

Current topics

Early detection and treatment of patients symptomatically at-risk for psychosis

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Over the last two decades, the treatment of psychosis has advanced substantially; yet, despite all progress, the immense individual and societal burden associated with psychosis, particularly due to schizophrenia, has largely stayed the same. Retrospective studies on the often years-long prodrome of psychotic disorders have shown that the vast majority of patients develop, among others, cognitive, perceptive, negative, and affective symptoms as well as precursors of positive symptoms and a significant loss of functioning even during the early phase of illness. Further, a long duration of untreated psychosis (DUP; time between the onset of the first frank psychotic symptom and the first adequate treatment) and a long duration of untreated illness (time between the onset of the first prodromal symptom and the first adequate treatment), have both been linked to a more negative outcome. For these reasons, an indicated prevention strategy of psychotic disorders and their negative consequences before they set in is regarded as the most promising approach to the management of these disorders.

Other than in universal preventive approaches, which utilize completely benign interventions broadly across the general population, indicated preventive approaches focus on patients with first signs of

the emerging disorder and use specific interventions, which are not necessarily completely benign. Thus, to limit the adverse effects and cost of treating individuals who may not require treatment, a reliable and valid early detection method is necessary to select patients who are at risk of developing psychosis.

Early detection of at-risk states of psychosis

Over the last two decades, two complementary main approaches to an early detection have been developed: (1) the ultra-high risk (UHR) criteria and (2) the basic symptom criteria.

Although differences predominately occur in timing the criteria and consideration of functional decline as well as in the consideration of disorganized and negative symptoms, the UHR criteria generally involve attenuated positive symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), and/or a combination of a genetic risk factor with a recent functional deterioration (Figure 2.1). Of these criteria, APS are consistently the most frequently endorsed, and are present in about 80% of UHR patients across studies [2]. They have therefore recently been proposed for inclusion in the forthcoming 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) due to be published in 2013 – and possibly in the *11th Revision of the International Classification of Diseases* projected for release in 2015 – as an attenuated psychosis syndrome (Figure 2.2) [3,4].

UHR criteria were originally designed to predict a high immediate risk of transition to psychosis within 1 year. Whilst the first studies seemed to support this assumption with 1-year transition rates of up to 50% [5–7], lower transition rates in recent studies have led to the generally accepted 1-year transition rate in UHR patients of about 20% [2]. Yet, even this lower estimate is several hundred times higher than the incidence rate in the general population of 0.035%, and studies with longer observation periods indicate a further increase in transition rates to psychosis beyond the first year to at least up to 35% [9]. More recently, interest in the longitudinal outcome of UHR patients beyond psychosis has grown. Initial studies on UHR patients undergoing diverse treatments, including antipsychotic medication, revealed remission rates

The ultrahigh risk criteria for transition to psychosis according to the Structured Interview for Psychosis-Risk Syndromes

Attenuated psychotic symptoms

Any one of the following symptoms that are qualitatively below the threshold of frank psychosis:

- **Abnormal or unusual thought content:** “magical” thinking that influences behavior and is inconsistent with subculture norms; ideas of reference and/or alien control (“Ich-Störungen”); paranoid, grandiose, somatic and/or other unusual ideas that are puzzling, preoccupying, or distressing and may affect functioning but are not held with delusional conviction
- **Abnormal suspiciousness,** ranging from slight mistrustful behavior and/or recurrent yet unfounded sense that people might be saying or thinking negative things about the person, to an anxious, unsettled state of mind with potential guarded presentation that may hinder the clinical interview
- **Perceptual abnormalities** (eg, acoustic, visual, olfactory, gustatory, tactile, somatic): persistent and puzzling perceptual distortions; recurrent unformed images, such as shadows, trails, or sounds (including hearing one’s own name being called); illusions, pseudohallucinations, and/or hallucinations that are perceived as external but not yet as real and distinct from the person’s thoughts (skepticism can be induced)
- **Abnormal organization of communication:** single incoherent words; temporarily going “off-track,” or some loosening of association, circumstantial or tangential speech; responsive to structuring of the interviews, prompts, or questions

AND

Symptoms have begun or worsened in quality in the past year

AND

Symptoms occurred at least once per week for the last month

Brief Limited intermittent psychotic symptoms

Any one of the following frank psychotic symptoms:

- **Delusions** including severe suspiciousness held with conviction that interfere with thinking and behavior
- **Hallucinations** perceived as real and distinct from the person’s thoughts that interfere with thinking and behavior (skepticism cannot be induced)
- **Formal thought disorders** such as unintelligible speech or loose, irrelevant, or blocked thoughts that do not respond to structuring of the interview

AND

Symptoms have begun in the past 3 months

AND

Symptoms occur currently at least several minutes per day at least once per month

Genetic risk plus recent deterioration

At least one **first-degree relative with history of any nonaffective or affective psychosis**

OR

Schizotypal personality disorder in patient

AND

Substantial functional deterioration in the past year (defined as a drop in the Global Assessment of Functioning score of at least 30% during the last month compared to the patient’s highest score in the previous 12 months)

Figure 2.1 The ultrahigh risk criteria for transition to psychosis according to the Structured Interview for Psychosis-Risk Syndromes (continues overleaf).

The ultrahigh risk criteria for transition to psychosis according to the Structured Interview for Psychosis-Risk Syndromes (continued)

General exclusion criteria

Past or present psychosis can be ruled out (ie, psychotic symptoms have never occurred for more than 1 hour per day and more than four times per week within 1 month and/or have never been disorganizing or dangerous)

AND

Symptoms are not sequelae of drug or alcohol use

AND

Symptoms are not better explained by another organic or mental disorder

Figure 2.1 The ultrahigh risk criteria for transition to psychosis according to the Structured Interview for Psychosis-Risk Syndromes (continued). Adapted from McGlashan et al [1].

Criteria of the attenuated psychosis syndrome proposed for the DSM-V

All six of the following:

- Characteristic symptoms: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency that it is not discounted or ignored:
 - delusions
 - hallucinations
 - disorganized speech
- Frequency/currency: symptoms must be present in the past month and occur at an average frequency of at least once per week in the past month
- Progression: symptoms meeting the first criterion must have begun or significantly worsened in the past year
- Distress/disability/treatment seeking: symptoms are sufficiently distressing and disabling to the patient and/or parent/guardian to lead them to seek help
- Symptoms are not better explained by any other DSM-V diagnosis, including substance-related disorder
- Clinical criteria for any DSM-V psychotic disorder have never been met

Figure 2.2 Criteria of the attenuated psychosis syndrome proposed for the DSM-V. Adapted from the American Psychiatric Association [3].

from their UHR status – but not necessarily from mental problems – of at least 50% within 1 year [11,12]. For the assessment of UHR criteria, special interview scales were developed that allow a sufficiently reliable rating when applied by trained clinicians (eg, the North-American Structured Interview for Psychosis-Risk Syndromes and the Australian Comprehensive Assessment of At-Risk Mental States) [1,13].

Whilst the information from different sources is integrated in the assessment of UHR criteria (eg, patient's report, third party's report, and interviewer's observations), the assessment of at-risk criteria according to the basic symptom concept exclusively relies on the report of the patient

and, therefore, on his/her self-perception and insight; the interviewer only makes sure that the reported complaint truly meets the definition of the basic symptom in question. Basic symptoms are subtle and subjectively experienced subclinical disturbances in drive and stress tolerance that affect thinking, speech, bodily and sensory perception, motor action, and central-vegetative functions. Such symptoms can occur decades before the onset of frank psychosis. By definition, they differ from what is considered to be one's "normal" mental self and are not evoked by substance misuse or somatic illness. They remain predominately private and apparent only to the affected person and are rarely directly observable to others. Due to the emphasis on the subjective and self-experienced character, basic symptoms differ from negative symptoms, which are now predominately assessed as deficits in behavior observable to others.

Spontaneously and immediately self-recognized as mental changes, basic symptoms are also distinct from frank or more severe attenuated psychotic symptoms that are experienced by the patient as real normal thinking and feeling. Yet, although insight that something is wrong with one's mental processes is present, some experiences might be so new and strange that they remain nearly inexplicable. Hence, a detailed description of these experiences usually requires help in the form of guided questioning by trained interviewers. The ability to experience basic symptoms with insight and to cope with them, however, often attenuates with progressive illness (ie, with emerging psychotic symptoms and more severe APS), but is restored upon remission.

There are two criteria used to assess basic symptoms: COgnitive-PERceptive basic symptoms (COPER; Figure 2.3) and COgnitive DISturbances (COGDIS; Figure 2.4) [14–17]. Despite their partial overlap in symptoms, the two criteria slightly differ in their predictive accuracy: whilst COPER performs better in ruling out subsequent psychosis (ie, has a lower rate of false-negative predictions and a higher sensitivity), COGDIS performs better in ruling in subsequent psychosis (ie, has a lower rate of false-positive predictions and a higher specificity). Naturalistic long-term follow-up studies reported transition rates to first-episode psychosis (FEP) within an average period of 10 years (minimum 5 years; no antipsychotic treatment before onset of psychosis) and within 4 years

(various treatments including antipsychotic treatment before the onset of psychosis), respectively, of 65% and 38% for COPER and 79% and 39% for COGDIS [18]. Across studies, the average 1-year transition rate of both basic symptom criteria is about 20% [14].

The basic symptom criteria: COGDIS

Any two of the following nine basic symptoms with at least weekly occurrence within the previous 3 months:

- **Thought interference:** an intrusion of completely insignificant thoughts that are not related to the intended thought and hinder concentration and thinking without resulting in a loss of the train of thoughts
- **Thought pressure:** a self-reported “chaos” of thoughts; a great number of random, different thoughts or images enter the mind and disappear again in quick sequences without the ability to suppress or guide them; the successive thoughts are completely unrelated to each other or to the intended content of the patient’s thinking
- **Thought blockages:** a subjective blocking of thought that can also be experienced as a sudden emptiness of thoughts, interruption of thoughts, fading (slipping) of thoughts, or losing the thread of thoughts. The original topic might subsequently be recalled or completely lost
- **Disturbance of receptive speech:** a disturbance in the immediate comprehension of simple words and sentences, either read or heard, that can result in giving up reading or avoiding conversations; it resembles “normal” problems with second languages, when a word is recognized as familiar but one cannot recall it, or its meaning is delayed
- **Disturbance of expressive speech:** self-experienced problems in producing appropriate words, sometimes also experienced as a reduction in active vocabulary; a self-recognition of verbal fluency, precision, and availability of language being slowed down
- **Disturbance of abstract thinking:** deficits in the comprehension of any kind of abstract, figurative, or symbolic phrases or contents as well as phenomena of concretism; an exceptional basic symptom that can either be self-reported or observed and rated when tested (eg, by asking to explain sayings or idioms)
- **Inability to divide attention** between simultaneous nondemanding tasks that each draw primarily upon a different sense that would not usually require a switching of attention; generally at least one demand is performed on a (semi-)automatic level and does not require full attention (eg, a patient may not be able to listen and pay attention to an oral presentation and take down notes at the same time; or cannot prepare a sandwich and talk to a family member at once)
- **Captivation of attention by details of the visual field** that catch and hold the look and attention; an ordinary visual stimulus or part of it stands out strikingly, appears almost isolated from the rest of the environment and is emphasized so that this single aspect of the environment catches and captures the attention completely; might also be described as a “fixation of perception” or “spell-bounding”
- **Unstable ideas of reference** with immediate insight into the pathological, “weird” nature of the feeling of reference (ie, a vague feeling that random events or comments and actions by others were related to oneself, while instantly knowing that this is impossible or at least most improbable). Other than in ideas of reference, the feeling of reference is not considered as reality-based, and no cognitive processes like reasoning or weighing pros and cons are involved before overcoming the idea (reality testing is completely intact)

Figure 2.3 The basic symptom criteria: COGDIS. Adapted from Schultze-Lutter et al [14].

The basic symptom criteria: COPER

Any one of the following ten basic symptoms WITH at least weekly occurrence within the prior three months AND first occurrence at least twelve months ago:

- **Thought interference** (see Figure 2.3)
- **Thought perseveration:** an obsessive-like repetition of banal thoughts or images of no emotional significance that can be related to all possible trivial past events; these “memories” are so unimportant and lacking in emotion that, even in the patient’s evaluation, they do not justify the excessive mental occupation given to them
- **Thought pressure** (see Figure 2.3)
- **Thought blockages** (see Figure 2.3)
- **Disturbance of receptive speech** (see Figure 2.3)
- **Decreased ability to discriminate between ideas and perception, fantasy and true memories:** a disturbance in the ability to surely distinguish internal, mentally generated events from external, perceived or experienced events, leading to a difficulty in locating the source of the experience/memory (not rated if the patient questions certain perceptions or does not fully trust himself anymore)
- **Unstable ideas of reference** (see Figure 2.3)
- **Derealization:** a change in how one relates emotionally to the environment with two potential forms:
 1. An alienation from the visual world (ie, how one sees the world). The environment appears unreal, changed and strange in a way that is often hard to describe. Here the individual feels estranged from the world and the usual emotional ties to the surroundings no longer exist or have become considerably weaker; a feeling of being disconnected from the environment.
 2. An increased emotional affinity for the environment. The environment, or certain isolated aspects of it, are exceptionally emotional impressive; often accompanied by rather positive or euphoric feelings
- **Visual or acoustic perception disturbances** with immediate complete insight. Unlike hallucinations or schizotypal perceptual distortions, perceptual basic symptoms are not regarded as real but are immediately recognized as a sensory or subjective problem. The knowledge that the misperception (eg, a wrong coloring, distorted shape or changed sound quality/intensity), has no counterpart in the real world is immediate and unquestioned

Figure 2.4 The basic symptom criteria: COPER. Adapted from Schultze-Lutter et al [14].

