Psychotic Disorders

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4.1 Schizophrenia

4.1.1 Introduction

Schizophrenia is a common paradigm of mental illness; it is characterized by a constellation of psychopathological aspects clinically and biologically related in a nonlinear, but rather coherent syndromic presentation and temporal pattern. Even if the clinical presentation and temporal distribution of symptoms across the lifespan have a variety of possibilities, the life perspective is that of a chronic condition, leading to cognitive and functional deterioration, which is not common to any other disease with a juvenile onset for the complexity of its different aspects.

A severe mentally ill is not necessarily a patient suffering from schizophrenia, but, when it happens, schizophrenia is probably the most frequent severe psychiatric illness.

Schizophrenia has represented since centuries madness itself like delusions are as a psychopathological entity. In delusion, you lose the qualitative features of the sentiment and perception of reality (what you believe firmly is not understandable

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and not shared in the common view of your peers, even considering the sociocultural background). However, while delusion itself is not typical of schizophrenia or any other disorder and can disappear with full recovery in other illnesses (i.e., mood disorders), when it happens in the context of this diagnosis, it may attenuate, become less or minimally important for patients' inner life and behavior (after an adequate treatment), but never be canceled. In the best situations, it may be referred to a past, closed experience, but never negated as true in the time it occurred.

This means that schizophrenia alterations in reality perception and sentiment become permanent in the autonoetic experience of the subject, that is, a permanently altered functioning of cognition supporting the long-term experience of consciousness itself.

Again, delusion experience alone is neither diagnostic nor characteristic of the illness. What is peculiar and practically always appreciable in all patients is the long-term change in cognition, in a wide sense.

This change in cognition is related to the "biogenesis" of the so-called positive symptoms (pathological mental activities absent in normal functioning), in their development and maintenance, but even more to the early progressive and chronic loss of some of the main components of vitality in every person experience: volition, engagement in life and relationship, affect, features that characterize the so-called schizophrenic autism (Bleuler), the prevalence of a (poor) inner world in a person's cognitive and affective investment in opposition to that in real world, and social life he could live.

Emil Kraepelin called this illness at the beginning of the twentieth century "Dementia Praecox"; this definition is impressive and strongly related to the absence, at that time, of any treatment improving symptoms and lives of the patients. Nowadays and since 50 years ago (this changed the paradigm of treatment of schizophrenia from support and assistance to care and cure), schizophrenia treatment is available starting from drugs that are effective in reducing the most acute and disturbing symptoms, but have a limited effect on the so-called negative symptoms (normal mental activities pathologically diminished in schizophrenia) and cognitive deficits developed. Nevertheless, their effects, even if limited to the "positive symptoms" treatment, are permissive toward the nonpharmacological treatment with psychosocial, neurocognitive, and sociocognitive rehabilitation that improve negative and cognitive symptoms.

This last part of the interventions, commonly delivered among patients with schizophrenia, has reached in the last 20 years much more milestones than drugs in building the hope of treatment of schizophrenia letting possible, also for this dramatic illness, terms as "remission" and also "recovery".

Nowadays, in most cases, schizophrenia is a treatable illness: this does not correspond to full restoring, usually, but a significant proportion of patients restore their life perspective, remaining a fragile population to be supported; they can go back to work, study, and have significant relationships. When this target is reached, the remaining part of the problem of schizophrenia is stigma, harder than for other psychiatric illnesses, due to the lack in comprehension of some experiences for the

nontechnicals and also to the behavioral evidence of strangeness or marginality of these lives.

This chapter will lead to a basic comprehension of phenomena appreciable in the illness, a knowledge of the main treatments and their effects, and of the main targets and instruments of treatment.

4.1.2 Definition and Epidemiology

Schizophrenia is a chronic psychotic disorder, typically deteriorating over time, which strongly affects daily functioning in a negative way, determining deficits in cognitive, emotional, and social domains. Symptoms are grouped in three main categories: positive, negative, and cognitive.

Schizophrenia affects almost 23 million people worldwide, with a lifetime prevalence in the general population that averages 0.7%, and an annual incidence of 15 per 100,000.

> Schizophrenia is among the top ten leading causes of disease-related disability in the world due to the pervasiveness of related deficits and life-long course.

