there is substantial risk that they will stay in the country where they train contributing to a phenomena frequently referred to as "brain drain" [16].

Expanding the psychiatrist workforce requires not only outreach to a new cohort of physicians but also retaining those physicians who are already in the field of psychiatry. As described above, issues of financial compensation are likely to be important. However, the burden of bridging the gap created by limited human resources and dysfunctional systems has had a huge toll on all physicians, including psychiatrists, with high rates of burnout. Defined as a combination of emotional exhaustion, depersonalization, and low personal accomplishment, burnout generates detrimental changes to physician attitudes, job satisfaction, and productivity. Reduced productivity, in turn, potentially affects access to care, demonstrated by associations of burnout with early retirement, reduced number of work hours, and intention to leave a current position or specialty [17]. The compounded effects of fatigue, stress, depression, and burnout also impact clinical decision-making, performance, and domains of quality of care including patient safety and patient satisfaction [18]. In response, training programs must also help psychiatrists and other physicians develop strategies to support their own wellbeing, while advocating for accountability and change at the level of institutions.

Distinctive and pertinent stressors experienced by psychiatry trainees include patient suicide, inadequate resources, threats to self-esteem and personal safety (i.e., violent patients), isolation, and secondary traumatic stress [19, 20]. Additional stressors faced by trainees in more recent years also include documentation burden incited by widescale implementation of electronic medical records. Addressing these specific challenges should be a priority for both psychiatry training programs and mental healthcare systems.

With increased calls to measure physician wellness as a quality indicator, there is impetus to improve physician wellness through concerted efforts at a healthcare system level, as well as through education and training [21]. Although many efforts have been focused at the individual physician level (in terms of enhancing resilience), organizational level interventions are often more effective in reducing burnout [22]. Thus, initiatives focused on physician wellness should include an effort to address system level issues and working conditions [23], such as reductions in workload, activities and meetings to boost teamwork and leadership, and adequate supervision. Psychiatrists should also have opportunities to receive positive and constructive feedback (including encouragement and appreciation) as well as easy access to mental health resources [22].

9.1.1.2 Aligning Training Priorities with Population Needs

Each training program should assess and realign training priorities according to the unique populations they serve. In many countries, there has been a growing recognition of the need to enhance training in child and adolescent psychiatry, geriatric psychiatry, and substance use disorders. Addressing workforce shortages in these areas will require a similar multi-pronged approach to expanding the mental health workforce in general: recruiting more psychiatrists into specialty training and developing more fellowship training programs. One recommendation has been to shorten

the requirement for general adult psychiatry training for those pursuing additional fellowship training [24]. However, given the overall shortage of general psychiatrists, additional efforts will be necessary. At a minimum, providing more focused training to all psychiatrists in these areas will be critical.

In order to meet the needs of an aging population, psychiatrists will need to further improve their skills in cross-collaboration with physicians in other branches of medicine given the complexities of treating mental illness in the setting of comorbid chronic medical illnesses and neuropsychiatric disorders (such as dementia) [25]. Although already included in psychiatry training, familiarity with medication side effects and drug–drug interactions will be even more critical for working with older adults who are particularly vulnerable to these complications [26]. Psychiatric training in substance use treatment should include not only foundational basics such as motivational interviewing and the stages of change model, but also protected time for buprenorphine training and practical experience in medication-assisted treatment [27].

9.1.1.3 Training in New Models of Care

Training additional psychiatrists and expanding psychiatric training to address the evolving needs of the population is unlikely to counterbalance the global burden of mental illness. As a result, new models of healthcare delivery are emerging in order to more effectively deploy the limited psychiatry workforce currently available (Fig. 9.2). Within these new models, the psychiatrist's role is conserved to directly

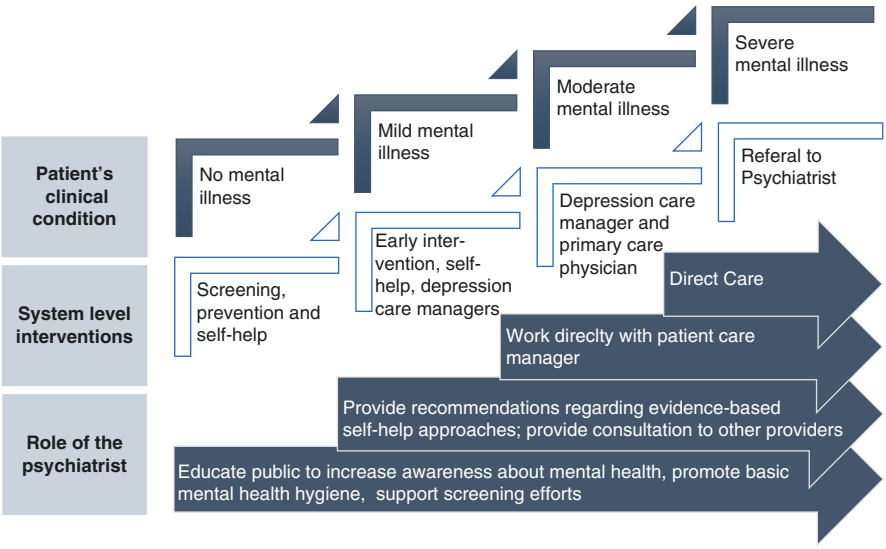

Fig. 9.2 The evolving role of the psychiatrist based on the severity of mental illness in new models of care such as "stepped care" and "integrated care" which aim to conserve limited psychiatric resources. Within these models, psychiatrists serve as consultants to teams who are directly managing patients with lower severity of the illness. Direct care is reserved for those patients with the highest complexity and level of need.

manage those individuals who need it most, while providing indirect oversight of a larger caseload, providing what is often referred to as population-based care. In stepped care, the goal is to provide the least expensive, effective treatment first and "step-up" to more resource intensive treatments as needed. In integrated care, this includes having psychiatrists and other mental health providers collocated in primary care settings as part of an interdisciplinary team.

Integrated care consolidates physical and mental health services in a systematic manner to improve the whole health of a person and increase access to care. This can be implemented in a number of ways, including co-location, in which behavioral health providers work nearby or within a primary care clinic, or a collaborative care model, in which team-based care is led by a primary care provider with support from a behavioral health care manager, and consultation from a psychiatrist, who provides guidance and treatment recommendations.

These new models of health delivery can expand access to care and improve health outcomes. A 2012 Cochrane Review of collaborative care showed significantly greater improvement in depression and anxiety outcomes compared with usual care, as well as secondary outcomes such as patient satisfaction with treatment, mental health quality of life, and rates of antidepressant use [28].

Training in integrated care should include the experience of providing psychiatric consultation in varied settings and working with and leading a multi-disciplinary team. In addition, trainees will also need to develop skills in measurement-based care [24], or in the use of standardized assessment tools to monitor and track symptoms and guide treatment decisions. Similarly, they will need to understand how to work with patient registries [29], which collect these types of measures across a cohort of patients, in order to identify which patients need a modification in their treatment plans.

In addition to improving mental health outcomes, collaborative care is also found to be more effective than care as usual in regards to illness burden and physical outcomes, particularly in patients with hypertension and comorbid depression, supporting the notion that patients should be treated as a whole, addressing both physical health and mental health concerns [30]. Significant disparities in physical health outcomes of patients with severe mental disorders with severe mental disorders remain a significant challenge. As studies continue to show significantly higher rates of medical comorbidity and lower life expectancies for patients with severe mental illness compared to the general population, there have been calls for psychiatrists to extend their role to managing general medical conditions of their patients, especially for patients with poor access to medical care [31]. By offering routine monitoring, screening, counseling, and first-line treatment for chronic medical conditions, especially hypertension, obesity, dyslipidemia, and diabetes, psychiatrists could improve the general health and quality of life of patients with mental disorders.

Recommendations for improving general medicine training in psychiatry include providing experiences in "reverse integrated care," a term referring to the delivery of primary care in a psychiatric clinical setting, or introducing an Integrated Medicine and Psychiatry (IMAP) curriculum that offers didactic and clinical practice in primary care throughout residency, focused on health

promotion, disease prevention, health screening, and basic management of common medical disorders in patients with severe mental disorders [32, 33].

9.1.1.4 Leveraging New Technologies

In addition to new integrated care models, advances in technology are expanding access to care through an explosion in telepsychiatry and online applications. Telepsychiatry, otherwise referred to as telemental health or telebehavioral health, is the delivery of mental health care at a distance, providing both psychiatric assessment and treatment to patients remotely. The earliest known use of telemedicine for psychiatry was in 1959 at the University of Nebraska Medical Center, where a two-way closed-circuit television system was used for medical student training throughout the university campus and for linking the medical center with distant hospitals in rural areas. Videoconferencing was later used by the university for delivery of group and individual therapy in the early 1960s [34].

More recently, telepsychiatry has moved from the early model of providing care from clinic-to-clinic to delivering psychiatric services directly to patients' homes [35]. Telepsychiatry has the potential to improve access to care for traditionally underserved communities, such as rural populations who suffer a shortage of mental healthcare providers, elderly individuals that face difficulty with mobility and commuting, and prisoners in correctional settings [36]. Several studies have also demonstrated that telepsychiatry is as effective as in-person care in regards to diagnosis, patient satisfaction, and symptom reduction in patients with different mental disorders including depression, substance use, and post-traumatic stress disorder [37].

It is increasingly clear that telepsychiatry should be included in psychiatric education and training, in line with the competency domains of patient care, interpersonal and communication skills, and system-based practice. Recommendations for training in telepsychiatry include integration of videoconferencing and telepsychiatry equipment into clinical practice, ensuring exposure to these technologies in a variety of clinical settings (inpatient, outpatient, and emergency rooms) and across subspecialties (such as consultation-liaison, forensics, and public psychiatry) [38].

Beyond telepsychiatry, technological advances in recent years have broadened mental health care from one-on-one videoconferencing interactions to smartphone apps used for myriad purposes, with over 10,000 apps currently related to mental health, out of 300,000 generally health-related apps available [39]. These apps can be (1) solely patient-facing—offering guided meditation, relaxation exercises, or coping strategies; (2) provider-facing—collecting the electronic medical record, standardized assessment scales, and psychopharmacologic references more readily accessible; or (3) interfacing between patient and provider—facilitating secure messaging, follow-up on progress of homework-based therapies such as cognitive behavioral therapy, tracking of medication adherence, or monitoring of symptoms such as mood, sleep, and appetite [40]. Further training is needed to increase psychiatrists' familiarity with potential risks (e.g., informed consent) related to the use of the apps in their treatments. Furthermore, attention should be devoted to the principles of beneficence, therapeutic alliance, confidentiality, safety, and consistency with therapeutic goals [40].

9.1.1.5 Training Additional Mental Health Providers

As part of a multi-pronged approach to address the mental health gap, it will be important to ensure that all physicians have a strong foundation in mental healthcare, as many of them will be on the front lines of treating psychiatric disorders. According to estimates from the World Health Organization, worldwide, less than 4% of training for physicians is dedicated to mental health [41]. A 2018 international survey of medical students found wide variation in training in psychiatry across countries, including some countries with no required training in psychiatry during medical school [42]. Thus, enhancing training in psychiatry at the level of medical school will be essential. All physicians should know how to recognize and treat common mental health conditions. They should also know how to track patient outcomes and when to refer patients to psychiatrists for more complex and/or treatment refractory cases.

In addition to expanding training in mental health for all physicians, it will be critical to expand the entire spectrum of mental health providers available, including nurses, social workers, and clinical psychologists. In recognition of the vast need, the field is also turning towards expanding the mental health team to include non-professional lay health workers such as community healthcare workers and peer support workers (or peers) [43]. Peers have personal experience with mental health problems and provide a unique perspective to the mental health team. In addition to providing informational and emotional support, peers may also serve as role models for patients with severe mental illness, increasing their hope for recovery [44]. There is also increasing evidence that for certain outcomes (such as hospitalizations, engagement in care, and empowerment), peer-based programs may have similar outcomes as non-peer-based programs when delivering evidence-based practices [44]. As these groups become more prevalent, psychiatrists will likely interface with a broad range of mental health providers.

9.1.2 Providing Affordable Care

Ensuring access to care is intimately impacted by the escalating cost of healthcare. For example, in 2017, the USA spent $3.5 trillion on healthcare (or $10,739 per person), the highest of any country. According to a 2019 USA survey, an estimated 65 million adults did not seek medical treatment for a health issue due to concerns about cost [45]. Unfortunately, this high cost is not necessarily linked to high quality. Despite its high cost, the USA is near the bottom of major health indices among the 36 nations of the Organization for Economic Cooperation and Development [45].

Many of the strategies focused on increasing *access* to care (described above) are also relevant to providing *affordable* care. For example, stepped care, integrated care, telepsychiatry, and self-care (through online apps) are all approaches that increase access to care while helping to curb overall healthcare costs. Additional strategies for addressing the cost of care include new payment models centered around "value", an increased focus on preventative care and early interventions, as well as resource management. All of these approaches have additional training implications (Table 9.2).

Table 9.2 Approaches for providing *affordable* mental healthcare and associated implications for training in psychiatry

Challenge: providing affordable care	
Solutions[a]	Training implications
Provide value-based care	• Train psychiatrists in "value-based" payment models • Expand training in identifying and tracking quality measures
Expand preventative care and early interventions	• Increase public awareness about mental health and address issues of stigma related to seeking treatment • Train lay public to recognize mental illness and intervene early • Expand training in maternal mental health and child and adolescent psychiatry
Manage resources	• Understand the financing of healthcare at the system level • Understand the cost of care (both diagnostic and treatment choices) associated with physician decisions • Incorporate a cost–benefit analysis into treatment decisions and avoid the use of unnecessary, expensive approaches to diagnosis and treatment • Develop skills in soliciting and discussing patient concerns around cost of treatment and implications for treatment compliance

[a]Note that these solutions are in addition to many of the strategies already outlined in Table 9.1, particularly providing training in new models of healthcare and new technologies as well as training an additional cohort of lay professionals

9.1.2.1 Value-Based Care

In order to address issues of both the high cost of healthcare and low quality, new payment models are emerging. The traditional fee-for-service model prevalent in many countries may promote unnecessary expenditures as payments are linked to the amount of services and tests rendered, regardless of patient outcomes. In response, "value-based" payment models realign payment incentives directly with patient health outcomes (not services)—with the goal to ultimately drive down total healthcare costs while preserving high-quality care. While the term "value-based care" often refers to financial value, it is critical that clinical decisions consider value within an ethical framework of beneficence, nonmaleficence, justice, and respect for autonomy [46].

Providing value-based care will require psychiatrists to identify and track quality measures. In fact, many of the solutions for increasing access to care are relevant to driving down costs. Value-based care requires providers to work collaboratively together to take care of a population of patients across their diverse needs. In many ways, recognizing and treating mental illness will become an increasingly important focus for all physicians as untreated mental illness is associated with poor outcomes across many chronic health conditions. As such, integrated care and the various associated skills (working with an interdisciplinary team, providing measure-based care, and population-based care) will be critical for psychiatrists to not only expand access to care but also help curb overall healthcare costs.

9.1.2.2 Preventative Care and Early Interventions

Since a huge proportion of healthcare dollars are spent on treating chronic medical conditions, driving down the cost of care will also mean providing more preventative care and early interventions. Delivering evidence-based early intervention services for those with first-episode psychosis has had promising outcomes with decreased hospitalization rates and increased rates of employment or school enrollment [47]. Providing preventative care and early interventions will require psychiatrists to address issues of stigma, increase awareness about mental health, and train the lay public to recognize and intervene early in mental illness. One example of an educational effort is Mental Health First Aid, a program intended to equip the general public with the skills to recognize mental illness and provide immediate support and assistance [48].

Since many psychiatric illnesses develop within childhood and early adolescence, providing enhanced training for all providers in child and adolescent psychiatry will be critical. Providing prevention and early intervention in mental health will also require enhanced training in maternal health and a focus on not only early childhood but also the prenatal period [49]. Training in psychiatry should include screening all pregnant women for intimate partner violence, use of alcohol, tobacco, and recreational drugs, as well as exposure to heavy metals and other environmental toxins. Ensuring adequate nutrition is also important. High levels of stress, depression, and anxiety among pregnant women is also likely to impact child development, thus identifying and treating maternal mental illness in the prenatal and postpartum period is likely to have a long-term benefits for both the mother and the child [50].

9.1.2.3 Resource Management

Providing affordable care will also require psychiatrists to become more versed in the cost of healthcare and their own role in resource management. Although an integral component of systems-based practice, psychiatry residents in one study reported relatively little training in resource management [51]. This is not surprising given the lack of standardization or transparency around healthcare costs. However, physicians have been estimated to control as much as 80% of healthcare costs which are closely linked to choices around diagnostic testing and treatment [52].

Psychiatrist training in resource management should include a basic understanding of the financing of healthcare at a macro (or system) level, as well as the costs to the individual consumer or patient. Physicians should understand when expensive treatment options are indicated and when they are not in order to avoid overuse of unnecessary, expensive approaches. Psychiatrists should be able to incorporate a cost-benefit analysis into their treatment decisions. In addition, they should develop skills necessary to speak with patients about the cost of treatment. They should be able to solicit and address patients' concerns about cost since they may be hesitant to bring up concerns about these financial aspects despite its potential impact on treatment compliance [53].

9.1.3 Delivering High-Quality Care

As highlighted above, major challenges in healthcare are not only centered around accessibility and affordability, but also in providing high-quality care.

Table 9.3 Approaches for delivering *high-quality* care mental healthcare and associated implications for training in psychiatry

Challenge: delivering high-quality care	
Solutions	Training implications
Embrace a culture of lifelong learning	• How to review the literature and interpret results of research studies • Quality improvement and adapting to new standards of care • Understanding the application of new research findings in neuroscience to the practice of psychiatry
Provide equitable, culturally-informed care	• Racial disparities, identifying and exploring implicit bias • Working with diverse communities, including refuges • Use of interpreters and family-based approaches • Applying principles of trauma-informed care to evaluation and treatment
Provide patient-centered care	• Shared decision-making, engaging patients as partners • Collaboratively setting treatment goals with patients

For psychiatry, like all specialties, this means making sure that care is both safe and effective. It also means making sure that care is patient-centered and equitable. Keeping pace with advances in the field and adopting new evidence-based practices requires adopting a culture of lifelong learning. These approaches have additional implications for training in psychiatry (Table 9.3).

9.1.3.1 Embracing a Culture of Lifelong Learning

According to the Accreditation Council for Graduate Medical Education (ACGME) which oversees graduate medical training in the USA, all residents "must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and life-long learning" [54]. The European Union of Medical Specialists (UEMS) also emphasizes the need for continuing medical education and professional development starting in medical school and continuing throughout a physician's career [55]. Although trainees are taught how to critically appraise scientific literature, translating research findings into clinical practice remains a challenge. Unfortunately, this challenge is not unique to trainees. Worldwide, across all medical specialties, there is a tremendous gap between well-defined, high-quality patient care, and current clinical practices [56].

Keeping pace with new emerging evidence-based practices will require that psychiatrists have training in how to review the literature, interpret the results of research studies, and adapt their own clinical practices to match new standards of care. Training in quality improvement as a strategy to assess performance, set goals, and measure progress will be a critical skill for all psychiatrists [57].

At the same time, there has been incredible growth in research technology and neuroscience. Historically, the biology of mental illness was (and in many cases still is) described as a "chemical imbalance" based upon a rudimentary understanding of

psychopharmacology at the level of the cellular receptors. Now a modern understanding of neuroscience and psychiatry includes advances in genetics, epigenetics, molecular pathways, and neural circuits. Providing trainees with a strong foundation in neuroscience will become increasingly important for the future practice of psychiatry [58].

9.1.3.2 Providing Equitable, Culturally-Informed Care

In recent years, the ACGME expanded expectations for psychiatry residents to include a variety of professional and clinical competencies, otherwise termed "Milestones". This includes "compassion, integrity, respect for others, [and] sensitivity to diverse patient populations", in which diversity is defined as "unique aspects of each individual patient, including gender, age, socioeconomic status, culture, race, religion, disabilities, and sexual orientation" [59].

Following the deinstitutionalization and the shift to community-based mental health centers started in the 1960s, consideration of cultural differences and its importance in tailoring person-centered care began to take hold in the USA [60]. Despite this shift, a 2001 report noted that minority groups "have less access and availability of care", and "tend to receive poorer quality mental health services…leav[ing] minority communities with a greater disability burden from unmet mental health needs" [61]. According to an analysis of pooled data from the National Institute of Mental Health Collaborative Psychiatric Epidemiology Surveys, "all racial and ethnic minority groups were significantly less likely than non-Latino whites to receive access to any mental health treatment", even when adjusted for socioeconomic factors including income, insurance coverage, and level of education [62].

Education and training in disparities and cultural competence will be crucial in preparing psychiatry trainees to deliver mental health care of the highest quality. As described above, it will also be important to increase minority group representation among mental health providers and leaders, to expand our workforce and better reflect the diverse population of patients we serve.

On a global scale, the United Nations High Commissioner for Refugees estimated a total of 41.3 million internally displaced people, 25.9 million refugees, and 3.5 million asylum seekers in 2019, comprising the "highest levels of displacement on record" [63]. Among these unprecedented numbers of individuals fleeing persecution and war-torn countries, psychiatrists and mental health providers will increasingly encounter patients from diverse backgrounds seeking treatment and evaluation for post-traumatic stress disorder, depression, anxiety, and psychological distress complicated by separation from family members, grieving and loss, socioeconomic difficulties, and post-migration stress [64].

In an increasingly transcultural landscape, psychiatry training must emphasize culturally-sensitive assessment and treatment, critical examination and exploration of one's own preconceived attitudes and implicit bias, and promotion of cross-cultural communication [65]. Working with migrant populations additionally requires practical knowledge and comfort with utilizing interpreters during

interviews, taking family-based approaches during mental health assessments, encouraging patients to provide open-ended personal narratives of their experience, and applying principles of trauma-informed care to evaluation and treatment [66]. Educators may also invest time in discussing the potential ethical implications and process of preparing forensic psychiatric evaluations in asylum proceedings or providing expert consultation to attorneys in refugee determination cases [67].

9.1.3.3 Providing Patient-Centered Care

Providing patient-centered care also means providing "recovery-oriented care". Recovery-oriented care engages patients as partners and collaborators in all aspects of their care. It involves patients in shared decision-making and identifies goals for treatment that are in line with patient priorities. For those with severe mental illness, goals of treatment may extend beyond symptom management and may focus more on quality of life issues such as education, employment, and expanding social networks.

With nearly unlimited access to information, patients are becoming more informed consumers. As such, knowledge is no longer the "exclusive domain of highly trained clinicians" [68]. Directing patients to reliable online resources will be increasingly important. As electronic medical records expand patient access through patient portals, patients can track their own labs and records, and often communicate directly online with their physicians. Learning how to work with patients in these new online venues will be critical.

9.2 Evolving Approaches to Medical Education

In the face of an evolving landscape, medical educators must identify and address new training priorities, often in the context of limited funding, time, and local expertise. In addition to identifying new priorities (or *what* to teach), programs will likely need to consider new models and approaches on *how* to teach. Just as the field of psychiatry is driven by challenges and opportunities, "medical education" is evolving in order to keep pace with the rapid advances in the field.

9.2.1 Principles of Adult Learning

Research into how adults learn has suggested that adult learners are not interested in just memorizing facts but applying new knowledge to practice. Information should be centered around solving problems and offering real-world examples. In the context of psychiatry, this means embedding learning into the clinical context. Adult learners also get more out of an experience if they can work autonomously, building on their prior experience. Learning is driven more by internal goals, making it important for instructors to understand what a learner wants to gain from an experience, and increasing their own motivation to learn [69].

While medical education has traditionally been lecture-based, there is growing evidence that lectures are not the most effective approaches for conveying knowledge and may be particularly poor in helping students to develop new skills. As a result, medical education is evolving to provide more opportunities for active engagement through case-based learning and team-based learning. Models such as flipped classrooms encourage students to learn materials on their own (instead of in a lecture-based format) and come to a classroom ready to apply this new information to practice [70]. Active approaches in the classroom are intended to reinforce learning and often include case discussions and role-play.

9.2.2 Developing a Collaborative Learning Model

One of the major challenges in medical education is ensuring that new knowledge conveyed in the classroom is translated into clinical practice. This often places educators in the position of driving change: not only developing new programs for students but also providing faculty development and continuing medical education opportunities for those supervisors and teachers who might not be as familiar with the latest advances, themselves. In translating knowledge to clinical practice, all psychiatrists will need to know how to apply quality improvement strategies to increase uptake of new evidence-based practices.

For cutting edge advances, the clinician-educators teaching on the front lines may not be the "traditional expert". At the same time, what it means to be an "expert" is evolving in an information age where knowing the information is not as important as knowing how to access the information. In order to keep pace with rapid advances in the field, clinical teaching faculty may be learning alongside with residents. While this challenges traditional educational models, it has the advantage of modeling lifelong learning.

9.2.3 Capitalizing on Shared Resources

Many programs do not have the local expertise, time, or money to develop new educational curricula to meet an ever-expanding list of training priorities. In addition, faculty may not be aware of some of the newer approaches to teaching and assessing learners. To meet this gap, several organizations provide specific resources for faculty involved in medical education. The Association for Medical Education in Europe (AMEE) is a worldwide organization with members from 90 countries around the world and provides a venue for sharing resources and approaches to medical education through their annual meeting and online platform (https://amee4.org). The Association for Academic Psychiatry and the American Association of Directors of Psychiatric Residency Training are similar organizations in the USA that are focused specifically on providing resources and training in medical education in psychiatry.

In addition, shared resources (such as webinars and portable online curricula) are becoming more prevalent. Examples of open access resources for medical

education include FOAM (Free Open Access Meducation), SlideShare, MedEdPORTAL, Kahn Academy, and TED (Technology, Education and Design) Talks. In addition, self-contained online learning programs have quickly become the major modality for continuing medical education, as they offer a way to provide standardized training to a large number of potential learners. Freely available Massive Open Online Courses (or MOOCs) also allow remote students to watch prerecorded lectures, take quizzes, join online chats, collaborate with other participants, and to track their progress [71]. These shared resources may be particularly valuable for those training efforts in low- and middle-income countries [42].

9.2.4 Integrating Training

While new models of patient care, such as integrated care, bring together primary care providers (doctors, nurses), depression care managers (often social workers or clinical psychologists), and psychiatrists, training for each of these providers remains siloed. Given the growing need for providers to work within multidisciplinary teams, it will become increasingly important for programs to develop more integrated training programs. In integrated training models, trainees have an opportunity to better understand other professional roles and develop skills in interprofessional teamwork and collaboration [72].

9.2.5 Assessing Outcomes

As with any learning activity, it is critical to establish specific learning objectives focused on knowledge, skills, and attitudes. The World Psychiatric Association has established a framework of minimum core competencies for all programs [15]. Identifying successful learning requires measuring learner gains across each of these domains. Within medical education, there has been a movement away from more subjective, and often impressionistic evaluations, to basing evaluations on observable skills. Objective Structured Clinical Examinations (OSCEs) are becoming more prevalent along with standardized patients, simulation, and virtual patients.