Studies combining UHR criteria, particularly APS, and basic symptom criteria, particularly COGDIS, indicate that the combined presence of APS and COGDIS signals the highest short-term risk of transition (within 1 to 2 years) compared to the presence of either criterion alone [10]. Further, in a recent meta-analysis of studies employing different at-risk criteria, the transition rate appeared to be influenced by the particular at-risk criteria that were employed, with higher rates reported in studies employing the basic symptom approach as compared to studies employing the UHR approach [19].

In conclusion, the 1-year incidence rates of psychosis in at-risk patients (predominately adult or mixed adult and adolescent samples)

are generally several hundred times higher than the 0.035% rate in the general population. However, the still high proportion of seeming false-positives, at least within shorter follow-up periods, has fostered ethical concerns about unnecessary preventive measures and stimulated a search for additional predictors. Further, about 18% of patients with FEP have the onset of the full-blown disorder before the age of 18 years, and an even more significant proportion of patients has the onset of the prodrome in childhood and adolescence [20]. Thus, it still remains to show that at-risk criteria are unaffected by potential developmental peculiarities and are also valid to a similar degree in these young age groups.

Other disturbances in at-risk states of psychosis

One indisputable general finding resulted from the studies searching for additional predictors to increase the predictive ability of existing at-risk criteria: irrespective of a future development of psychosis, people presenting at mental health services with at-risk criteria suffer from a large variety of other psychopathological symptoms or even mental disorders. The most common symptoms and disorders include depressive disorders and social phobia, functional deficits (including deficits in stress coping strategies), and deficits in social cognition, and affect regulation and meta-cognition, such as negative beliefs about an individual's own ability to control events. Further, among others, at-risk persons exhibit neurocognitive deficits (particularly in verbal fluency and memory, working memory, and processing speed), electrophysiological aberrations indicative of a gating deficit, local reductions of gray matter (particularly in cingular structures), and deficits in functional MRI indicative of a hypofunction of the prefrontal cortex, as well as aberrations in PET and MRS studies pointing toward disturbances in serotonergic and dopaminergic neurotransmission, and an increased level of anandamide in the cerebrospinal fluid. In addition, they report a reduced quality of life that is similarly impaired to that of FEP patients.

In light of the impressive and still growing evidence of deficits in this group of help-seeking patients, above and beyond their potential risk of psychosis, their clinical status clearly meets DSM-IV-TR criteria of a mental

disorder that is “conceptualized as a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress (...) or disability (ie, impairment in one or more important areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom” [21]. Therefore, these patients should be considered as “ill” and in need of treatment.

Early intervention in at-risk states of psychosis

Despite the need for treatment for present symptoms and problems, early intervention studies have mainly focused on the prevention of future psychotic symptoms above the threshold for full-blown psychosis. Though the number of early intervention studies is still limited and study samples had often been small, encouraging results have already been reported from pharmacological and psychotherapeutic trials. And a recent review of five randomized controlled studies (two based on medication, two on psychological or psychosocial treatment, and one on a neuroprotective fatty acid treatment) concluded that receiving any focused treatment was associated with a lower risk of developing psychosis as compared to no treatment or treatment as usual, indicating a relative risk of 0.36 (95% CI, 0.22–0.59) in the treatment group at the time of treatment cessation [22]. In most studies, however, this “preventive” effect was not stable after treatment cessation, indicating a delay rather than a prevention of psychosis.

Initial early intervention studies in UHR and related samples, each comprising only approximately 60 participants, were modeled on treatments for full-blown psychosis and mainly applied low-dose medication with antipsychotic drugs (risperidone and olanzapine) with or without additional psychotherapy or cognitive–behavioral psychotherapy, not excluding use of antipsychotics [23–25]. A phase-specific treatment approach was followed in the German Research Network on Schizophrenia, in which two larger early intervention trials were conducted, each including approximately 120 patients. One study explored the effects of cognitive–behavioral therapy in at-risk patients identified by COPER and/or an adapted UHR genetic risk criterion [26]; the other

studied the effects of low-dose amisulpride in at-risk patients reporting APS or BLIPS [27]. The studies differed in the length of the treatment period (between 6 months and 2 years) and terminated according to study protocols irrespective of the clinical state.

However, studies are frequently evaluated under the presumption that an intervention can only be regarded as successful when its effects remain after treatment cessation. Yet to do so, a successful intervention with long-term effect would have to override the impact of a highly complex interplay of genetic, epigenetic, neurodevelopmental, and psychosocial factors that start at conception and determine the risk of, and progression to, psychosis. In somatic disorders with longstanding risk conditions, long-term rather than short-term intervention is therefore a common strategy (eg, in the prevention of stroke). As implied by the concept of indicated prevention, however, this would certainly require treatment strategies with a very favorable cost–benefit ratio for at-risk individuals. Thus, current concepts of an effective prevention in terms of time-limited interventions should be reconsidered.

A promising new road to the prevention of psychosis, which is not modeled on treatments of frank psychosis but a unique opportunity in the early states, is based on a recent neuroprotective intervention study. In this randomized controlled study of a 3-month high-dose treatment with omega-3 fatty acids in a sample of 81 UHR patients [28], the effectiveness in preventing transition and improving current symptoms indicated that it may indeed be possible to develop benign interventions particularly for the at-risk state, independent of their effectiveness in manifest psychosis, that, furthermore, have lasting effect after treatment cessation. Though a long-term effect of a well-tolerated substance would be the most desired and would present a therapeutic breakthrough, these first results still have to be confirmed and extended, particularly with regard to truly long-term effects spanning years. Moreover, it will be necessary to investigate whether such preventive treatment is also efficient in adults past the main years of brain development. Also, should larger replication studies reveal that a short-term intervention is not as sufficient as the first study has suggested, long-term tolerability of high doses of omega-3 fatty acids will have to be studied.

In summary, it is most important to intensify basic research efforts in these early stages and to develop new special early intervention approaches from these findings. Furthermore, recent observations indicate that at least the temporal variance of risk estimation by UHR criteria is broader than originally expected. Therefore, improved enrichment strategies or clinical staging algorithms that allow a more individualized risk classification or stratification have to be developed to increase the homogeneity of individual risk levels in study samples; this might prove a necessary precondition for conclusive risk-adapted prevention trials. However, after preventive intervention strategies have proven their efficacy in studies on at-risk patients seeking help in specialized services, the next challenge will be to prove the effectiveness of an early intervention at epidemiological level (ie, with regard to all subjects at increased risk of developing psychosis and not only the subsample of those seeking help early).

To conclude, although the first one and a half decades of early detection and intervention research in psychosis have already produced encouraging results, much remains to be done before evidence-based, detailed intervention guidelines can be developed and implemented into clinical settings. Until then, the rather vaguely defined guidelines formulated in 2005 by the International Early Psychosis Association (IEPA) writing group (Figure 2.5), which are due to be updated, will have to serve as a general framework to the clinical handling of people exhibiting potential at-risk symptoms of psychosis.

First-episode psychosis

Eóin Killackey

FEP presents a great opportunity to provide quality interventions, positively engage the patient in treatment of the psychosis, and minimize the secondary disability that can stem from psychosis. The 2005 IEPA guidelines on the interventions for FEP are summarized in this chapter.

Two important dimensions of interventions for FEP are the timing of the intervention (and therefore DUP) and the quality of the intervention (the sustained provision of comprehensive phase-specific treatment).

Treatment guidelines of the International Early Psychosis Association writing group

If young people with an at-risk mental state are actively seeking help for the distress and disability associated with their symptoms, they need to be:

- Engaged and assessed
- Offered regular monitoring of mental state and support
- Offered specific treatment for other syndromes, such as depression, anxiety, or substance misuse, and assistance with problem areas such as interpersonal, vocational, and family stress, if present
- Provided with psychoeducation and encouraged to develop coping skills for subthreshold psychotic symptoms
- Offered family education and support
- Provided information in a flexible, careful, and clear way about risks for mental disorders as well as about existing syndromes

Such care can be carried out in a low stigma environment, such as home, primary care, or a youth-friendly office-based setting

Antipsychotic medications are not usually indicated unless the person meets criteria for a DSM-IV/ICD-10 psychotic disorder. Exceptions should be considered when rapid deterioration is occurring; severe suicidal risk is present, and treatment of any depression has proved ineffective; or aggression or hostility are increasing and pose a risk to others. If antipsychotics are considered, ideally, atypical medications should be used in low doses and considered as a “therapeutic trial” for a limited period. If there is benefit and resolution of symptoms after 6 weeks, the medication may be continued with the patient’s consent for a further 6 months to 2 years, following explanation of risks and benefits. After this period, a gradual attempt to withdraw the medication should be made if the patient agrees and there has been a good recovery. If the patient has not responded to one atypical antipsychotic, another may be tried if the above indications still exist

If young people with an at-risk mental state are not seeking help, then regular contact with family members or friends may be an appropriate strategy

The evidence of the effectiveness of treatments aimed specifically at reducing the risk of transition to psychosis (eg, cognitive and family therapy, antipsychotic medication, or experimental neuroprotective drug strategies) remains preliminary. More data are required and the risk–benefit ratio of various interventions needs to be determined

Figure 2.5 Treatment guidelines of the International Early Psychosis Association writing group. Adapted from the International Early Psychosis Association Writing Group [29].

Although this topic is beyond the scope of this book, identification and treatment of people at risk of psychosis have resulted in the reduction of DUP to zero.

Often, as a result of both the nature of onset of psychosis and resource issues in mental health care systems, there are prolonged delays in initiating effective treatment for FEP. Although there was previously some debate, prolonged DUP is now known to be independently associated with poorer response and outcome. The clinical staging model being applied to mental illnesses suggests that identification of patients in the earliest

phases of psychotic disorders allows for more optimal treatment, and is likely to reduce the burden of disease while it is active. Any improvements in long-term outcome should be seen as a bonus, rather than as a prerequisite for improving clinical standards during early illness.

FEP tends to be more responsive to treatment than subsequent episodes; later phases of illness tend to be less stable and may evolve over time, making definitive diagnosis more difficult. The umbrella term “psychosis” accommodates this syndromal flux and comorbidity, and allows treatment to be commenced for all prominent syndromes before a definitive diagnosis, such as schizophrenia, can be or has to be applied. Thus, whether core schizophrenia can be diagnosed is not crucial for effective treatment in FEP. A notable example is that cannabis use is common in FEP and can cause confusion and delay in treating the psychotic episode. Significant cannabis use appears to be a risk factor for the onset of schizophrenia, as well as an aggravating factor for the subsequent course. It is crucially important, therefore, that there is no disconnect between the management of the substance abuse and the mental disorder; rather, a unified approach is called for. Recommendations for treatment of FEP are listed in Figure 2.6.

Recommendations for treatment of first-episode psychosis

- Strategies to improve the treatment of first-episode psychosis include better mental health literacy, more informed primary care, and greater responsiveness of public and private psychiatry to possible cases. Community-wide education systems should be developed to improve understanding of how psychotic disorders emerge in a previously healthy person and how to seek and obtain effective advice, treatment, and support
- A high index of suspicion and a low threshold for expert assessment should be set
- Entry and retention within specialist mental health services is often based on a reactive, crisis-oriented model, in which patients must reach a threshold of behavioral disturbance, risk, disability, or chronicity before they are retained. This model is a poor use of resources and creates unnecessary trauma, demoralization, and therapeutic nihilism in patients, families, and clinicians. Instead, services should aim for proactive retention of patients throughout the first 3–5 years of illness, combining developmental (youth) and phase-specific perspectives
- Initial treatment should be provided in an outpatient or home setting, if possible. Such an approach can minimize the trauma, disruption, and anxiety of the patient and family, who are usually poorly informed about mental illness and have fears and prejudices about in-patient psychiatric care. In-patient care is required if there is a significant risk of self-harm or aggression, if the level of support in the community is insufficient, or if the crisis is too great for the family to manage, even with home-based support

Figure 2.6 Recommendations for treatment of first-episode psychosis (continues overleaf).

Recommendations for treatment of first-episode psychosis (continued)

- In-patient care should be provided in the least restrictive environment. Optimal in-patient units should be streamed by phase of illness and developmental stage, be relatively small in size, and be staffed adequately, so that one-to-one nursing of highly distressed, suicidal or agitated young people is possible, without locking sections of the unit or secluding the patient, unless this is absolutely necessary. The use of traditional psychiatric intensive care, a pragmatic intervention that lacks a solid evidence base, is especially traumatic for these patients. Where streaming is not possible, a special section may be created in a general acute unit for young recent-onset patients
- Pharmacological treatments should be introduced with great care in medication-naïve patients to do the least harm while aiming for the maximum benefit. Appropriate strategies include graded introduction, with careful explanation, of low-dose antipsychotic medication, plus antimanic or antidepressant medication, where indicated. Skilled nursing care, a safe and supportive environment, and regular and liberal doses of benzodiazepines are essential to relieve distress, insomnia, and behavioral disturbances secondary to psychosis, while antipsychotic medication takes effect
- The first-line use of atypical antipsychotic medication is recommended on the basis of better tolerability and reduced risk of tardive dyskinesia. In the longer term, the risk–benefit ratio may change for some patients (eg, if weight gain or sexual side effects associated with the atypical agents develop). Typical antipsychotic medications may then be one of the options considered
- Initial assessment should include a baseline computed tomography scan, neurocognitive screen, neurologic examination for movement disorder, electrocardiogram, body mass index, and a fasting serum glucose level
- Psychosocial interventions, especially cognitive–behavior therapy (CBT), are an important component of early treatment, providing a humane basis for continuing care, preventing and resolving secondary consequences of the illness, and promoting recovery. CBT may also be helpful for comorbid substance use, mood and anxiety disorders, and improving treatment adherence
- Families and, whenever possible and appropriate, other members of the patient's social network, should be supported actively and educated progressively about the nature of the problem, the treatment, and the expected outcomes. If there are frequent relapses or slow early recovery, a more intensive and prolonged supportive intervention for families is required
- If recovery is slow and remission does not occur despite sustained adherence to two antipsychotic medications (at least one of which is an atypical medication) for 6 weeks each, early use of clozapine and intensive CBT should be considered seriously
- Early use of clozapine should also be considered if suicide risk is prominent or persistent

Figure 2.6 Recommendations for treatment of first-episode psychosis (continued). Adapted from McGorry et al [30].