Historically, the risk of developing schizophrenia over one's lifetime was thought to be similar among males and females, but recent large-scale studies revealed a slightly higher incidence among males (male/female relative risk = 1.4). The age of onset ranges between adolescence and early adulthood, with sex-related differences. Indeed, male patients show first symptoms of the disease earlier (age of onset: 20–28 years) compared to females (age of onset: 26–32), with a mean difference of onset of about 6 years. The later age of onset in women is associated with higher attainment of social role functioning before illness, which is related to a longitudinal better outcome.

The overt onset of illness is frequently anticipated by the presence of prodromal symptoms, detectable since early adolescence and consisting in one or more of the following clinical manifestations: social withdrawal and isolation, impaired social/scholastic function, bizarre thoughts, speech or behavior, neglected personal hygiene, blunted and inadequate affect, and loss of personal initiative. Delayed attainment of various developmental milestones, cognitive impairments during childhood or adolescence, neurological "soft signs" and poor social adjustment have been linked to an increased likelihood of developing schizophrenia. However, it is still unclear whether such impairments represent risk factors per se or early manifestations of the disease.

Concerning epidemiological differences in the worldwide distribution of the disease, a near-uniform global distribution suggests a relative independence from cultural and ethnical factors.

Nonetheless, ethnical and sociocultural environment may indirectly represent determinants of illness, since they can be associated with significant risk factors for the disease such as migration and urbanization.

4.1.3 Etiopathogenesis

Despite a multitude of studies, to date etiology of schizophrenia is still unclear. Schizophrenia is considered a multifactorial disease, associated with genetic and environmental factors that structure the phenotype of the illness by interacting with each other. Although no single DNA mutations or specific gene variation are able to directly cause the disease, genetic variations and gene–environment interactions together determine over 80% of the liability for developing schizophrenia. In this context, epigenetic represents the bridge between gene and environment, and a growing number of studies have been focusing on the analysis of its neurobiological effects.

> Epigenetics do not determine DNA code alterations, but modulate gene expression by modifying DNA structure.

Genome-wide association studies revealed a large set of genetic loci associated with schizophrenia, each with a minimal effect in determining disease susceptibility. Among these, the most relevant are those involved in neurotransmission and immune response/modulation. Genetic alterations such as single-nucleotide polymorphisms (SNPs) and copy number variants (CNVs) located within these loci of interest are able to significantly contribute to the development of the illness. Moreover, a growing body of evidence suggests that abnormalities in genetics-mediated brain maturation during the early teen years (and especially that of the hub areas in the brain) might be crucial to the development of the disorder.

Nowadays, the strongest etiopathogenetic theory revolves around the concept of "schizophrenia vulnerability." It is hypothesized that individual genetic liability interacts with other environmental and biological risk factors, leading together to develop schizophrenia once a critical threshold is crossed.

4.1.3.1 Heritability

A family history of schizophrenia in a first-degree relative represents one of the most widely replicated risk factors for the disorder. However, as discussed above, heritability follows a complex, multigenic, nonmendelian transmission pattern, probably involving reduced genetic penetrance (variants that do not express in every carrier as disease), gene-expression variability (variants that express differently between carriers), and gene–gene interactions. Schizophrenia shows indeed a higher incidence in certain families, despite over two-thirds of the cases occur sporadically without an aggregation in familial clusters. The concept of familiarity is a topic of

main interest, since family members share both genetic heritage and life experiences (environmental aspects), and thus represents an actual demonstration of the *gene* × *environment* etiopathogenetic theory. Familiar studies and comparisons between twins and sibling clearly indicate a higher risk of schizophrenia in relatives of affected patients, compared with the general population. Indeed, lifetime risk in first-degree relatives of patients is 6.5%, and it rises to more than 40% in monozygotic twins of affected subjects. However, despite the same genetic substrate and family environment, the rate of concordance between homozygous twins deviates from the theoretical expected rate of concordance of 100%, evidencing the crucial role of external contributing risk factors.

4.1.3.2 Environmental Risk Factors

A multitude of epidemiological studies have highlighted the presence of a large number of environmental factors associated with an increased risk for schizophrenia. Among these, there are both biological and psychosocial risk factors that may occur from antenatal and perinatal periods until early adulthood. However, once again, it is important to underline that none of these elements are necessary or sufficient to cause schizophrenia alone but only increase the likelihood by a small percentage.

Overall, the main environmental factors that seem to have a greater impact on the susceptibility of developing the disease are urbanicity, substance use/abuse, and childhood trauma. Although the causal mechanism is still unclear, it has been hypothesized that the different environmental stressors ultimately impact on brain structure and function through a common neurobiological pathway, the dysregulation of the striatal dopaminergic neurotransmission ("stress sensitization").