Using observable standards, trainees are expected to meet certain competency-based milestones and perform certain Entrustable Professional Activities (EPAs) as they progress through their training. These approaches are intended to provide more objective measures of progress throughout training, allowing for a more customized approach to each learner based upon their unique strengths and areas for improvement. In fact, there have been some proposals to set graduation standards on a competency-based model as opposed to a time-based model [23, 73]. These types of models pose many challenges but may help in shortening training for some advanced learners. Although the length of training in psychiatry varies greatly across countries [23], the World Psychiatric Association has recommended a minimum three year curriculum [15].

As value-based payment models progress, psychiatrists are likely to be evaluated directly by their performance across several quality performance indicators and

their compliance with evidence-based standards. As part of a comprehensive 360-degree evaluation, feedback from patients will also become increasingly important information along with input from other members of the treatment team.

9.3 Conclusions

Addressing unmet needs in psychiatry training requires identifying emerging priorities in the field and preparing psychiatrists to address the challenges ahead while capitalizing on new opportunities. Within psychiatry, like other fields of medicine, issues surrounding healthcare accessibility, affordability, and quality have been major drivers of change—each pointing towards critical priorities for training. In order to address these evolving training priorities, it will become essential for training programs to leverage shared resources and identify new strategies to engage adult learners. Advances in neuroscience, technology, and health service delivery models are likely to continue to evolve, making a commitment to quality improvement and lifelong learning particularly critical for the future of psychiatry.

References

1. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, Silove D. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. Int J Epidemiol. 2014;43:476–93.
2. Liu G, Jack H, Piette A, Mangezi W, Machando D, Rwafa C, Goldenberg M, Abas M. Mental health training for health workers in Africa: a systematic review. Lancet Psychiatry. 2016;3:65–76.
3. Skokauskas N, Fung D, Flaherty LT, et al. Shaping the future of child and adolescent psychiatry. Child Adolesc Psychiatry Ment Health. 2019;13:1–7.
4. World Health Organization. Global health and aging. 2011. https://www.who.int/ageing/publications/global_health.pdf. Accessed 9 Jul 2019.
5. Institute of Medicine. Retooling for an aging America: building the health care workforce. Washington: The National Academies Press; 2008.
6. Huecker MR, Azadfard M, Leaming JM. Opioid addiction. In: StatPearls. Treasure Island: StatPearls Publishing; 2019.
7. Brenner AM, Balon R, Coverdale JH, Beresin EV, Guerrero APS, Louie AK, Roberts LW. Psychiatry workforce and psychiatry recruitment: two intertwined challenges. Acad Psychiatry. 2017;41:202–6.
8. Pinto da Costa M, Giurgiuca A, Holmes K, et al. To which countries do European psychiatric trainees want to move to and why? Eur Psychiatry. 2017;45:174–81.
9. Association of American Medical Colleges. Medical school affordability and student aid. AAMC News. 2018. https://news.aamc.org/for-the-media/article/affordability-and-student-aid/.
10. Brin DW. Taking the sting out of medical school debt. AAMC News. 2017. https://news.aamc.org/medical-education/article/taking-sting-out-medical-school-debt/.
11. Golberstein E, Busch S. Mental Health insurance parity and provider wages. J Ment Health Policy Econ. 2017;20:75–82.
12. Pierre JM, Mahr F, Carter A, Madaan V. Underrepresented in medicine recruitment: rationale, challenges, and strategies for increasing diversity in psychiatry residency programs. Acad Psychiatry. 2017;41:226–32.

13. Malone P. Addressing social determinants of mental health: a resident's perspective. New York Country Psychiatric Society Magazine. 2016. https://bluetoad.com/publication/?i=350457&article_id=2618857&view=articleBrowser. Accessed 9 July 2019.
14. Roberts LW, Maldonado Y, Coverdale JH, Balon R, Louie AK, Beresin EV. The critical need to diversify the clinical and academic workforce. Acad Psychiatry. 2014;38:394–7.
15. Belfort E, Lopez-Ibor M-I, Hermans M, Ng R. WPA recommendations: principles and priorities for a framework for training psychiatrists; 2017.
16. Eastwood JB, Conroy RE, Naicker S, West PA, Tutt RC, Plange-Rhule J. Loss of health professionals from sub-Saharan Africa: the pivotal role of the UK. Lancet. 2005;365:1893–900.
17. Dewa CS, Loong D, Bonato S, Thanh NX, Jacobs P. How does burnout affect physician productivity? A systematic literature review. BMC Health Serv Res. 2014;14:325.
18. Dewa CS, Loong D, Bonato S, Trojanowski L. The relationship between physician burnout and quality of healthcare in terms of safety and acceptability: a systematic review. BMJ Open. 2017;7:e015141.
19. Fothergill A, Edwards D, Burnard P. Stress, burnout, coping and stress management in psychiatrists: findings from a systematic review. Int J Soc Psychiatry. 2004;50:54–65.
20. Boscarino JA, Adams RE, Figley CR. Secondary trauma issues for psychiatrists. Psychiatr Times. 2010;27:24–6.
21. Wallace JE, Lemaire JB, Ghali WA. Physician wellness: a missing quality indicator. Lancet. 2009;374:1714–21.
22. Panagioti M, Panagopoulou E, Bower P, Lewith G, Kontopantelis E, Chew-Graham C, Dawson S, van Marwijk H, Geraghty K, Esmail A. Controlled interventions to reduce burnout in physicians. JAMA Intern Med. 2017;177:195.
23. Nawka A, Kuzman MR, Giacco D, Malik A. Challenges of postgraduate psychiatric training in Europe: a trainee perspective. Psychiatr Serv. 2010;61:862–4.
24. Juul D, Colenda CC, Lyness JM, Dunn LB, Hargrave R, Faulkner LR. Subspecialty training and certification in geriatric psychiatry: a 25-year overview. Am J Geriatr Psychiatry. 2017;25:445–53.
25. Yaffe K. Moving beyond dualism to advance geriatric neuropsychiatry. Am J Geriatr Psychiatry. 2016;24:339–41.
26. Raue PJ, McGovern AR, Kiosses DN, Sirey JA. Advances in psychotherapy for depressed older adults. Curr Psychiatry Rep. 2017;19:57.
27. National Institute on Drug Abuse (NIDA). Overdose death rates. 2019. https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed 26 Jun 2019.
28. Archer J, Bower P, Gilbody S, Lovell K, Richards D, Gask L, Dickens C, Coventry P. Collaborative care for depression and anxiety problems. Cochrane Database Syst Rev. 2012;10:CD006525.
29. Nelson EC, Dixon-woods M, Batalden PB, et al. Patient focused registries can improve health, care, and science. BMJ. 2016;354:i3319.
30. van Eck van der Sluijs JF, Castelijns H, Eijsbroek V, Rijnders CAT, van Marwijk HWJ, van der Feltz-Cornelis CM. Illness burden and physical outcomes associated with collaborative care in patients with comorbid depressive disorder in chronic medical conditions: a systematic review and meta-analysis. Gen Hosp Psychiatry. 2018;50:1–14.
31. Vanderlip ER, Raney LE, Druss BG. A framework for extending psychiatrists' roles in treating general health conditions. Am J Psychiatry. 2016;173:658–63.
32. McCarron RM, Bourgeois JA, Chwastiak LA, Folsom D, Hales RE, Han J, Rado J, Rivelli S, Scher L, Yu A. Integrated medicine and psychiatry curriculum for psychiatry residency training: a model designed to meet growing mental health workforce needs. Acad Psychiatry. 2015;39:461–5.
33. Annamalai A, Rohrbaugh RM, Sernyak MJ. General medicine training in psychiatry residency. Acad Psychiatry. 2015;39:437–41.
34. Wittson CL, Benschoter R. Two-way television: helping the medical center reach out. Am J Psychiatry. 1972;129:624–7.

35. Fletcher TL, Hogan JB, Keegan F, Davis ML, Wassef M, Day S, Lindsay JA. Recent advances in delivering mental health treatment via video to home. Curr Psychiatry Rep. 2018;20:56.
36. Chakrabarti S. Usefulness of telepsychiatry: a critical evaluation of videoconferencing-based approaches. World J Psychiatry. 2015;5:286–304.
37. Hilty DM, Ferrer DC, Parish MB, Johnston B, Callahan EJ, Yellowlees PM. The effectiveness of telemental health: a 2013 review. Telemed J E Health. 2013;19:444–54.
38. Saeed SA, Johnson TL, Bagga M, Glass O. Training residents in the use of telepsychiatry: review of the literature and a proposed elective. Psychiatry Q. 2017;88:271–83.
39. Torous J, Roberts LW. Needed innovation in digital health and smartphone applications for mental Health. JAMA Psychiat. 2017;74:437–8.
40. Torous J, Bauer A, Chan S, Boland R, Ramo D. Smart steps for psychiatric education: approaching smartphone apps for learning and care. Acad Psychiatry. 2018;42:791–5.
41. World Health Organization. Mental health atlas 2011. Geneva: World Health Organization; 2011. p. 1–81.
42. Ng RMK, Chan TF, Shields G, Pinto da Costa M. Global mental health and psychiatry education. In: Innovations in global mental health. Cham: Springer; 2019.
43. Pitt V, Lowe D, Hill S, Prictor M, Se H, Ryan R, Berends L. Consumer-providers of care for adult clients of statutory mental health services (Review). Cochrane Database Syst Rev. 2013;(3):CD004807. https://doi.org/10.1002/14651858.CD004807.pub2.
44. Cabassa LJ, Camacho D, Velez-Grau CM, Stefancic A. Peer-based health interventions for people with serious mental illness: a systematic literature review. J Psychiatr Res. 2017;84:80–9.
45. West Health, Gallop. The U. S. Healthcare Cost Crisis. 2019. https://news.gallup.com/poll/248123/westhealth-gallup-us-healthcare-cost-crisis-report.aspx. Accessed 9 July 2019.
46. Moriates C, Arora V, Shah N, editors. Ethics of cost conscious care. Understanding value-based healthcare. New York: McGraw-Hill Education; 2015.
47. Bello I, Lee R, Malinovsky I, et al. HHS public access. Psychiatr Serv. 2018;68:318–20.
48. Wong EC, Collins RL, Cerully JL. Reviewing the evidence base for mental Health first aid. Rand Health Q. 2015;5:19.
49. Mental Health America Prevention and Early Intervention in Mental Health. Prenatal period to early childhood. http://www.mentalhealthamerica.net/issues/prevention-and-early-intervention-mental-health. Accessed 30 Jul 2010.
50. Satyanarayana VA, Lukose A, Srinivasan K. Maternal mental health in pregnancy and child behavior. Indian J Psychiatry. 2011;53:351–61.
51. Arbuckle MR, Weinberg M, Barkil-oteo A, Stern DA. The neglected role of resource manager in residency training. Acad Psychiatry. 2014;38:481–4.
52. Detsky AS, Verma AA. A new model for medical education: celebrating restraint. JAMA. 2012;308:1329–30.
53. Barkil-Oteo A, Stern DA, Arbuckle MR. Addressing the cost of Health care from the front lines of psychiatry. JAMA Psychiat. 2014;71:619–20.
54. ACGME. Accreditation council for graduate medical education common program requirements. 2017, pp. 1–27.
55. European Union of Medical Specialists. Continuing medical education & professional development; 2013. https://www.uems.eu/areas-of-expertise/cme-cpd.
56. Institute of Medicine Committee on Quality of Health Care in America. Crossing the quality chasm: a new health system for the 21st century. 2001. https://doi.org/10.1200/JCO.2003.01.044.
57. Arbuckle MR, Weinberg M, Cabaniss DL, Kistler SC, Isaacs AJ, Sederer LI, Essock SM. Training psychiatry residents in quality improvement: an integrated, year-long curriculum. Acad Psychiatry. 2013;37:42–5.
58. Ross DA, Travis MJ, Arbuckle MR. The future of psychiatry as clinical neuroscience: why not now? JAMA Psychiat. 2015;72:413–4.
59. ACGME and ABPN. The psychiatry milestone project. 2015. https://www.acgme.org/acgmeweb/Portals/0/PDFs/Milestones/PsychiatryMilestones.pdf. Accessed 23 Nov 2016.

60. DelVecchio Good M-J, Hannah SD. “Shattering culture”: perspectives on cultural competence and evidence-based practice in mental health services. Transcult Psychiatry. 2015;52:198–221.
61. Office of the Surgeon General (US), Center for Mental Health Services (US), National Institute of Mental Health (US). Mental Health: culture, race, and ethnicity: a supplement to mental Health: a report of the surgeon general. Rockville: Substance Abuse and Mental Health Services Administration; 2001.
62. Alegría M, Chatterji P, Wells K, Cao Z, Chen C, Takeuchi D, Jackson J, Meng X-L. Disparity in depression treatment among racial and ethnic minority populations in the United States. Psychiatr Serv. 2008;59:1264–72.
63. The UN Refugee Agency. Figures at a Glance. 2019. https://www.unhcr.org/en-us/figures-at-a-glance.html. Accessed 22 Jul 2019.
64. Kronick R. Mental health of refugees and asylum seekers: assessment and intervention. Can J Psychiatry. 2018;63(5):290–96.
65. Corral I, Johnson TL, Shelton PG, Glass O. Psychiatry resident training in cultural competence: an educator’s toolkit. Psychiatric Quarterly. 2017;88(2):295–306.
66. Wylie L, Van Meyel R, Harder H, Sukhera J, Luc C, Ganjavi H, Elfakhani M, Wardrop N. Assessing trauma in a transcultural context: challenges in mental health care with immigrants and refugees. Public Health Rev. 2018;39(1).
67. Prabhu M, Baranoski M. Forensic mental health professionals in the immigration process. Psychiatr Clin North Am. 2012;35(4):929–46.
68. DeBronkart D. The patient’s voice in the emerging era of participatory medicine. Innov Clin Educ Prog. 2018;53:350–60.
69. Knowles MS, Holton EF, Swanson RA. The adult learner. 8th ed. Abington: Routledge; 2015.
70. Tolks D, Schäfer C, Raupach T, et al. An introduction to the inverted/flipped classroom model in education and advanced training in medicine and in the healthcare professions. GMS J Med Educ. 2016;33:1–23.
71. Harder B. Are MOOCs the future of medical education? BMJ. 2013;346:f2666.
72. Morphet J, Hood K, Cant R, Baulch J, Gilbee A, Sandry K. Teaching teamwork: an evaluation of an interprofessional training ward placement for health care students. Adv Med Educ Pract. 2014;5:197–204.
73. Dias MC, Riese F, Tasman A. Curriculum development for psychiatric training. In: Fiorillo A, Volpe U, Bhugra D, editors. Psychiatry in practice: education, experience, and expertise. Oxford: Oxford University Press; 2016. p. 149–64.

Unmet Needs During Residency Training Programmes in Psychiatry

10

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10.1 Introduction

Training is essential to equip aspiring psychiatric specialists with the skills that they need to provide excellent care [1]. In many countries these skills are primarily acquired during dedicated postgraduate training programmes, which doctors enter following the completion of their undergraduate medical degrees [2]. These

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programmes build on the knowledge and skills that doctors have already begun to accumulate during their undergraduate training [3]. Terms for defining participants of postgraduate training programmes vary around the world, with 'resident' common in North America, while other terms, such as 'trainee', 'house officer' and 'registrar' are favoured elsewhere. For consistency, we will use the term resident throughout this chapter.

In this chapter we consider some of the challenges that residents in psychiatry face in their training programmes and outline the most important unmet needs. This will be achieved by examining the current literature and also through perspectives from different countries around the world. These vignettes aim to highlight the similarities and differences of the training experience in a range of settings. In addition to evidence from the literature, the chapter will also include the narrative experiences and personal reflections of the authors. It will explore the common themes that emerge and advance potential solutions, which may offer a chance to challenge some of these unmet needs. Although wider evidence and perspectives will be considered, we will focus on residents and early career psychiatrists' views on their challenges and how they believe these could be addressed.

10.2 Education for Early Career Psychiatrists Across the World

There is a general consensus that a minimum of three years of postgraduate psychiatric training is required for a psychiatrist to be able to provide competent and effective care to patients with mental disorder [4]. This is in addition to a good quality psychiatric education during medical school, including both theoretical and practical exposure [5]. The World Psychiatric Association (WPA) has recently released a position statement on the basic qualities required in order to become a psychiatrist [6]. Nevertheless, psychiatric training varies significantly across the world and even within countries [7]. A joint survey by the World Health Organization (WHO) and WPA has found that 30% of the national partners of the WHO had no psychiatric training programme, all of which were low- and middle-income countries (LMIC) [2]. A more recent survey conducted by the WPA has found that 10% of the WPA's member societies reported having only one year of psychiatric training and another 30% of societies reported having less than three years of training [8]. A worldwide survey of medical students organised by the International Federation of Medical Students' Associations (IFMSA) found that psychiatry is a mandatory part of the student curriculum in 81 countries, except Ethiopia and Nigeria [5]. The lack of expertise in psychiatric training, the limited resources dedicated to the training of mental health professionals and the lack of mental health policy in these countries have contributed to the shortage, or even absence, of trained mental health professionals [9]. Additionally, the brain drain caused by the emigration of qualified mental health professionals from LMIC to high-income countries (HIC) only serves to exacerbate the problem [10, 11]. In this chapter we will focus on the unmet needs of residents in existing training programmes, however, we recognise that there is a

broader question from a global perspective about overall training capacity and the failure of the system to adequately train enough psychiatrists.

At a time of economic challenge, residents are concerned about wider resourcing issues for mental health, including the funding of training, the number of working hours and the pressure of the whole mental health workforce, creating a dysfunctional environment affecting the quality of training [12]. To address these differences and challenges, some residents decide to migrate to another country in order to access better academic and employment opportunities, especially single women [10, 11, 13–16].

Notwithstanding these challenges, across the world there are several innovative opportunities that residents can benefit from. Many of these initiatives are led by residents themselves. One opportunity is represented by the Exchange Programme promoted by the European Federation of Psychiatric Trainees (EFPT), in which residents can do an exchange in other European country, experiencing a different training programme and mental health care system [17]. Another opportunity is the EFPT Porto Research Award, which recognises the best research conducted by a psychiatric resident, based on a donation of the Local Organizing Committee of the 23th EFPT Porto Forum of 10,000€ to encourage psychiatric residents to conduct research in the upcoming years [18].

Despite the changes that have taken place in psychiatric practice in recent decades, much specialist training and continuous professional development (CPD) in Europe continues to be based on old-fashioned paradigms that do not fully equip the newly qualified specialist for contemporary practice as a competent clinician [19]. Several efforts have been made by national and international bodies to describe the gap between the training and practice of early career psychiatrists. In particular, the Early Career Psychiatrists' Committees of the European Psychiatric Association (EPA) and of the WPA have carried out several surveys in different countries to identify the areas with the most significant educational needs, with recommendations about how to address such gaps. The areas identified include psychopathology, psychotherapy, prevention and early intervention, drug management and the treatment of physical diseases in patients with mental disorders [8, 20, 21].

Early career psychiatrists have reported other difficulties in their training, including the lack of practical knowledge to manage the transition phase from residency to independent practice, managing the risk of burnout, skills for dealing with the media, opportunities to be involved with professional and scientific societies and skills for handling difficult patients and colleagues [20, 22–24].

Recent debates about the future of psychiatry have questioned the role of psychiatrists and the training that should be provided [25]. Undoubtedly the future will witness the increased usage of technology in clinical practice, including new formats of care delivery, not yet envisioned [1, 26]. One suggestion is to have more joint collaborations with other specialties and professionals which can benefit the discipline, its professionals and the care provided to patients [27].

The size of the WPA's Early Career Psychiatrists Section has noticeably increased in recent years, having members in all the continents of the world. It offers several opportunities for early career psychiatrists across the world to meet, supported by

the WPA. There are travel fellowships to attend the WPA Congress, a dedicated conference track for ECPs, and innovative sessions using technology (such as the WPA 3 min Competition and, more recently, the Digital Interactive Theater).

10.3 Europe

This first vignette will explore training across a whole continental region. While there are significant variations between individual countries within the region, there are also several political, professional and scientific organisations concerned with training operating at a European level.

10.3.1 Landscape

There are a number of definitions of what Europe pertains to. Various political and health organisations categorise Europe differently in terms of the areas and nations included. The WHO provides a definition that stretches to the Caucasus, across Siberia and includes Israel [28]. The European Union (EU) is an evolving political and trading bloc, which includes within it and incorporates nearby countries, a range of economic and political entities, such as the Eurozone and the Schengen Area [29].

A number of supranational organisations exist within this complex framework that have particular relevance for training in psychiatry. The EFPT is an umbrella association for national resident associations from more than 30 European countries [30]. The Union Européenne des Médecins Spécialistes (UEMS) Section of Psychiatry aims to 'promote the highest standard of care for people who are affected by mental health problems in Europe through postgraduate training and continuing medical education of psychiatrists' [31]. The European Psychiatric Association (EPA) is the major scientific society for psychiatrists and its 'activities address the interest of psychiatrists in academic research and practice throughout all stages of career development' [32]. These organisations work together to address problems in training programmes by advocating for improvements, including the harmonisation of training throughout Europe [33]. Recently an initiative has been established to examine this issue in more detail, called the Task Force for Education in European Psychiatry [34].

10.3.2 Challenges

The EFPT conducts an annual survey, which collects information about the situation of training in psychiatry in its member countries. This has now been running for a number of years, providing a rich longitudinal picture of training and its evolution across the continent. The results have demonstrated that the basic parameters of training programmes vary considerably between countries and sometimes even

within countries. The length of residency varies from just two years to a maximum of six years for a single specialty, although in countries where dual training is possible, this can be even longer [35]. In the European Union, the length of training varies from four years, up to seven years [36]. This is in line with the minimum duration of training required for professional certification to be recognised within the EU [37]. In several countries training is not standardised nationally, which can make it difficult to get a unified picture of residents' experiences [13]. Other concerns identified by residents include problems in certain countries in gaining access to training programmes and financial problems resulting from salary limitations.

The EPA issued a guidance paper in 2014 on postgraduate psychiatric training in Europe, reviewing the available literature. The limited information published at that time reflected a broad variation in training programme structures, quality assurance mechanisms and levels of satisfaction with the experience of training. It goes on to review the curricula in six northern and western European countries, comparing the length of training, compulsory elements of training and assessment structure. The authors recommend that information about curricula in European countries should be more freely available to aid comparison between them. The authors advocate that training should be harmonised across Europe and suggest that a European level examination in psychiatry might help to drive improvement [38].

The UEMS Section of Psychiatry has produced guidelines on training requirements for the speciality of psychiatry, based on the charter on training of medical specialists in the EU [39]. These set out minimum expectations for training, for example, that residents should receive at least one hour of personal supervision each week. They recommend that training should be a minimum of five years full time equivalent and should be possible to complete by working less than full time.

In collaboration with EFPT, the UEMS Section of Psychiatry developed a practical tool to establish the level of compliance with these standards on the ground, called Test Your Own Training (TYOT). This is a freely available web platform that residents can complete on the EFPT or UEMS Section of Psychiatry website [40]. Participants complete 27 questions related to different aspects of the guidelines. The programme generates a total final score and the participants receive instant feedback on whether their answers meet the guidelines.

An analysis of the preliminary data showed that compliance with the guidelines is poor. The mean overall score was just 42% for 77 respondents from 27 countries. Just less than half of residents received a copy of the relevant national guidelines at the start of training, while another large proportion reported knowing that such guidelines existed. This reduced significantly for the European guidelines, with the majority having no idea of the existence of such a document. Almost half of respondents stated that they did not have the option to complete training less than full time. Over half reported problems accessing psychotherapy training during working hours as part of the curriculum. One in four described paying for mandatory parts of training themselves. The particularly problematic issues identified by the respondents were that training needs were subordinated to service demands (71%), feeling unsafe in the working environment (30%), staying in unacceptable hospital accommodation (21%) and feeling punished for seeking help when unwell (16%) [41].

Research conducted with residents has showed that the main concerns in Europe are related to the discrepancies between the stated national programme and the lived experience of residents, especially around delivery of specific training opportunities, access to psychotherapy training and research experience [42, 43]. Levels of recruitment into psychiatry, inadequate working conditions, access to information, access to research opportunities and training are amongst the key areas where residents identify that their needs remain unmet [1, 44–46].

10.3.3 Potential Solutions

EFPT and the UEMS Section of Psychiatry both advocate that any effective improvement in the residency programmes in Europe should involve the residents themselves. EFPT publishes a series of statements, which are reviewed and updated annually. These statements provide a consensus view about issues that are important to residents. Many pertain to the quality of training itself and the experience of residents [47].

One solution that has been repeatedly advanced is harmonisation of training across Europe, to ensure that all training programmes meet similar minimum standards [33]. An examination has been postulated as one way that this could be implemented. This has been effectively utilised in over 30 other specialties and is being considered by the UEMS Section of Psychiatry [48]. An exam may help to push up standards and promote free movement of psychiatrists, although if implemented badly, it may risk creating an additional burden for residents [49].

From the residents' perspective, harmonisation of curricula is perhaps less important than ensuring more consistent and effective quality assurance of training [50]. The results from TYOT suggest that there is often a significant gap between theory and reality. Aspirational guidelines are therefore not enough and robust inspection of compliance with regulations, with requirements for rapid rectification of any deficits, are essential. One component of this is ensuring a high quality of supervision [51, 52]. As well as ensuring that supervision takes place as expected, it is also important that supervisors are adequately trained and supported in their roles [53, 54].

Working conditions, including salaries and working hours, are one obvious target for improvement [55]. These aspects can remain closely linked with the overall economic prosperity and labour regulations of the respective country; however, improvements can frequently be achieved with small changes developed in collaboration with residents [44]. Aspects that are particularly amenable to improvement are around the health and safety of residents [56]. Flexible training for residents with family or other caring responsibilities would also support a better quality of life [57].

Equitable access to training opportunities is another important target for improvement. EFPT recommends that residents should have access to a full range of clinical placements, including in community settings and in a variety of psychiatric specialties, such as child and adolescent psychiatry and old age psychiatry. The UEMS Section of Psychiatry guidelines recommend a minimum of 120 hours

of theoretical teaching in psychotherapy and 100 hours of supervision [39]. There should also be adequate opportunities to gain training and experience in research, with EFPT stating that all residents should have a 'basic knowledge of research methodologies' [47].

10.4 United Kingdom

This second vignette considers the situation within one constituent country within the European region, looking at how the issues discussed above play out in a national context. It also considers specific issues affecting training and practice for residents in the country itself.

10.4.1 Landscape

There are 33 medical schools, with licences to award UK medical degrees from the General Medical Council (GMC) in the UK [58]. Recent studies have highlighted that 80% of UK medical students come from only 20% of UK schools and that these were more likely to be from selected schools [59]. There have therefore been widening participation schemes set up within the UK to encourage more students from disadvantaged backgrounds to enter medical school.