As stated, FEP is a prime opportunity for intervention. The earlier and more appropriately this intervention begins, the better. An optimal and sustained intervention at this point has the greatest possibility of reducing the secondary disability wrought by psychosis. In addition, it increases the probability of better quality-of-life outcomes for the patient. To achieve these objectives, a goal-oriented framework focused on

recovery is required, rather than a mindset that concentrates on chronicity and disability. Good practice in this area is to stay abreast of the development of pharmaceutical and psychological therapies targeted at FEP, incorporate evidence-based guidelines developed around FEP into clinical practice, and convey optimism and hope to those experiencing FEP and to their families and friends.

Cognitive dysfunctions in schizophrenia

Steffen Moritz

Many patients with schizophrenia display severe neurocognitive dysfunction in a wide variety of domains, most notable memory and executive functioning. These dysfunctions are in most cases present at the first exacerbation but, unlike Kraepelin's initial concept of "dementia praecox" at the end of the nineteenth century, do not necessarily progress during the course of the illness, beyond age-related decrement. Although neurocognitive deficits are not obligatory for diagnosis, the necessity for their identification and treatment in schizophrenia is increasingly acknowledged.

In the past decade, a large body of empirical evidence has been accumulated showing that cognitive disturbances are important determinants of functional outcome variables such as social relationships and work status. For example, in a meta-analysis, it was demonstrated that memory dysfunction is a particularly strong predictor of functional outcome in schizophrenia [31]. In addition, there is increasing recognition of the impact of neuropsychological dysfunction on a number of treatment-related variables, such as insight and coping skills.

Neurocognitive dysfunction may also exert a negative impact on compliance with medication. For example, several psychotropic agents, especially benzodiazepines and anticholinergic medications, with the latter often being prescribed to attenuate the side effect of conventional neuroleptics, are known to have potential adverse effects on neurocognition in some patients. When such side effects remain unnoticed, drug discontinuation may occur, especially if the patient considers that the adverse side effects outweigh the benefits of drug treatment.

Evaluation of negative medication effects is also essential, given that many patients are already cognitively impaired before treatment, potentially compromising the outcome of psychotherapeutic or psychoeducational treatment. Memory problems and dysfunctions in abstract logical thinking may severely limit the outcome of insight-based psychotherapeutic interventions. A compromised capacity to store information, as evidenced by many psychiatric patients, as well as older patients with or without mental illness, may also lead to forgetfulness about taking medication and the purpose and contents of psychotherapy, with forgetting about the latter being a further risk factor for noncompliance. Recently, we found that approximately one third of patients with schizophrenia do not take their medication as prescribed because of prospective memory problems.

Once neurocognitive problems have been detected, there are a number of strategies that can be used to deal with such dysfunctions in psychiatric patients. With regard to memory problems, clinicians should repeat essential information regularly, check from time to time that patients are indeed grasping the core aspects of therapy, give the most essential information in written form (especially on medication and dosage, but also for cognitive-behavioral intervention and stress management) and, when appropriate, involve relatives in the session so that they can remind patients in their own homes. To illustrate, the effects of psychoeducation are usually more effective when relatives are involved. Patients with decreased sustained attention benefit from more frequent but shorter therapeutic sessions. In addition, there is evidence that cognitive remediation programs are effective for at least some patients. The administration of second-generation antipsychotics may ameliorate some neurocognitive symptoms (possibly via the improvement of negative symptoms), or at least may not aggravate neurocognitive dysfunctions. However, in view of conflicting new evidence on the neurocognitive effects of atypical antipsychotics, a seemingly closed chapter has been reopened.

Clinicians may want to evaluate whether medications that are potentially harmful to memory, such as benzodiazepines and anticholinergic agents, are still necessary or could at least be diminished in dosage. In any case, the presence of memory and other neurocognitive problems

should not be disregarded as a minor problem or lesser evil given their possible impact on compliance with medication, insight, treatment, and functional outcome. In addition, cognitive dysfunctions may cause increased stress at work or school, because many jobs necessitate intact selective attention, vigilance, and memory. To compensate for neurocognitive problems, the impaired patient must devote more effort to a task than individuals whose cognitive functioning is normal. However, this causes stress, a major risk factor for renewed exacerbation of psychiatric symptoms according to the widely accepted vulnerability–stress model of psychiatric illness. This creates a vicious circle when job demands are not suited to the patient’s cognitive abilities.

Cognitive biases and metacognitive training in schizophrenia

In addition to neurocognitive impairment, cognitive biases (or cognitive distortions) are being increasingly investigated. This line of research encompasses a wide variety of response styles and cognitive distortions. Prominent biases are jumping to conclusions (eg, hasty decision making), deficits in theory of mind (eg, failure to empathize with others and to deduce motifs), a bias against disconfirmatory evidence, overconfidence in errors, negative self-schemata, and monocausal attributional styles. There is evidence that these styles are related to the emergence and maintenance of psychotic symptoms, especially delusions, in concert with other factors. Importantly, these cognitive distortions seem to precede psychotic breakdown and the patient is not fully aware of them (ie, many patients lack metacognitive insight into these problems). Hence, a training program, entitled metacognitive training (MCT), has been developed (Figure 2.7). Its eight modules aim to raise the patient’s awareness of these distortions and to prompt the patient to critically reflect on, complement, and change his or her current repertoire of problem solving. Thus, its main purpose is to change the “cognitive infrastructure” of delusional ideation. As psychosis is rarely an instantaneous incident, changing the appraisal of one’s cognitions and social environment may act prophylactically on psychotic symptoms. The modules are administered in the framework of a group intervention program. Several studies

Summary of each metacognitive training module		
Module	Target domain	Description of core exercises
1. Attribution: blaming and taking credit	Self-serving bias versus depressive attributional style	Different causes of positive and negative events must be contemplated. For example, "a friend was talking behind my back"; dominant interpretation: "friend is not trustworthy" (blaming others); alternatives: "I have done something bad" (blaming self), "she is preparing a surprise party for my birthday" (circumstances). Explanations that take into account various causes are preferred to monocausal explanations. The negative consequences of self-serving attribution are repeatedly highlighted
2. Jumping to conclusions, I	Jumping to conclusions; liberal acceptance; bias against disconfirmatory evidence	Motifs contributing to hasty decision making are discussed and its disadvantages are stressed. Fragmented pictures are shown that eventually display objects. Premature decisions often lead to errors, emphasizing the benefits of cautious data gathering. In the second part, ambiguous pictures are displayed. Here, a quick survey leads to the omission of details demonstrating that first impressions may often reveal only half the truth
3. Changing beliefs	Bias against disconfirmatory evidence	Cartoon sequences are shown in backward order, which increasingly disambiguate a complex scenario. After each new picture, patients are asked to (re-)rate the plausibility of four interpretations. Although the initially most likely interpretation prevails in some pictures in the course of the exercises, patients are "led up the garden path" on others. Thus, patients learn to withhold strong judgments until sufficient evidence has been collected, and encouraged to maintain an open attitude toward counter-arguments and alternative views
4. Empathy, I	Theory of mind, first order	Facial expression and other cues are discussed for their relevance to social reasoning. Pictures of human faces are presented in the exercises. The group should guess what the depicted character(s) may feel. The correct solution often violates a first intuition, demonstrating that relying on facial expression alone can be misleading. In the second part, cartoon strips are shown that either must be completed or brought into the correct order. Participants are shown that social inferences should involve multiple cues

Figure 2.7 Summary of each metacognitive training module (continues opposite).

Summary of each metacognitive training module (continued)		
Module	Target domain	Description of core exercises
5. Memory	Overconfidence in errors	Factors that foster or impair memory acquisition are discussed first, and examples for common false memories are presented. Then, complex scenes (eg, beach) are displayed with two typical elements removed (eg, towel, ball). Owing to logical inference, gist-based recollection and liberal acceptance, many patients falsely recognize these lure items in a later recognition trial. The constructive rather than passive nature of memory is thus brought to the participants' attention. Patients are taught to differentiate between false and correct memories by means of the vividness heuristic
6. Empathy, II	Theory of mind, second order; need for closure	Different aspects guiding theory of mind (eg, language) are discussed with respect to both their heuristic value and fallibility for social decision making. Then, cartoon sequences are presented, and the perspective of one of the protagonists must be considered, which involves discounting knowledge available to the observer but not available to the protagonist. For the majority of sequences, no definitive solutions can be inferred, which is unsatisfactory for patients with an enhanced need for closure
7. Jumping to conclusions, II	Jumping to conclusions/liberal acceptance	As in module I, the disadvantages of quick decision making are outlined with regard to events related and unrelated to psychosis. In the exercises, paintings are displayed, for which the correct title must be deduced from four response options. On superficial inspection, many pictures tempt false responses
8. Mood and self-esteem	Mood and self-esteem	First, depressive symptoms, causes, and treatment options are discussed. Then, typical depressive cognitive patterns in response to common events are presented (eg, overgeneralization, selective abstraction), and the group is asked to come up with more constructive and positive ones. At the end, some strategies are conveyed to help patients to transform negative self-schemata and elevate their mood

Figure 2.7 Summary of each metacognitive training module (continued). Reproduced with permission from Moritz et al [32].

assert the feasibility of this approach as well as its efficacy. MCT can be downloaded cost-free in 23 languages from www.uke.de/mkt. A number of self-conducted as well as independent investigations have affirmed the feasibility, safety, and efficacy of this approach as an add-on treatment to standard intervention. Since 2008, an individualized version called MCT+ has also been available from www.uke.de/mkt_plus.

Suicidality in schizophrenia

Martin Lambert

Suicide is the most frequent cause of death in patients with schizophrenia. Estimates of completed suicides by patients with schizophrenia range from 4% to 13%, similar to the range seen in affective disorders [33,34]. This is approximately four times higher than in the period before deinstitutionalization (1913–1960) [35], which has been interpreted as suggesting that the suicide rate has risen markedly since the onset of deinstitutionalization. However, recent re-evaluation of previous studies has concluded that the suicide rate is in fact lower, at approximately 5%, and that this rate is 7–10 times higher than in the general population [36]. Approximately 40–50% of individuals with schizophrenia either consider or attempt suicide [37–39]. In the prodromal and/or untreated psychotic phase before first treatment contact, 5–15% of patients with schizophrenia attempt suicide [40]. The high proportion of suicide attempts that result in death can be explained by the high autoaggression of the attempts.

In general, it can be assumed that psychoreactive and social consequences of schizophrenia are the primary causes of suicidal behavior, especially when accompanied by a depressive affect. There are various risk factors for suicide attempts and completed suicide in schizophrenia; some of them are similar to those in the general population, and others are specific to the disorder itself (Figure 2.8). Most patients fulfill several of these risk factors concurrently, so there are certain risk constellations that are especially predictive for suicidal behavior. For example, a high risk was found for single, unemployed males with severe forms of schizophrenia, previous suicide attempt(s), and concurrent depressive episodes

Risk factors related to suicidal behavior

- Previous suicide attempts and actual suicidal ideation and/or plans
- Recent depressive episode and/or lifetime major depressive episode(s), especially in combination with hopelessness
- Long duration of untreated psychosis; possibly also long duration of untreated illness
- Severe forms of the disorder; paranoid subtype with suspiciousness and agitation in the absence of negative symptoms, impulsivity
- Comorbidity, such as substance use disorder or obsessive–compulsive disorder
- Poor adherence to treatment or service disengagement
- Socially isolated single males; lack of support and/or occupation; homelessness
- Relatively higher premorbid functioning before onset of psychosis (eg, higher education); relatively higher cognitive functioning including intelligence and self-expectations; greater insight into illness, but also problem-solving deficits
- First 10 years of illness; frequent short hospitalizations in past year; first 6 months after discharge from hospital
- Repeated unsuccessful antipsychotic treatment attempts with side effects (especially akathisia)

Figure 2.8 Risk factors related to suicidal behavior.

and/or substance abuse disorders. In summary, the main factors to be taken into account when assessing risk of suicidal behavior in patients with schizophrenia are previous suicide attempts, recent or past affective symptoms or syndromes, recent suicidal thoughts, threats or suicidal behavior, poor adherence to treatment, fears of the impact of illness on a patient's life, and substance abuse.

Prevention of suicidal behavior and suicide is likely to result from ongoing community and professional education, early detection, and early intervention, as well as active treatment of the underlying causes. The latter mainly includes treatment of affective symptoms and syndromes, improving adherence to treatment, use of medication that may have special antisuicidal effects, and ongoing special vigilance when patients have a number of risk factors, especially if the impact of the disease on the patient's functional level and quality of life is significant.