Pregnancy and birth complications, together defined as "obstetric complications," have been individuated as early risk factors for schizophrenia, as different studies reported a higher number of these events among patients. Obstetric complications can be grouped in three main categories: complications of pregnancy (bleeding, preeclampsia, diabetes, maternal malnutrition, maternal infections, Rh incompatibility), abnormal fetal development (low birth weight, congenital malformations, small head circumference), and complications of delivery (asphyxia, uterine atony, emergency cesarean section). Concerning parents, among other relevant biological risk factors, is also reported higher maternal/paternal age, due to an increased likelihood of de novo mutation and aberrant epigenetic regulation correlated with age.

Adverse childhood experiences and trauma (sexual/physical/psychological abuse, neglect, parental death or separation, and bullying) have been extensively investigated and associated with increased odds of developing psychosis in adulthood. Particularly, childhood trauma has been associated with the most severe forms of positive symptomatology and affective symptoms. Life events that bring negative changes in personal circumstances and/or involve an element of threat occurring in a period ranging between 3 months and 3.6 years before the onset of the illness are the most involved in inducing psychotic transition.

Other relevant stressors occurring during early stages of life and associated with the development of schizophrenia are *urbanicity*, defined as growing up or moving

to an urban environment, and *migration*. These factors are associated with a mean twofold increased risk for the disease, although the specific mechanisms underlying these data are not fully understood yet. It has been hypothesized that both urbanicity and migration are associated with a large cluster of environmental stressors (i.e., social inequality, isolation, discrimination, lack of appropriate accommodation, lower social status) that together contribute to the increased incidence of psychosis.

Besides environmental and social stressors, epidemiological studies individuated a large set of risk factors associated with schizophrenia. Among these, *substance abuse* is probably the most important determinant of the disease, after genetic liability. Schizophrenia is indeed associated with the use/abuse of several substances, such as cannabis, psychostimulants (cocaine and amphetamines), or hallucinogens, and these harmful habits have been widely reported to induce psychotic symptoms. In this context, cannabis plays a major role, representing the most frequently involved psychoactive substance in psychotic onsets. Besides being able to induce and worsen positive symptoms, several prospective epidemiological studies consistently reported an association between cannabis use and greater risk for schizophrenia. A relationship between degree of abuse (dose and frequency of consumption, THC concentration) and risk of psychosis has been extensively demonstrated as well. Moreover, frequent use of cannabis, especially at a younger age, and high potency THC not only increase the risk of schizophrenia of several times but are also associated with earlier onset, more severe positive symptoms, greater cognitive impairment, and worse long-term clinical and functional outcome.

4.1.3.3 Neurobiological Correlates

A multitude of cross-sectional studies strongly support the presence of structural and functional brain alterations in schizophrenia. Whole brain and gray matter volume reductions are largely described, particularly in frontal, temporal, and postcentral cortical regions. Moreover, increased ventricular size, conditioned by atrophy, is a frequent finding. Structural magnetic resonance imaging (MRI) has been used to investigate longitudinal volume changes, finding a progressive decline in both the first-episode psychosis and chronic patients. Notably, a large body of evidence suggests that longitudinal progression of cortical thinning of frontal and temporal areas correlates with deficits in several cognitive domains. Alterations in brain connectivity seem to play a crucial role in schizophrenia as well. Diffusion tensor imaging (DTI) studies indicate a decreased integrity of the microstructure of the white matter (WM). Interestingly, disruption of WM integrity seems to be progressive along the course of the disease. In particular, structural alterations in the myelin sheet seems to play the major role in the disruption process of the WM, hampering neuronal signaling. Taken together, these structural alterations result in impaired neurofunctional networks, as shown by positron emission tomography (PET), spectroscopy, and functional-MRI studies. Specifically, patients with schizophrenia are characterized by decreased cortical glutamatergic and dopaminergic activity, associated with cognitive and negative symptoms, and by increased dopaminergic synthesis and signaling in the striatum, underlying positive symptomatology.

Over the last decade, in vivo imaging approaches have significantly contributed to elucidate neurotransmitter abnormalities underling the disorder, strongly contributing to the development of new and integrated etiopathogenetic theories.

Overall, schizophrenia is characterized by a dysregulation of multiple neurotransmitters in multiple pathways, with main alterations involving dopaminergic and glutamatergic systems.

