

New Directions in Psychiatry

Maurizio Pompili
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Andrea Fiorillo
Norman Sartorius
Editors

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ISBN 978-3-030-42636-1

ISBN 978-3-030-42637-8 (eBook)

<https://doi.org/10.1007/978-3-030-42637-8>

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The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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

1

Gaia Sampogna, Mario Luciano, Valeria Del Vecchio, Vincenzo Giallonardo, Benedetta Poci, 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.

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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 schizophrenia 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-HT_{1A} 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 in turn 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