The optimal management of suicidality in schizophrenia involves early detection and regular assessment of suicidal ideation, immediate and effective interventions to ensure safety, selection of psychosocial interventions based on the patient's needs, and pharmacotherapy directed primarily at psychotic and depressive symptoms (Figure 2.9). Pharmacological treatment for suicidality should consist of additional supportive medication to alleviate the emotional pressures. This alleviation can be achieved with sedative or anxiolytic drugs, such as benzodiazepines, or antipsychotic

Recommendations for the management and treatment of suicidal behavior in schizophrenia	
Strive for early detection and regular assessment	<ul style="list-style-type: none">• The risk of suicide and suicidal behavior in schizophrenia is significant and matches that of affective disorders. The clinician needs to be alert to subtle hints of suicidality, particularly during high-risk periods. Suicide in schizophrenia is often not impulsive, as it is commonly believed
Assess risk factors and risk constellations	<ul style="list-style-type: none">• Assessment of risk factors and risk constellations is vital in the management of suicidal behavior in schizophrenia. This includes, for example, initial assessment of duration and severity of suicide intent, previous suicidal ideation or attempt, mediating factors (both risk and protective factors [see Figure 2.8]), phase and severity of psychotic (eg, command hallucinations) and associated symptoms (eg, agitation), degree of subjective distress, level of affective disturbance, access to lethal means, supervision and support available, potential for treatment nonadherence or service disengagement, and patient's initial response to clinical interventions proposed. Check that patient has not made recent attempt that might require immediate treatment
Ensure immediate safety	<ul style="list-style-type: none">• Ensure patient's immediate safety by providing constant supervision and removal of any potential means to self-harm until an appropriate intervention has been decided upon
Decide on appropriate management plan	<ul style="list-style-type: none">• Determine who will be the primary clinician involved and facilitate the establishment of a therapeutic alliance between the patient and that clinician throughout the high-risk period• Liaise with patients' other treating clinicians, check immediately available interventions, and consult with senior clinical staff if high suicide risk is determined. Liaise with carers regarding recent and past history of factors that might indicate increased suicide risk. Determine degree of supervision needed to minimize likelihood of a suicide attempt, balancing degree of suicide intent, willingness to comply, variability of mental state, and reliability of the least restrictive options available. Decide on necessary treatments, and negotiate options with the patient (eg, hospitalization)
Initiate management plan	<ul style="list-style-type: none">• Supervision: Provide an adequate level of supervision by staff or carers with clear instructions about risk, degree of monitoring, frequency of clinical reviews needed, and responses required if a deterioration is observed (eg, who and how to consult if problems arise)• Safety: Remove access to means of self-harm (eg, razors, knives, cords, guns, medications, and poisons). Limit exposure to immediate stressors and, if necessary, provide containment within a safe setting (eg, hospital, with clear instructions to carers about limitations on patients' freedom)• Personal contact and counseling: Provide initial counseling and treatment while establishing rapport, understanding, and trust; explore cognitions that influence level of suicidality; encourage an understanding that suicide ideation is a transient although painful phenomenon related to illness; instill hope in recovery through treatment; and finally negotiate a suicide contract• Initiate treatment: Reduce associated distress due to psychosis or suicide ideation with anxiolytics (eg, benzodiazepines) and/or antipsychotics. Attempt to influence psychosocial factors that might reduce suicidality (eg, practical assistance with homelessness, access to social milieu)

Figure 2.9 Recommendations for the management and treatment of suicidal behavior in schizophrenia (continues opposite).

Recommendations for the management and treatment of suicidal behavior in schizophrenia (continued)

Provide optimal pharmacologic treatment	<ul style="list-style-type: none"> Medication(s) to treat suicidality in schizophrenia should fulfill the following criteria: (1) eliminate positive symptoms, (2) enhance quality of life through improved depressive symptoms, anxiety, and social functioning, (3) be free of extrapyramidal symptoms, and (4) decrease substance use. Clozapine has been shown to have a substantial effect on both attempted and completed suicide. It should be considered in patients showing significant suicidal behavior, though other atypical antipsychotics may be useful in patients for whom clozapine is either contraindicated or otherwise undesirable
Review management	<ul style="list-style-type: none"> Regularly review and negotiate the above interventions with the patient, carers, and other clinicians involved. Ensure clear lines of clinical accountability and decision making

Figure 2.9 Recommendations for the management and treatment of suicidal behavior in schizophrenia (continued). Adapted from Power et al [41].

drugs or, particularly in the long term, clozapine. Patients for whom clozapine is appropriate are those who have made serious suicide attempts on other medications, and are likely to follow the generally accepted guidelines for taking clozapine. If patients refuse clozapine or are unable to tolerate it, there is no evidence to assist in making the choice among the other antipsychotic drugs. Overall, a second-generation antipsychotic drug would be superior to a first-generation agent, based on the greater tolerability, enhanced effect on depression, and possibly lower risk of noncompliance. The pharmacotherapy of the underlying disorder should also be re-evaluated with respect to efficacy and tolerability.

Nonadherence and service disengagement in schizophrenia

Britta Galling, Liz Rietschel, Martin Lambert

Introduction

Poor adherence to medication as well as to treatment in general (referred to as treatment engagement or service disengagement) is one of the main treatment problems in schizophrenia. Rates of medication nonadherence within the first 2 years after hospital discharge are approximately 50–75% [42], and 20–40% for service disengagement within the first 18 months [43,44]. However, current reviews on medication nonadherence suggest

that these rates are probably even higher [42]. A variety of risk factors have been identified, which increase the risk of medication nonadherence and poor treatment engagement. The prediction of nonadherent behavior by these risk factors is complicated, as they can change and interfere with each other over time. Consequences of medication nonadherence and service disengagement are manifold and lead to a poor course of illness and worse overall prognosis. A variety of clinical interventions have been described for an improvement in treatment engagement and specifically in medication adherence. However, an integrated approach gives the highest chance for long-lasting improved adherence in individual patients. This chapter provides a brief yet detailed overview of various aspects that play a role in medication nonadherence and treatment disengagement.

Definition

Adherence is defined as the extent to which a patient complies with the physician recommendations. Unlike compliance, adherence focuses on following the course of action that was mutually agreed upon by the patient, the physician and, when appropriate, the caregivers.

An essential prerequisite for adherence is that the patient has been adequately informed, understands different therapeutic treatment options, and has chosen an appropriate treatment in accordance with the physician. The participation of the patient in the process of the decision-making (ie, shared decision-making) is already well established in other medical domains. It is based on the general societal trend for more autonomy and self-determination, better information availability on the internet and other media, and the advancement of patients' rights. However, patients' rights to shared decision-making involve difficulties in daily practice for several reasons, which can be especially significant in case of psychiatric disorders. First, patient involvement lessens the aspect of the paternal and directive relationship between a patient and a physician. Second, it requires good communication skills on part of the physician, which are usually not sufficiently taken into account during their professional education. Third, the decision-making ability in patients, especially in

those suffering of psychosis, is often challenged and can be limited, at least temporarily.

At present, shared decision-making is the best-defined concept for facilitating patient involvement in antipsychotic management for those suffering from schizophrenia.

Models of adherence

There are two overlapping categories of adherence to therapy:

1. Medication adherence, which refers to the antipsychotic medication, other psychotropic drugs (eg, mood stabilizers), somatic medication (eg, antihypertensive therapy), or the overall drug treatment. Studies have shown that nonadherent behavior usually affects the overall drug treatment and is not limited to medication for a particular disorder. The stage of adherence is expressed by the percentage of medication that was not taken as prescribed:

- full adherence: <20% of the medication missed;
- partial adherence: 20–80% of the medication missed; and
- full nonadherence: >80% of the medication missed.

Furthermore, a special category of nonadherence includes the so-called “medication refusers.” These patients, due to persistent nonadherence, have never received antipsychotic or other drug treatment in the required duration and/or amount. An epidemiological study assessing adherence in 605 first-episode patients found that 18.8% of the patients belonged to that group [43].

2. Adherence to the entire treatment regimen (treatment engagement), where nonadherence is defined as the overall therapy dropout rate. In the majority of cases, patients drop out after multiple attempts to continue with treatment. Clinical studies show that 20–40% of the patients abort overall therapy in the first 12–18 months after hospital discharge [43–45].

Examination methods

There is no gold standard for the measurement of adherence, and the determination of individual adherence is based on an assessment of

a patient’s current behavior. The following methods can be employed in adherence assessment:

- a patient’s own declaration (assessed by an interview and/or questionnaires);
- assessment by a physician or pharmacist (assessed by an interview and/or questionnaires);
- reports by family members or caregivers;
- assessment of medication collection/purchase;
- observation of intake (eg, hospital ward, therapeutic flat share);
- pill counting;
- calculation of medication availability over time;
- Medication Event Monitoring System® (electronic monitoring of extraction of capsules/pills from a container); and
- in vitro diagnosis (ie, blood sample analysis).

In 161 adherence studies conducted from 1971 to 2006, Velligan et al found that 124 studies (77%) were based solely on subjective statements (eg, by patients or clinicians; Figure 2.10) [46]. However, the measurement methods have been reported to differ considerably with regards to their

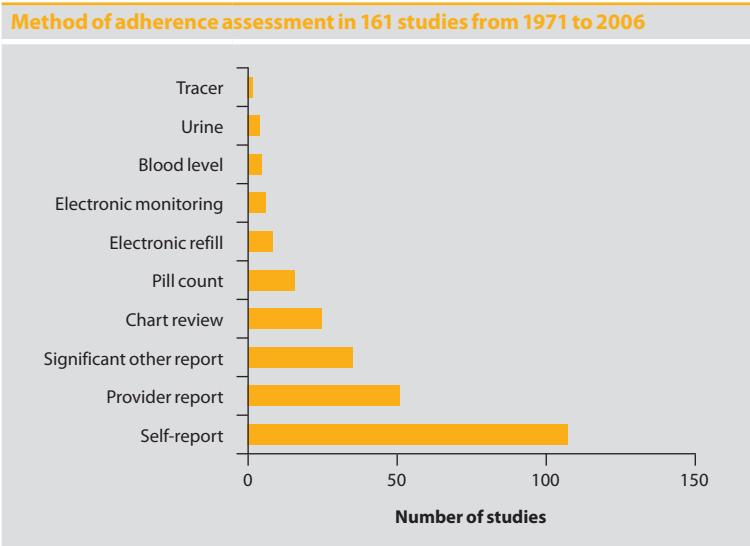


Figure 2.10 Method of adherence assessment in 161 studies from 1971 to 2006. Reproduced with permission from Velligan et al [46].

validity. Velligan et al showed clear differences in adherence rates 3 months after inpatient discharge depending on the measurement used (subjective patient statements: 55%; counting pills: 40%; blood level: 23%) [46]. These results suggest that the extent of nonadherence in patients with schizophrenia is larger than previously believed.

Frequency

Studies on the frequency of partial or complete antipsychotic treatment adherence show large methodological differences, especially with regards to the measurement of adherence, duration of the studies, and study populations. An important limitation of almost all studies is that, in most cases, unrepresentative (nonepidemiological) patient cohorts were analyzed. Real high-risk nonadherence patients were often not included and not analyzed, as they mostly do not take part in “informed consent” studies. The methodological heterogeneity causes a significant variance in the determined nonadherence rates, which range from 20% to 89%. If only the studies with reliable methodology are included, the 1-year nonadherence rates are approximately 40–50%, and up to 75% of patients are partially or wholly nonadherent within 2 years after discharge from a hospital [46]. The following conclusions can be made regarding the frequency of nonadherent behavior:

- The studies with fewer selectively chosen patient populations have higher rates of partial or complete nonadherence. This insight must be taken into account in interpreting the majority of adherence studies.
- In nonselected cohorts there is, as mentioned earlier, a subgroup of patients known as medication refusers, who, when not treated under monitoring conditions, do not accept antipsychotic medication, at least for some period of time.
- The rates of partial or complete nonadherence rise with increasing duration of treatment.

Causes and risk factors

Knowledge of risk factors of partial or complete nonadherence is vital for planning an effective treatment regimen that is simple to adhere to. Different authors have proposed different systematization of risk factors,

including categories based on patient-associated factors, relationship-related aspects (ie, family and social support), and factors associated with the care system (Figure 2.11).

In order to fully understand the risk factors for nonadherence, it is important to remember that they are not static, but rather can be positively influenced by treatment. It is not necessarily the risk status at admittance that determines the adherence, but whether and how the risk factors evolve during treatment. For example, a patient's familiarity with the disease influences adherence; however, it is less important whether a patient is familiar with the disease when admitted than it is how effectively he is informed about the disease during the course of treatment. The same is true for other factors, including the presence of a comorbid addictive disorder, attitude toward treatment, supportive therapeutic alliance, and an adequate medication supply system.

Consequences

It is well known that partial or complete nonadherence (to medication or to the entire treatment) is an important factor in the course of the disease and the prognosis. Accordingly, nonadherent behavior is directly or indirectly associated with the following consequences:

- increased recidivism (psychotic or comorbid) leading to higher doses of antipsychotic medication, increased polypharmacy, and more adverse events;
- partial response or nonresponse to treatment and therapy resistance;
- increased inpatient treatment with higher costs;
- increased emergencies;
- chronicity of schizophrenic and comorbid symptoms;
- a decreased level of functioning and quality of life; and
- increased suicide attempts.

It is important to understand that these consequences can be caused even by partial nonadherence.

Therapeutic measures for improved adherence

The complexity of the problem of nonadherence becomes clear in clinical experience: some patients enjoy the benefits of treatment and willingly

Risk factors for partial and complete nonadherence

Patient-associated factors	<ul style="list-style-type: none"> • Poor insight into disease and treatment • Negative attitude or subjective response toward medication • Shorter illness duration (first-episode psychosis) • Comorbidity, especially persistent substance use disorder • Cognitive impairment • Fear of side effects and addiction • Fear of stigma • Past nonadherence • Demographic factors such as lower age and male gender • Social factors such as living alone and unemployment
Other factors (including relationship-related aspects and factors associated with the care system)	<ul style="list-style-type: none"> • Insufficient therapeutic alliance • Insufficient family and social support • Deficient care systems, including long latency time and lack of finances to afford appropriate medication • Complex route of medication administration • Severity of adverse events

Figure 2.11 Risk factors for partial and complete nonadherence. Based on data from Lacro et al [47] and Goff et al [48].

take medication, others do not like and do not take medication, yet others dislike some aspects of treatment but take medication as prescribed. There is no single intervention that can solve the problem of nonadherence. Instead there are a number of possible interventions, which should be adapted to the patient's individual condition, and which need to be further adjusted over the course of treatment.