The basic process for becoming a consultant psychiatrist in the UK is detailed in the below Fig. 10.1:

10.4.2 Challenges

Psychiatry has struggled for a long time to recruit enough residents [60]. This has led some to characterise psychiatry as a 'recruiting, not a selecting, specialty' [61]. Medical students cite concerns around prognosis of patients, worries about a lack of scientific basis and a lack of evidence around diagnosis [62].

Paralleled with recruitment struggles are retention difficulties [63]. Doctors have also cited the poor public image of psychiatry, a lack of respect from other specialities, a lack of resources and work-related stress.

Some doctors feel that training is threatened by credentialing, a process whereby additional training in discrete areas of practice can be obtained outside of standard training programmes. The British Medical Association (BMA) sees this process as a risk to high-quality structured speciality training [64], whereas the GMC sees this as complementary to existing training curricula [65].

Furthermore, some doctors see the recruitment of physician associates as another threat to training and doctor numbers; with the BMA raising concerns about who will supervise these new healthcare professionals and the clinical governance of their practice [66].

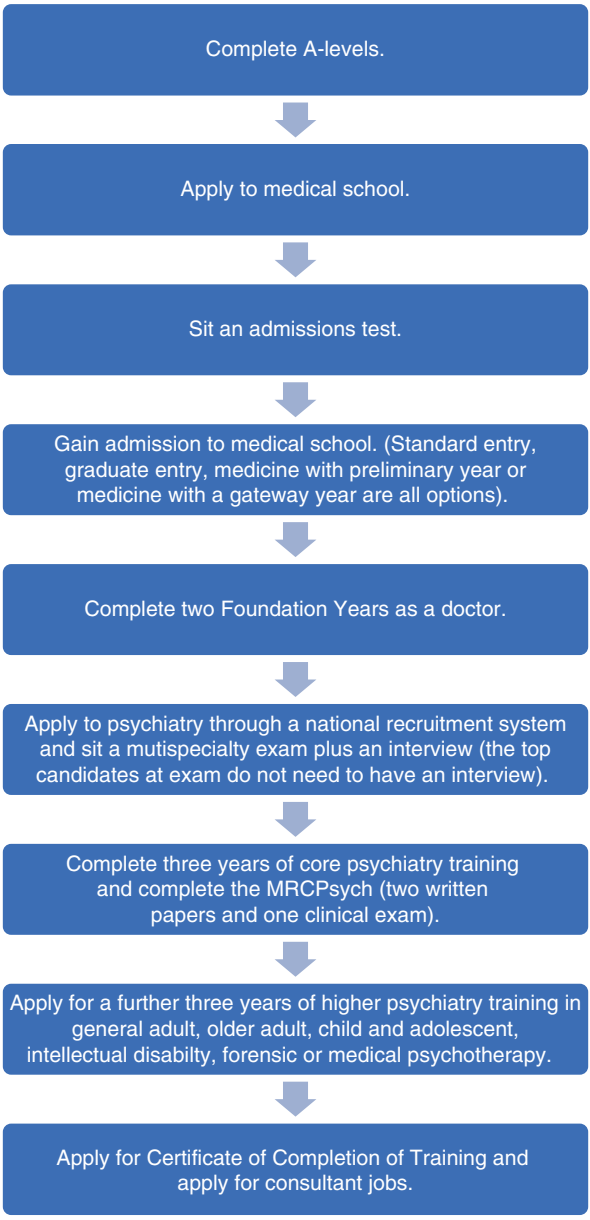

Fig. 10.1 UK journey to become a psychiatrist

Finally, although a problem for all junior doctors, tuition fees for UK Universities rose to £9000 a year in 2012. This means that UK medical students can expect on average to have debts from fees and accommodation on graduation of £64,000, according to the government's own figures [67], which would take them years to pay from their junior doctors' salary.

10.4.3 Possible Solutions

The Royal College of Psychiatrists launched its 'Choose Psychiatry' campaign in 2017 which aims to increase recruitment into psychiatry by targeting medical students. This varied programme has connected to medical student psychiatry groups across the UK, attended careers fairs and launched publicity campaigns, including short films illustrating the role of the psychiatrist. In 2018 recruitment to core psychiatry training was up by a third [68].

In 2017, psychiatry residents themselves strove to improve the quality of training with the report 'Supported and Valued?' which brought together data collected from 11 regional focus groups of residents, and was followed by a national survey [69]. This document provided core recommendations, such as regular supervision and protected teaching time, as well as desired recommendations such as greater career autonomy and enhanced junior doctor forums. This document was published and has been promoted widely.

Run-through child and adolescent psychiatry training, which is a 6-year programme, was first piloted for posts beginning in 2018 and continues in 2019 [70]. Competition for the first year was fierce, with 94 applicants for 11 posts. This follows the recommendations for run through training made by the Centre for Workforce Intelligence, which was commissioned by the UK Government in 2014 to analyse how to meet the demand for psychiatrists in the UK [71].

Furthermore, since 2018, applicants to Core Training can bypass the interview process if they achieve a certain score in the Specialty Recruitment Assessment, which involves questions on professional dilemmas and clinical problems [70].

In more general measures, the government announced in 2018 that there would be 1500 additional medical student places at five new medical schools, as well as adding to numbers at existing establishments [72]. These new student places will prioritise recruitment into areas where there are doctor shortages or in certain specialities. Increasing numbers of medical students may well benefit psychiatry in the long run.

The GMC is endeavouring to make the UK doctor workforce more flexible and, as part of this, enable more doctors to switch between specialities [73]. To achieve this the GMC introduced the Generic Professional Capabilities framework which delineates the skills of the doctor through nine domains, seven of which would apply to any doctor, with specialist skills in the remaining two areas [74]. Doctors in other specialities may more easily retrain as psychiatrists in the future.

10.5 Training in Brazil

The third vignette focuses on training within the largest country in South America, the Federal Republic of Brazil.

10.5.1 Landscape

In Brazil there is a lack of electronic information about psychiatric training programmes. In fact, most services do not have a website providing information about the curriculum [75].

In Brazil, the residency programme in psychiatry lasts for three years [76]. In the first year the resident is placed in a psychiatric hospital, where they will care for the most seriously unwell patients in inpatient wards. Some services are provided in psychiatric beds located within general hospitals and others are in stand-alone psychiatric hospitals. Residents complete theoretical classes and present clinical cases, alongside their practical duties. The medical residency programme is considered the best form of training and expertise in the country. The Council of Medical Residency of the Brazilian Psychiatric Association (ABP) recommends a training distribution of 10–20% for theoretical assignment and 80–90% for supervised clinical practice [77].

Adult psychiatry residents treat a range of patients and conditions during the first year, including both female and male patients, adults, children and adolescents, as well as patients with substance use disorders. Also in the first year, residents do internships in neurology and emergency psychiatry. In the second and third year, residents will have supervised exposure to patients in an outpatient setting. Here, a wide range of patients will be seen, including those with diagnoses of mood disorders, schizophrenia, eating disorders and substance use disorders. Additionally, residents will provide liaison services for other specialties in the general hospital. In the third year residents also offer individual psychotherapy and group therapy and work on psychogeriatric and forensic units [78].

An optional fourth year allows residents to further specialise in areas such as child and adolescent psychiatry, forensic psychiatry, psychogeriatrics, addictions, sleep medicine or psychotherapy.

10.5.2 Challenges

In Brazil, not all residency programmes provide comprehensive training in psychotherapy. In the southern part of Brazil, the focus of most psychiatric services is on psychodynamic psychotherapy, due to the influence of psychoanalysis from neighbouring Argentina. Many residency programmes lack a more comprehensive overview of psychotherapeutic modalities, resulting in many residents taking additional courses in order to improve their psychotherapeutic skills.

The use of simulation as a method to learn about managing complex cases is often neglected during residency training. Role-plays can help to internalise learning of both clinical and psychotherapeutic management [79].

Possibly the greatest challenge in Brazil is the disparity between what is learnt from the academic literature and the precarious nature of the Brazilian mental health infrastructure [80]. For example, it may be that the best medication for a particular patient is too expensive, so the professional is obliged to adapt the management plan accordingly.

10.5.3 Possible Solutions

One solution is to identify how gaps in training might be filled through other institutions. For example, attending scientific activities such as lectures, conferences and participating in an association in the local region are ways to improve academic knowledge. An example of an association in Brazil is the Núcleo de Psiquiatras em Formação da Associação de Psiquiatria do Rio Grande do Sul, located in the southernmost state of Brazil [23]. Created in 1988, it is an association that facilitates collaboration between residents from different services; it develops scientific activities as a way to complement and fill the gaps in residents' places of education. One of the activities involves the presentation of clinical cases by one medical resident and comments from psychiatrists from other services, as a way of gaining an understanding of different approaches. Another activity is the discussion of a film. Such 'cinemeducation' helps the learning process by increasing empathy in the doctor-patient relationship [81].

It is important for those completing the programme to leave psychiatric residency with competency not only in cognitive-behavioral therapy (CBT) and psychodynamic psychotherapy, but also of specialist therapies, such as dialectic behavioural therapy, interpersonal therapy, systemic and family therapy. Therefore, efforts should be made to provide access to such training opportunities. The search for other possible solutions to make up for the deficits in formal education are essential to keep residents updated so that they can help their patients more effectively.

10.6 Africa

The fourth and fifth vignettes are from opposite ends of the African continent, comparing and contrasting the experiences of training in South Africa in the south and Egypt in the north.

10.7 South Africa

10.7.1 Landscape

South Africa has the highest number of psychiatrists in the Southern Africa region, with over 700 psychiatrists registered with the Health Professionals Council of South Africa (HPCSA) in 2012 [82]. South Africa also has one of the highest number of psychiatrist graduates per year in the region, with 27 psychiatrists graduating per year for the decade up to 2015 [83]. This makes the country's training programmes important not only for psychiatric care in the country, but also in the region as a whole.

South Africa currently has eight medical schools that offer specialist training in psychiatry [84]. Psychiatric residents register with one of these medical schools but are employed and work at Department of Health (DOH) hospitals during their

training. At these hospitals, they will be supervised by specialists, also employed by the DOH, with respect to academic, clinical and research needs. These specialist psychiatrists, together with residents, are joint appointees between a university and a hospital where they are employed. This means that although they are employed by a government hospital, they also provide academic input to a university. This academic input includes attending to all the academic needs of the residents, including research supervision, teaching and clinical supervision.

Although universities provide the training of psychiatrists, the College of Psychiatrists examines and provides the required qualification for psychiatrists [84]. The College of Psychiatrists sets the curriculum, decides on training requirements and administers examinations [85]. In order to become registered as a psychiatrist, candidates must pass a College of Psychiatrists' entry examination, complete four years of training as a psychiatric registrar, pass the College of Psychiatrists' final examinations and complete a master's research project. During the four years of training, they must complete the forensic and child psychiatry rotations, in addition to general psychiatry. Psychotherapy training is also mandatory during training.

South Africa's College of Psychiatrists offers four subspecialty qualifications, namely child, forensic, geriatric and neuropsychiatry. Training in a subspecialty requires further two years of training time in a relevant department and successfully completing an exit examination.

10.7.2 Challenges

One of the main challenges that psychiatry residents face in South Africa is the quality of the available resources, both human and non-human. Medical schools are distributed throughout various parts of South Africa. As a result, there is a significant discrepancy in distribution of psychiatrists across the country, with urban areas having a much higher density of psychiatrists than the rural areas [82]. There were seven psychiatrists in rural facilities across South Africa in 2014; this translates to 2% of all psychiatrists in the public sector. Rural provinces, like Eastern Cape and Limpopo (each with one medical school) have very few psychiatrists compared to provinces with big cities like Western Cape and Gauteng. There are certain training hospitals, affiliated to some of the training universities, that may have one or no psychiatrist. Residents then depend on psychiatrists that are based at geographically distant hospitals to assist with tuition and supervision. Most of the time residents continue to work with little or no supervision. The centres with fewer specialist psychiatrists also have limited capacity to supervise residents with research work. They are also poorly resourced with respect to equipment and, sometimes, medication availability. This leads to residents often conducting research with little or no guidance. As a result, the specialist requirements may not be fulfilled within the allocated 4 years of training. Some residents may complete the time allotted for the training programme, but have to leave the training post and try to complete the examinations at a later stage. Many leave to pursue other careers, without ever becoming psychiatrists.

Another challenge that psychiatric residents face is a large and increasing clinical burden. Over and above the academic requirements upon them, residents are expected to offer and prioritise service delivery in the public sector in government hospitals where they are employed and receive their salaries. Psychiatric residents make up more than half of doctors employed by the government in psychiatry, serving the majority of the country's population. Often, they find themselves, doing only clinical work during official working hours, while academic work is done after hours, on weekends and during leave. This results in many residents not meeting the necessary academic requirements, burning out and dropping out of the programme. In other cases, residents complete the programme and become specialists, but feel ill-prepared for the task of being a psychiatrist.

A further challenge that residents face is the discrepancy between training and expected practice as a psychiatrist. Although psychiatric training is geared towards preparation to manage psychiatric disorders adequately, it does not train residents for psychiatric practice overall. Besides managing psychiatric disorders, psychiatric practice requires patients' advocacy, community education and mobilisation, health system management and leadership skills.

Importantly, currently there is very little, if any, training in the use of technology or social media during the psychiatric training programme. Thus, recently-qualified early career psychiatrists are ill-equipped to face the challenges that the digital age brings. As patients become more familiar with social media and technology, the onus falls upon the psychiatric residents to equip themselves for the changing landscape of technology. In fact, the College of Psychiatrists in South Africa does not require any training in electronics or leadership as part of training to become a psychiatrist [85].

Lastly, South Africa is a large and diverse country. Not only is there an uneven spread of resources, there is also an uneven presentation of pathology. People who train in one centre may therefore be more exposed to managing substance use disorders, while others trained in a different location may have far less experience in psychiatric presentations related to substance use.

10.7.3 Possible Solutions

Given the several challenges, some of which were highlighted above, possible solutions are necessarily varied. One major solution is a deliberate, concerted introduction of digitalisation of psychiatric training and practice. The possible benefits for psychiatry are multiple. Academic teaching, research and clinical supervision can all be done through tele-psychiatry. Thus, skills and personnel that are not physically available in the vicinity of training centres can easily reach residents, thus improving the quality of their training, despite resource limitation. In addition, psychiatric residents will become early career psychiatrists that are more familiar with the digital world that they practice psychiatry in.

Another aspect of psychiatric practice that needs attention is the joint appointment between universities and DOH. Residents need uniform, adequate and protected academic time within their regular employment. For residents to achieve the

expected academic outputs, the necessary academic resources need to be provided. Not only will the protection of academic time lead to better academic outputs, but will also help in preventing burnout and reducing drop-out rates [86]. It is important to clarify the relationship between the Departments of Higher Education and Health in overseeing the employment and training of residents who are joint appointees. This should aim to prevent such residents being subject to the changing demands of such an environment and provide greater consistency.

10.8 Egypt

10.8.1 Landscape

Postgraduate training in medicine in Egypt, including psychiatry, takes place under two systems: the academic system, offered by universities, and the Fellowship of the Egyptian Board programme, through the Ministry of Health. The academic system leads to a scientific degree at master's, and subsequently at the higher doctoral level, through both clinical and research training activities. The procedures of the academic system are regulated by the higher education Unified Law No. 49 (1972) and each university has also additional regulations. In general, postgraduate students must attend a certain percentage of the practical activities and lectures, undergoing continuous assessment, usually comprising written, practical and clinical parts leading to summative final exams. Students registered for masters' or doctoral degrees must also write and defend a research thesis. This is obligatory for residents in university hospitals, especially if they expect to continue as academics in their universities. Doctors who do not work in universities also choose to pursue this training pathway due to its high quality and in order to gain a scientific degree. On the other hand, the fellowship system is mainly clinically focused, and assessment is primarily of participants' clinical skills and knowledge [87].

There is no unified training across different universities. Each university has its own programme and regulations. When it comes to psychiatry training, the most prominent difference is that some universities have comprehensive psychiatry and neurology training during residency, integrated within a single department (e.g., Ain Shams University Neurology and Psychiatry Department). This means that residents have to spend half their training in the neurology unit, gaining further knowledge of neurological history and clinical examination, the biological aspects of disorders, managing medical problems and reviewing critical cases. This cross-training is considered an advantage in light of recent calls to acknowledge the overlap between neurology, psychiatry and neuroscience. Advocates have suggested revising the length of neuropsychiatry training for psychiatry residents [88, 89]. In other universities, the psychiatry department is now separate from neurology and acts as an individual silo. Thus, neurology training is less extensive, with more time and focus given to social aspects and psychotherapy. These are adequately covered in the merged system as well, but over a shorter period.

For years, university training was the gold standard and was pursued by doctors from both the Ministry of Health and private practice. However, this system is not suitable for those who do not want to work in research or prepare a thesis as part of their scientific degrees. Those who wish to be recognised as psychiatric specialists, but prefer to undertake training that is more clinically orientated are able to pursue the fellowship pathway. There are two fellowship pathways that can be pursued in Egypt. The first is the fellowship of the Egyptian Board of Psychiatry. The Psychiatry Board requires four years of supervised training that must be conducted in accredited hospitals before sitting the final examination. Psychiatry residents have to spend their training period in general psychiatry, child psychiatry, old age psychiatry and emergency psychiatry. Addictions and other psychiatric specialty placements can also be completed according to the availability of services. Rotations between services are flexible and candidates may start in general adult psychiatry and then rotate to the other specialties, according to service needs and availability [90]. The second is the fellowship of the Arab Board of Psychiatry. Training systems, even the language of training, varies across Middle Eastern and Arabic countries. The Arab Board qualifies psychiatrists to be recognised in several countries in the region. The duration of clinical training is four years. During the first year, the resident must possess enough experience and qualifications to take the first part of the examination. The resident must be given priority to train in general psychiatry (18 months at least) and to develop experience in diagnosing and treating acute and chronic cases. The resident should attend educational meetings and related seminars every week. In the following years, the resident must gain more skills in general psychiatry and other specialist areas of psychiatry (such as child and adolescent psychiatry, old age psychiatry, alcohol and substance abuse, etc.) [91].

It is also noteworthy that some postgraduate students would prefer to pursue an international qualification like the Membership of the Royal College of Psychiatrists (MRCPsych) or the Fellowship of the Royal Australian and New Zealand College of Psychiatrists (FRANZCP) [92, 93]. However, those students mostly plan to work and train abroad or even to migrate permanently.

10.8.2 Challenges

Psychiatric training in Egypt shares many challenges with other countries. The main issue seems to be the lack of unified training amongst universities in the academic pathway. Thus, despite being overall of a similar quality, the training of residents varies across the country. This is more evident when comparing training in psychiatry departments that are incorporated with neurology to the stand-alone ones. While all medical schools adapt the biopsychosocial model, some schools are more biologically oriented and others are more focused on social and psychological aspects.

Another major challenge is that trainers are busy with service provision due to the low number of mental health professionals. They have to cover the gap between service and demand, which leaves little time to provide training. However, this also

has a positive side, as it allows for more 'hands-on' training in real life situations through shadowing senior colleagues.

Residents themselves have a similar situation, often being preoccupied with service provision. Most of the lectures and structured training sessions take place during working hours, while residents are already involved in other activities. With such a workload, burnout is a risk for both trainers and residents, which aggravates the problem.

As a LMIC, the cost of training is another point that many residents worry about. With many residents having to cover the costs of training out of their own pockets, this is not an easy task. One of the major challenges noted in Egypt is stigma. Many residents avoid choosing psychiatry as a career due to the negative attitudes expressed by their families, colleagues and even patients.

Residents have reported feeling unsatisfied with their psychotherapy training and highlight that it needs more standardisation and supervision. This differs between different training centres, but overall psychotherapy training needs to be revised. A similar issue is noted with forensic psychiatry training, which is limited only to certain hospitals.

Finally, research skills training is limited mainly to the academic pathway. Indeed, while research skills and critical appraisals appear in all training curricula, it is only in the academic pathway that residents are required to defend a thesis, where practical research training is mandatory.

10.8.3 Possible Solutions

One possible approach is to revise different curricula and address the real needs of residents, while trying to reach a unified training programme. Flexible training hours and schedules should be considered, while protected hours for scientific activities and research should be implemented and enforced in all workplaces. This also applies for trainers, who should have protected hours devoted to meeting residents, responding to their queries and providing support and advice. On the other hand, resilience training and peer support might help decrease burn out symptoms and help residents stay motivated.

In order to overcome the low number of mental health professionals and increase the number of medical students choosing psychiatry, combating stigma by ongoing campaigns that start amongst undergraduates are needed. Also, campaigns should target the negative attitude amongst other medical specialities and families of doctors [94].

Another solution for the low number of mental health professionals is the training of primary health care physicians to help bridge the service gap and allow more time for better training and service delivery.

Addressing the concerns of residents, those responsible for overseeing training programmes might want to consider standardisation of psychotherapy training across the country, make arrangement to ensure that all residents receive at least a basic training in forensic psychiatry and incorporate research skills in to all training

programmes. This will help them develop critical appraisal skills and the ability to differentiate good research when engaging with continuing professional development.

10.9 Discussion

The five vignettes presented in this chapter aim to give an overview of some of the unmet needs for psychiatric residents in diverse parts of the world. It does not provide a comprehensive insight in to all global regions, but hopefully provides a reasonable barometer of the challenges faced. The literature was highly variable, with some areas rich in published data, while others have very limited record of formal enquiry in this subject.

10.9.1 Common Themes

Across the world psychiatric residents face many similar challenges. Despite the wide variation in the resources available, residents from many different settings identify pressure on the clinical service as an issue. High demand, sometimes coupled with unsupportive administrative structures, create a tension between service provision and training. This can mean that protected time for learning is either non-existent or subordinated to the needs of the service. In some countries this can lead to residents struggling to acquire the necessary competencies in the allocated timeframe. Linked to these pressures, working conditions are often sub-optimal for residents, with low pay, inadequate supervision and poor work/life balance frequent concerns. Consequently, residents are at risk of experiencing burnout before they have even graduated as specialists [95].

Another significant area for concern is the availability and quality of training in particular domains. Commonly cited areas are neurology and psychotherapy, as well as a variety of sub-specialties of psychiatry, such as forensics and addiction medicine. Others pinpoint non-clinical skills, such as research and leadership as being inadequately catered for within certain training programmes [25].

Stigma against the profession remains a serious issue in many countries. This can act as a deterrent to students choosing to pursue psychiatry. Recruitment problems can then exacerbate the workforce crisis, putting even greater pressure on residents to prioritise service provision over training [94].

10.9.2 Contrasts

Despite the many similarities in residents' experiences globally, a number of differences persist. One key issue is the degree of standardisation in training within and between countries. In several countries, residents may have completely different opportunities depending on where they train or which pathway they choose to undertake. While such variability may have advantages for some, by providing

options to tailor training to the individual resident, it risks creating psychiatric specialists with uneven and incomparable qualifications [38].

The vignettes above draw on the experiences of countries and regions with highly variable resources. The experience of training is highly dependent on these resources, which can determine burden of clinical work, availability of formal training and have significant ramifications for the quality of life of residents.

Another discrepancy is the varying attitudes to the role of other professional groups. In some settings other professional groups are perceived to be vital allies, who offer the potential to reduce the clinical burden on residents, freeing them up to focus on their training needs. At the other end of the spectrum, new roles for allied professionals are seen as encroaching on the territory of residents, threatening to reduce the opportunities they have for training. This tension highlights differing perspectives on the fundamental role of the psychiatrist [96].

10.10 Conclusions

Given the many challenges and unmet needs identified by residents, solutions are urgently needed to improve the experience of training. This is particularly important in light of the workforce recruitment problems that pose considerable threats to the quality of patient care [97].

The obvious solution requires the provision of more resources for the training and support of residents. These could be directed to ensuring that residents have protected time to train and to safeguard the working conditions of trainees. Additional support for trainers is also essential, so that they have the necessary time and training themselves to provide adequate supervision [98].

The use of enhanced pedagogical and technological approaches can also support better training in psychiatry. Newer techniques, such as simulation and the use of the humanities in teaching, can be used to give residents a richer and more rounded experience of training. Telepsychiatry can be used to bridge the gap that geography imposes on residents training further away from established academic centres [25].

Greater harmonisation of training across regions offers the opportunity to drive up standards and reduce variability in the training experience. Careful thought must be given to how a comprehensive education can be provided that covers the full range of skills that a fully qualified specialist needs to practice effectively. Robust quality assurance mechanisms need to be in place to ensure that such standards are actually implemented on the ground in a sustainable way [39].

Finally, for solutions to stand a chance of success, they must involve residents themselves. There has been a burgeoning number of organised associations of residents at all levels, from local areas, up to the global scale [23]. Those responsible for designing and delivering training schemes are recommended to work with such organisations, as well as eliciting input from residents locally.