The first step: physician–patient relationship and participative decision making

Physician–patient relationship

An attitude to sickness in general and to any disease in particular is strongly influenced by the societal factors, varies significantly by culture, and evolves with time. A disease and its symptoms are thus a phenomena, which could be considered and evaluated differently from variable viewpoints of doctors, patients, and the society. This is especially true for psychiatric diseases such as schizophrenia. Hence it is important to take into account that in the treatment of psychosis, the patients' concepts of disease, corresponding treatment designs, and expectations of treatment are strongly influenced by the experiences and attitudes of the patient. An important prerequisite for improving adherence is to address

and understand these perceptions and attitudes and to take them into account while planning treatment. A decisive factor in this process is the quality of communication and interaction between the person providing the treatment and the patient. An effective physician–patient interaction provides the patient with necessary information and an opportunity to contribute to the therapeutic decision making, which improves the process of diagnosis, understanding of and coping with the disease, and therefore the adherence to therapy and the efficiency of treatment.

Communication in the physician–patient relationship

The physician–patient interaction is strongly characterized by an asymmetry, which resonates in all communication processes. The doctor is active, performs the usual professional role, and knows the rules and procedures of the clinical setting. He or she possesses expert knowledge and uses technical terminology. The patient, on the contrary, is more passive, and due to the illness, which is usually a dramatic event for the patient, may be unsettled, anxious, and stressed. He or she is torn out of their normal daily life, is dependent on specialists, has only layperson knowledge, and may be unfamiliar with the clinical setting. In patients with psychosis, such an asymmetry in the physician–patient relationship can have a significant influence on adherence. The goal for a physician must therefore be to build a relationship with a patient that is as symmetrical as possible, where the patient is informed about the disease and therapy decisions can be made together. This process of “shared decision-making” should be the first step to increasing the patient’s willingness to adhere to treatment.

Shared decision-making

The term shared decision-making was defined in 1982 by the President’s Commission for the Study of Ethical Problems in Medication and Biomedical and Behavioural Research [49]. However, in a 2006 review comparing different studies on shared decision-making, Makoul et al found that the definition of this term had remained largely unchanged [50].

The general and most important idea of shared decision-making is that the physician should attempt to inform the patient as well as potential

caretakers about the disease and therapy options. In doing so, the physician imparts his or her knowledge advantage to the patient, and after this stage the therapy decisions should be made together.

According to Makoul et al physicians have variable understanding of shared decision-making, and assumptions vary widely regarding how to proceed in working with the patient to select appropriate therapy (Figure 2.12) [50]. Some doctors assume that it is their responsibility to convince the patient to take the most appropriate medication; others think that their role is to recommend a medication, and to leave the final decision of whether or not to agree to it to the patient. This discrepancy hinders the ability to compare the research on the effectiveness, and of other factors involved in shared decision-making.

At the start of therapy and during the course of the disease, individual factors that influence short- and long-term risks for nonadherence and therapy dropout should be raised frequently by physicians and assessed in collaboration with the patient.

Further therapeutic measures for improving adherence

There is no single measure that can solve the problem of nonadherence. A number of interventions can be implemented based on the patient's individual conditions. Most patients profit from multimodal therapeutic approaches, which can change over the course of treatment. Risk factors can fluctuate over a period of time and influence one another. Accordingly, it is important to regularly check therapy adherence and adjust the interventions.

The following therapeutic measures can be used to help improve adherence:

- **Cognitive-behavioral therapy:** The first step in the behavioral therapy involves identification of cognitive and behavioral patterns that negatively influence the patient's wellbeing. During the course of therapy, the patient learns certain techniques that can be utilized to alter these patterns. For example, negative attitudes toward medication use can be discussed and cognitively restructured, and new strategies for regular therapy participation can be worked out. The educational part of the behavioral therapy

Essential elements of shared decision-making

1. Define/explain the problem

Factors that seem problematic to the physician may not be important to the patient, and vice versa; a patient may be concerned with some factors that may be incidental in the physician's perspective. Therefore, it is not enough to simply inform the patient of the diagnosis. The physician must understand and address the patient's perception of the disease and any concerns that may arise and interfere with treatment

2. Present options to solve the problem

Any discussion between the physician and the patient about potential solutions to the problems and challenges faced by the patient is indispensable. The physician's role is mainly to provide education and further information on the origins and the course of disease and different approaches to therapy

3. Consideration of advantages and disadvantages of treatment

Considering all the advantages and disadvantages of a specific treatment strategy is an important step in physician–patient communication, especially when the physician's and patient's opinions differ widely. The patient's personal values and preferences should be considered and taken into account during the decision-making process. For example, if the patient has an impression that he will not benefit from the therapy or may be harmed by side effects, extra time should be dedicated to discuss these attitudes

4. Discussion of patient's abilities and self-efficacy

Patients with psychosis frequently have difficulties with therapy adherence because of forgetfulness and lack of structure and organization in their lives. Furthermore, patients with psychiatric diseases tend to lack self-confidence, which is associated with lower expectations in one's ability to deal with the disease. Consequently, some patients may think that they are unable to change their current condition and confine themselves to a passive role during the therapy process. Physicians should discuss this aspect and ensure that the patients understand that they can influence the treatment and the prognosis by adopting a more proactive approach

5. Physician's knowledge and recommendations

In this step, the physician should list all possible treatment strategies and identify the best approach. The physician should not seem patronizing, but rather consider himself a consultant. The patient should not feel like he is being pushed toward a certain treatment

6. Ensuring patient's understanding

The next step is to ensure that the patient understands what is being said. Therefore, complex terms should be either avoided or precisely explained. The physician also has to be certain that he fully understands all the patient's expectations, fears, and concerns

7. Making or delaying decisions

The final step involves a decision on the treatment strategy and a mutual agreement by the physician and patient on that approach. One cannot assume that this will be possible at the end of the initial consultation. Additional time and consultations may be necessary depending on the form and degree of the disease, psychological strain, and patient's opposition. The patient should not feel pressured to make a decision immediately. If desired, additional appointments should be made to further discuss various treatment strategies and concerns

Figure 2.12 Essential elements of shared decision-making. Adapted from Makoul et al [50].

(both family and individual education) includes information about the basis of the disease and available treatment options. Such education can reduce the recidivism rate due to noncompliance by approximately 20% [51].

- **Adherence therapy (compliance therapy)** is a short-term intervention (usually with 4–6 sessions), based on motivational conversation with a patient. The effectiveness of this intervention has been clinically proven: patients that have participated in this therapy had a five-time higher chance of adhering to treatment.
- **Cognitive–motivational addiction therapy** is useful for patients with a comorbid addiction disorder. This therapy is used to motivate the patient to end substance abuse and can be offered both in group and individual therapy settings.
- **Assertive community treatment:** In this form of therapy patients are, if necessary, treated at home. Patients are also given an emergency number, which they can call to receive immediate help and support in case of a crisis. This form of therapy is especially recommended for ambulatory patients, who rarely have appointments in the clinical setting and regularly cease using their medication.
- **Person-to-person or family-to-family assistance:** Experienced and informed patients are increasingly given an opportunity to aid other patients. The credibility of such patients is very high as they themselves have experienced the disease and have learned to live with it. The same applies to informed family members, who can pass on their knowledge to other families. Both strategies can improve medication adherence of affected individuals.
- **Destigmatizing the disease:** People with psychiatric diseases are often stigmatized by society. The symptoms of schizophrenia, especially, can sometimes cause the behavior of affected people to breach many of the societal norms, which can lead to extreme stigmatization. Therefore, patients usually have to deal not only with the symptoms but also with the stigma, which can cause such a degree of shame and suffering that it is known as the

“second disease.” Not only can this limit the patient’s quality of life but it can also have a great influence on the treatment and course of the disease. An open conversation on the subject of stigmatization within the doctor–patient interaction is therefore indispensable.

- **Dialogue and medicinal compliance:** Physicians need to address negative convictions that patients may have regarding their treatment, which can affect adherence. Potential topics for discussion involve likely assumptions regarding medication efficacy, potential for addiction, and undesirable side effects.
- **Technical support for medicinal compliance:** Patients with repeated nonadherence can profit from measures that simplify the administration of medication. For example, a switch from multiple daily doses to a once-a-day dose or depot medication may improve compliance. If applicable, continuous supervision of medication administration (eg, Medication Event Monitoring System™ or a nursing service) can provide necessary support, at least until the autonomous adherence is assured. In addition, it has been shown that depot medications can and should be used preventively in first-episode patients or patients with nonadherence risk factors. Every appointment should include a short screening for treatment adherence, and the patient’s attitude toward medication should be assessed routinely.

Co-occurring substance abuse in schizophrenia

Martin Lambert

Co-occurring substance use disorders, often termed “dual diagnosis” or “comorbidity,” are a serious and common issue among patients with schizophrenia, and frequently remain under-recognized and poorly addressed. Up to 90% of people with schizophrenia smoke cigarettes [52–54], and 40–60% use other substances [55]. Comorbid substance abuse (excluding tobacco smoking) appears to be more prevalent (up to 75%) among young people with FEP [46], as well as among those who are homeless or have come to the attention of the criminal justice system. The most frequently abused substances are cannabis, alcohol, and

psychostimulants, mirroring patterns of use evident within the general population, although abuse of more than one substance is relatively common (20–40%) [56,57]. Most patients start using before the onset of psychosis (with regular cigarette use usually starting first), which most probably reflects the typical temporal order of onset of both disorders.

A number of hypotheses have been proposed to explain the high rate of co-occurring substance use among people with psychosis, including the following:

- psychosis increases risk for substance use;
- substance abuse increases risk for psychosis; and
- common factors increase risk for both disorders.

The “self-medication” hypothesis proposes that individuals with psychosis are more prone to substance abuse because they selectively abuse particular substances in order to “treat” specific symptoms of their psychotic illness. Despite the intrinsic appeal of this model, supporting evidence is limited, and factors associated with substance abuse in the general community also apply to those with psychosis (eg, cost, availability, use for intoxication and relaxation, peer group use, and acceptance). Nevertheless, people with psychosis do consistently report abusing substances to relieve feelings of dysphoria, anxiety, and boredom, and it is likely that some patients continue to abuse substances to help cope with a range of psychosocial problems (eg, family conflict, trauma, financial problems, lack of vocational opportunities, and social anxiety).

The hypothesis that substance abuse is a risk factor for psychosis has received support from a number of recent longitudinal cohort and population-based studies. Regular cannabis use appears to be associated with an approximately twofold increase in the relative risk of developing schizophrenia or other psychosis outcomes. However, although cannabis use (particularly adolescent-onset and heavy use) is a risk factor for later psychosis, the incidence of schizophrenia does not appear to be increasing despite elevated rates of cannabis use in the general community. This suggests that the relationship between cannabis use and psychosis is particularly complex, and further studies examining the interaction of genotype, developmental processes, and cannabinoid exposure are required. However, a recent population-based study in positively selected people

(without psychosis risk factors) and long-term follow-up showed that cannabis use was linked to the development of psychosis and resistance to treatment in case of ongoing cannabis use [58].

An alternative hypothesis for the high rate of co-occurring substance abuse disorders among individuals with psychosis is the possibility that common underlying biological, personality, or environmental factors increase vulnerability for both disorders. For example, both disorders are associated with dysfunction within the brain's reward system, as well as frontal executive deficits, whereas certain personality traits (eg, sensation seeking, impulsivity, and negative affect) have been implicated in the etiology of co-occurring psychosis and substance use disorders. Certain personality traits (eg, antisocial personality disorder) as well as environmental experiences also increase risk for both disorders.

Cigarette smoking is associated with considerable morbidity and mortality among people with schizophrenia, yet interventions are not routinely offered to this population despite evidence for their effectiveness. Smoking also places a substantial financial burden on such individuals, who spend a large proportion of their weekly income on cigarettes.

Abuse of other substances has a significant impact on both treatment course and outcome, and many patients do poorly in standard treatment settings. Indeed, co-occurring substance use disorders are associated with lower rates of remission, frequent use of health care services and increased rates of relapse and hospitalization, blood-borne virus infections (eg, human immunodeficiency virus), suicide, violent behavior, incarceration, and early death. In addition, persistent substance abuse affects medication adherence, service engagement, health care costs, and housing stability, and substantially increases the burden on patients, their families, and the health care system. Although this often leads to clinicians feeling pessimistic toward this population, many individuals with FEP achieve remission and/or a reduction in the severity of substance abuse after entry to treatment, and a significant reduction in substance abuse is likely to be associated with improved clinical outcomes.

It is essential that all patients with psychosis are assessed for co-occurring substance use, given the high rate of substance use within this population and the associated negative outcomes (Figure 2.13).

Recommendations for the management and treatment of substance use disorder in schizophrenia

Assessment	<ul style="list-style-type: none"> • Screen all patients for substance use and other psychiatric disorders (eg, social phobia) • Determine severity of use and associated risk-taking behaviors (eg, injecting practices, “unsafe sex”) • Exclude organic illness or physical complications of substance use • Seek collateral history: families or close supports should be involved where possible
Treatment principles	<ul style="list-style-type: none"> • First engage patient, adopting a nonjudgmental attitude • Educate patient: <ul style="list-style-type: none"> – Give general advice about harmful effects of substance use – Advise about safe and responsible levels of substance use – Make individual links between substance use and patient’s problems (eg, cannabis use and worsening paranoia) – Inform patient about safer practices (eg, using clean needles, not injecting alone, practicing “safe sex”) • Treat psychotic illness and monitor patient for potential side effects • Help patient establish advantages and disadvantages of current use, and motivate patient for change • Evaluate need for concurrent substance-use medications (eg, methadone, acamprosate) • Refer patient to relevant clinical and community services, as appropriate • Devise relapse prevention strategies that address both psychosis and substance use • Identify triggers for relapse (eg, meeting other drug users, being paid, family conflict) and explore alternative coping strategies
General interventions	<ul style="list-style-type: none"> • Explore reasons for substance use, including relationship to psychiatric symptoms, antipsychotic treatment, and feelings of social isolation • Address patient’s motives and degree of commitment toward treatment of both their psychotic illness and substance use • Adopt concrete problem-solving approach with patient, where appropriate • Set tasks that are simple and readily achievable (eg, keeping a diary of substance use or psychotic symptoms; regularly taking medication; keeping appointments) • Focus on specific skills to deal with high-risk situations, and consider use of role play (eg, learning how to say “no” to a dealer or drug-using friends) • Suggest alternatives to substance use for coping with stressful situations (eg, exercise, contacting a support person) • Treat comorbid anxiety with behavioral techniques (eg, breathing exercises, progressive muscular relaxation) • Remain supportive and emphasize any gains made • Encourage participation in alternative activities and contact with non-substance-using peer group (discuss available resources with local community health center or mental health service)
Motivational enhancement techniques	<ul style="list-style-type: none"> • Motivational interviewing is a useful therapeutic approach, based on a model conceptualizing stages through which behavioral change occurs. It emphasizes the role of both ambivalence and relapse within the process of change. This therapeutic approach aims to match appropriate treatment options with the patient’s motivational level, based on the patient’s current stage within the cycle

Figure 2.13 Recommendations for the management and treatment of substance use disorder in schizophrenia. Adapted from Meister et al [59,60].

The assessment should include a detailed history of the type, amount, pattern, and circumstances of substance use, negative consequences associated with use (including the impact on mental and physical health, and social and occupational functioning), the degree of physiological dependence, the interaction between psychosis and substance use, relevant risk issues (eg, accidental or deliberate overdose and aggressive behavior when intoxicated), reasons for use, previous attempts to control use and past treatment, and motivation/readiness to change substance use. Assessment is most accurate if the clinician establishes a collaborative therapeutic alliance, using an empathic nonjudgmental approach. Biomedical investigations (eg, γ -glutamyl transpeptidase, urine drug screen) and collateral information should also be sought, because patients may minimize their level of substance use. It is important to assess for any level of use, because people with schizophrenia are often more sensitive to the effects of psychoactive substances and experience greater adverse effects than would typically be expected.

Psychosis in the context of co-occurring substance use presents clinicians with a particularly difficult diagnostic challenge, especially as many psychoactive substances can induce psychotic symptoms during periods of intoxication or withdrawal. That said, psychosis can also occur with prolonged abuse, and there is growing evidence that substance-induced psychotic episodes occur more frequently among individuals with substance use disorders. Although substance-induced psychotic symptoms are typically transitory in nature, generally lasting less than a week in most cases, there is a small but growing amount of literature to suggest that, in a minority of chronic users, psychotic symptoms can last substantially longer than a month (especially among those with underlying schizoid or schizotypal traits). Nevertheless, the priority of initial assessment should be to identify treatment-relevant syndromes (such as the triad of psychosis, substance abuse, and depression), and to start appropriate treatment. Indeed, those with substance-induced psychosis should not be excluded from treatment, especially as there is evidence to suggest that they are a particularly high-risk group for later transition. In this regard, the interaction between substance abuse and psychotic symptoms should be monitored longitudinally to ensure accuracy of the initial diagnosis.

It is important to acknowledge that many clinicians feel overwhelmed or not sufficiently skilled to manage patients with co-occurring disorders. Many are often pessimistic regarding outcomes and believe that substantial time and effort are required for little return. It is therefore not uncommon for clinicians to want limited involvement with such patients, and to try to refer them elsewhere. However, the reality is that few physicians have had specialized training in managing co-occurring disorders, and practitioners need to acknowledge that substance abuse is a common concomitant of a psychotic illness. It should be borne in mind that appropriate interventions have been shown to be beneficial, and clinicians need to remain optimistic with realistic long-term expectations.

Comprehensive treatment planning involves discussing the assessment with the patient (and key support/carer if the patient consents), providing education about the link between psychosis and substance abuse outcomes, identifying clear treatment goals, and discussing potential pharmacological and psychosocial interventions. The approach should be integrated, such that both the psychosis and the substance abuse are addressed simultaneously in a comprehensive treatment package. Effective pharmacological treatment of the psychotic illness with antipsychotic agents is critical, because improved medication adherence increases the effectiveness of adjunctive psychosocial interventions. In this regard, patients should be offered simplified medication regimens, as well as clear information about potential interactions between their prescribed medication and abused substances. Those who are consistently nonadherent may benefit from switching to a longer-acting depot antipsychotic, although limited research has been conducted to examine the effectiveness of this approach. Benzodiazepines should be used with caution because of their interaction with alcohol and other depressants, as well as their potential for abuse. Limited pharmacological trials for substance abuse have been conducted among patients with schizophrenia, but most addiction treatments appear to be safe and effective in combination with antipsychotics. Nicotine replacement therapies and bupropion have both been successfully and safely used in patients with schizophrenia.

Assertive outreach with intensive case management has been found to improve engagement and retention, as well as treatment outcomes, in those with co-occurring disorders; however, few such programs exist. Nevertheless, ensuring that the patient's immediate needs are addressed, as well as offering practical assistance with everyday tasks, enhances engagement and increases motivation for treatment. Life-long abstinence may be a particularly difficult goal to achieve for this population, and it is more useful to adopt a harm reduction framework focused on reducing the harm associated with the substance abuse and its consequences. In general, psychosocial interventions for substance abuse need to be modified for people with schizophrenia (eg, adopting a concrete problem-solving approach or the use of role play), given the negative symptoms, cognitive difficulties, and poor self-efficacy associated with this disorder. Motivational interviewing remains an important component of treatment, in terms of identifying the pros and cons of continuing or ceasing substance use, and accepting treatment, addressing ambivalence, building self-efficacy, identifying and implementing relevant strategies for change, encouraging new skills, and rehearsing relapse prevention strategies (for both the psychosis and the substance abuse). It is important that "lapses" are not viewed as failures, but should rather be discussed early in treatment as being something that is to be expected and viewed as an opportunity to refine the patient's set of coping strategies.

Lack of vocational opportunities, homelessness, and contact with drug-abusing peers are obvious drivers of continued substance abuse, and these should be addressed early in treatment. Vocational and educational goals are also important motivators for change, and relevant support agencies should be included in treatment planning to ensure that relevant opportunities are considered. Links to alternative social networks and support groups are also essential. Finally, families play a particularly important role in supporting and monitoring treatment, as well as building self-efficacy and self-esteem, and should be involved early in treatment planning, with the patient's consent. Carers may need additional support themselves, because family conflict is common when patients have co-occurring disorders.

Childhood trauma in schizophrenia

Ingo Schäfer and Philippe Conus

Trauma and its consequences have long been a neglected issue in patients with schizophrenia and other psychotic disorders. However, over the past decade, interest in this topic has markedly increased. The existing evidence consistently shows a high prevalence of early trauma, especially childhood sexual abuse (CSA) and childhood physical abuse (CPA), in the lives of people with psychosis. In a recent critical review of 20 carefully selected studies on patients with psychotic disorders, 42% of the female patients reported CSA and 35% reported CPA. In male patients, these figures were 28% and 38%, respectively. At least one form of abuse (CSA or CPA) was found in 50% of the patients, irrespective of gender [61]. A slightly lower prevalence of CSA and/or CPA has been reported in studies focusing on patients with bipolar disorder, but this is likely to be due in part to the dearth of studies exclusively exploring these adverse experiences in bipolar patients.

Population-based studies suggest that childhood trauma may be a causal factor for psychosis. In almost all existing studies, a history of trauma was related to psychotic symptoms during either adolescence or adulthood. For example, in a prospective study of 4045 individuals aged 18–64 years drawn from the Netherlands Mental Health Survey and Incidence study (NEMESIS), participants who had experienced emotional, physical, or sexual abuse before the age of 16 were more likely to develop positive psychotic symptoms according to several different definitions during a 3-year follow-up period, after adjusting for a wide range of potential confounding factors (adjusted odds ratio 7.3) [62].

Research into the consequences of early trauma suggests that both psychological and neurobiological factors may contribute to the development of schizophrenia and other disorders. At the psychological level, the focus has been on cognitive factors and their interplay with emotions. Neurobiological theories include alterations of the hypothalamic–pituitary–adrenal axis and an altered function of the dopaminergic system. Although some of these mechanisms have been linked to a range of mental health problems, others (eg, information processing abnormalities) might

represent distinct processes specifically associated with schizophrenia and other psychotic disorders.

Psychotic patients with a history of childhood trauma have a more severe clinical profile across a variety of measures compared with those without these experiences. They have an earlier onset of the illness, a higher number of hospitalizations and a more severe clinical course. Patients with childhood trauma are more likely to have been revictimized later in life, have more current or lifetime substance abuse, and suffer from more lifetime episodes of major depression. Victims of abuse also have higher levels of current depression and anxiety, and report more dissociative symptoms than patients without these experiences. One of the most prevalent consequences of childhood abuse is posttraumatic stress disorder (PTSD). In clinical samples, the disorder is in most cases related to childhood abuse, and in a smaller group of patients to experiences later in life. Whereas about 3–5% of individuals in the general population fulfill a current diagnosis of PTSD [63], the prevalence of the disorder in samples of patients with schizophrenia is 17–46% [64,65]. Rates of current PTSD in individuals with bipolar disorder range from 11% to 24% [66,67].

In a study of patients with schizophrenia in vocational training, victims of childhood abuse had a poorer level of participation, were less able to sustain intimacy, and were more prone to emotional instability. Finally, abused patients have frequently been found to report more suicidal ideation and suicide attempts. Although similar findings with regard to the consequences of early trauma have been reported independent of psychiatric diagnosis, more specific differences have also been reported concerning the type and content of psychotic symptoms. In patients diagnosed with schizophrenia, those who suffered CSA or CPA have repeatedly been found to have more “positive symptoms” (eg, hallucinations, ideas of reference, and thought insertion) and fewer “negative symptoms” than those without a history of abuse. Although findings about the interrelationship of childhood trauma and delusions, thought disorder, and “negative symptoms” remain inconsistent, the link between childhood trauma and hallucinations has repeatedly been replicated and seems to exist across diagnostic boundaries including schizophrenia spectrum disorders, affective psychosis, personality disorders, and dissociative disorders, and also in the general

population. Finally, associations can be found between childhood trauma and the actual content of psychotic symptoms; for example, schizophrenia patients with a history of childhood abuse tend to hear more malevolent voices with hallucination themes such as threat, guilt, and humiliation.

Given the strikingly high number of patients with a history of trauma and the obvious clinical problems related to this issue, recommendations have been published to design trauma-sensitive services for people with severe mental illness. They call for a more systematic assessment of trauma history, better staff training, and modification of standard services to recognize particular safety, control and boundary issues that such patients face. With regard to assessment, research suggests that instruments for identification of childhood trauma and PTSD developed for the general population are also appropriate for use among people with psychosis. Some useful observations are summarized in the following box.

Discussing previous trauma with patients who have schizophrenia

- It is important to ask patients with schizophrenia about a possible exposure to trauma:
 - Without asking, only 10–30% of trauma histories are identified [68].
 - Although trauma is very rarely a part of clinical assessment (because of other priorities for assessment, fear of destabilizing patients, doubt about veracity of reported trauma, fear of blaming families), 85% of patients who have lived through such events are relieved when they are offered an opportunity to talk about them [68].
- When trauma is discussed with a patient:
 - It is often a progressive process: it is not necessary to gather all details at once and patients need time to gradually expose what they went through.
 - Clinicians need to be available and to positively reinforce the efforts that patients make to talk about such issues.
 - It is also important to evaluate the risk for victimization, recurrence of trauma, and suicide.

Trauma-specific treatments aim to directly address the effects of abuse. Although, no sound evidence is available for differential pharmacological approaches, several psychotherapy treatments have proved effective in patients with psychosis who have experienced childhood trauma. Patients with early and complex trauma may benefit from integrated treatment programs with an emphasis on psychoeducation, stabilization, and the development of safe coping skills. Other approaches focus on PTSD. Several case studies and open trials reported that exposure-based treatments of PTSD can be used safely and effectively in patients with schizophrenia [69,70]. More recently, a randomized controlled trial of a group-based cognitive-behavioral intervention for PTSD, with an emphasis on cognitive restructuring rather than exposure therapy, has yielded promising results in patients with severe mental illness [71]. Independent of the strategy chosen, trauma treatments for patients with schizophrenia should take place within the context of a comprehensive and integrated service, where all aspects of the disorder can be addressed in a coherent fashion, combining case management, medication, and psychotherapy of the various comorbidities that may occur. Clearly, more research is needed to further develop and evaluate treatment approaches appropriate for this vulnerable population and to integrate them into routine practice.

New antipsychotics and antipsychotic formulations

Tim Lambert

In patients with schizophrenia, antipsychotics are the cornerstone of therapy for the management of an acute episode of psychosis and for prevention of relapse. They provide the bedrock upon which psychosocial treatments can be applied in order to achieve remission. Due to their lower risk of extrapyramidal adverse effects and their (variable and arguably modest) beneficial effects on the negative, affective, and cognitive symptoms of schizophrenia, the so-called atypical or second-generation antipsychotics (SGAs) are often utilized in preference to the older, conventional first-generation antipsychotics (FGAs). However, despite the oral SGAs having a preferable risk-benefit ratio, rates of persistence

on these medications, dimensional improvements, and general social integration differ extensively.

The complex nature of the disease and the fact that responsiveness to any single agent is largely idiosyncratic, suggests that psychiatrists should have a broad palette of agents at their disposal in order to attempt to individualize treatment. That the rates of adherence are only marginally better with the latest medications compared to the FGAs, suggests that any individualized treatment plan also needs to consider ways of dealing with nonadherence, and this may require considering new forms of delivery of the required agent such as rapidly disintegrating tablets, sublingual preparations, and injectable short- and long-acting formulations. In the years to come, newer delivery methods such as patches, aerosols, implants, and gas-forced subcutaneous injections will extend our ability to administer agents to patients who are unable to maintain their adherence.