References

1. Pinto da Costa M, Palavra IR, Fung P, Tawfik F, Santos M, Sitanggang S, et al. The future of psychiatry commission. Lancet Psychiatry. 2018;5(1):15–6.
2. World Health Organisation and World Psychiatric Association. Atlas of psychiatric education and training across the world. Geneva: World Health Organisation; 2005.
3. Bhugra D, Ventriglio A, Kuzman MR, Ikkos G, Hermans MH, Falkai P, et al. EPA guidance on the role and responsibilities of psychiatrists. Eur Psychiatry. 2015;30(3):417–22.
4. Edgard B, Lopez-Ibor M, Hermans M, Ng R. WPA recommendations: principles and priorities for a framework for training psychiatrists; 2017.
5. Pinto da Costa M, Dima K, Ng RMK. Undergraduate psychiatric education: a snapshot of medical students across the world. World Psychiatry. 2019;18(2):243–4.
6. Bhugra D, Ventriglio A, Castaldelli-Maia J, Ryland H, Wilkes C, Sonmez E, et al. WPA position statement: good psychiatric practice; 2017.
7. Grover S, Sahoo S, Srinivas B, Tripathi A, Avasthi A. Evaluation of psychiatry training in India: a survey of young psychiatrists under the aegis of research, education, and training foundation of Indian Psychiatric Society. Indian J Psychiatry. 2018;60(4):445–60.
8. Ng R, Hermans M, Belfort E, Bhugra D. A worldwide survey on training provisions for psychiatric trainees in WPA member associations. Int Rev Psychiatry. 2019. https://doi.org/10.1080/09540261.2019.1648241.
9. World Psychiatric Association. Mental health atlas; 2017.
10. Pinto da Costa M, Giurgiuca A, Holmes K, Biskup E, Mogren T, Tomori S, et al. To which countries do European psychiatric trainees want to move to and why? Eur Psychiatry. 2017;45:174–81.
11. Pinto da Costa M, Giugiuca A, Andreou E, Baessler F, Banjac V, Biskup E, et al. Women, partners and mothers – migratory tendencies of psychiatric trainees across Europe. Front Public Health. 2019;7:143.
12. Fiorillo A, Luciano M, Giacco D, Del Vecchio V, Baldass N, De Vriendt N, et al. Training and practice of psychotherapy in Europe: results of a survey. World Psychiatry. 2011;10(3):238.
13. Baessler F, Riese F, Pinto da Costa M, de Picker L, Kazakova O, Kanellopoulos A, et al. Becoming a psychiatrist in Europe: the title is recognized across the European Union, but what are the differences in training, salary and working hours? World Psychiatry. 2015;14(3):372–3.
14. Kilic O, Sonmez E, Erzin G, Guloksuz S, Pinto da Costa M. What is the role of personal characteristics of psychiatric trainees in Turkey on their mobility and migration? Asian J Psychiatr. 2019;42:30–1.
15. Pinto da Costa M. A challenge of the 21st century: brain migration in psychiatry. Int Psychiatry. 2012;9(3):75.
16. Giurgiuca A, Rosca AE, Matei VP, Giurgi-Oncu C, Zgarbura R, Szalontay AS, et al. European Union mobility, income and brain drain. The attitudes towards migration of Romanian psychiatric trainees. Rev Cercet Interv Soc. 2018;63:268–78.
17. Dias M, Orlova M, Pinto da Costa M. Training abroad? Not so difficult. The Lancet Global Health. 2013;1:e136.
18. Pinto da Costa M. Global mental health: what is your role in this movement? Acta medica portuguesa. 2015;28(3):275–6.
19. Oakley C, Malik A. Psychiatric training in Europe. Psychiatrist. 2010;34:447–50.
20. Riese F, Oakley C, Bendix M, Piir P, Fiorillo A. Transition from psychiatric training to independent practice: a survey on the situation of early career psychiatrists in 35 countries. World Psychiatry. 2013;12(1):82–3.
21. Fiorillo A, Malik A, Luciano M, Del Vecchio V, Sampogna G, Del Gaudio L, et al. Challenges for trainees in psychiatry and early career psychiatrists. Int Rev Psychiatry. 2013;25(4):431–7.
22. Jovanovic N, Podlesek A, Volpe U, Barrett E, Ferrari S, Rojnic Kuzman M, et al. Burnout syndrome among psychiatric trainees in 22 countries: risk increased by long working hours, lack of supervision, and psychiatry not being first career choice. Eur Psychiatry. 2016;32:34–41.

23. Fiorillo A, Pinto da Costa M, Nakamae T, Puspanathan P, Riese F, Picon F, et al. Associations of early career psychiatrists worldwide: history, role, and future perspectives. Middle East Curr Psychiatr. 2016;23:3–9.
24. Beezhold J, Bendi N, Pinto da Costa M. Managing difficult people in the workplace. In: Fiorillo A, Volpe U, Bhugra D, editors. Psychiatry in practice. Oxford: Oxford University Press; 2016.
25. Bhugra D, Tasman A, Pathare S, Priebe S, Smith S, Torous J, et al. The WPA-lancet psychiatry commission on the future of psychiatry. Lancet Psychiatry. 2017;4(10):775–818.
26. Leite FO, Cochat C, Salgado H, Pinto da Costa M, Queiros M, Campos O, et al. Using Google Translatê(c) in the hospital: a case report. Technol Health Care. 2016;24(6):965–8.
27. Kristufkova A, Pinto Da Costa M, Mintziori G, Vasquez JL, Aabakke AJM, Fode M. Sexual health during postgraduate training-European survey across medical specialties. Sex Med. 2018;6(3):255–62.
28. World Health Organisation. WHO Europe 2019 [cited 2019 16th April]. http://www.euro.who.int/en/home.
29. European Union. The EU in brief 2019. https://europa.eu/european-union/about-eu/eu-in-brief_en.
30. European Federation of Psychiatric Trainees. The European Federation of Psychiatric Trainees 2019 [cited 2019 29th May]. www.efpt.eu.
31. UEMS Section of Psychiatry. The purpose of the UEMS Section of Psychiatry 2019. http://uemspsychiatry.org.
32. European Psychiatric Association. About the European Psychiatric Association 2019. https://www.europsy.net.
33. Brittlebank A, Hermans M, Bhugra D, Pinto da Costa M, Rojnic-Kuzman M, Fiorillo A, et al. Training in psychiatry throughout Europe. Eur Arch Psychiatry Clin Neurosci. 2016;266(2):155–64.
34. European Psychiatric Association. Task force for education in European psychiatry 2019. https://www.europsy.net/general-task-forces/.
35. Oakley C, White O, Bailey S. Dual training in psychiatry: where now? Psychiatr Bull. 2009;33(6):231–4.
36. De Picker L, Nobels A. [Heterogeneity in psychiatry training in Europe: competition or collaboration?]. Tijdschr Psychiatr. 2019;61(3):175–81.
37. The European Parliament and the Council. DIRECTIVE 2005/36/EC Official Journal of the European Union; 2005.
38. Mayer S, van der Gaag RJ, Dom G, Wassermann D, Gaebel W, Falkai P, et al. European Psychiatric Association (EPA) guidance on post-graduate psychiatric training in Europe. Eur Psychiatry. 2014;29(2):101–6.
39. Union Europeenne des Medecins Specialistes Section of Psychiatry. Training requirements for the specialty of psychiatry 2017.
40. European Federation of Psychiatric Trainees. Test your own training 2019. efpt.eu/tyot/.
41. Szczegielniak A, Ryland H. TYOT: the trip advisor of training 2019. http://uemspsychiatry.org/tyot-the-trip-advisor-for-training/.
42. Gargot T, Donde C, Arnaoutoglou NA, Klotins R, Marinova P, Silva R, et al. How is psychotherapy training perceived by psychiatric trainees? A cross-sectional observational study in Europe. Eur Psychiatry. 2017;45:136–8.
43. Pinto da Costa M, Guerra C, Malta R, Moura M, Carvalho S, Mendonca D. Psychiatry training towards a global future: trainees' perspective in Portugal. Acta Medica Port. 2013;26(4):357–60.
44. Nawka A, Kuzman MR, Giacco D, Malik A. Mental health reforms in Europe: challenges of postgraduate psychiatric training in Europe: a trainee perspective. Psychiatr Serv. 2010;61(9):862–4.
45. Fiorillo A, Del Vecchio V, Luciano M, Sampogna G, Beezhold J. This is why there is hope for psychiatry. World Psychiatry. 2014;13(1):98–9.
46. Gama Marques J, Pantovic Stefanovic M, Mitkovic-Voncina M, Riese F, Guloksuz S, Holmes K, et al. Equal access for all? Access to medical information for European psychiatric trainees. Psychiatry Res. 2016;238:150–2.

47. European Federation of Psychiatric Trainees. Statements 2016 [cited 2019 28th May]. http://efpt.eu/4584-2/about/statements/.
48. Mathysen D, Rouffet J, Tenore A, Papalois V, Sparrow O, Goldik Z. UEMS-CESMA guideline for the organisation of European postgraduate medical assessments; 2015.
49. Union Europeenne des Medecins Specialistes Section of Psychiatry. Newsletter, vol. 1; 2014.
50. Kuzman MR, Giacco D, Simmons M, Wuyts P, Bausch-Becker N, Favre G, et al. Psychiatry training in Europe: views from the trenches. Med Teach. 2012;34(10):e708–17.
51. Simmons M, Barrett E, Wilkinson P, Pacherova L. Trainee experiences of Child and Adolescent Psychiatry (CAP) training in Europe: 2010-2011 survey of the European Federation of Psychiatric Trainees (EFPT) CAP working group. Eur Child Adolesc Psychiatry. 2012;21(8):433–42.
52. Karageorge A, Llewellyn A, Nash L, Maddocks C, Kaldelis D, Sandhu H, et al. Psychiatry training experiences: a narrative synthesis. Australas Psychiatry. 2016;24(3):308–12.
53. Duvivier RJ, van Geel CCJ, Mulders P, Ackermans E. A different look at the quality of psychiatry education: trainee perspective. Tijdschr Psychiatr. 2019;61(3):148–52.
54. Julyan TE. Educational supervision and the impact of workplace-based assessments: a survey of psychiatry trainees and their supervisors. BMC Med Educ. 2009;9:51.
55. Morrow G, Burford B, Carter M, Illing J. Have restricted working hours reduced junior doctors' experience of fatigue? A focus group and telephone interview study. BMJ Open. 2014;4(3):e004222.
56. Peters M, Hasan O, Puddester D, Garelick A, Holliday C, Rapanakis T, et al. Doctors' health: taking the lifecycle approach. BMJ. 2013;347:f7086.
57. Rich A, Viney R, Needleman S, Griffin A, Woolf K. 'You can't be a person and a doctor': the work-life balance of doctors in training-a qualitative study. BMJ Open. 2016;6(12):e013897.
58. General Medical Council. Bodies awarding UK medical degrees 2019. https://www.gmc-uk.org/education/how-we-quality-assure/medical-schools/bodies-awarding-uk-medical-degrees.
59. Medical Schools Council. Selecting for excellence 2014. https://www.medschools.ac.uk/our-work/selection/selecting-for-excellence.
60. Choudry A, Farooq S. Systematic review into factors associated with the recruitment crisis in psychiatry in the UK: students', trainees' and consultants' views. BJPsych Bull. 2017;41(6):345–52.
61. Mukherjee K, Maier M, Wessely S. UK crisis in recruitment into psychiatric training. Psychiatrist. 2013;37(6):210–4.
62. Curtis-Barton MT, Eagles JM. Factors that discourage medical students from pursuing a career in psychiatry. Psychiatrist. 2011;35(11):425–9.
63. Barras C, Harris J. Psychiatry recruited you, but will it retain you? Survey of trainees' opinions. Psychiatrist. 2012;36(2):71–7.
64. British Medical Association. Response to proposals on credentialing 2019. https://www.bma.org.uk/-/media/files/pdfs/collective%20voice/influence/uk%20governments/bma%20response%20to%20gmc%20proposals%20on%20credentialing%20final%20280119.pdf?la=en.
65. General Medical Council. Introducing regulated credentials 2015. https://www.gmc-uk.org/-/media/documents/Introducing_Regulated_Credentials_Consultation_W_form_FINAL_distributed.pdf_61589419.pdf.
66. British Medical Association. Physician associates in the UK 2016. https://www.bma.org.uk/-/media/files/pdfs/collective%20voice/policy%20research/education%20and%20training/physician-associates-in-the-uk-2016-v2.pdf?la=en.
67. Department of Health. Expansion of undergraduate medical education 2017. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/600835/Medical_expansion_rev_A.pdf#page=22.
68. Rimmer A. Number of trainees choosing psychiatry is up by a third. BMJ. 2018;361:k2535.
69. Royal College of Psychiatrists. Supported and valued? A trainee-led review into morale and training within psychiatry 2017 [cited 2019 28th May]. https://www.rcpsych.ac.uk/docs/default-source/training/training/ptc/supported-and-valued_final_20-april.pdf?sfvrsn=fb77df45_0.

70. North West Postgraduate Medical Deanery. CT1 core psychiatry training recruitment guidance documents 2018. https://www.nwpgmd.nhs.uk/ct1_psy_recruit_guidance_docs.
71. Centre for Workforce Intelligence. In-depth review of the psychiatrist workforce 2014 [cited 2019 28th May]. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/507557/CfWI_Psychiatrist_in-depth_review.pdf.
72. Health Education England. New medical schools to open to train doctors of the future 2018. https://www.hee.nhs.uk/news-blogs-events/news/new-medical-schools-open-train-doctors-future.
73. General Medical Council. New standards to boost flexibility of doctors' training 2017 [cited 2019 28th May]. https://www.gmc-uk.org/news/news-archive/new-standards-to-boost-flexibility-of-doctors-training.
74. General Medical Council. Generic professional capabilities framework 2017. https://www.gmc-uk.org/education/standards-guidance-and-curricula/standards-and-outcomes/generic-professional-capabilities-framework.
75. Coêlho BM, Zanetti MV, Lotufo NF. Residência em psiquiatria no Brasil: análise crítica. Rev Psiquiatr Rio Gd Sul. 2005;27:13–22.
76. Ministry of Education and Culture. Content of medical residency programs; 2006.
77. Fernandes RL, Citero VA, Nogueira-Martins LA, Mari JJ. Psychiatry career in Brazil: regional disparities, differences and similarities in an international context. Int Rev Psychiatry. 2013;25(4):486–92.
78. Comissão de Residência Médica em Psiquiatria da Associação Brasileira de Psiquiatria. Programa Mínimo para Residência Médica em Psiquiatria 2019 [cited 2019 12th June]. http://portal.mec.gov.br/index.php?option=com_docman&view=download&alias=6534-psiquiatria-sesu-rm&Itemid=30192.
79. King J, Hill K, Gleason A. All the world's a stage: evaluating psychiatry role-play based learning for medical students. Australas Psychiatry. 2015;23(1):76–9.
80. Zisook S, Balon R, Björkstén KS, Everall I, Dunn L, Ganadjian K, et al. Psychiatry residency training around the world. Acad Psychiatry. 2007;31(4):309–25.
81. Dave S, Tandon K. Cinemeducation in psychiatry. Adv Psychiatr Treat. 2011;17(4):301–8.
82. De Kock JH, Pillay BJ. A situation analysis of psychiatrists in South Africa's rural primary healthcare settings. Afr J Prim Health Care Fam Med. 2017;9(1):e1–6.
83. Colleges of Medicine South Africa. Psychiatrists qualifying per year. Johannesburg; 2015.
84. Szabo CP. Training psychiatrists in South Africa. Afr J Psychiatry. 2013;16(1):3–7.
85. Colleges of Medicine South Africa. Welcome to the Colleges of Medicine of South Africa 2019 [cited 2019 28th May]. https://www.cmsa.co.za.
86. Rotenstein LS, Torre M, Ramos MA, Rosales RC, Guille C, Sen S, et al. Prevalence of burnout among physicians: a systematic review. JAMA. 2018;320(11):1131–50.
87. Abdelaziz A, Kassab SE, Abdelnasser A, Hosny S. Medical education in Egypt: historical background, current status, and challenges. Health Prof Educ. 2018;4(4):236–44.
88. Fitzgerald M. Do psychiatry and neurology need a close partnership or a merger? BJPsych Bull. 2015;39(3):105–7.
89. Shalev D, Jacoby N. Neurology training for psychiatry residents: practices, challenges, and opportunities. Acad Psychiatry. 2019;43(1):89–95.
90. EgyFellow. EgyFellow programme 2019 [cited 2019 28th May]. http://www.egyfellow.mohealth.gov.eg/scientific_source/curr.aspx.
91. Arab Board. Psychiatry specialty 2019. http://arab-board.org/node/43211.
92. Royal College of Psychiatrists. Exams 2019. https://www.rcpsych.ac.uk/training/exams.
93. Royal Australian and New Zealand College of Psychiatrists. Assessments - college-administered 2019. https://www.ranzcp.org/pre-fellowship/assessments-college-administered.
94. Sartorius N, Gaebel W, Cleveland H-R, Stuart H, Akiyama T, Arboleda-Flórez J, et al. WPA guidance on how to combat stigmatization of psychiatry and psychiatrists. World Psychiatry. 2010;9(3):131–44.
95. Kumar S. Burnout in psychiatrists. World Psychiatry. 2007;6(3):186–9.

96. Union Europeenne des Medecins Specialistes Section of Psychiatry. Profile of a psychiatrist 2018. http://uemspsychiatry.org/wp-content/uploads/2012/01/UEMS-PS-PROFILE-OF-A-PSYCHIATRIST-2018.pdf.
97. Brenner AM, Balon R, Coverdale JH, Beresin EV, Guerrero APS, Louie AK, et al. Psychiatry workforce and psychiatry recruitment: two intertwined challenges. Acad Psychiatry. 2017;41(2):202–6.
98. Health Education England. Stepping forward to 2020/21: the mental health workforce plan for England 2017. https://www.hee.nhs.uk/sites/default/files/documents/Stepping%20forward%20to%20202021%20-%20The%20mental%20health%20workforce%20plan%20for%20england.pdf.

Unmet Needs in Youth Mental Health: Transforming Models of Care to Improve Outcomes

11

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11.1 Introduction

Mental health is a key health issue faced by young people globally. Mental disorders are a leading contributor to the total burden of disease for 10–24 year olds [1] and are considered the "chronic diseases of the young" [2] due to their pattern of onset and major impact. The majority (75%) of mental disorders emerge prior to 24 years of age, with the number of new cases peaking in late adolescence and early adulthood [3]. This peak period of onset coincides with a major life event: the transition from adolescence to adulthood. This is a time of significant personal growth and potential that can shape an individual's life trajectory. The ramifications of experiencing a mental disorder during this developmental period can be immense and include poor social functioning, reduced educational and vocational attainment, and financial insecurity [4, 5]. The lost productivity often associated with mental illness, reflecting lower employment, absenteeism, presenteeism, and premature death, places a large burden on the community. In Australia alone, the annual financial cost of mental illness in young people is estimated between $6.29 and $10.6 billion [6, 7].

Despite these devastating impacts, the treatment gap for mental illness is overwhelmingly high [8]. This is most apparent in young people who, despite demonstrating the highest incidence, prevalence, and burden of mental illness, have the poorest access to mental health care [9]. In recognition of this, transformational reform of mental health services to improve the care of young people has occurred, although mostly in developed nations, with positive results [10]. In this chapter, we outline these promising service innovations and highlight how youth models of care can be further strengthened.

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11.2 The Need for Youth Mental Health Service Reform

Young people's poor access to mental health services reflects a number of individual and structural barriers related to the design of mental health services and young people's help-seeking behaviours. Seeking help for a mental disorder can be a challenging and complex process for young people. They are often reluctant to seek help, which can stem from a range of beliefs such as wanting to solve their own problems, perceived stigma of mental illness, negative attitudes towards services, and confidentiality concerns [11]. Initially, young people are likely to seek informal help through family or friends [12]. The first contact with professional help is most likely to occur via primary health care services, namely general practice [13]. However, the culture of these settings and their focus on physical health can make them unsuitable for young people with mental health problems who are often reluctant to disclose emotional problems to general practitioners [11].

The poor resourcing and design of the specialist mental health system also forms a critical barrier to care for young people. Child and adolescent services, with their focus on the needs of young children, are better placed to manage disorders that typically emerge pre-puberty (e.g., ADHD, conduct disorder, and developmental disorders) than adult-type disorders that begin to emerge during adolescence (e.g., mood, psychotic, substance use, and personality disorders). Although many child and adolescent services have extended their eligibility criteria to include adolescents as old as 18 years, they are often ill equipped to manage older adolescents, particularly those with severe presentations. Adult mental health services are similarly unsuitable for this population, as they are not designed to meet the clinical, developmental, and cultural needs of young people with emerging mental illness. With a predominant focus on middle-aged patients with severe and persistent psychotic disorders, adult services fail to cater for the large proportion of young adults with less severe non-psychotic disorders [5]. Young people with emerging or subthreshold mental health symptoms, who equally require expert care, are a further subgroup disadvantaged by the design of adult mental health services. This clinical group typically presents with insufficient symptom specificity and intensity to meet adult-type diagnostic criteria, making them ineligible for adult services and essentially locking them out of community-based care.

The adoption of a paediatric-adult model of care for mental health is a serious design flaw. The arbitrary split at 18 years of age coincides with the age range where the incidence of new cases of mental illness peaks. This creates major service discontinuity for the substantial proportion of young people who require ongoing care and need to transition to adult services. In the UK, less than 5% of young people make an optimal transition to adult mental health services [14], with this percentage reflecting a transition process that is often inadequately planned, communicated, and delivered [14, 15]. This often leads to young people falling through the gaps (even despite being referred to adult services), service disengagement, poor mental health outcomes, and young people feeling anxious and fearful about transitioning to adult services [14–17].

There are also arguments against the paediatric-adult split from a biological and cultural perspective. The divide between child/adolescent and adult mental health services at 18 years of age does not reflect the changing landscape of adolescence. It is now well recognized that the transition to mature adulthood does not cease at 18 years and extends well into the mid to late twenties [18, 19]. This lengthened period of transition, termed emerging adulthood, reflects a range of biological, maturational, and societal trends [18]. This includes accelerated pubertal timing, protracted brain maturation, and delayed independence and initiation of adult roles [20–23]. These have implications not only on how mental health services should be designed and delivered for young people, but also on a heightened risk of mental illness. Although the causes remain unclear, mounting evidence is available to suggest that the mental health of young people has deteriorated over recent generations [24–27]. This underscores the imperative for mental health systems to meet the mental health needs of young people within a twenty-first century clinical infrastructure.

11.3 New Models of Mental Health Care for Young People

The service discontinuity created by the configuration of the traditional mental health system means that provision of care is weakest precisely when it should be the strongest [5]. A new approach to mental health care is needed to enhance young people's access to care and to ensure that the quality and continuity of care effectively meets their clinical, developmental, and cultural needs. They require a discrete treatment model that differs to those suitable for children and older adults, but with seamless linkages across these streams [28]. Youth-specific services are necessary due to the distinct needs of young people and the complex and evolving pattern of morbidity and symptomatic fluidity seen in this population [29]. Young people who are experiencing the early stages of a mental disorder often present with a range of comorbidities, particularly substance abuse and complex personality traits, which underscore the need for an integrated approach to their mental health care. As well as acknowledging this heterogeneous pattern of clinical presentation, services need to be responsive to the cultural and developmental needs that are unique to young people, which are often not catered for in adult services [30]. This includes a young person's individual and group identity as well as their help-seeking needs and behaviours. This means that services need to be youth-friendly in that they are accessible and delivered in community-based, non-judgemental, and non-stigmatizing settings.

The diversity and complexity of need among young people requires a layered approach to care where different service levels area available that have the capacity to manage the high volume of presentations as well as the full spectrum of need. Service levels that can cover the range, complexity, and severity of mental illness seen in young people include e-health, primary, or enhanced primary care services for those with mild-to-moderate mental ill-health, and specialized back-up services for those with complex or severe presentations [29]. These systems should be guided

by key principles of mental health care for young people (Box 11.1). For any system to succeed, both individual and service level barriers to care need to be addressed, including young people being able to recognize the need for help and knowing where to seek care, and services providing care that is accessible, acceptable, affordable, and appropriate to the young person's developmental phase and stage of illness [29].

Box 11.1 Key Principles for Systems of Mental Health Care for Young People. Reproduced from McGorry et al. [29] with Permission

- Youth participation at all levels, to enable the creation of youth-friendly, stigma-free cultures of care that provide what young people and their families really need
- Care that represents the epidemiology of mental ill-health in young people and acknowledges the developmental culture of emerging adults
- A holistic, preventive, and optimistic framework that emphasizes early intervention and offers a comprehensive, evidence-informed, stepped care, which is governed by risk–benefit considerations and shared decision-making, with key targets of social and vocational outcomes
- An integrated practice unit in which providers of care are organized around the needs of the young person and his or her family, and through which a dedicated team of clinical and non-clinical personnel provide the full cycle of care for the young person's disorder; this approach fundamentally changes the way clinicians are organized to deliver care
- Elimination of discontinuities at peak periods of need for care during developmental transitions
- Positive and seamless links between services for young children and adults
- Flexible tenure and re-entry to care as needed during the crucial period of transition from childhood to adulthood

Over the last decade, reform in the delivery of youth mental health services has gained momentum. This was built on the success of the early psychosis movement in the 1990s, which generated evidence for the effectiveness of early intervention [31, 32] and supported service transformation at a global scale [33]. The success of the early psychosis model of reform encouraged a broader application of early diagnosis and specialized treatment that covered the full range of emerging mental disorders in young people, including mood and anxiety disorders, substance use disorders, eating disorders and personality disorders [29, 34]. The transformation of mental health services for young people began in Australia through an innovative and evidence-informed approach ("headspace"), which has subsequently flowed to other nations [28, 35–38]. While models of care across countries may differ in order to adapt to local contexts, a common aim of these global reforms is to develop a youth mental health stream that fully integrates care for young people, in order to provide seamless and appropriate coverage of mental health care from adolescence to mature adulthood (at around 25 years of age), with soft transitions between child and adult mental health care.

11.4 Australia's Response: Headspace

Headspace, the National Youth Mental Health Foundation, was established in 2006 with the mission to promote and support early intervention for young people aged 12–25 years with a range of mental disorders [28]. The headspace model of care is comprised of 16 core components (Fig. 11.1), which currently represent best practice to deliver and reform youth mental health care [39]. Headspace is an enhanced primary care model that provides young people with a range of integrated mental health, drug and alcohol, physical and sexual health, and vocational supports. In addition to these four key streams of care, headspace offers suicide postvention services in high schools and provides local community awareness campaigns that enhance young people's help-seeking behaviour, enable families and local service providers to identify emerging mental health concerns in young people early, and strengthen referral pathways into the service [29]. A key component of the headspace model is to establish youth-friendly, easy to access centres that target young people's core health needs in a multidisciplinary care model with close links to local specialist services and community organizations [39]. This provides a stigma-free, soft entry point to care that is more likely to promote service access and engagement among young people. Youth participation and engagement are central pillars of the model and also contribute to creating a non-stigmatizing environment by ensuring that services are provided within a setting that is accessible, non-judgemental, and youth-friendly.

Headspace provides early intervention within an integrated and preventive framework that offers evidence-informed stepped care guided by risk-benefit considerations and shared decision-making, with social and vocational outcomes as the key targets [29]. Simple and brief psychosocial approaches are typically used as first-line treatments, with pharmaceutical approaches used in young people who do not respond to initial psychosocial interventions or who present with more severe

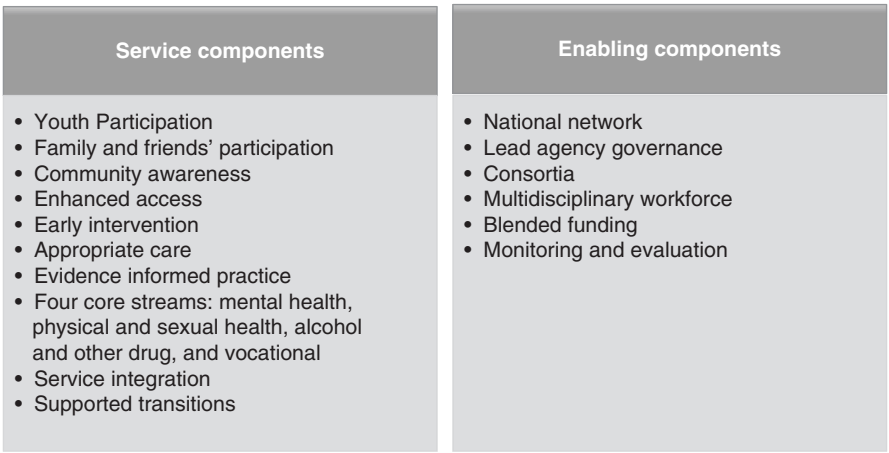

Fig. 11.1 The 16 core components of the headspace model [39]

symptoms or risk [29]. This approach allows care to be matched to a young person's stage of illness, with an emphasis on delivering the right evidence-based interventions at the right time (i.e., early during the course of mental illness) to improve patient outcomes and reduce the risk of illness progression [34]. This aligns with the clinical staging model, which differentiates early and mild clinical features from those that are more severe and established [34]. The clinical staging model is particularly relevant to youth given that the onset of mental illness is most common at this stage of life and the poor specificity of their clinical symptom profiles means that treatment approaches will differ to those for a full-threshold illness. Although traditional diagnostic systems fail to recognize the very early symptoms of mental ill-health seen in young people, headspace data have shown that these early stages of illness are often associated with significant distress and functional impairment, risk of self-harm and suicidal ideation, and substance abuse [40–42]. These alone, as well as their risk of persistence, indicate a genuine need for care with a strong emphasis on interventions that are appropriate and preventive.

The success of headspace has resulted in it being scaled up to 110 national centres, with an additional 30 centres or satellite centres recently committed by the Australian government. The outcomes of headspace have been favourable across a number of areas. Headspace has played an integral role in enhancing access to mental healthcare, particularly for a number of marginalized and at-risk groups, including those who reside in regional areas, Indigenous young people, and those who identify as LGBTI [43]. In the 2018/2019 financial year, a total of 99,892 young people accessed a headspace centre and 32,142 accessed eheadspace, its online and phone service [44]. Outcome studies have shown promising results with 60% of headspace clients experiencing significant symptomatic and/or functional improvement [40]. An independent evaluation of headspace revealed further positive outcomes, including reduced suicidal ideation and self-harm, and fewer days absent from school or employment [43]. In addition, young people and their families are highly satisfied with the services they receive at headspace [43, 45].

11.5 Global Developments in Youth Mental Health

The youth mental health reform achieved in Australia has spread to other parts of the globe, with the UK, Ireland, Canada, USA, Europe and Asia adopting similar, culturally appropriate models [10]. In Ireland, reform has led to the development of Jigsaw (previously Headstrong), which operates in 10 communities and has led to accessible and effective community-based mental health services for young people aged 12–25 years [46]. In the UK, the establishment of Youthspace, a youth-based mental health service in Birmingham, has led to the commissioning of an integrated care pathway for individuals aged 0–25 years [37]. Numerous other global developments have occurred, including the creation of headspace in Denmark, Israel and Iceland, and allcove in California; the establishment of ACCESS Open Minds in Canada, which aims to transform mental health services for young people aged 11–25 years [47]; the scaling up of "The Foundry" model in British Columbia; and

the launch of @ease in the Netherlands. In Europe, the child and adolescent psychiatry field has recognized the need for transformation and created an emerging "Transition Psychiatry" field. The International Association for Youth Mental Health has held five successful conferences. The International Early Psychosis Association has transformed and expanded into IEPA: Early Intervention in Mental Health. The creation of the journal "Early Intervention in Psychiatry" has promoted scientific research, translation of knowledge, and evidence-based reform in early intervention. Together, these transformations have begun to fill the serious gap in providing accessible, stigma-free, multidisciplinary, developmentally appropriate and effective mental health care to young people.

11.6 Where to Next for Youth Mental Health?

While service innovation across the globe has shown promising outcomes for young people [10], youth mental health reform remains an area of ongoing refinement. Further work is needed to fully capitalize on the potential of early intervention for young people with mental ill-health and to reduce the substantial unmet need they continue to experience. Recently, areas for improvement to strengthen the capacity of the headspace model have been highlighted and include stronger national oversight to ensure integrative commissioning as well as stronger financial models and additional funding streams to provide a longer tenure of care, improve model fidelity, and support core streams (e.g., alcohol and other drug and vocational interventions) [48].

A further area of development is strengthening the headspace model to effectively address the full spectrum of complexity and severity of mental illness. Headspace provides mostly short-term services to young people with mild-to-moderate mental health needs, although a substantial subset of clients present with higher levels of need [29]. The 40% of headspace clients who do not show significant symptomatic and/or functional improvements have more complex or severe forms of mental ill-health that cannot be adequately addressed within the current provision of headspace centres. They require more specialized, intensive, and extended tenure of care than can be currently offered at headspace, which may include mobile home-based and outreach care, specific disorder-based expertise, and acute and sub-acute residential care. Accessing acute tertiary services is often not possible for these young people as they are not unwell enough to meet the high threshold for service entry. This represents a critical blind spot in youth mental health care, with young people who are falling through this service gap described as the "missing middle". The repercussions can be immense, as already seen in Australia, where nearly three-quarters of young people with complex disorders who should qualify for entry to community-based mental health services are denied access despite presenting with significant morbidity and functional impairment. Inadequate investment in specialist community mental health care for young people has had flow on effects, with young people and their families seeking care via hospital emergency departments during times of crisis, which has led to increased

mental health-related emergency department visits [49]. Yet management within emergency settings is often counterproductive for young people with mental ill-health where they can face traumatic or harmful care.

A current priority for reform is enhancing service provision for the "missing middle" of young people. This requires substantial and ongoing investment for, and strengthening and integration of, youth mental health systems to adequately treat the full spectrum of presentations [50]. A key outcome is to establish seamless transitions as well as patient management from primary to tertiary care and coordination with social systems through a vertically integrated system. In 2013, the Australian Government began to address this gap through the funding of six "enhanced headspace" services, which are linked with a local cluster of headspace centres and deliver evidence-based early psychosis services. The next direction of the headspace model is to similarly embed services for young people who present with complex and severe presentations across the full diagnostic spectrum of mental disorders.

11.7 Conclusion

The peak onset and large burden of mental disorders on adolescents and young adults clearly indicates the need for early and preventive intervention programs directed towards the life stage of youth. The traditional and current mental health system has meant that young people, who have the greatest need for care, are faced with services that are inaccessible, create treatment discontinuity at critical periods, and are inappropriate for their developmental, cultural, biological, and psychosocial needs. The creation of youth-specific stigma-free early intervention models has reduced barriers to care for young people and improved their outcomes. Built on this success, a new wave of reform is needed to strengthen these services and to ensure that access and quality of care is equitable for all young people across the entire spectrum, complexity and severity of mental illness [48, 51]. While investment in child and adult mental health services remains essential for preventive and seamless care across the lifespan, a discrete stream for young people is crucial to appropriately and effectively meet their needs. Providing evidence-based care within a system that is both accessible and acceptable to young people (such as headspace and similar service models) should continue as good practice in youth mental health care while further evidence is accumulated and models of care are strengthened.

References

1. Mokdad AH, Forouzanfar MH, Daoud F, Mokdad AA, El Bcheraoui C, Moradi-Lakeh M, et al. Global burden of diseases, injuries, and risk factors for young people's health during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2016;387:2383–401.
2. Insel TR, Fenton WS. Psychiatric epidemiology: it's not just about counting anymore. Arch Gen Psychiatry. 2005;62:590–2.

3. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593–602.
4. Gibb SJ, Fergusson DM, Horwood LJ. Burden of psychiatric disorder in young adulthood and life outcomes at age 30. Br J Psychiatry. 2010;197:122–7.
5. McGorry PD. The specialist youth mental health model: strengthening the weakest link in the public mental health system. Med J Aust. 2007;187:S53–6.
6. Hosie A, Vogl G, Carden J, Hoddinott J, Lim S. A way forward: equipping Australia's mental health system for the next generation: EY and ReachOut Australia; 2015.
7. Access Economics. The economic impact of youth mental illness and the cost effectiveness of early intervention. Melbourne: Access Economics Pty Limited; 2009.
8. Patel V, Saxena S, Lund C, Thornicroft G, Baingana F, Bolton P, et al. The Lancet Commission on global mental health and sustainable development. Lancet. 2018;392:1553–98.
9. Burgess PM, Pirkis JE, Slade TN, Johnston AK, Meadows GN, Gunn JM. Service use for mental health problems: findings from the 2007 National Survey of Mental Health and Wellbeing. Aust N Z J Psychiatry. 2009;43:615–23.
10. Hetrick SE, Bailey AP, Smith KE, Malla A, Mathias S, Singh SP, et al. Integrated (one-stop shop) youth health care: best available evidence and future directions. Med J Aust. 2017;207:S5–18.
11. Rickwood DJ, Deane FP, Wilson CJ. When and how do young people seek professional help for mental health problems? Med J Aust. 2007;187:S35–9.
12. Rickwood DJ, Mazzer KR, Telford NR. Social influences on seeking help from mental health services, in-person and online, during adolescence and young adulthood. BMC Psychiatry. 2015;15:40.
13. Lawrence D, Johnson S, Hafekost J, Boterhoven De Haan K, Sawyer M, Ainley J, et al. The mental health of children and adolescents. Report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing. Canberra: Department of Health; 2015.
14. Singh SP, Paul M, Ford T, Kramer T, Weaver T, McLaren S, et al. Process, outcome and experience of transition from child to adult mental healthcare: multiperspective study. Br J Psychiatry. 2010;197:305–12.
15. Perera RH, Rogers SL, Edwards S, Hudman P, Malone C. Determinants of transition from child and adolescent to adult mental health services: a Western Australian pilot study. Aust Psychol. 2017;52:184–90.
16. Dunn V. Young people, mental health practitioners and researchers co-produce a Transition Preparation Programme to improve outcomes and experience for young people leaving Child and Adolescent Mental Health Services (CAMHS). BMC Health Serv Res. 2017; 17:293.
17. Singh SP. Transition of care from child to adult mental health services: the great divide. Curr Opin Psychiatry. 2009;22:386–90.
18. Arnett JJ, Žukauskienė R, Sugimura K. The new life stage of emerging adulthood at ages 18–29 years: implications for mental health. Lancet Psychiatry. 2014;1:569–76.
19. Sawyer SM, Azzopardi PS, Wickremarathne D, Patton GC. The age of adolescence. Lancet Child Adolesc Health. 2018;2:223–8.
20. Lebel C, Beaulieu C. Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci. 2011;31:10937–47.
21. Twenge JM, Park H. The decline in adult activities among U.S. adolescents, 1976-2016. Child Dev. 2019;90:638–54.
22. Australian Institute of Health and Welfare. Australia's welfare 2017. Australia's welfare series no. 13. AUS 214. Canberra: AIHW; 2017.
23. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev. 2003;24:668–93.
24. Weinberger AH, Gbedemah M, Martinez AM, Nash D, Galea S, Goodwin RD. Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. Psychol Med. 2018;48:1308–15.

25. Collishaw S. Annual research review: secular trends in child and adolescent mental health. J Child Psychol Psychiatry. 2015;56:370–93.
26. Sellers R, Warne N, Pickles A, Maughan B, Thapar A, Collishaw S. Cross-cohort change in adolescent outcomes for children with mental health problems. J Child Psychol Psychiatry. 2019;60:813.
27. Twenge JM. Time period and birth cohort differences in depressive symptoms in the U.S., 1982–2013. Soc Indic Res. 2015;121:437–54.
28. McGorry PD, Tanti C, Stokes R, Hickie IB, Carnell K, Littlefield LK, et al. Headspace: Australia's National Youth Mental Health Foundation - where young minds come first. Med J Aust. 2007;187:S68–70.
29. McGorry PD, Goldstone SD, Parker AG, Rickwood DJ, Hickie IB. Cultures for mental health care of young people: an Australian blueprint for reform. Lancet Psychiatry. 2014;1:559–68.
30. McLaren S, Belling R, Paul M, Ford T, Kramer T, Weaver T, et al. 'Talking a different language': an exploration of the influence of organizational cultures and working practices on transition from child to adult mental health services. BMC Health Serv Res. 2013;13:254.
31. Correll CU, Galling B, Pawar A, Krivko A, Bonetto C, Ruggeri M, et al. Comparison of early intervention services vs treatment as usual for early-phase psychosis: a systematic review, meta-analysis, and metaregression. JAMA Psychiatry. 2018;75:555–65.
32. van der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, et al. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. Schizophr Res. 2013;149:56–62.
33. McGorry PD. Early intervention in psychosis: obvious, effective, overdue. J Nerv Ment Dis. 2015;203:310–8.
34. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust N Z J Psychiatry. 2006;40:616–22.
35. Illback RJ, Bates T. Transforming youth mental health services and supports in Ireland. Early Interv Psychiatry. 2011;5:S22–7.
36. Iyer SN, Boksa P, Lal S, Shah J, Marandola G, Jordan G, et al. Transforming youth mental health: a Canadian perspective. Ir J Psychol Med. 2015;32:51–60.
37. Vyas NS, Birchwood M, Singh SP. Youth services: meeting the mental health needs of adolescents. Ir J Psychol Med. 2014;32:13–9.
38. McGorry P, Bates T, Birchwood M. Designing youth mental health services for the 21st century: examples from Australia, Ireland and the UK. Br J Psychiatry. 2013;202:S30–5.
39. Rickwood D, Paraskakis M, Quin D, Hobbs N, Ryall V, Trethowan J, et al. Australia's innovation in youth mental health care: the headspace centre model. Early Interv Psychiatry. 2019;13:159–66.
40. Rickwood DJ, Mazzer KR, Telford NR, Parker AG, Tanti CJ, McGorry PD. Changes in psychological distress and psychosocial functioning in young people visiting headspace centres for mental health problems. Med J Aust. 2015;202:537–42.
41. Scott EM, Hermens DF, Naismith SL, White D, Whitwell B, Guastella AJ, et al. Thoughts of death or suicidal ideation are common in young people aged 12 to 30 years presenting for mental health care. BMC Psychiatry. 2012;12:234.
42. Rickwood DJ, Telford NR, Parker AG, Tanti CJ, McGorry PD. Headspace – Australia's innovation in youth mental health: who are the clients and why are they presenting? Med J Aust. 2014;200:108–11.
43. Hilferty F, Cassells R, Muir K, Duncan A, Christensen D, Mitrou F, et al. Is headspace making a difference to young people's lives? Final report of the independent evaluation of the headspace program. Sydney: Social Policy Research Centre; 2015.
44. Headspace. Annual report 2018–2019. Headspace National Youth Mental Health Foundation; 2019.
45. Rickwood D, Nicholas A, Mazzer K, Telford N, Parker A, Tanti C, et al. Satisfaction with youth mental health services: further scale development and findings from headspace – Australia's National Youth Mental Health Foundation. Early Interv Psychiatry. 2017;11:296–305.

46. O'Keeffe L, O'Reilly A, O'Brien G, Buckley R, Illback R. Description and outcome evaluation of Jigsaw: an emergent Irish mental health early intervention programme for young people. Ir J Psychol Med. 2015;32:71–7.
47. Malla A, Iyer S, Shah J, Joober R, Boksa P, Lal S, et al. Canadian response to need for transformation of youth mental health services: ACCESS Open Minds (Esprits ouverts). Early Interv Psychiatry. 2019;13:697–706.
48. McGorry P, Trethowan J, Rickwood D. Creating headspace for integrated youth mental health care. World Psychiatry. 2019;18:140–1.
49. Hiscock H, Neely RJ, Lei S, Freed G. Paediatric mental and physical health presentations to emergency departments, Victoria, 2008-15. Med J Aust. 2018;208:343–8.
50. McGorry PD, Hamilton MP. Broken promises and missing steps in mental health reform. Med J Aust. 2017;206:487–9.
51. McGorry PD, Ratheesh A, O'Donoghue B. Early intervention - an implementation challenge for 21st century mental health care. JAMA Psychiatry. 2018;75:545–6.

Classification Systems of Mental Disorders: Where Did We Go Wrong?

12

Hans-Jürgen Möller

12.1 Earlier Classification Systems of Mental Disorders: Their Principles, Limitations and Limited Improvements

For a long time, the first steps towards classifying mental disorders were based on clinical observations. At the end of the nineteenth century, Kraepelin attempted to establish a classification of mental disorders on the basis of traditional descriptions and cross-sectional and longitudinal clinical research. Among other disorders, Kraepelin's system included dementia praecox (later named schizophrenia by E. Bleuler) and manic-depressive disorder [1]. After being discussed intensively [2], his approach became accepted almost globally and, together with input from others (like Kurt Schneider's concept of first rank symptoms), formed the principal base for the conceptualisations of psychotic disorders in the early versions of the International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM). Both these disorder-based classification systems later included all the empirical knowledge available from the fields of clinical studies and basic research [3]. In particular, the most recent versions of these two systems consider many findings from cross-sectional and longitudinal clinical studies, epidemiology, neurobiology, neuropharmacology, neurogenetics, molecular biology, brain imaging, etc. [1].

All classification approaches to date are based on psychopathological symptoms. Originally, these symptoms were simple clinical descriptions, but in recent decades they were assessed with the help of special assessment procedures, such as standardised rating scales or structured interviews. A lot of successful work in recent years has improved the psychometric quality of these instruments in terms of their validity and reliability [4].

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Psychopathological symptoms can be clustered by multivariate analyses into syndromes and individuals or samples can then be characterised by using syndrome scores, which can be seen as dimensions of psychopathology. These syndrome scores can be applied, e.g., to characterise the psychopathological symptoms of a person by using the individual scores or of a sample, cross-sectionally or longitudinally, by using mean scores and standard deviations.

The next step is to classify people with a prominent depressive syndrome as having a depressive syndrome, those with a prominent paranoid-hallucinatory syndrome as having a paranoid-hallucinatory syndrome, etc. This classification approach, which not only refers to the score values of the syndrome but defines a certain value as pathological, can be called a syndromal classification. The cut-off scores related to this classificatory syndromal approach [3] can be derived from the normal distribution of the scores in the average population and from the scores in defined clinical samples (norm values and reference values approach, respectively).

It has to be noted that, in general, people seeking help in psychiatry do not only have symptoms of one syndrome but also have symptoms that belong to other syndromes, albeit with mostly lower intensity and thus lower rating scores [5]. This syndromal/dimensional description and classification was popular for a short time in the 1970s and seems to have regained interest in the last 10 years, apparently because of the disappointments concerning the validity and reliability of disorder-related classification (e.g., [6]).

Of interest is that such a syndrome-/dimension-based description/diagnosis seems to have similar predictive power, e.g., in terms of outcome parameters, as a diagnosis in the frame of a disorder-related classification [5, 7]. However, a syndrome-/dimension-related approach seems to have some advantages over a disorder-related classification system [8–10].

A disorder-related classification, also referred to as a categorical classification—as mentioned above, a syndromal/dimensional approach can also be a categorical classification!—has been widely used in recent decades and is the main approach used in the various versions of DSM and ICD, among others. It combines symptom patterns/syndromes with potential causes and course characteristics in constructs of diseases/disorders such as dementia, schizophrenic disorder, bipolar disorder and depressive disorder and the related subtypes of these disorders. Each of these disorders is characterised by one or two prominent syndromes, but other syndromes can also be present, although mostly at a lower intensity [11]. While in the traditional disorder-related classification system and in the early versions of DSM and ICD an individual's diagnosis referred to only one disease or disorder and other potential concurrent diagnoses were not permitted because of hierarchical rules, the modern versions of ICD and DSM allow comorbidity in the sense that a person can have both a major depressive disorder and a general anxiety disorder, for example [12]. These kinds of comorbidities are quite common.

These principles of classifying mental disorders can be found in all kinds of syndromal or classification systems. To increase the reliability of diagnoses, the later versions of DSM and ICD also included a special operationalization. The more or less worldwide acceptance of these classification systems can be seen as an

important step forward in psychiatric diagnostics, especially in terms of reliability and to a lesser degree in terms of validity. However, these systems still have many limitations. Especially with the growing neurobiological knowledge the discordance between diagnostic entities and their neurobiological background has become increasingly problematic. Thus, besides their reliability, the validity of the current systems has been continuously questioned and further developments and improvements were seen to be urgently required. For this reason, a lot of work was put into developing DSM-5 and ICD-11.

This chapter focusses mainly on DSM-5. It does not consider ICD-11 because the final version is not yet available and the principal approach and content is very similar to DSM-5 [13]. The chapter does not describe the content of DSM-5 in detail but focusses on different kinds of problems in its development and structure. In this respect, the chapter follows my previously published arguments [14–16].

12.2 DSM-5: Problems in Its Development and Structure

In DSM-5, the disorder (or disease) categories are not based on neurobiological findings, despite the efforts of the DSM-5 consortium to do so [17]. This corresponds with the general state of research in psychiatry. The original aim to include biological markers was not fulfilled. DSM-5 does consider the traditional evaluation of brain changes in neurocognitive disorders but not modern biomarkers, e.g., for Alzheimer dementia. Research groups had proposed to include biological markers for a variety of diseases on different diagnostic levels, ranging from the "old" dexamethasone suppression test [18] to a new serum marker approach for depression [19]. However, in the view of the DSM-5 consortium these markers and other approaches, e.g., magnetic resonance imaging-based markers in schizophrenia (e.g., [20, 21]), were not sufficiently well developed or replicated. The consortium even chose to omit amyloid-related biomarkers for Alzheimer's disease, although these are considered to be quite advanced [22–24]. The omission of biological markers means that psychiatric diagnosis is still primarily based on the symptoms and course of a disorder.

An additional main aim of DSM-5 was to use a dimensional diagnostic system, i.e., a syndrome-based approach, instead of or in addition to a categorical diagnostic system [25]. This would have made the latest DSM revision even more atheoretical than the previous one, DSM-IV [3]. However, while preparing the revision the DSM-5 working groups decided not to pursue this objective. This was mainly a pragmatic decision but was also related to stakeholders' serious concerns that a dimensional system would be incompatible with treatment guidelines and create problems with existing drug licences [26]. Nevertheless, traces of this dimensional approach can be found in DSM-5. These include transnosological specifiers (e.g., the mixed feature specifier), evaluations of severity (e.g., global evaluations of schizophrenia symptom domains), cross-cutting dimensional evaluations and some aspects of the diagnosis of substance use and dependence. The DSM-5 section on substance use and dependence illustrates the main problem of a symptom-oriented

dimensional approach, i.e., ultimately cut-off scores have to be set to determine whether or not a disorder is present [3], but defining cut-off scores is the first step in a reverse development from a dimensional to a categorical approach.

From the perspective of a psychometric approach, which can be considered to be the highest standard, the "dimensional approaches" of the DSM-5 generally do not appear to be very sophisticated, particularly in view of the available psychometric and statistical options [27–32]. Also surprising is that when reverting from a dimensional to a categorical approach, DSM-5 used arbitrary cut-off scores instead of standard scores from the general population. In a dimensional classification system, the ideal approach is to use a broad spectrum, comprehensive scale that assesses all the relevant symptoms and defines "cases" on the basis of norm or reference values. The decision not to adopt this approach may have been pragmatic, i.e., it would have placed too great a time burden on doctors.

The tension between a categorical approach on the one hand and a dimensional one on the other becomes clear when we consider schizophrenic and affective disorders. Originally, the DSM-5 consortium was keen to use a "psychotic spectrum" to classify schizophrenic and bipolar disorders and to provide an optional dimensional subdivision; however, in the end they did not follow through on this idea because of numerous theoretical [5, 33–35] and pragmatic concerns [25]. Although many people found this idea to be plausible (because it represented a return to the concept of the "Einheitspsychose" [unitary psychosis] [36]), closer consideration reveals several associated problems. For example, why should the system include bipolar disorder but not unipolar depression, in view of the known overlaps between these two disorders [37–40]? And, to continue in the same line of thought, why not also include generalised anxiety disorder [41]? The definition of "psychotic", i.e., the presence of delusional symptoms and hallucinations, is also not as clear as it might first appear to be [36]. Does a diagnosis of a "psychotic disorder" require positive symptoms to be present or is it sufficient that positive symptoms could potentially be present, e.g., in a disorder such as mania or depression? Recently, for example, some authors (e.g., [42]) have classified mania and bipolar depression primarily as psychotic disorders, but not major depression. The reasons for this varying classification are unclear.

Field trials of DSM-5 classifications yielded some low scores for interrater reliability [43]. For example, the kappa coefficient for MDD was only 0.28 [3]. This poor interrater reliability may have been a result of the study methods [44] and the high prevalence of comorbidities among the participants, but further studies are required to determine whether it was also related to the new DSM-5 diagnostic concepts. The counterargument that the interrater reliability of DSM-IV was also low is hardly reassuring, in particular because the two versions were assessed with different methods and the DSM-5 consortium specified improved interrater reliability as a goal of the new system [45]. One would expect an improved approach to diagnosis to have a higher interrater reliability, although a main objective of the DSM-5 consortium was to improve the validity of the system, not just the reliability. The use of a different approach to assess DSM-5 and DSM-IV makes it difficult to directly compare the interrater reliability of the two versions.

In contrast to the poor DSM-5 interrater reliability for MDD, the interrater reliability for schizophrenia and bipolar disorder, for example, were fairly good, as was that for schizoaffective disorder. Therefore, we can conclude that the DSM-5 diagnostic criteria for MDD are not sufficiently clear and show too much overlap with other disorders. When we consider the association or overlap with other disorders [43], referred to in the DSM as comorbidity, it becomes apparent that this feature would be better referred to as partial cosyndromality, e.g., of depressive symptoms with anxiety symptoms (generalised anxiety disorder, PTSD). This cosyndromality can explain the above-mentioned problems related to differential diagnosis [46]. The low MDD interrater reliability scores are similar to the scores for generalised anxiety disorder but higher than those for anxious depressive disorder, a category that was omitted in DSM-5. Jaspers' hierarchical principle may provide an explanation for the low reliability scores, i.e., because symptoms of depression and anxiety are so prevalent in psychiatric disorders, they are not specific for a certain disorder and consequently cannot easily be separated into two distinct disorder groups.

In DSM-5, clinicians can provide supplementary descriptions of patients on the level of syndromes, e.g., they can specify that a patient with a schizophrenic disorder has predominant "negative symptoms". This supplementary information covers both severity assessments (similar to the global assessments of eight schizophrenia symptom domains) and cross-cutting dimensional assessments. It thus represents an important tool for clinicians because it allows them to personalise the diagnosis of individual patients, which can be important, e.g., for drug treatment. Despite their usefulness, most of these supplementary assessments were placed in the final section of the new DSM, Section III ("Emerging Measures and Models"), i.e., their use is not mandated but just suggested for further exploration. This is similar to the situation with the multiaxial diagnoses in DSM-IV, which were not well accepted and have been omitted from DSM-5. Consequently, we have to ask ourselves whether clinicians will perform the voluntary, "emerging" assessments, which are more complicated and comprehensive than standard assessments. The likelihood that the supplementary assessments will not be routinely performed is high because they still need to be developed further and their conceptual penetration is inadequate. Furthermore, they have severe shortcomings as regards psychometrics, i.e., they include more self-rating than observer scales, some of the self-rating scales are very simple and some of the items appear to rather be orienting interview questions and not suitable for psychometric assessments, which should correspond with the usual validity and reliability criteria. Observer-rated instruments are known to differentiate better between disorders than self-rating instruments and the findings of the latter do not necessarily match those of the former [47].