This chapter considers new antipsychotics that are reaching the clinic, as well as new formulations, particularly the development of crystal-based long-acting injectable antipsychotics (LAIs).

New drugs – not a case of “me-tooism”

The development of truly novel antipsychotic treatments appears to have reached a plateau, marked by the disbanding of central nervous system research groups in some major pharmaceutical companies and the exhumation of previously discovered but undeveloped medications to fill the need for a broader palette of options. In this respect there may be some concern that the most recent developments are examples of “me-too” drugs, rather than those that add clinically meaningful depth to the pharmacopoeia. Essentially, the newer agents are serotonin/dopamine antagonists (SDAs) and thereby share a mode of action common to nearly all SGAs (exceptions include amisulpride). Furthermore, many of the “new” antipsychotics that are discussed in this chapter (eg, iloperidone, asenapine, lurasidone, and paliperidone) have been around for some time. Iloperidone, first developed in the early 1990s, has had an especially chequered pathway to US approval. Similarly, asenapine was developed in the early 1990s; and paliperidone is a primary metabolite of the long-standing antipsychotic staple risperidone, which has been available since 1993.

Despite this, it would be unwise to dismiss “me-too” drugs out of hand. There is little doubt that responsiveness can be a particularly individual matter in schizophrenia. Although, 30% of patients are likely to be refractory to standard treatments [72], there always exists the possibility that in any one particular person, there may be a match between the multireceptor targeting profile of newer drugs and the patient’s particular neuropharmacological sensitivity, which may allow clozapine to be avoided. Although these agents are based on the centrality of dopamine antagonism as an essential component of their action – at least with respect to positive symptoms – their broader range of receptor affinities has been used to differentiate them in terms of tolerability and putative effectiveness with respect to other dimensional targets such as negative, cognitive, and affective symptoms. Apart from clozapine, any differences in positive symptom efficacy between the newer (atypical or SGA) medications and the FGAs is likely to be of marginal clinical significance. Effects at other targets may appear to be somewhat more robust, although apparent differences may be exaggerated by a combination of primary improvements through the manipulation of specific receptor interactions combined with the absence of more deleterious actions by the FGAs as they are discontinued. For example, the neuroleptic deficit syndrome along with akinesia and other immediate motor/cognitive effects might be considered a typical profile of FGAs. As these effects “wash out” and the newer, less toxic agents are added, emergent qualities of superior efficacy against cognitive deficits may actually reflect a different effect.

Although alternatives to direct dopamine and serotonin antagonism have been sought, such as agents acting on the glutamate pathways (see page 55), neuropeptide Y, serotonin receptor 2A antagonists, and many others, none have emerged as a replacement for the existing classes of SGAs. Some, as will be discussed, may have a role in adjunctive therapy, to target dimensions such as cognition and negative symptoms.

The following sections will first discuss the new oral antipsychotics, then some of the newer agents in early phase trials, and finally consider the role of LAIs, particularly the crystal-based agents (paliperidone palmitate and olanzapine pamoate).

Whether or not breakthrough drugs do emerge in the decades to come, their potential may still be undermined by one of the critical failures in psychiatric health care – that of ensuring adherence to treatment over the longer term.

Adverse events associated with specific receptor signaling

What can we expect from the new antipsychosis medications? Many antipsychotics come to market with a thorough Phase III testing period behind them. However, in many of these studies, which have been designed for the purposes of regulatory approval, there are particular limits on the populations studied. When the medication is released into the real clinical setting, physicians often determine what the “real world” average doses are, and what the main side effects experienced by the patients are likely to be for their typical cohort. Before clinicians are able to obtain such experience, it is often helpful to look at the preclinical pharmacology as this may help in identifying effects that may occur as a consequence of the interaction with various receptors. Figure 2.14

Clinical aspects of iloperidone, asenapine, and lurasidone			
	ILO	ASEN	LUR
Indication*	Acute schizophrenia	Acute schizophrenia, maintenance schizophrenia, bipolar disorder	Acute schizophrenia
Dosing	BID	BID	OD
Formulations	Oral	Sublingual (do not swallow; no food for following 10 mins)	Oral (with food)
Up titration	4 days titration	Up to 7 days titration (maintenance)	To target dose
Metabolism	CYP2D6; 3A4	UGT1A4; CYP1A2A	CYP3A4
EPS	Flat/low	Dose dependent	Dose dependent
Sedation	Some	Most	Some (dose dependent)
Cardiac	Potential QTc effects	Low	Low
Weight/metabolics	Low/moderate	Low/moderate	Low

Figure 2.14 Clinical aspects of iloperidone, asenapine, and lurasidone. *Indication may differ by country/region. ASEN, asenapine; BID, twice daily; EPS, extrapyramidal symptoms; ILO, iloperidone; LUR, lurasidone; OD, once daily.

compares pharmacology of three recently released medications: asenapine, iloperidone, and lurasidone [73,74].

Figures 2.15 and 2.16 compare receptor affinities of various antipsychotic medications and the clinical therapeutic and adverse effects that have been associated with various receptor types and are discussed in this section.

Weight gain

Kroeze et al provide evidence that the drugs most associated with weight gain are those that are antagonists of the histamine H₁ receptor and to a lesser extent α₁ adrenergic receptors [75]. There is also an association between the serotonin 5-HT₆ and 5-HT_{2C} receptor antagonists or inverse agonists, although the latter by itself is not predictive of weight gain. Based on this model one could expect weight gain to occur in asenapine, paliperidone, and iloperidone to a greater extent than lurasidone. In the absence of long-standing use, the comparative rates of sequelae of weight gain such as the metabolic syndrome and diabetes, are not sufficiently established.

Extrapyramidal side effects

All new agents are SDAs and thus may be expected to have lower extrapyramidal symptoms (EPS) than FGAs. With no intrinsic anticholinergic effects (which may lessen apparent EPS) some “atypicality” may be afforded by a higher 5-HT_{2A} to D₂ receptor occupancy ratio (iloperidone)

Receptor affinities of various antipsychotic medications									
	D ₂	5-HT _{2A}	5-HT _{2C}	5-HT _{1A}	H ₁	α ₁	α ₂	M ₁	5-HT ₇
Asenapine	+++	+++	++++	+++*	++	+++	+++	0	+++
Iloperidone	+++	++++	++	+	++	++++	+++	0	
Lurasidone	+++	+++	±	+++*	0	±	+	0	++++
Paliperidone	+++	+++	±	±	++	++	±	0	
Sertindole	+++	++++	+++	±	±	+++	±	0	
Clozapine	±	+++	+++	+	+++	+++	+++	+++	±
Olanzapine	++	+++	++	0	++++	++	±	++	
Risperidone	+++	++++	+	±	+++	+++	++	0	+++
Haloperidol	+++	±	0	0	±	++	±	0	0

Figure 2.15 Receptor affinities of various antipsychotic medications. *Partial agonism. 5-HT, serotonin; α, adrenergic; D, dopamine; H, histamine; M, muscarinic.

Therapeutic and adverse effects of binding to target receptor

Receptor	Therapeutic	Adverse
D₂, D₃	<ul style="list-style-type: none"> Reduces positive symptoms 	<ul style="list-style-type: none"> EPS: dystonia, parkinsonism, akathisia, tardive dystonia, rabbit syndrome Neurohormonal (hyperprolactinemia) NIDS
D₁	<ul style="list-style-type: none"> Increases PFC function (agonism) 	<ul style="list-style-type: none"> Cognitive effects (antagonism)
α₁	<ul style="list-style-type: none"> Improves cognition under high stress 	<ul style="list-style-type: none"> Postural hypotension, dizziness, reflex tachycardia Potentiates hypotensive effect of prazosin May enhance weight gain
α₂	<ul style="list-style-type: none"> May potentiate antipsychotic effects and reduce EPS 	<ul style="list-style-type: none"> Blocks antihypertensive effect of clonidine
H₁	<ul style="list-style-type: none"> Sedation (acute, short-term use only) 	<ul style="list-style-type: none"> Sedation, drowsiness, weight gain
M₁ (antagonism)	<ul style="list-style-type: none"> Reduces EPS 	<ul style="list-style-type: none"> Memory effects (dysmnnesia)
M₁ (agonism)	<ul style="list-style-type: none"> Improves cognition 	<ul style="list-style-type: none"> Not known
5-HT_{2A/2C}	<ul style="list-style-type: none"> Reduces EPS Improves cognition and reduces negative symptoms 	<ul style="list-style-type: none"> Weight gain (5-HT_{2C} in association with other receptors)
5-HT₇	<ul style="list-style-type: none"> Ameliorates depression; improves cognition 	<ul style="list-style-type: none"> Not known
5-HT_{1A} (agonism)	<ul style="list-style-type: none"> Enhanced dopamine release in PFC and motor areas Anti-aggressive, anxiolytic, and mood stabilizing 	<ul style="list-style-type: none"> Worsens EPS in full agonism
NMDA complex	<ul style="list-style-type: none"> Cognitive (agonist) 	<ul style="list-style-type: none"> Neurotoxicity, psychosis

Figure 2.16 Therapeutic and adverse effects of binding to target receptor. 5-HT, serotonin; α, adrenergic; D, dopamine; EPS, extrapyramidal symptoms; NIDS, neuroleptic deficit syndrome; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex.

and the possible influence of potent α₂ antagonism (eg, asenapine, iloperidone). There may also be an effect from partial 5-HT_{1A} agonism (eg, asenapine, lurasidone), which putatively may reduce EPS through a reduction in raphe to striatum serotonergic tone.

Sedation

Whereas physicians tend to rate weight gain and EPS as being more important than sedation, it is the latter that patients and their families

often complain about. Aside from management of an acute relapse, complaints of sedation should be taken seriously and attempts made to lessen this side effect. Based on the pharmacology of asenapine and iloperidone, these drugs could be expected to be more sedative than lurasidone due to H_1 and α_1 blockade. Early reports, however, suggest that asenapine has the most sedation, followed by iloperidone and (dose dependently) lurasidone. Like all side effects that are influenced by multiple endogenous and exogenous conditions, this will require individual assessment in the clinic. Other side effects of note for each medicine can be found in early reviews.

Similarly, comparative efficacy can be estimated to some degree from these reports. Lurasidone has been studied using olanzapine as an active comparator. Essentially there was no difference in efficacy between lurasidone (40–120 mg/day) and olanzapine 15 mg/day, although there were differences in the range and degree of side effects, particularly weight gain, favoring lurasidone [76,77]. Asenapine trials have mainly been short-term and placebo-controlled studies. When olanzapine was used as an active comparator (not a direct head-to-head comparator), asenapine showed a similar to somewhat lower efficacy profile depending on how the results are interpreted. Iloperidone has been trialed by active comparators, but no studies were clearly designed as head-to-head comparisons (rather, placebo was the main comparator). Similarly, these findings do not answer the question of whether the symptom efficacy is on par with standard medications, although there is no doubt that they perform better than placebo. At this early stage of clinical use, postmarketing studies should be expected, where head-to-head comparisons are performed with well-established agents in appropriately selected populations and are sufficiently well-powered.

At the same time it is important not to focus on the nominal class of agent (FGAs vs SGAs), as this distinction has become somewhat vague. In keeping with the dictum that all treatment should be individualized, this approach should push clinicians toward examining the risks and benefits of each medication and tailoring them to the individual's specific need and/or vulnerability to adverse effects.

Agents targeting the metabotropic glutamate system

Brief mention should be made of the metabotropic glutamate receptor (mGluR) agonists and positive allosteric modulators. Group I mGluRs (mGluR1 and 5) are located postsynaptically, where they may play a role in modulating both glutamate and dopamine neurotransmission. Group II mGluRs (mGluR2 and 3) are found presynaptically, and are thought to directly modulate the release of glutamate. These agents could be considered to be a new generation of treatment due to their very different pharmacological targets when compared to dopamine antagonists and inverse agonists (ie, standard antipsychotics). A full description of progress in the development of these agents is beyond the scope of this chapter, however, a brief summary of research to date will be presented.

Whereas the precise mechanisms by which mGluR agonists and positive allosteric modulators may be effective in schizophrenia has not been elucidated, an early proof of concept trial of an mGlu2/3 agonist showed promise. A more recent and larger study in patients with schizophrenia was deemed “inconclusive” as neither the study agent nor the active comparator (olanzapine) could be differentiated from placebo. Clearly, further studies using mGluR agonists are required.

It can be argued that positive allosteric modulators may be closer to the “physiological state,” in that they may increase the effect of the natural ligand but only when it is binding to the orthostatic site. Although such agents are under development, none have received extensive investigation in patients with schizophrenia to date. It is useful to keep these agents in mind, as they may provide a method of targeting specific deficits (eg, cognition, motivation) when used as part of rational polypharmacy with antidopaminergics. However, early toxic outcomes (eg, seizures) in patients receiving mGluR2/3 agonists suggest that very careful attention should be paid to the risk–benefit ratio of these agents.

Form versus formulation

As discussed in the chapter on adherence, the actual effectiveness of medication may be a function of the patient’s understanding of the costs and benefits of their treatment, a realization of whether they have an illness,

and how intense it is, as well as the known efficacy and tolerability of the medicine. All of these factors influence the patient's preference and thus the rate of adherence (Figure 2.17). No matter how good or poor a medication is on paper, it will not help if the patient does not take it.

Although the new SDA-based medicines do not appreciably change the paradigm of antipsychotic action, immediate outcome gains can be made by improving the adherence to treatment, thereby enhancing the overall clinical effectiveness. For this reason antipsychotic formulation has become a mainstream clinical issue. As shown in Figure 2.18, for most oral medications, nonadherence is covert and it is difficult to detect without objective tests such as therapeutic drug monitoring. The next best strategy involves using the medication possession ratio, although this might not be suitable in all service delivery contexts.