A final question is why Section III includes only some established scales and why work was clearly put into developing new, mostly simple global assessments. For example, only a few available self-rating instruments are included, e.g., the Patient Health Questionnaire (PHQ-9) to assess depression severity, the National Stressful Events Survey PTSD Short Scale (NSESS) to assess PTSD symptoms and the Brief Dissociative Experience Scale (DES-B) to assess dissociative symptom severity. For other disorders, however, such as panic disorder, social anxiety

disorder and generalised anxiety disorder, Section III does not include severity assessment tools. Thus, the list of included assessment instruments seems to be incomplete and not well thought through. Clinician-rated instruments are only provided for a few disorders, e.g., the clinician-rated severity of psychosis and of somatic symptom disorder. It would be interesting to know how the DSM-5 consortium decided which instruments to include and which to omit.

12.3 How Can We Overcome the Mistakes of the Past? New Horizons

As is clear from the above descriptions, DSM-5 is far from what the working groups and psychiatrists in general were expecting. This is mostly not the fault of the working groups, however, but is related to the inherent, not easily solvable problems of classifying mental disorders and our still limited understanding of the complex phenomena of psychiatric disorders. Of great importance in this context is the above-mentioned point that DSM-5 contains few references to neurobiology, despite the availability of so many relevant neurobiological findings, because the relationship between the traditional disorder constructs and neurobiological factors is mostly only weak. For example, genome-wide association studies have produced a wealth of new genetic findings, but each of the genetic alterations they have found explains only a small portion of the symptomatic phenotype or outcome prediction. This is even true when multiple genetic findings are combined into so-called polygenetic risk scores, which only explain a small additional amount of variance [48–52]. Similarly, imaging findings of structural alterations of the brain, for example, were not specific enough to be seen as biomarkers of schizophrenia or psychosis, although interesting associations, e.g., with the at-risk mental state (ARMS) for psychosis and predictive capacity for the transition of the ARMS into psychosis, were described [20, 21, 53]. Consequently, some experts, e.g., in neurogenetics, suggested not to use these classical disorder constructs and to develop something new that primarily considers neurobiological parameters [54], although others have said that we should consider combining neurobiological parameters with psychological dimensions rather than psychopathological symptoms [55]. Some experts are convinced that such a neurobiologically oriented approach should be the primary one and therefore see DSM-5 as an interim solution that will be increasingly replaced by a “brain circuit classification of mental illness” [56] in the framework of the Research Domain Criteria (RDoC) project [55, 57–59].

The RDoC is based mainly on five psychological domains/constructs (negative valence systems, positive valence systems, cognitive systems, systems for social processes and arousal/regulatory systems) that cover only a limited range of psychological dimensions but are assumed to be more closely related than traditional psychopathological dimensions to measurable neurobiological conditions. Each domain/construct is subdivided into several features. For example, the positive valence systems consist of the subdimensions approach motivation, initial responsiveness to reward, sustained responsiveness to reward, reward learning and habit,

illustrating that research in this domain is focussed on the reward system. Research into the reward system has also been performed in relation to symptoms of depression and negative symptoms. Many questions about the RDoC approach still remain unanswered. For example, we need to determine whether the RDoC can explain all aspects of the psychopathological phenomena specified above and how we can best apply the knowledge gained on these basic psychological phenomena to the more complex psychopathological phenomena encountered in routine clinical practice. Another issue of interest is whether the neurobiological background of changes in these domains/constructs is identical across diagnostic entities and their hypothetical causes. Although this new approach looks promising, we need to ensure that it does not just represent a more neurobiologically oriented phenomenology but really represents progress towards providing explanations for clinical phenomena, e.g., that findings of disturbed circuits in the brain really are a pathogenetic explanation for psychiatric disorders and can be used as a basis for treatment interventions (other than brain stimulation). Questions similar to these were recently the subject of a forum discussion in the journal *World Psychiatry* [60]. The RDoC is mainly relevant for research, however, and even its supporters see it as a work in progress that will gradually evolve and gain a clear profile over time and thus cannot yet be applied in routine clinical care.

Unlike the focussed neurobiological approach of the RDoC, the psychopathological symptom approach is considered to be a suitable basis for a symptom-oriented classification system that is based on modern methods of quantitative classification. According to a large number of empirical studies, psychopathology tends to be rather dimensional than categorical and research supports the hypothesis that symptoms are on a continuum rather than being discrete. Studies have also shown how psychopathological dimensions can be arranged hierarchically, ranging from a "broad spectrum level" dimension to specific and narrow clusters of symptoms. In this way, a quantitative approach solves the "problem of comorbidity" by explicitly modelling patterns of co-occurring signs and symptoms within a detailed and variegated hierarchy of dimensional concepts, with direct clinical usefulness. This interesting approach is currently being realised by the "Hierarchical Taxonomy of Psychopathology (HiTOP) Consortium" [61], but it has been widely criticised for various reasons. Besides methodological issues, such as the required quality of the rating scales and the persistency of cross-sectional findings in the long term, criticism was expressed about the translation into clinical settings. The model's lack of course- and cause-related aspects were considered especially problematic [62].

A new, more simplistic approach to define disorders was attempted by a small working group during the development of DSM-5 and ICD-11 [63]. This group tried to explore the feasibility of a meta-structure based on 11 validating criteria comprising both clinical features and risk factors (i.e., shared genetic risks factors, familiarity, shared specific environmental risk factors, shared neural substrates, shared biomarkers, shared temperamental antecedents, shared abnormalities of cognitive or emotional processing, symptom similarity, high rates of comorbidity, course of illness, treatment response). DSM-IV disorders were allocated to one of five clusters as a starting premise. A team of experts then reviewed the literature to

determine within-cluster similarities in the 11 predetermined validating criteria and discovered that those similarities were consistently greater than between-cluster similarities. The five clusters were neurocognitive (identified principally by neural substrate abnormalities), neurodevelopmental (identified principally by early and continuing deficits), psychosis (identified by clinical features and biomarkers for information processing deficits) and emotional/internalising (identified principally by the temperamental antecedent of disinhibition). The group found this meta-structure promising and tried to change the chapter order in DSM-5 to reflect it. This meta-structure appears to be an interesting theoretical framework that might also be helpful for future classification systems.

A more general theoretical framework is offered by the modular approach suggested by Zielasek and Gaebel [64]. This approach is based on the assumption that all mental functions are the outcome of modularly and hierarchically organised subsystems that interact with each other.

As mentioned above, multiaxial diagnoses, including the dimension of comorbid somatic disorders, are unfortunately no longer present in DSM-5, apparently because they were hardly used. Of interest is that when the DSM first included the multiaxial diagnostic approach, it was considered to be a significant advancement that would allow diagnoses to be refined and individualised [3]. As a result, expectations were high that it would yield comprehensive datasets that would enable progress in psychiatric classification and diagnosis on the basis of a multifactorial pathogenetic approach. Although from a pragmatic perspective one can understand the decision to omit the multiaxial diagnoses in DSM-5, it may mean that we no longer have the chance to gather large amounts of data. We can only hope that future revisions of the DSM will reintroduce this approach and thus provide this important opportunity again.

12.4 Conclusion

In retrospect, it is difficult to evaluate which mistakes were made during the development of the newest versions of the DSM classification system and which approach would be the most fruitful in the future. The hope that DSM-5 would represent a radical change that would solve all the problems of psychiatric classification was unrealistic for principal and pragmatic reasons. This difficulty has been understood throughout the long journey to modern classification systems, even by those who were optimistic at first. The hope that we can solve the complicated puzzle by one or the other means seems to be unreasonable. Using neurobiological parameters alone as classifiers does not do justice to the fact that mental disorders also have other facets. Consequently, we still need to use a sophisticated descriptive approach that covers disease symptoms, courses and potential causes and is carefully underpinned by relevant neurobiological findings from the various disciplines. Stratifications based on these findings and supported by information from biomarkers should be able to optimise classifications in terms of diagnosis, prognosis and

prediction of treatment outcome. This conservative strategy seems to be meaningful and superior to more radical solutions. We can hope that ultimately this approach, combined with big data research, might improve the current classification systems.

References

1. Moller HJ. Systematic of psychiatric disorders between categorical and dimensional approaches: Kraepelin's dichotomy and beyond. Eur Arch Psychiatry Clin Neurosci. 2008;258(Suppl 2):48–73.
2. Palm U, Moller HJ. Reception of Kraepelin's ideas 1900-1960. Psychiatry Clin Neurosci. 2011;65:318–25.
3. Moller HJ. Problems associated with the classification and diagnosis of psychiatric disorders. World J Biol Psychiatry. 2005;6:45–56.
4. Moller HJ. Standardised rating scales in psychiatry: methodological basis, their possibilities and limitations and descriptions of important rating scales. World J Biol Psychiatry. 2009;10:6–26.
5. Moller HJ, Jager M, Riedel M, et al. The Munich 15-year follow-up study (MUFUSSAD) on first-hospitalized patients with schizophrenic or affective disorders: assessing courses, types and time stability of diagnostic classification. Eur Psychiatry. 2011;26:231–43.
6. van Os J, Fahy TA, Jones P, et al. Psychopathological syndromes in the functional psychoses: associations with course and outcome. Psychol Med. 1996;26:161–76.
7. Van Os J, Gilvarry C, Bale R, et al. A comparison of the utility of dimensional and categorical representations of psychosis. UK700 Group. Psychol Med. 1999;29:595–606.
8. van Os J. The dynamics of subthreshold psychopathology: implications for diagnosis and treatment. Am J Psychiatry. 2013;170:695–8.
9. van Os J, Kapur S. [Psychosis: from diagnosis to syndrome]. Ned Tijdschr Geneeskd. 2010;154:A1874.
10. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry. 2016;15:118–24.
11. Moller HJ, Falkai P. The psychosis continuum: diagnosis and other phenotypes. Eur Arch Psychiatry Clin Neurosci. 2011;261:1–2.
12. Moller HJ. The relevance of negative symptoms in schizophrenia and how to treat them with psychopharmaceuticals? Psychiatr Danub. 2016;28:435–40.
13. Reed GM, First MB, Kogan CS, et al. Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. World Psychiatry. 2019;18:3–19.
14. Moller HJ. Possibilities and limitations of DSM-5 in improving the classification and diagnosis of mental disorders. Psychiatr Pol. 2018;52:611–28.
15. Moller HJ, Bandelow B, Bauer M, et al. DSM-5 reviewed from different angles: goal attainment, rationality, use of evidence, consequences-part 2: bipolar disorders, schizophrenia spectrum disorders, anxiety disorders, obsessive-compulsive disorders, trauma- and stressor-related disorders, personality disorders, substance-related and addictive disorders, neurocognitive disorders. Eur Arch Psychiatry Clin Neurosci. 2015;265:87–106.
16. Moller HJ, Bandelow B, Bauer M, et al. DSM-5 reviewed from different angles: goal attainment, rationality, use of evidence, consequences—part 1: general aspects and paradigmatic discussion of depressive disorders. Eur Arch Psychiatry Clin Neurosci. 2015;265:5–18.
17. Kupfer DJ, Regier DA. Neuroscience, clinical evidence, and the future of psychiatric classification in DSM-5. Am J Psychiatry. 2011;168:672–4.
18. Carroll BJ. Biomarkers in DSM-5: lost in translation. Aust N Z J Psychiatry. 2013;47:676–8.
19. Papakostas GI, Shelton RC, Kinrys G, et al. Assessment of a multi-assay, serum-based biological diagnostic test for major depressive disorder: a pilot and replication study. Mol Psychiatry. 2013;18:332–9.

20. Koutsouleris N, Borgwardt S, Meisenzahl EM, et al. Disease prediction in the at-risk mental state for psychosis using neuroanatomical biomarkers: results from the FePsy study. Schizophr Bull. 2012;38:1234–46.
21. Koutsouleris N, Davatzikos C, Borgwardt S, et al. Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of psychiatric disorders. Schizophr Bull. 2013;40:1140. https://doi.org/10.1093/schbul/sbt142.
22. Blennow K, Hampel H, Weiner M, et al. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol. 2010;6:131–44.
23. Ewers M, Sperling RA, Klunk WE, et al. Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. Trends Neurosci. 2011;34:430–42.
24. Hampel H, Frank R, Broich K, et al. Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. Nat Rev Drug Discov. 2010;9:560–74.
25. Moller HJ. Development of DSM-V and ICD-11: tendencies and potential of new classifications in psychiatry at the current state of knowledge. Psychiatry Clin Neurosci. 2009;63:595–612.
26. Moller HJ. Is there a need for a new psychiatric classification at the current state of knowledge? World J Biol Psychiatry. 2008;9:82–5.
27. Egli S, Riedel M, Moller HJ, et al. Creating a map of psychiatric patients based on psychopathological symptom profiles. Eur Arch Psychiatry Clin Neurosci. 2009;259:164–71.
28. Lage D, Egli S, Riedel M, et al. Exploring the structure of psychopathological symptoms: a re-analysis of AMDP data by robust nonmetric multidimensional scaling. Eur Arch Psychiatry Clin Neurosci. 2012;262:227–38.
29. Lage D, Egli S, Riedel M, et al. Combining the categorical and the dimensional perspective in a diagnostic map of psychotic disorders. Eur Arch Psychiatry Clin Neurosci. 2011;261:3–10.
30. Steinmeyer EM, Klosterkotter J, Moller HJ, et al. [Personality and personality disorders II. The specificity of the DAPP-model as a diagnostic system for personality disorders]. Fortschr Neurol Psychiatr 2002;70:641–6.
31. Steinmeyer EM, Klosterkotter J, Moller HJ, et al. [Personality and personality disorders I. Universality and sensitivity of dimensional personality models as diagnostic systems for personality disorders]. Fortschr Neurol Psychiatr 2002;70:630–40.
32. van Os J, Delespaul P, Wigman J, et al. Beyond DSM and ICD: introducing "precision diagnosis" for psychiatry using momentary assessment technology. World Psychiatry. 2013;12:113–7.
33. Maier W, Zobel A, Wagner M. Schizophrenia and bipolar disorder: differences and overlaps. Curr Opin Psychiatry. 2006;19:165–70.
34. Moller HJ. The forthcoming revision of the diagnostic and classificatory system: perspectives based on the European psychiatric tradition. Eur Arch Psychiatry Clin Neurosci. 2008;258(Suppl 5):7–17.
35. Moller HJ. The consequences of DSM-5 for psychiatric diagnosis and psychopharmacotherapy. Int J Psychiatry Clin Pract. 2014;18:78–85.
36. Moller HJ. Dichotomy versus spectrum concept in approaching psychotic disorders: are we ready to make the final decision? In: Soldatos C, Ruiz P, Dikeos D, Riba M, editors. Proceedings of the WPA Thematic Conference on Intersectional Collaboration 4th European Congress of INA and the 1st Interdisciplinary Congress of HSAPRS, Athens, Greece, Nov 29 to Dec 2, 2012. Pianoro, Italy: Medimond s.r.l.; 2014. pp. 1–5.
37. Andrews G, Brugha T, Thase ME, et al. Dimensionality and the category of major depressive episode. Int J Methods Psychiatr Res. 2007;16(Suppl 1):S41–51.
38. Carroll BJ. Bringing back melancholia. Bipolar Disord. 2012;14:1–5.
39. Maj M. Mood disorders in ICD-11 and DSM-5. Die Psychiatr. 2013;10:24–9.
40. Maj M, Pirozzi R, Magliano L, et al. Phenomenology and prognostic significance of delusions in major depressive disorder: a 10-year prospective follow-up study. J Clin Psychiatry. 2007;68:1411–7.
41. Starcevic V, Portman ME. The status quo as a good outcome: how the DSM-5 diagnostic criteria for generalized anxiety disorder remained unchanged from the DSM-IV criteria. Aust N Z J Psychiatry. 2013;47:995–7.

42. Tohen M, Strakowski SM, Zarate C Jr, et al. The McLean-Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. Biol Psychiatry. 2000;48:467–76.
43. Regier DA, Narrow WE, Clarke DE, et al. DSM-5 field trials in the United States and Canada, part II: test-retest reliability of selected categorical diagnoses. Am J Psychiatry. 2013;170:59–70.
44. Clarke DE, Narrow WE, Regier DA, et al. DSM-5 field trials in the United States and Canada, part I: study design, sampling strategy, implementation, and analytic approaches. Am J Psychiatry. 2013;170:43–58.
45. Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: classification and criteria changes. World Psychiatry. 2013;12:92–8.
46. Kendler KS, Neale MC, Kessler RC, et al. Major depression and generalized anxiety disorder. Same genes, (partly) different environments? Arch Gen Psychiatry. 1992;49:716–22.
47. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR∗D: implications for clinical practice. Am J Psychiatry. 2006;163:28–40.
48. Dudbridge F. Power and predictive accuracy of polygenic risk scores. PLoS Genet. 2013;9:e1003348.
49. Santoro ML, Ota V, de Jong S, et al. Polygenic risk score analyses of symptoms and treatment response in an antipsychotic-naive first episode of psychosis cohort. Transl Psychiatry. 2018;8:174.
50. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511:421–7.
51. Ward J, Graham N, Strawbridge RJ, et al. Polygenic risk scores for major depressive disorder and neuroticism as predictors of antidepressant response: meta-analysis of three treatment cohorts. PLoS One. 2018;13:e0203896.
52. Zhang JP, Robinson D, Yu J, et al. Schizophrenia polygenic risk score as a predictor of antipsychotic efficacy in first-episode psychosis. Am J Psychiatry. 2019;176:21–8.
53. Koutsouleris N, Davatzikos C, Bottlender R, et al. Early recognition and disease prediction in the at-risk mental states for psychosis using neurocognitive pattern classification. Schizophr Bull. 2012;38:1200–15.
54. Craddock N, Owen MJ. The beginning of the end for the Kraepelinian dichotomy. Br J Psychiatry. 2005;186:364–6.
55. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013;11:126.
56. Stahl SM. The last Diagnostic and Statistical Manual (DSM): replacing our symptom-based diagnoses with a brain circuit-based classification of mental illnesses. CNS Spectr. 2013;18:65–8.
57. Cuthbert BN, Kozak MJ. Constructing constructs for psychopathology: the NIMH research domain criteria. J Abnorm Psychol. 2013;122:928–37.
58. Insel T. Director's blog: transforming diagnosis; 2013.
59. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167:748–51.
60. Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry. 2014;13:28–35.
61. Krueger RF, Kotov R, Watson D, et al. Progress in achieving quantitative classification of psychopathology. World Psychiatry. 2018;17:282–93.
62. Wittchen HU, Beesdo-Baum K. "Throwing out the baby with the bathwater"? Conceptual and methodological limitations of the HiTOP approach. World Psychiatry. 2018;17:298–9.
63. Andrews G, Goldberg DP, Krueger RF, et al. Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity? Psychol Med. 2009;39:1993–2000.
64. Zielasek J, Gaebel W. Modern modularity and the road towards a modular psychiatry. Eur Arch Psychiatry Clin Neurosci. 2008;258(Suppl 5):60–5.

Stigma: An Old Unmet Need in Psychiatric Practice

13

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13.1 Introduction

Stigma, the pervasive devaluation and marginalization of people with mental illnesses, has become a matter of major concern for public health officials, academics in social psychiatry, and an important practical issue for health providers involved in the care of people with mental illnesses. It is an even larger issue for people who have a mental illness and their family members, who also experience stigma directly and by association. Numerous international and national organizations have now included stigma reduction as one of their policy aims. This chapter will provide an overview of mental health-related stigma reduction as an old and unmet need in the mental health field and review some of the international and national initiatives currently underway to combat this problem. The chapter will close with some discussion of future challenges and directions.

13.1.1 Historical Perspectives

Medieval European attitudes toward people with a mental illness were relatively benign. Mental illnesses were considered to be part of the divine plan for mankind and the mentally ill were kindly treated and allowed to run at large, or to dwell in almshouses without constraint unless they were demonstrated to be dangerous [1]. The pejorative use of the term stigma, reflecting a mark of degradation, probably

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appeared in the late sixteenth or early seventeenth centuries in Europe. Prior to that time, stigma was more broadly understood to indicate a tattoo or mark that may have been used for decorative or religious purposes, or alternatively, for utilitarian reasons such as branding criminals (to indicate they had transgressed a law) or slaves (to indicate their ownership) [1].

Similar to Medieval European culture, early Islamic cultures viewed mental disturbances as illnesses with no particular moral meaning, guilt, or shame attached. Family members were mostly responsible for those with a mental illness unless they became a serious danger to themselves or others, in which case they were hospitalized. While patients were restrained and sometimes beaten when confined, the systematic abuses that accompanied the rise of European asylums during the period of the "Great Confinement" in the seventeenth century were not evident, suggesting that mental illnesses did not elicit as much stigma in the Islamic world as in European societies [2, 3].

The explicitly derogatory application of the term stigma most likely appeared in European societies when mental illnesses became linked with sin. The inquisitorial approach to witches, represented in the *Malleus Maleficarum* (The Witches' Hammer), is a good representation of the negative and condemning attitudes toward mental illnesses that existed in Christian cultures from the rise of rationalism in the seventeenth century to the present. Indeed, the witch trials described in the Malleus contain numerous clear characterizations of mental illnesses, such as schizophrenia or depression, though, in their day, witches were not considered to be ill, but in pact with the devil [4].

By comparison, in Chinese cultures, mental illnesses have been associated with shame and guilt at least since the dawn of Confucian ethics (551–479 BC). Confucianism expects social relationships to be harmonious and positive and mental illnesses are considered to be a source of dissonance. As well as being a moral transgression against social norms, mental illnesses are a moral transgression against one's ancestors. Thus, the main reason for stigma in Chinese cultures is that mental illnesses tarnish the family honour, past, present, and future [5].

In eighteenth century in Europe, it has been developed the notion that individuals who were socially deviant were also physically deviant. An individual's physical characteristics, such as the shape of the nose, the colour of the eyes, or the shape of the head, were considered to reflect a predisposition to a mental illness as well as an individual's character, inclinations, and capacity [6]. By the nineteenth century, madness had been firmly linked to heredity through a degenerative taint in the family. Important thinkers of the day agreed that heredity was the source of most mental illnesses. Also, it was now commonplace to think that people who were mentally ill displayed morphological stigmata such as pointed ears, stunted growth, or cranial abnormalities [7].

Degeneracy theory remained popular in Europe and North America until World War I, when the role of environmental stressors and trauma became more widely recognized. It was influential in the eugenics movement, and discouraged physicians from seeking cures during the asylum era. It made overcrowded and

inadequate institutions more acceptable and it also meant that mental illnesses were linked with other forms of degeneration, which then conferred the enduring stereotype of moral incapacity [7].

Banishment and marginalization have been consistent societal responses to people with mental illnesses. Prior to the asylum era, people who were mentally ill may have been thrown outside of the doors of the city left to meander aimlessly. There are old documents from the Middle Ages that describe ships whose cargo was "fools", giving rise to the "ship of fools" narrative, where mentally ill were cast adrift with no port to disembark [8]. In some locations, the mentally ill were exported "down the river" to clean the towns; a foreshadowing of the more recently used "Greyhound Therapy" where health authorities buy a bus ticket to get rid of troublesome mental patients to another jurisdiction.

Despite what they became, the earliest asylums were intended to be protective. In Spain, for example, Father Gilbert Jofré established the first asylum in Valencia in 1410 after witnessing a crowd teasing a mentally ill man. Early Islamic hospitals (ninth and tenth centuries) included sections for the care of people with mental illnesses that were open to visitors. Although unpleasant, these were places where physicians practiced their physiologically oriented medicine with diversions such as dancing, theatrical performances, and recitations. In some hospitals, patients were led to the mosque to pray [2].

Over time, asylums became synonymous with incarceration and brutality, and a preferred means of environmental banishment. Even today, in parts of the world where segregation in a mental hospital is not possible, mentally ill may be chained to trees or immovable objects to prevent them from wandering about and to segregate them from the community [9]. In Indonesia, for example, 19,000 people are currently shackled or locked in small cramped spaces (called pasung). This occurs even though pasung has been banned since 1977 and the Government has ratified the Convention on the Rights of Persons with Disabilities in 2011 guaranteeing equal rights for persons with disabilities. With the support of religious and traditional healers, mentally ill people continued to be shackled as family members struggle to cope given the lack of mental health care and support services [10].

The Cummings' *Closed Ranks* provides a unique view of Canadians' perceptions of mental hospitals and their role in the treatment of the mentally ill [11]. Despite deplorable conditions in early psychiatric hospitals, members of the public often held an unshakable belief in their ability to treat the mentally ill. The Cummings attributed the population's belief in the efficacy of mental hospitals to a patterned response involving social and physical isolation. The ordinary citizen felt little social responsibility for the plight of the mentally ill and remained happily uniformed about the nature of psychiatric hospitals, mental illnesses, and their treatments [12].

Against this backdrop, one important and immediate consequence of deinstitutionalization was the demand placed on local communities to host a group which traditionally had been segregated to large and far-away institutions. The enduring reason for institutional care had been the separation of unwanted individuals from

everyday society to places where they could be effectively forgotten. An immediate consequence of deinstitutionalization was the demand placed on communities to host unwanted groups of people, thus making stigmatization more likely. To be successful, the community mental health movement would have required a wholesale revision of conventional social attitudes toward the mentally ill. Subsequently, the increased contact between the mentally ill and the general public resulting from deinstitutionalization caused considerable friction and challenges to the placement of community mental health facilities and the creation of the "not on our street" or "not in my backyard" mentality [13].

13.1.2 Contemporary Perspectives

Contemporary perspectives of stigma have evolved over time from the relatively understated, where stigma is a mark of shame [14], to the more complex construct, where stigmatization is a multi-faceted social process based on the exercise of power to devalue, exclude, and marginalize [15]. Figure 13.1 depicts three eras of stigma discourse corresponding to three of the most recent policy paradigms shaping mental health service delivery in the twentieth and twenty-first centuries. Initially, stigma was considered to be a consequence of institutionalization. Following deinstitutionalization, stigma became a consequence of the increased visibility of the mentally ill in the community as a result of failed community care. More recently, stigma has become understood as a barrier to recovery and viewed as a social rights issue [9 p. 87].

In his seminal work, Goffman [14] described mental illness-related stigma as the most deeply discrediting of all stigmatized conditions. He outlined a number of damaging effects including devaluation, status loss, and social marginalization, all

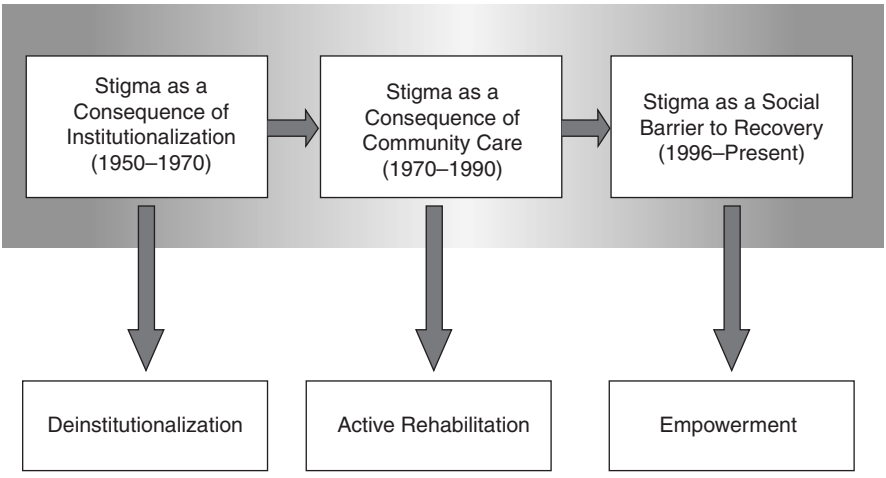

Fig. 13.1 Three eras of stigma discourse

of which had the function of rendering a whole person into one that was irredeemably tainted. In subsequent work Goffman [16] was highly critical of mental hospitals for their stigmatizing effects, thus reinforcing the concept that the negative and debilitating effects of mental illnesses were more a result of the way in which psychiatry was organized, rather than of any inherent characteristic of the illnesses themselves. Stigmatization was viewed as the by-product of the social organization of psychiatry and psychiatric services. Indeed, one of the motivations behind the massive deinstitutionalization that took place in the late twentieth century was the idea that community care would go a long way to destigmatize mental illnesses. However, the stigma followed patients out of the hospitals into the streets where they were more visible and disconcerting [9].

Psychological models of stigma have examined the way in which labels are connected to cultural stereotypes and the content of these. They have identified how cognitive and attributional processes lead to the development and maintenance of negative and erroneous stereotypes, which forms the cognitive scaffolding for stigmatized views. Attribution theory describes a process that begins with a label, that triggers a stereotyped attribution, which, in turn, evokes a negative emotional response (prejudice), and a behavioural expression (discrimination). People who hold moral views of mental illnesses based on attributions that emphasize blameworthiness, dangerousness, or unpredictability, are more likely to respond in angry and punitive ways and they are more supportive of coercive legislation and treatment practices [17, 18].

Link and Phelan [15] have incorporated these social and psychological elements into a broader process map which ties stigmatization to the interactions between individuals and groups. Initially, the social group identifies and labels a difference that is deemed to be socially salient. The label is then linked to negative stereotypes and labelled people are socially categorized in ways that make a clear distinction between *us* and *them*. Once labelled and categorized in this way, individuals experience status loss and discrimination. In this model, stigmatization is entirely predicated on powerful social forces that have the ability to create and maintain unequal access to social, economic, and political power.

Figure 13.2 depicts a cycle of stigma that spirals to deepen social disabilities and the illness itself [19, p. 3]. This is the operational model that was used by the World Psychiatric Association's global anti-stigma program. It stresses that stigma is a vicious cycle that will continue unless the circle is interrupted. Most importantly, the cycle defines access points where interventions might be undertaken and where there is room for action by professionals, social services, hospitals, community agents, and other advocates. In the context of this model, there is no one who cannot contribute to stigma reduction and its consequences. Similar cycles were conceptualized at the level of the family, depicting how stigma reduces social support that can be provided to the ill person; and at the level of programs and services, where services are underfunded and of poor quality.

Over time, we have moved from models emphasizing the psychological aspects of stigma, to multi-factorial models that consider the social, psychological, and ecological components of stigmatization.

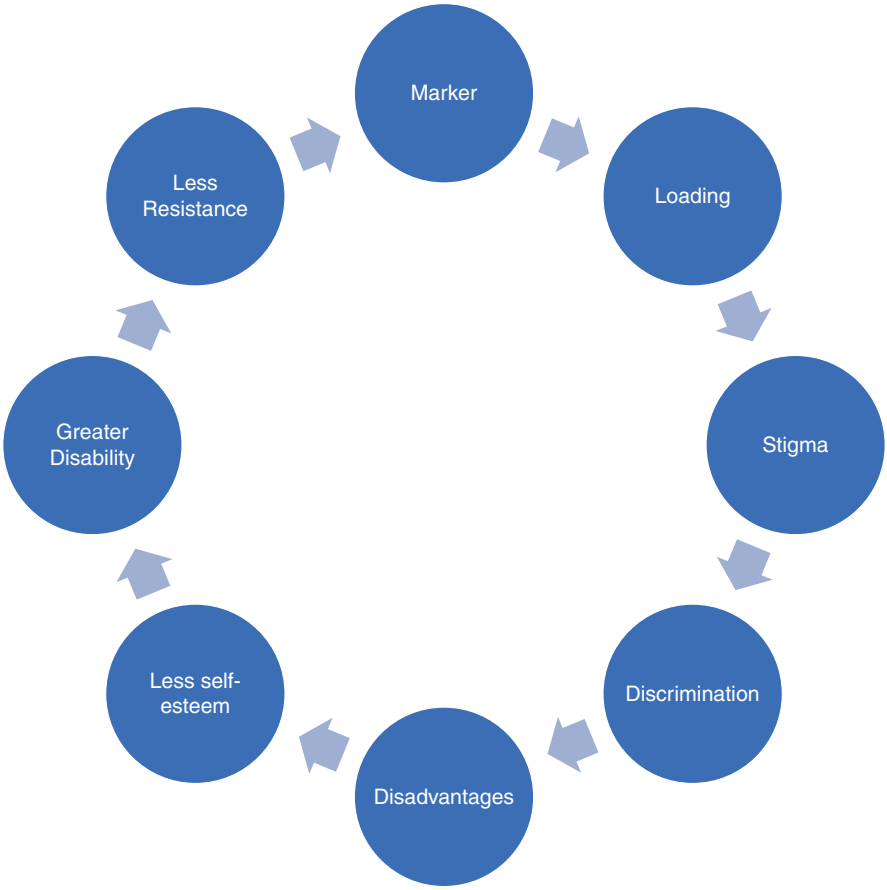

Fig. 13.2 Vicious cycle of stigmatization

13.1.3 The Emergence of a Social Model of Disability

Historically, people with physical or mental impairments were viewed as having suffered an unfortunate tragedy requiring medical treatments and charity-focused social welfare programs. During this era, the medical model of disability focused on the chain reaction of risk factors, disease onset, impairment, disability, and handicap. People with disabilities were viewed as different from other functional members of society and directed toward separate tracts of government policy. The government track for normal, healthy members of the community focused on developing potential, whereas the track for disabled persons regarded them as defective and systematically excluded them from mainstream society. The focus

was on fixing the individual so that they could better align with mainstream social practices in a society that was filled with barriers to full and effective social participation [20].

Contemporary discourse focuses on understanding disabilities from a social perspective. The "social model" of disability (or sometimes "socio-political model") represents a paradigm that emerged in the context of the disability rights movement of the 1960s, which refocused the agenda from issues of treatment, cure, protection, and acceptance of impairment as a positive dimension of diversity, to a human rights perspective that promotes full social inclusion of people with disabilities. Unlike previous models, the social model deliberately severed the link between a physical or mental impairment and any social disability. Impairments are no longer viewed as the cause of an individual's economic, political, or social disadvantage [21]. Rather, social inequalities are considered to flow from social structures. People are disabled because the social environment has failed to adjust to their needs [22].

In 2006, the Convention on the Rights of Persons with Disabilities was adopted (coming into force in 2008). It is the most up-to-date international legal instrument designed to specify and protect the rights of persons with physical and mental disabilities. It puts forward a social model of disability, recognizing that it is the level of accommodations (or lack thereof) of a society that determines the degree to which an impairment becomes a disability [23]. One limitation of the convention is that it has equated an illness with a disability. In the context of mental illnesses, the majority of individuals do not have socially relevant impairments, so are not "disabled" in the sense of the convention. Nevertheless, by adopting a social model, the convention has created an important climate for change and has challenged signatories to remove attitudinal and structural barriers that prevent people with impairments from becoming full and effective members of society. In so doing, it firmly rejects the view that disabled people are objects of charity and in need of medical and social protections [24]. Recently, the UN Committee, set up to monitor the implementation of the convention, has come under criticism for its "absolutist" interpretation of the convention prohibiting all forms of involuntary detention and treatment as well as substitute decision making of people with mental health or psychosocial disabilities, notwithstanding any danger to self or others. Szmukler [23] has suggested that this interpretation (though not legally binding in international law) will threaten the rights of others, the family, and the public; and subsequently increase mental illness-related stigma. As a result of the Committee's interpretation, a large number of signatories have expressed their disagreement, indicating that it will have serious and adverse consequences for people with mental illnesses and psychosocial disabilities; indeed, potentially undermining some of the hard-won critical rights [25]. Clearly, future compromises will be necessary in order to realize the vision of the Convention in creating socially inclusive communities for people with disabilities.

13.2 Prevalence of Stigma and Stigma Impact

13.2.1 Public Stigma

It is difficult to estimate the frequency of mental illness-related stigma expressed by members of the public. Social desirability can influence the extent to which people are willing to admit that they hold prejudicial beliefs or participate in socially distancing or discriminatory activities [26]. Also, as national anti-stigma initiatives proliferate, members of the public become even more sensitized concerning the "socially desirable" response that they should provide with the result that population estimates may be seriously biased [9]. Secondly, estimates of stigma differ depending on the measurement instrument used. For example, Corrigan and colleagues found that measures of difference yielded significantly higher endorsements compared to measures of stereotypes [26]. Thirdly, stigmatized views of mental illnesses are likely to be shaped by culture, tradition, access to education, access to health services, beliefs about aetiology, the diagnosis of the individual, previous contact with someone who has had a mental illness, and a host of other factors. Thus, endorsements for common stereotypes will vary widely by culture [27].

The World Values Survey (worldvaluessurvey.org) offers an opportunity to examine social distance expressed toward "emotionally unstable people" across different countries. An advantage of this survey is that all countries provide large representative samples, use the same survey tool, and have rigorous translation and back-translation procedures. In addition, countries span a range of economic development indices. In each country, respondents are asked to pick from a list individuals they would not want to have living in their neighbourhood. We used the longitudinal component to estimate the proportion of samples aggregated over five survey waves (from 1981 to 2009) who identified "emotionally unstable people" as a group they would not like to have living in their neighbourhoods. Fig. 13.3 shows a box and whisker plot of these results. The shaded box shows the 25th and 75th percentiles, with the middle line showing the median (50th percentile). The whiskers extend out to the extreme values on either end of the distribution. These are the average values across five successive waves of the survey (undertaken from 1981 to 2009), representing 163,729 respondents.

This figure shows that there is considerable variability across the 72 countries represented; but in half of the countries, the social distance expressed toward emotionally unstable people was pervasive, ranging from 32% to 58% of the sample. As with all multi-cultural research, it is not clear how individuals in various countries understood the term "emotional instability," what specific stereotypes were triggered, or what range of mental illness-related behaviours might have been included under this label. Similarly, it is not known the extent to which social desirability response sets may have biased (probably underestimated) results. Nevertheless, these results portray a picture of pervasive social intolerance.

Another way of looking at the prevalence of mental illness-related stigma is to ask people who have a mental illness whether they have experienced prejudice and discrimination because of their current or past emotional ill health. A strength of

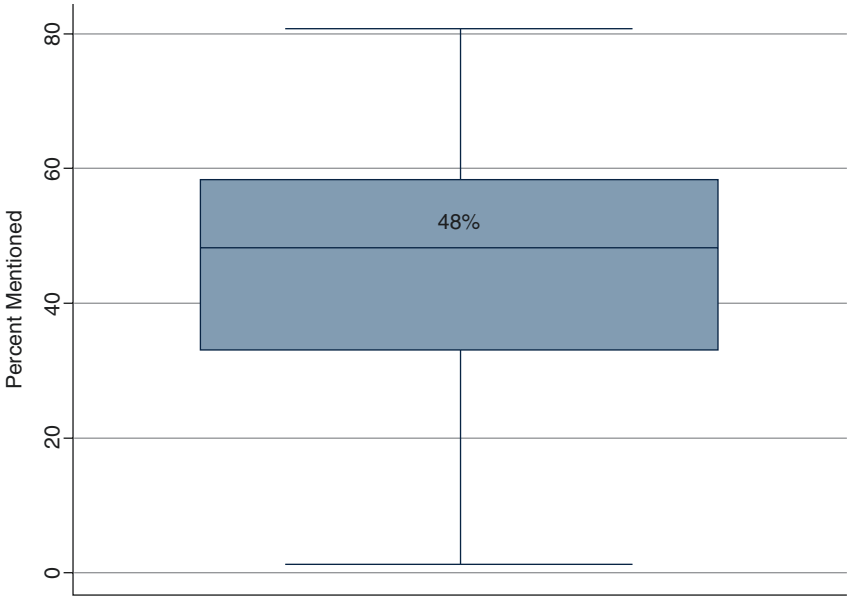

Fig. 13.3 Proportion of samples indicating that they would not like to have "emotionally unstable people" living in their neighbourhood

this approach is that it is not based on hypothetical situations reflecting what members of the public think they would do, but directly analyzes real life experiences of people who have been stigmatized. As an example, Thornicroft and colleagues examined patterns of experienced and anticipated discrimination against people with schizophrenia in 27 countries participating in the INDIGO network (International Study of Discrimination and Stigma Outcomes) [28]. Researchers at each site purposively selected a sample of 25 individuals who, in their judgement, were representative of people with a clinical diagnosis of schizophrenia who were in treatment with local services (n = 732). While experienced discrimination was apparent in all samples, there was significant variability. In most countries, half of the sample reported five or more areas of negative discrimination; the most frequent being in making or keeping friends, discrimination from relatives, keeping or finding a job, and intimate relationships. Positive discrimination where individuals received some benefit because of their diagnosis (e.g., pensions, housing, treatment) was rare, and occurred in less than 10% of the sample. Respondents were more likely to anticipate discrimination, than to have experienced it. For example, 69% anticipated discrimination in finding or keeping work, whereas less than half had actually experienced discrimination. Similarly, 60% of participants anticipated discrimination in the context of intimate relationships, whereas more than half (56%) had not experienced it. This may be reflective of the situation where individuals avoid placing themselves in discriminatory relationships if they anticipate that they will be treated negatively because of their mental illness. This interpretation was

borne out in a subsequent INDIGO study examining anticipated and experienced discrimination by people with depression [29]. Respondents scoring high on the anticipated discrimination items decided to give up and not pursue their goals. In this study, respondents from the most developed countries (measured using the Human Development Index) experienced significantly higher levels of discrimination.

In Canada, a survey module assessing the frequency and impact of perceived stigma (the Mental Health Experiences Scale) has been used in two national population surveys; in 2010 (n = 10,389; 72% response) [30] and 2012 (n = 25,113; 69% response rate) [31] to assess stigma experiences of people who have used mental health services in the previous year. In both surveys, the frequency of stigma experienced was considerable, in the range of 30% to 40% of the 8.3% of the Canadian population who accessed mental health services in the previous year. Between 2.0% and 6.4% (depending on the disorder category) reported discontinuing treatment because of discrimination, unfair treatment, or embarrassment [31]. While it is generally supposed that stigmatization is an inevitable component of the experience of a mental illness, these results suggest that it may not be part of people's current (past year) experiences. Half or more of those accessing services in the previous year did not report stigmatization, though they may have experienced it earlier in their lives. The finding from the 2010 survey [30] showing that younger respondents reported significantly greater stigma is consistent with this possibility. Respondents who did not meet the criteria for a Composite International Diagnostic Interview (CIDI) mental disorder were less likely to report stigma, which is consistent with the view that diagnostic labelling plays an important role in the stigma process. Finally, the levels of reported stigmatization were surprisingly similar between disorder groups, all in the range of 30–40%, but those who self-rated their mental health as moderate or fair, were more likely to report stigma (38% for moderate or fair compared to 25% for very good or excellent). Both mental health itself, and the perception of mental health status, may contribute to perceptions of stigma or, alternatively, stigma may be an important determinant of poor mental health status. It is not possible to sort out the direction of the relationship with cross-sectional data [31].

13.2.2 Stigma Impacts

People growing up in a specific culture are aware of the stigmatized views about people with a mental illness. The negative attitudes of others, which are attached to a diagnostic label, become personally relevant when one learns that one has a mental illness. Self-stigma occurs when these negative public views are internalized and negatively impact the self-esteem and self-identify of the individual [15]. Brohan and colleagues [32] examined the degree to which self-stigma was reported by random samples of 1340 mental health service users with schizophrenia, psychosis, or schizoaffective disorders who were members of mental health charity organizations in 14 European countries. Almost half (41.7%) reported moderate or high levels of

self-stigma using the Internalized Stigma of Mental Illness Scale—a 29 item scale that assesses self-stigma along five dimensions (alienation, stereotype endorsement, perceived discrimination, social withdrawal, and stigma resistance). As with levels of public stigma, they noted significant between-country variations on all four dimensions. Lower self-stigma was associated with feelings of empowerment and higher numbers of social contacts suggesting that interventions that target these factors may help to reduce self-stigma.

Self-stigma has been associated with a range of negative social and clinical outcomes, including lower quality of life, lack of empowerment, shame, blame, increased symptom severity, and reduced help-seeking, to name a few [32, 33]. Corrigan and colleagues [34] talk about the "why try" effect that occurs when self-esteem and self-efficacy prevent people from achieving important goals, such as failing to pursue work, independent living opportunities, or social interactions. People who view public stereotypes as legitimate (and apply them to themselves) suffer greater harm to their self-esteem and self-efficacy. Others, who may view public stereotypes as invalid, may experience righteous indignation and use these feelings to become empowered and develop a positive self-identity.

As well as having direct effects on the individual who has a mental illness, stigma may indirectly affect all of those around them. As previously described, Sartorius and Schulze [19] describe vicious cycles of stigmatization that interact to affect the individual who has a mental illness, their family members, and professional caregivers. The individual with a mental illness, once marked as "different" will experience a number of social disadvantages including inequitable access to care, poorer quality of care, reduced self-esteem, and additional stresses that may amplify the individual's disability making them a greater target for public stigma. In turn, this may have important negative consequences for the family. They may experience stress, feel shame, guilt, and worry, and experience a loss of family esteem and reserves, making it difficult to provide the social supports necessary for recovery. Mental health services are also chronically underfunded. They are typically the first to have budget cuts and the last to experience budget growth. As a result, it is difficult to provide high-quality, recovery-oriented care. In many parts of the world, medications needed for the treatment of mental illnesses are unavailable because they are deemed to be "too expensive"—another way of saying that people with a mental illness are not worth the cost. These individual, family, and structural pressures coalesce to perpetuate impairment and disability.

13.3 Interventions to Reduce Stigma

13.3.1 International Programs

World Psychiatric Association Stigma Section

The World Psychiatric Association (WPA) is an association of national psychiatric societies aimed to increase knowledge and skills necessary for work in the field of

mental health and the care for individuals living with mental illnesses (www.wpa-net.org). The Stigma Section of the World Psychiatric Association, through its network of international members, engages in activities designed to reduce prejudice and discrimination due to mental disorders and improve social inclusion for people living with mental illnesses and their family members.

The Stigma Section has three major goals. The Section's first goal is to disseminate information about stigma due to mental disorders through academic and technical publications, as well as symposia and courses offered at WPA regional meetings and congresses. Secondly, the Section aims to advance scientific knowledge about stigma through collaborative research and evaluation. Finally, the Section provides training opportunities to support the development of effective programs to fight stigma because of mental disorders. Since 2014, members of the Stigma Section have contributed over 100 scholarly papers, manuscripts, and books and made numerous presentations at symposia and academic conferences. The Section works with local sites to host the biennial *Together Against Stigma* Conference. The location changes, depending on the local host and attracts stigma researchers from around the globe. The most recent conferences were held in Copenhagen, Denmark in 2017 and in Singapore in 2019.

Open the Doors

Open the Doors was established in 1996 with the intention of fighting the stigma associated with schizophrenia. The goals of the program are to examine the nature of stigma and its consequences in different sociocultural settings, and to develop methods that could be used to prevent or reduce it. Recognizing that there was insufficient data describing the scope and impact of stigma from the perspective of people living with schizophrenia (and their family members), the program places high priority on gaining the perspective of people with direct experiences of schizophrenia regarding their experiences with prejudice and discrimination.

Open the Doors was ultimately implemented in 18 low-, middle-, and high-income countries: Austria, Brazil, Canada, Chile, Egypt, Germany, Greece, India, Italy, Japan, Morocco, Poland, Romania, Slovakia, Spain, Turkey, USA, and the United Kingdom. In addition, Australia worked in partnership with *Open the Doors*. Activities conducted by teams in each of these countries under the umbrella of the *Open the Doors* program have included: surveys of knowledge and attitudes (in 14 countries); publications in newspapers and magazines (14) and scientific journals (13); the development of a speaker bureau involving people with schizophrenia, family members, and/or professionals (12); the development of education programs for health professionals (12), journalists (11), primary or secondary students (9), psychiatrists (9), families (8), clergy (5), and general practitioners (7); stigma watch or stigma busting programs (6); art presentations and competitions (6) and theatre or dramatic presentations (4); anti-stigma awards (5), story workshops (3), and other miscellaneous interventions ranging from movie screenings to public days of solidarity with people experiencing schizophrenia.

Meeting for Minds (M4M)
Meeting for Minds (M4M) is a non-profit organization currently operating in five countries, aiming to become a unified, global catalyst for ground breaking change in mental health research. While MFM acknowledges all mental health support groups and the invaluable work they do, the program emphasizes the one often overlooked, yet vital component: the insight and knowledge of those who have lived experience of mental illnesses and those who care for them. The overall goal of M4M is to create a new and innovative style of research into disorders of the brain that supports collaborative research with people with lived experience of mental illness as partners in research. Activities conducted by the program have included formal scientific research, public fora and lecture series, workshops, and other events held through partnerships with existing groups such as *Spacecubed*, an organization dedicated to creating new, innovative solutions to mental health problems in Australia.

The Global Anti-Stigma Alliance (GASA)
The GASA program is an informal grouping bringing together national programs with the help of the WPA Stigma Section. Established in 2012 at the Ottawa, Canada *Together Against Stigma* Conference, alliance members share learning, methodologies, best practices, materials, and the latest evidence to achieve improved outcomes for individuals facing prejudice and discrimination as a result of living with a mental illness. The program draws anti-stigma researchers and national programmatic initiatives from around the world, and is actively seeking additional members. Currently, members hail from over 16 countries.

13.3.2 National Programs

The following programs are national anti-stigma initiatives, in ten countries. Abbreviated descriptions of programs are presented in alphabetical order by country, and program name.

13.3.2.1 Australia

Beyondblue
Beyondblue is a co-funded government initiative across all eight governments in Australia. The program began as a basic awareness campaign, aiming to raise awareness about youth and depression. Originally established as a five-year program, *beyondblue* has since evolved to encapsulate good mental health for the entire population of Australia, with a focus on anxiety, depression, and suicide prevention. Since 2015, *beyondblue*'*s* strategic plan has shifted into a settings-based focus on the family home, the workplace, schools, and the community as a whole. The program's goals are stigma reduction, improving mental health literacy, and getting support to people at the right time. The *beyondblue* website offers a wealth of information, including downloadable resource packs, online programs, information videos, and more. The website receives close to 100,000 visitors per month on their

community fora, reaching up to 10,000 unique posts per month. Other activities have included social media campaigns, the provision of online support serves (i.e., information phone line, online forum support, and web chat), and online training programs and resources. All programs and resources are embedded within the *beyondblue* website.

SANE Australia

SANE Australia was originally launched in 1986 as the Schizophrenia Australia Foundation. Over the past years, the organization has had a number of foci, but stigma reduction has remained a common element throughout. *SANE* primarily focuses on reducing the stigma surrounding complex or poorly understood mental illnesses including schizophrenia, bipolar disorder, personality disorders, eating disorders, Post Traumatic Stress Disorder (PTSD), and trauma. In addition to stigma reduction, the program focuses on policy development and advocacy, ensuring that the needs of people affected by complex mental illnesses are reflected in public policy and the health and social service systems. The program aims to reach all Australians affected by complex mental illnesses including those living with a mental illness, their families, friends, and colleagues. *SANE* works collaboratively with the media, community groups, governments, and institutions (i.e., the police force, legal services, etc.), serving adults aged 18 years and older. Activities conducted by *SANE* include: Stigma Watch, an initiative comprising response to community concerns about stigmatizing language used in the media and the production of training materials and guidelines for media professionals; public awareness campaigns, which include components such as conversation starters, improving understanding of complex mental illnesses, and eliminating self-stigma associated with these illnesses; and online help available on the program's website (https://www.sane.org/), moderated 24/7 by mental health professionals.

13.3.2.2 Canada

Opening Minds

Opening Minds, launched in 2009, is the largest systematic effort in Canadian history focused on reducing stigma related to mental illnesses. Established by the Mental Health Commission of Canada, the program seeks to change Canadians' attitudes and behaviours toward people living with mental illnesses to ensure they are treated fairly, as full citizens with equal opportunities to contribute to society. *Opening Minds* takes a population-based approach, with the ultimate goal being that the program's stigma reduction message benefits all Canadians with lived experience of a mental illness. The goal is for these individuals to never experience stigma at home, school, or work; to receive timely and equitable care from health care providers; and to receive useful support and correct information regarding how to seek help and how to reach recovery. To accomplish these goals, *Opening Minds* targets four key groups: (1) youth; (2) the workplace (including employees and employers); (3) health care providers (including practicing physicians, nurses, students in health-related disciplines, administrative and support staff); and (4) the media (including journalism students, and those currently employed in the media). *Opening Minds* engages in

three major activities: (1) formal evaluation of existing anti-stigma programs in Canada so that those that are found to be effective can be replicated; (2) delivery and promotion of evidence-based programs; and (3) the development of toolkits where none exist. The program's youth initiative, *Headstrong*, was also launched in 2014, and is modelled after the most effective of over 25 youth anti-stigma programs across Canada formally evaluated by *Opening Minds*.

Bell Let's Talk (See letstalk.bell.ca)

Bell Let's Talk began in September 2010. At that time, most Canadians were not talking openly about mental illnesses. They were still very much taboo subjects. The goal of *Bell Let's Talk* day was to open a national conversation about Canadians' mental health. This national program has four pillars of action: anti-stigma; care and access; research; and workplace mental health. For one day each year, Bell donates 5 cents for messages of support on the Bell network. On the first Let's Talk Day, Canadians made 66,079.236 calls and texts resulting in a donation of over $3 million to add to the $50 million start-up funding originally committed by Bell. Over time, messages have steadily grown to over 145,442,699 interactions (in 2019). In September 2015, Bell announced a further 5-year commitment and a total pledge of $100 million. A telephone survey of 1007 randomly selected Canadian adults conducted by Nielsen Consumer Insights showed that 57% of Canadians believed that the stigma associated with mental illness had been reduced compared to five years earlier, 70% indicated that they thought attitudes about mental health issues had changed for the better, and 81% indicated they were more aware of mental health issues. To date over $100 million dollars has been donated to a host of community mental health initiatives, including mental health initiatives, $1.4 million to crisis and distress line callers, $0.5 million to children and youth programs, $800 thousand to train staff and volunteers, and $300 thousand to individuals supported through technology-based mental health programs. In addition, Bell has funded the first Mental Health and Anti-stigma research chair at Queen's University with a 10-year funding commitment. This makes the *Bell Let's Talk* program the largest corporate sponsorship for mental health in Canadian history.