To make nonadherence overt, the use of LAIs is the most effective way of knowing when a patient is receiving their medication (or not, depending on the service structure). In the case of direct medication supervision, dissolvable tablets offer the next best avenue of ensuring that the medicine is likely to have been ingested. A similar case can be made for liquid forms, such as for risperidone. If tablets or capsules have to be used, than persistent adherence is much more likely if there is a simple medication regimen (eg, once daily, at a time that allows for any peak side effects to occur during sleep). Additionally, the once-daily medication may be beneficial if it can be taken independently of food, a potential problem when prescribing ziprasidone and lurasidone, for example. As side effects may contribute to a patient's negative assessment of a medication, providing mechanisms to reduce the difference between high peak to trough levels seen with most oral medications may be useful. The OROS® technology used with paliperidone capsules flattens the daily peak–trough profile and may contribute to the low overall rate of EPS.

Of the new medications discussed here, paliperidone has both the OROS once-daily technology for oral delivery, and a newer crystal-based LAI form. Asenapine is administered by a sublingual tablet. However, asenapine and iloperidone are given twice daily, whereas lurasidone is given once daily, but must be taken with food. In other words, the kinetic profile affects delivery of the medication, which in turn may impair

The views of clinicians and patients on therapeutic effectiveness of treatment

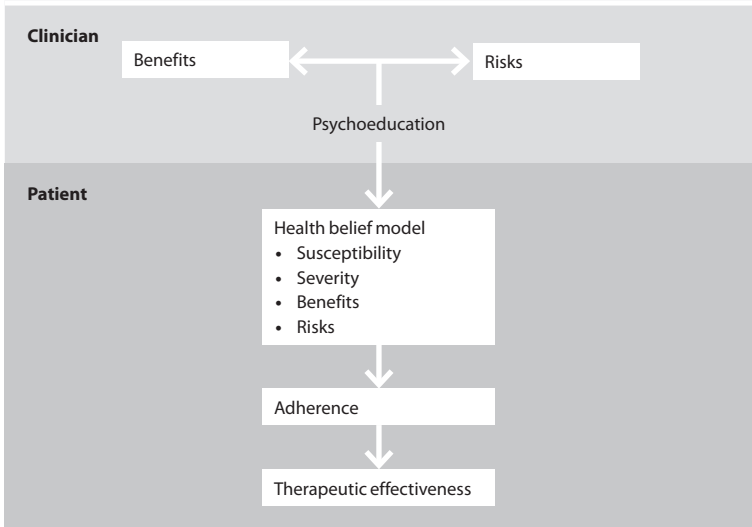


Figure 2.17 The views of clinicians and patients on therapeutic effectiveness of treatment.

Relationship between nonadherence and relapse

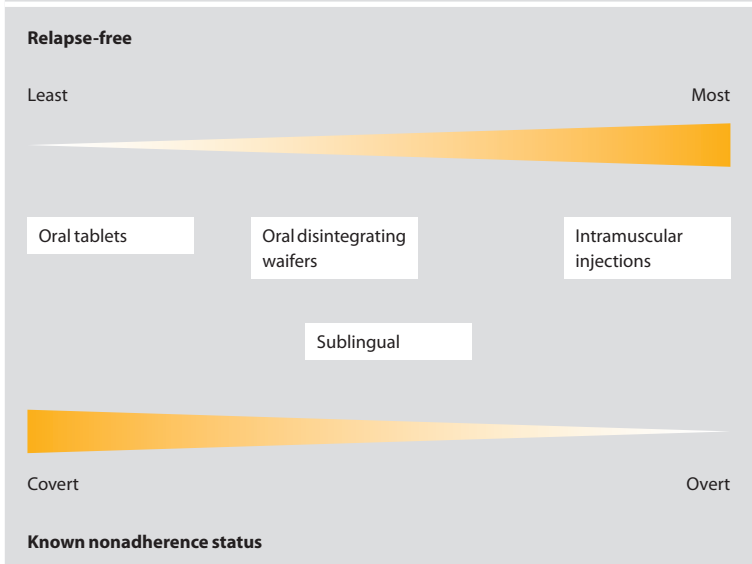


Figure 2.18 Relationship between nonadherence and relapse.

effectiveness through poor adherence if there is no adequate external medication-taking support.

New developments in the use of long-acting antipsychotics in the treatment of schizophrenia

As discussed elsewhere in this chapter (see page 27), rates of non- and partial adherence in schizophrenia are very high, with about two-thirds of patients missing significant amounts of oral medication in any 12-month period [78]. LAI antipsychotics have been developed with the aim of improving the long-term treatment of schizophrenia, primarily through improving the parlous rates of nonadherence. Relative to older antipsychotics, more recently developed antipsychotics combine variable efficacy at a broader range of targets with improved motor, neurocognitive, and neurohormonal tolerability. Long-acting forms of these agents might therefore be expected to combine better adherence with the benefits associated with the new generation agents. Whilst it should be emphasized that antipsychotic medication forms the key part of an individualized comprehensive treatment plan, which should include psychosocial interventions, a detailed discussion of the nonpharmacological management of schizophrenia is beyond the scope of this section, which reviews the use of LAIs in the practical management of schizophrenia.

Various lines of evidence support the use of LAIs, also known as “depots.” These include randomized controlled trials, open studies, and mirror studies, which are further supported by comparing continuous to intermittent therapy as well as by expert opinion in most clinical practice guidelines. In the recent ADHERE study, LAIs demonstrated improved patient adherence when compared to oral antipsychotics (97.7% vs 42.3%) [79]. Differentially high LAI adherence rates have also been found in other settings, including the USA and Australia. The regular administration schedule of LAIs also facilitates rapid identification of patients who are overtly nonadherent, allowing clinicians to determine whether suboptimal treatment responses are due to a lack of efficacy or nonadherence issues.

There are now three SGA LAIs available in the clinic: risperidone LAI (RLAI), olanzapine pamoate LAI (OLAI), and paliperidone palmitate LAI

(PLAI). An overview of these agents can be found in Figure 2.19, which shows that there is a number of differences between the formulations, including the need for initiation/loading strategies, requirements for oral supplementation to offset the time to steady state, time to onset of antipsychotic actions, range of injection frequencies, sites of injection, mechanical issues of storage and reconstitution, and the need for special precautions.

Comparison of second-generation antipsychotic long-acting injections			
	RLAI	PLAI	OLAI
Formulation	• Microsphere	• Crystal	• Crystal
Initiation/loading strategy	• Not possible	• Yes: day 1, then day 8, then monthly	• Yes: variable, depends on oral equivalence target
Requires oral supplementation	• Yes: 3+ weeks if switching from oral; • No: if switching from LAI	• No	• Not usually
Onset of clinical effect	• ≥4–5 weeks	• ≤1 week	• ≤1 week
Injection frequency	• 2-weekly	• Once-monthly	• 2- or 4-weekly [§]
Injection site	• Gluteal; deltoid*	• Deltoid; gluteal	• Gluteal
Reconstitution	• Powder in vial	• Prefilled syringes	• Powder in vial
Storage	• Refrigerated	• Room temp	• Room temp
Available doses*	• 25, 37.5, 50 mg	• 25, 50, 75, 100, 150 mg [†]	• 210, 300, 405 mg
Special precautions	• Take out of the fridge 30 minutes before use	• None	• Postinjection syndrome; requires mandatory 3-hour observation and transport protocols to be in place*, [‡]

Figure 2.19 Comparison of second-generation antipsychotic long-acting injections.

*Availability may differ by country; [†]in the USA PLAI doses are shown as paliperidone palmitate and so the equivalences to those in the table are 39, 78, 117, 156, 234 mg, respectively; [‡]protocols may reflect what an allowable facility entails, who will monitor, who will take the patient to and from the injection facility, and procedures for dealing with the postinjection syndrome, if it occurs; [§]to achieve an equivalence of 20 mg/day of oral olanzapine, no 4-weekly OLAI dose is approved at present. OLAI, olanzapine long-acting injection; PLAI, paliperidone long-acting injection; RLAI, risperidone long-acting injection. Adapted from Haddad et al [80].

Paliperidone palmitate

Paliperidone is the major active metabolite of risperidone and the palmitate ester of paliperidone and is one of only two crystal-based LAIs available at present. PLAI crystals are provided in an aqueous, rather than an oil-based, suspension that utilizes nanoparticle technology. There are many advantages to using crystal-based LAIs: primarily their onset of action is usually within the first week (as with oral antipsychotics). Thus, treatment may be commenced in situations of acute relapses, and the effectiveness of the treatment may be established even after short administration periods, which is in distinct contrast to FGA LAIs and RLAI that have a lag period before providing sufficient antipsychotic release without oral supplementation. Furthermore, this agent can be administered in either the deltoid or the gluteal muscles, and in fact allows for some control of the release kinetics depending on the injection site (deltoid has a greater C_{max} and is recommended for at least the first two loading doses). The structure of the nanoparticles allows for a relatively long apparent half-life and the standard injection frequency is monthly.

Although efficacy data on PLAI are limited at this time, an intramuscular gluteal injection of long-acting paliperidone was shown to be significantly more effective than placebo in treating a first episode of schizophrenia in two double-blind, randomized studies. In 518 patients with schizophrenia, once monthly PLAI administered over 13 weeks produced clinically meaningful improvements across all efficacy measures: positive and negative syndrome scale total ($P < 0.001$ vs placebo), positive and negative symptom scores ($P \leq 0.05$), and clinical global impression severity scores ($P \leq 0.006$) [81]. These findings have been confirmed in a 9-week study in which the PLAI responder rate (without oral supplementation) was 2.5-fold higher than that of placebo (37% vs 14% with $\geq 30\%$ improvement in positive and negative syndrome scale total score) [82]. Relative to placebo, PLAI was generally well tolerated with a similar incidence of treatment-emergent events and low rates of EPS (5% vs 6%) [82]. In another placebo-controlled recurrence prevention study, PLAI significantly delayed time to relapse compared with placebo, without unexpected adverse events [82]. Although head-to-head comparative trials will be needed to confirm these results, the efficacy

and tolerability of paliperidone support its use as a viable treatment option in the acute management of psychosis. This is a game-changing development considering that older depots did not allow for an effective and safe acute use strategy.

To date, few studies have investigated the efficacy of SGA LAIs in the prevention of relapse as a primary clinical end point. However, available data indicate that SGA LAIs significantly reduce relapse rates. PLAII appears to be effective in relapse prevention. In a 6-month “real-world” study in stabilized patients with schizophrenia ($n=408$), PLAII significantly delayed the time to relapse ($P<0.0001$) and produced a threefold reduction in the rate of relapse (10% vs 34% for placebo) [83]. Studies of longer duration are expected for PLAII in order to establish its long-term effectiveness.

PLAII may also play an important role in helping to differentiate those with resistance to treatment versus true treatment-refractory schizophrenia. The former implies the possibility of modifiable reasons for poor outcome, whereas the latter suggests that adequate treatment has been applied (ie, medications have reached their target receptors in optimal concentrations for optimal periods, and appropriate psychosocial interventions transacted), but there has been little or insufficient response. After examining various resistance-to-treatment factors, it is common to find that adherence to past treatments cannot be confirmed. This leads to an important question as to whether the so-called resistance to treatment was simply inadequate effectiveness due to nonadherence.

Ultimately, the only sure test of whether adherence issues are at the root of the poor outcomes is to ensure adherence through a trial of an LAI. A priori end-points should be defined in order to gauge the success of LAI intervention. Preceding such a trial, the following factors should be established: (i) the trial time frame; (ii) symptoms or outcome dimensions that are expected to improve; (iii) how the symptoms should be measured and by whom; and (iv) the minimal/threshold shifts required to determine drug responsiveness. By setting the threshold for improvement in a manner that is readily discernible by the treatment team, it usually becomes clear within 3 months whether LAI is having an effect, although up to 5 or 6 months may be required in some cases. For those

who respond, continuing maintenance with LAI is recommended, while issues of adherence to oral treatments are addressed. However, when patients show no response and treatment-refractory disease seems likely, it is important to switch to clozapine as soon as possible. Delays in the initiation of clozapine may lead to less robust responses, and maintaining LAI treatment with no real therapeutic benefit and many potential risks poses ethical concerns.

Advantages of PLAI in the clinic

Not all benefits of new medications and formulations lie in the pharmacology alone. In case of PLAI, the following may facilitate its use in overstretched community psychiatric settings and thereby enhance the efficiency of services:

- injections once every month;
- no special storage requirements such as cold chain;
- different needle sizes available for varying patient body-mass index;
- provision of prefilled syringes with no need to spend time preparing a suspension;
- deltoid or gluteal injections (although not researched adequately to date, the ability to give the injection in the deltoid may also be seen as an advantage for quicker, less stigmatizing delivery, both from the patient's and service's points of view);
- no 3-hour observation period required;
- no requirement to monitor transport to and from the injecting facility;
- may be given anywhere (eg, patient's home, work, office).

Conclusion

This section has reviewed medications for schizophrenia that have been recently released as well as those approaching release. Whereas the newer oral antidopaminergic agents do not have new mechanisms of action (being SDA drugs), their broader range of effects at key receptors allows their overall cost–benefit profile to be sufficiently different. The individualization of treatment requires a broad palette of options when treating schizophrenia, and new agents may “work” in particular cases where others have failed. Such targeted multireceptor approaches may

be effective through a “magic shotgun” approach, rather than that of a “magic bullet.”

The problem of nonadherence underlies all management of chronic disease states. The acceptance of, and the direct approach to, managing such states increasingly lies with new formulations of existing medications that clearly highlight overt nonadherence. Crystal-based LAIs may represent one of the advantages of new delivery systems providing better adherence and outcomes in the longer term.

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