13.3.2.3 Denmark

One of Us

En Af Os, or *One of Us* is a population-based anti-stigma program in Denmark. A strong network of partner organizations, including The Danish Health Authority, the philanthropic foundation TrygFonden, the Danish Regions, The Danish Mental Health Fund, The National Board of Social Services, The Psychiatry Network, KL (Local Government Denmark), and The Danish Committee for Health Education, was formed in 2010 to extend the program's coverage. The program's overall goal is to improve life for all Danes by promoting inclusion and combatting mental illness-related discrimination. More specifically, the organization aims to: increase knowledge about mental illnesses, reduce stigmatization, and promote social inclusion. Similar to the Canadian *Opening Minds*, the Danish program has five main target groups: (1) youth, (2) the workplace (labour market), (3) service users and

relatives, (4) staff in health and social services, and (5) the media. Activities conducted by *One of Us* have included: ambassador training for community members with lived experience of a mental illness; social contact activities (i.e., talks led by ambassadors); media response information and materials for journalists that guide responsible reporting on mental health-related issues; and dialogue toolkits, packages of materials designed to challenge and promote reflection among professionals in healthcare, social sectors, job centres, and educational settings about how to talk about and with individuals living with mental illnesses.

13.3.2.4 United Kingdom

Time to Change

Time to Change is an anti-stigma program based in London, United Kingdom. The program was established in October 2007. Overall, the program takes a population-based approach, aiming to reduce stigmatizing attitudes and behaviours among all individuals in the United Kingdom, including those with and without experiences of a mental illness. More recently, the program has begun to take a global approach, extending their reach to anti-stigma programming in low-income countries within the Commonwealth. At the heart of all work conducted through the program is the concept of "lived experience", with individuals sharing their stories and experiences living with a mental illness and the associated stigma. *Time To Change* targets four main focus areas, where community champions are developed: (1) the workplace; (2) the youth; (3) the media; and (4) the general community. Within the community, the program campaign operates several programs, including the community leadership work as well as social media and communications to the general public. Activities conducted by *Time to Change* have included: the development of community champions, both in the general population and more specifically, in workplaces (ranging from sharing lived experiences in a formal setting, to speaking up when witnessing stigmatizing behaviour); school-based activities, including downloadable resources and free, online toolkits available to students and teachers; and formal challenging of harmful or stigmatizing mental health-related messaging in the media.

SANE (UK)

SANE is a leading mental health charity that aims to reach all individuals with lived experience of a mental illness in the United Kingdom. In 2003, *SANE* founded the Prince of Wales International Centre for *SANE* Research in Oxford, where leading researchers are investigating the yet unknown causes of schizophrenia and psychosis. Research in general plays a central role to *SANE's* programming, the services offered, and the program's approach to reaching its desired outcomes. The program aims to meet three overarching objectives: (1) reduce the impact of mental illnesses (e.g., reduce stigma and distress, increase support); (2) improve treatment and care by increasing knowledge about mental illnesses; and (3) influence policy and public attitudes by increasing understanding of mental illnesses. *SANE* engages in a range of activities, from research, to campaigning for the rights of individuals living with mental illnesses, to providing emotional support, guidance, and information to those

affected by a mental illness, including families and caregivers. The mental health support services provided by the program are confidential and non-judgmental, and delivered by a team of mental health professionals and trained volunteers. The program also offers *SANEline*, a national after-hours mental health helpline run by trained volunteers who offer support and guidance for those affected by mental illnesses. *SANEline* is open all year round from 4:30 to 10:30 p.m. The program addresses negative portrayals of mental illness in the media, and also helps individuals who have lived experience with mental health problems speak to journalists, broadcasters, and researchers to share their stories.

13.3.2.5 Netherlands

Samen Sterk

Samen Sterk Zonder Stigma (*Together Strong Against Stigma*) is an anti-stigma program based in the Netherlands. The overall goal of the program is to eliminate the prejudice and discrimination associated with mental illnesses. Taking a population-based approach, the program targets the following groups: (1) mental health professionals, (2) the workplace, (3) the media, (4) the community, and more recently, (5) youth. Among mental health professionals, *Samen Sterk* aims to improve awareness around the stigmatization of mental illnesses within the mental health care system, in addition to making healthcare professionals aware of self-stigma. Within the general workplace, the program aims to encourage employees and employers to have open discussions about mental health and mental illnesses. *Samen Sterk* encourages media professionals to report responsibly, in a non-stigmatizing fashion, on mental health-related news stories. Finally, *Samen Sterk* reaches youth in school settings, working with educational professionals, school administrations, students, and parents. Activities conducted by the program have included: curating ambassadors within the community (i.e., individuals with lived experience of a mental illness who share their stories with others through workshops, talks, etc.); the creation of toolkits and training for healthcare professionals; the development of *CORAL*, a decision making tool designed for employers and employees with respect to disclosing a mental illness; and the creation of non-stigmatizing reporting guidelines for media professionals.

13.3.2.6 New Zealand

Like Minds, Like Mine

Like Minds, Like Mine is a comprehensive, national campaign based in New Zealand. Established in 1997, the program grew out of a recommendation following an inquiry into mental health care and discrimination against those living with mental illnesses (the 1996 Mason Report). The program aims to counter prejudice and discrimination related to mental illnesses. *Like Minds, Like Mine* takes a population-based approach, targeting people who have the potential to exclude, particularly in workplace and community settings. The program aims to emphasize the removal of barriers to social inclusion for the most excluded groups, including: people with severe mental illnesses, Māori and Pacific people who are more likely to begin their journey through a mental illness in a position of social disadvantage, and people

under the age of 25 years. The program's messaging primarily targets the following groups: (1) the media, (2) the workplaces, and (3) the community. Activities conducted by *Like Minds, Like Mine* have included guidelines for responsible media reporting, public awareness campaigns, and a wealth of online resources for minimizing stigma in any environment, accessible through the program's website.

13.3.2.7 Portugal

UPA Movement

Developed by Encontras, a Portuguese NGO, the UPA Movement (*United to Help*) began in Portugal in 2007. The focus of the program is to eradicate prejudice and discrimination and improve the lives of those living with mental illnesses. The UPA Movement aims to reach the entire Portuguese population, with particular efforts targeted toward youth and the workplace. *A Song for Mental Health* was the UPA Movement's first national campaign. Over the course of 10 months, a new song was released by a popular, high-profile Portuguese musician. Each song was about a theme related to stigma and mental illness, and was released on television, radio, and billboards around the cities of Portugal. Since then, the UPA Movement has also engaged in other activities, including the development of the *Make a Difference* program, school-based interventions targeting Portuguese youth and teachers, as well as providing community-based psychosocial rehabilitation programs and services to community members.

13.3.2.8 Scotland

See Me

See Me is an anti-stigma initiative based in Glasgow, Scotland. Since its inception in 2002, the program has taken a settings-based focus, targeting workplaces, schools, and health, and social care. The broader community as a whole is also described by the program as one of the main settings of interest. Social contact theory (i.e., sharing stories of people with lived experience with a mental illness) is the cornerstone of the program. More recently, the program's focus on policy and practice within each of the identified settings of interest has increased significantly. In the past, *See Me* has focused on delivering high-profile awareness campaigns. While the program will continue to provide public campaigns, more recently, resource allocation has been weighted more heavily towards policy and practice (i.e., implementing training and increasing knowledge within health and social care). This represents a shift to a more comprehensive focus. Activities conducted by *See Me* have included: providing knowledge and training to teachers and students within school settings; the creation of a four-stage, e-learning program for workplaces to develop an improvement plan regarding mental health-related policy and practice; and a variety of activities with the Social Movements division, including multi-day training programs, "conversation-starting" awareness campaigns, and lived experience talks designed to empower community members to become champions of mental health and anti-stigma messaging.

13.3.2.9 Spain

1decada4

1decada4 (*1 in 4)* is an anti-stigma program based in Andalusia, Spain. The program is a cross-sector strategy shared across three agencies of the Department of Health. Five institutions are collectively under the umbrella of *1decada4*. The program began in 2007 with the overall goal of combating the prejudice, discrimination, and violation of rights experienced by people with mental health problems and championing the recovery of people with lived experience and their families. This program has taken a population-based approach, aiming to change stigmatizing attitudes and behaviours within the general population. More specifically, the program aims to reach the following target groups: (1) healthcare professionals; (2) service users and families; (3) schools and universities; (4) media; and (5) workplaces. Activities conducted by *1decada4* have included social media campaigns, the production of short documentary films, the development of a *Media Reporting Guide*, and various training courses and workshops.

Obertament

Obertament (*Open Mind*) is an anti-stigma program based in Barcelona, Catalonia, in Spain. The program was founded in 2010 and aims to improve the lives of all individuals living with mental illnesses. The program takes a population-based approach, aiming to reach all of Catalonia. A large regional survey, created in partnership with the Health Department of Catalonia, suggests that *Obertament's* campaigns reach between 9 and 11% of the Catalan population (the total population of Catalonia is approximately 7.5 million). The primary target groups of interest include: (1) media; (2) youth (education); (3) primary healthcare; and (4) workplace. Activities conducted by *Obertament* have been the development of the *Media Observatory*, which includes media guidelines for reporting on mental health-related topics and educational workshops for journalists; the development of online toolkits; activism training for the general population, which has helped to create a powerful network of anti-stigma champions throughout Catalonia; and the *What's Up!* project, which aims to raise awareness about stigma and increase mental health literacy among school-aged youth.

13.3.2.10 United States of America

Bring Change to Mind

Founded by actress and activist Glenn Close in 2010, *Bring Change to Mind* (*BC2M*) is a non-profit organization dedicated to encouraging dialogue about mental health, and to raising awareness, understanding, and empathy. The overall mission of *B2CM* is to end the prejudice and discrimination surrounding mental illnesses. Three major objectives (or pillars) guide the program: (1) creating national advocacy and awareness campaigns; (2) developing a national student-led high school club program, and (3) building a storytelling movement that works to end the stigma in the USA. Activities conducted by the program have included: supporting a

national dialogue about mental health through Public Service Announcements; developing evidence-based, peer-to-peer high school, and undergraduate programs; and providing platforms for individuals to share, connect, and learn about mental health and mental illnesses.

The Carter Centre
The Mental Health Program at the Carter Center was launched 35 years ago, established by former First Lady Rosalynn Carter. The initiative focuses on promoting awareness about mental health issues, informing public policy, achieving equity for mental health care comparable to other health care, and reducing prejudice and discrimination against individuals living with mental illnesses. The Rosalynn Carter Fellowships for Mental Health Journalism have been in existence for 21 years. This program provides stipends and training to journalists to support responsible reporting on topics related to mental health and substance use issues. The program currently awards journalists from the USA, Colombia, Qatar, and the United Arab Emirates, and has previously awarded journalists in Romania, South Africa, and New Zealand. Components of the program include social media support from previous fellowship recipients, as well as annual meetings with advisory groups. While professional journalists are the direct target group for the Fellowships for Mental Health Journalism, several broader target groups are indirectly impacted by the program, including policymakers and the general public (as consumers of media). The messaging that these journalists take back to their communities creates a snowball effect, educating countless additional individuals on language which supports accurate, non-stigmatized, and balanced reporting about mental health-related issues.

13.3.3 Smaller Anti-Stigma Programs

In addition to the programs described above, there are a number of anti-stigma activities underway across the globe spearheaded by local advocates, health providers, family members, people with mental illnesses, and a host of other social and policy people. These activities are typically unpublished or published in local journals and so are less apparent than the large international and national programs described in the previous sections. For example, Beldie and colleagues [35] catalogued anti-stigma activities in 14 midsize European countries (Austria, Belgium, Croatia, Czech Republic, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden, Switzerland, and Turkey). Eight of these countries had country-wide national programs and all had regional projects or campaigns. With the exception of three countries, anti-stigma programming was supported by the government, though the level of funding varied considerably. In many countries, work was supported by the pharmaceutical industry and in many cases, funding came from a variety of sources. Unlike the programs described above that undertook sustained anti-stigma activities, in these countries' activities were of short duration, sometimes restricted to a special day. Even where campaigns were of longer duration, activities occurred in short bursts. On the whole, anti-stigma activities

did not seek to empower people with mental illnesses and their families and there was no comprehensive effort to include people with mental illnesses or their families in the planning or implementation of these activities. Program evaluation has not been given much attention so it is unclear how effective these activities have been. This situation likely typifies much of the local anti-stigma work occurring throughout the world.

13.3.4 Interventions Targeting People with a Mental Illness

Development of interventions to address self-stigma is a relatively new area of activity, but one that seems to hold some promising results. However, the field is still in its infancy and much work is needed to solidify theoretical orientations, key ingredients, efficacy, and sustainability.

In 2016, Tsang and colleagues [36] conducted a systematic review and meta-analysis of 14 self-stigma reduction programs for people with serious mental illnesses (schizophrenia, schizophrenia spectrum disorder, bipolar disorder, or major mood disorder). Most of the programs adopted a psychoeducational approach with a combination of other components such as Cognitive Behavior Therapy (CBT), social skills training, goal attainment, and narrative therapy. The duration of the programs ranged from 10 to 40 sessions with sample sizes of 20–205 participants (total of 1131 participants; 879 in treatment and 452 in control groups). Two interventions were peer-led. Nine studies showed significant improvements and two showed sustainable effects. The authors concluded that most self-stigma programs appear to be effective; however, more research is needed. Similar findings were reported in an earlier critical review of the literature [37]. In the 14 articles reviewed, approaches varied considerably. Eight reported significant improvements in self-stigma.

In 2014, Yanos and colleagues [38] illustrated the variety of interventional approaches available by comparing the similarities and differences between six self-stigma programs. The *Healthy Self-Concept* intervention is a 12-week manualized group-based psychoeducational intervention focusing on individuals who had experienced their first episode of psychosis. The *Self-Stigma Reduction Program* is a 16-week manualized intervention using a combination of group and individual sessions. Psychoeducation, CBT, motivational interviewing, social skills training, goals setting, and action planning were all addressed. The *Ending Self-Stigma Program* is a 9-session manualized psychoeducational program. Sessions combine information, reflection, experience sharing, mutual support, discussion, skills and strategy practice, interactive exercises, and home-based practice. The *Narrative Enhancement and Cognitive Therapy* program is a structured manual-based group intervention with 20 sessions with personal sharing, psychoeducation, cognitive restructuring techniques, and narrative enhancement. *Coming Out Proud* is an approach that focuses on encouraging participants to explore and consider disclosure as a primary method of overcoming self-stigma. This is a 3-session, manualized group intervention that is solely peer-led. While it is primarily consciousness

raising, it does include some methods that are derived from motivational interviewing. Finally, the *Anti-stigma Photovoice Intervention* has participants take pictures and record narratives that relate to their experiences. It is a 10-week group-based intervention led by peer facilitators. It includes psychoeducation about stigma, experiential exercises to reduce endorsement of stereotypes about mental illnesses, and personal narratives about the pictures taken. The status of research on these interventions is minimal, but promising.

13.4 Future Challenges and Directions

13.4.1 Using Legislation to Promote Social Equity

In this context, equity is understood as providing individuals with what they need. This is to be differentiated from "equality" where everyone gets the same, regardless of their underlying need.

Though the public health importance of mental disorders has been recognized for more than two decades [39, 40], they are still not afforded the same policy and program priorities as other, equally disabling conditions. The majority of the world's population still has little or no access to mental health treatments, and most countries significantly underfund mental health programming. In many parts of the world, large custodial institutions still provide the only available source of psychiatric beds—institutions that have been widely associated with poor psychosocial outcomes and significant human rights violations [41]. Treatment inequities are examples of a deeply engrained process of structural stigmatization that results in widespread discrimination and human rights violations. As we move toward a new generation of stigma reduction initiatives rooted in the discourse illuminated in the UN Convention on the Rights of People with Disabilities [24], a key challenge will be identifying the legislative tools and policy levers that can be used to reduce social inequities for people with mental illnesses and promote their full and effective social participation.

In their book *Mental Illness, Discrimination and the Law* Callard and colleagues [42] provide ten central principles that can focus legislative action designed to promote social justice and reduce discrimination against people with mental disorders. The first is that "mental health" reform must go beyond health legislation and encompass sectors such as housing and education, to create a strong lattice of legal tools. Second, legislation must be accompanied by adequate enforcement so that rights and entitlements are enacted and this must not rely on those who have been wronged to seek redress. Instead, mechanisms to establish enforceable duties on sectors and bodies to protect and promote the rights of people with mental illnesses must be created. Third, legislative reform must go hand in hand with the political participation of those who have mental health problems. Meaningful involvement by people with mental illnesses in the development of legal solutions will be an important tool to ensure that reforms are beneficial, effective, and welcomed by those who are affected by them. Fourth, legislative reforms should seek to recognize

and support the exercise of people's capacity. Fifth, to be successful, legislative reforms will require support from key stakeholders in a number of different constituencies. This means that mental health advocates will have to make strong alliances with representatives in other sectors. Sixth, legislative clarity in the definition of terms used (such as disability, mental illness, and discrimination) will be paramount to ensure the rights and entitlements of people who have mental illnesses. Seventh, legislative reform should go hand in hand with strengthening mental health user organizations. The empowerment and self-advocacy of people with mental health problems and their representative organizations should be a priority. Eighth, legislative and policy reform should not exacerbate the problems of people with mental illnesses. Ninth, legislation should be enacted to ensure the full and effective participation of people with mental health problems; not as a form of charitable support. Finally, legislative action should give significant attention to deepening government accountability, transparency, and quality standards with respect to planning and enacting services and supports for people with mental health challenges. Underlying these principles is the idea that creative and animated human rights thinking can push us toward new ways of using the law to promote social justice for people with mental illnesses.

13.4.2 Building a Knowledge Base for Anti-Stigma Programming

Although countries are increasingly active in anti-stigma programming, evaluation of the effects of these programs, their sustainability, their transferability to other settings (such as low-income countries), or their overall cost-effectiveness is not well known. Validated fidelity criteria (or theories of change) which would identify the active ingredients in a program have not been widely addressed. Therefore, the clear articulation of the principles and procedures underliying anti-stigma programs that can be meaningfully tested using rigorous methods remains an important public health priority. In most countries, particularly in middle- and low-income countries, the funding for mental health research and evaluation is meagre or non-existent. Even in high-income countries, the funds available for mental health service evaluation is minimal, hit or miss, and incommensurate with the burden caused by mental disorders [43].

At least four of the large anti-stigma programs described above have built ties with university-based researchers in an effort to conduct outcome evaluations—the World Psychiatric Association's global program, *Open the Doors* [19], The UK's *Time to Change* [44], New Zealand's *Like minds Like Mine* [45], and *Canada's Opening Minds* [46]. Partnerships such as these demonstrate that community-university alliances are an important tool for developing and documenting best practices in stigma reduction. They also form a nexus of knowledge exchange between policy makers, providers, and researchers. In future, partnerships and networks such as these should expand to include young researchers from low- and middle-income countries who require training opportunities, networks of practice, and researcher collaborations. This would not only broaden our

understanding of how programs developed in high-income countries might translate into low- or middle-income countries, it could play an important role in global knowledge exchange. The challenge will be to find stable funding to promote these global efforts.

13.5 Summary and Conclusions

There is no doubt that stigmatization of mental illnesses remains a key public health challenge and an important human rights issue for people who have a mental illness and their family members. This chapter has provided an overview of mental health-related stigma reduction activities and reviewed some of the international and national initiatives currently underway to combat this problem. While the Convention on the Rights of Persons with Disabilities has provided an important rallying point for anti-stigma activities, sustained country-wide or international anti-stigma programs that employ best or promising practice are not yet the norm. More often there several underfunded activities that occurs in short bursts with little attention to effectiveness. Significant treatment inequities still exist across the globe and the majority of people world-wide who have a mental illness do not have access to treatments and community supports. Large and ill-equipped institutions are still the norm. Therefore, stigma reduction continues to be an old and unmet need in mental health.

References

1. Mora G. Stigma during the medieval and renaissance periods. In: Tasman A, Fink PJ, editors. Stigma and mental illness. Washington: American Psychiatric Press; 1999. p. 41–52.
2. Dols MW. Insanity and its treatment in Islamic society. Med Hist. 1987;31:1–14.
3. Fabrega H Jr. Psychiatric stigma in non-western societies. Compr Psychiatry. 1991;32(6):534–51.
4. Anderson RD. The history of witchcraft: a review with some psychiatric comments. Am J Psychiatry. 1970;126(12):69–77.
5. Tsang HWH, et al. A cross-cultural study of employers' concerns about hiring people with a psychotic disorder: implications for recovery. Soc Psychiatry Psychiatr Epidemiol. 2007;42:723–33.
6. Goldstein DE. Deranged psychopaths and victims who go insane: visibility and invisibility in the depiction of mental health and illness in contemporary legend. In: Blank TJ, Kitta A, editors. Diagnosing folklore. Jackson: University of Mississippi; 2015.
7. Shortt SED. Victorian lunacy. Cambridge: Cambridge University Press; 1986.
8. Arboleda-Florez J, Stuart H. From sin to science: fighting the stigmatization of mental illnesses. Can J Psychiatry. 2012;57(8):457–63.
9. Stuart H, Arboleda-Florez J, Sartorius N. Paradigms lost: fighting stigma and the lessons learned. Oxford: Oxford University Press; 2012.
10. Human Rights Watch. Living in hell. Abuses against people with psychosocial disabilities in Indonesia. s.l.: Human Rights Watch; 2016.
11. Cumming E, Cumming J. Closed ranks: an experiment in mental health education. Cambridge: Harvard University Press; 1957.
12. Stuart H. Canadian perspectives on stigma because of mental illness. In: Streiner D, Cairney J, editors. Mental disorder in Canada: an epidemiologic perspective. Toronto: University of Toronto Press; 2010. p. 304–30.

13. Dear MJ, Taylor SM. Not on our street. Brondesbury Park: Pion Limited; 1982.
14. Goffman E. Stigma: notes on the management of spoiled identity. Englewood Cliffs: Prentice-Hall; 1963.
15. Link BG, Phelan JC. Conceptualizing stigma. Annu Rev Sociol. 2001;27:363–85.
16. Goffman E. Asylums: essays on the social situation of mental patients and other inmates. Garden City: Anchor Books; 1961.
17. Hindshaw SP, Stier A. Stigma as related to mental disorders. Annu Rev Clin Psychol. 2008;4:367–93.
18. Corrigan P, et al. An attribution model of public discrimination towards persons with mental illness. J Health Soc Behav. 2003;44(2):162–79.
19. Sartorius N, Schulze H. Reducing the stigma of mental illness. Cambridge: Cambridge University Press; 2005.
20. Harpur P. Time to be heard: how advocates can use the convention on the rights of persons with disabilities to drive change. Valparaiso Univ Law Rev. 2011;45:1271–96.
21. Kayees R, French P. Out of the darkness into light? Introducing the convention on the rights of persons with disabilities. Hum Rights Law Rev. 2008;8:1–34.
22. Jongbloed L. Disability policy in Canada: an overview. J Disabil Policy Stud. 2003;13:203–9.
23. Szmukler G. "Capacity", "best interests", "will and preferences" and the UN Convention on the Rights of Persons with Disabilities. World Psychiatry. 2019;18(1):34–41.
24. Stuart H. United Nations convention on the rights of persons with disabilities: a road-map for change. Curr Opin Psychiatry. 2012;25:365–9. https://doi.org/10.1097/YCO.Ob013e328356b7ed.
25. Caldas de Almeida JM. The CRPD Article 12, the limits of reductionist approaches to complex issues and the necessary search for compromise. World Psychiatry. 2019;18(1):46–7.
26. Corrigan PW, et al. The public stigma of mental illness means a difference between you and me. Psychiatry Res. 2015;226:186–91.
27. Seeman N, et al. World survey of mental illness stigma. J Affect Disord. 2016;190:115–21.
28. Thornicroft G, et al. Global pattern of experienced and anticipated discrimination against people with schizophrenia: a cross sectional survey. Lancet. 2009;373:408–15.
29. Lasalvia A, et al. Cross-national variations in reported discrimination among people treated for a major depression worldwide: the ASPEN/INDIGO international study. Br J Psychiatry. 2015;207:507–14.
30. Stuart H, et al. Stigma in Canada: results from a rapid response survey. Can J Psychiatr. 2014;59(10 Suppl 1):S27–33.
31. Patten S, et al. Perceived stigma among recipients of mental health care in the general Canadian population. Can J Psychiatry. 2016;61:480–8.
32. Brohan E, et al. Self-stigma, empowerment and perceived discrimination among people with schizophrenia in 14 European countries: the GAMIAN-Europe study. Schizophr Res. 2010;122:232–8.
33. Ritsher JB, Phelan JC. Internalized stigma predicts erosion of morale among psychiatric outpatients. Psychiatry Res. 2004;129:257–65.
34. Corrigan PW, Larson JE, Rusch N. Self-stigma and the "why try" effect: impact on life goals and evidence-based practices. World Psychiatry. 2009;8(2):75–81.
35. Beldi A, et al. Fighting stigma of mental illness in midsize European countries. Soc Psychiatry Psychiatr Epidemiol. 2012;47:1.
36. Tsang HWH, et al. Therapeutic intervention for internalized stigma of severe mental illness: a systematic review and meta-analysis. Schizophr Res. 2016;173:45–53.
37. Mittal D, et al. Empirical studies of self-stigma reduction strategies: a critical review of the literature. Psychiatr Serv. 2012;63(10):974–81.
38. Yanos PT, et al. Interventions targeting mental health self-stigma: a review and comparison. Psychiatr Rehabil J. 2014;38(2):171–8.
39. Murray CJL, Lopez AD. The global burden of disease. Geneva: World Health Organization; 1996.
40. Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: the global burden of disease study. Lancet. 1997;349:1436–42.
41. World Health Organization. Mental health atlas 2017. Geneva: World Health Organization; 2018.

42. Callard F, et al. Mental illness, discrimination and the law. Fighting for social justice. Chichester: Wiley; 2012.
43. Stuart H. Building an evidence base for anti-stigma programming. In: Arboleda-Florez J, Sartorius N, editors. Understanding the stigma of mental illness: theory and interventions. Chichester: Wiley; 2008. p. 135–46.
44. Hederson C, Thornicroft G. Evaluation of the time to change program in England 2008-2011. Br J Psychiatry. 2013;202:S45–8.
45. Thornicroft C, et al. Impact of the "Like Minds, Like Mine" anti-stigma and discrimination campaign in New Zealand on anticipated and experienced discrimination. Aust N Z J Psychiatry. 2014;48(4):360–70.
46. Stuart H, et al. Opening minds in Canada: background and rationale. Can J Psychiatry. 2014;59(10 Suppl 1):S8–S12.