Historically, the "*dopamine hypothesis*" was the first proposed to explain etiopathogenesis of schizophrenia. It was based on two main observations: the efficacy of antipsychotic drugs acting by blocking dopamine mesolimbic D2 receptors in managing psychotic symptoms, and the capacity of drugs increasing dopamine, such as amphetamine, to induce psychotic symptoms. Schizophrenia was therefore hypothesized to be caused by the hyperactivity of subcortical mesolimbic D2 pathways. However, this theory was not able to explain the presence of negative and cognitive symptoms, neither the frequent lack of response to antipsychotic D2-blocking activity. Subsequent studies showed that cognitive and negative symptoms were associated with reduced prefrontal cortical activity, leading to a reconceptualization of the dopamine hypothesis implying a prefrontal hypodopaminergia as the primary alteration. However, as mentioned before, dopaminergic dysfunction does not comprehensively explain the full range of clinical features of the disorder, not including alterations of other neurotransmitter systems known to be dysregulated in schizophrenia. Among these, the *glutamatergic system* is highly implicated in the etiopathogenesis of the illness, representing the major excitatory pathway in the central nervous system involved in critical processes such as neural development, synaptic plasticity, and cognition. Glutamate dysregulation was hypothesized to be involved in the etiopathogenesis of schizophrenia as a consequence of the observed psychotogenic effects of phencyclidine and its derivative ketamine, drugs antagonizing the glutamatergic *N*-methyl-D-aspartate receptor (NMDAr). Following studies consistently reported a widespread reduction of glutamatergic signaling among patients with schizophrenia.

However, there is much more to psychosis than dopamine and glutamate, and there is much more to treatment of psychosis than D2 antagonism. For instance, serotoninergic hyperactivity (specifically at 5HT2a receptor) has been hypothesized to underlie positive symptoms. In fact, serotonin was examined early for a role in schizophrenia because of the psychomimetic actions of its agonists, such as lysergic acid diethylamide (LSD) and mescaline. Moreover, drugs with serotoninergic antagonist action seem to improve psychotic symptoms. Dysregulation of other neurotransmitters, such as GABA and choline, have been reported as well, although less consistently and with marginal effects on clinical outcomes, but rather on cognition.

More recently, an etiopathogenetic model attempted to integrate glutamatergic and dopaminergic alterations of schizophrenia. Specifically, it has been proposed that a deficient cortical glutamatergic transmission, associated with diminished prefrontal activity, may lead to increased striatal dopamine synthesis and release by hypo-activating GABAergic transmission, which physiologically inhibits striatal dopamine activity.

However, although intriguing, even this integrated model only partially elucidate the broad range of neurobiological alterations and does not take into account the high inter-individual variability observed among patients with schizophrenia.

Indeed, rather than a unique disorder characterized by high neurobiological and clinical variability, schizophrenia is being reconceptualized as a spectrum of chronic psychotic disorders (or "*schizophrenias*") sharing a multitude of biological and phenotypic features. In this view, treatment-resistant schizophrenia (TRS) has been proposed as a different subtype of schizophrenia, defined as "normodopaminergic." TRS occurs in approximately one third of patients diagnosed with schizophrenia and is characterized by persistence of positive symptoms despite adequate antipsychotic treatment, detectable from illness onset. Studies reported that TRS patients, differently from responders, show normal striatal dopaminergic synthesis and higher cortical glutamate levels. Consistently, clozapine is the only effective antipsychotic in TRS and the only antipsychotic showing a glutamatergic receptor affinity, thus further suggesting the presence of two (at least) distinct neurobiological subtypes of schizophrenia.

4.1.4 Clinical Presentation

Schizophrenia is characterized by a great heterogeneity of clinical manifestations and outcome, resulting in a merge of positive, negative, and cognitive symptoms whose severity varies across patients and through the course of illness. In the great majority of affected subjects, schizophrenia has a devastating impact on functional outcome, determining long-term disability.

Besides the structural feature of no insight on delusions and hallucinations, patients affected by schizophrenia usually lack insight on the illness itself, being unaware of it and its potential consequences, thus not recognizing the need for treatment and showing poor compliance to therapy.

For this reason, a god patient–doctor relationship and psycho educational interventions on illness, its consequences, and positive perspectives given from an adequate treatment are of extreme importance.

4.1.4.1 Positive Symptoms

Positive symptoms are more prominent during acute exacerbations and include the reality distortion symptoms of hallucinations and delusions, as well as disorganized thoughts, speech, and behavior.

Box 4.1: Positive Symptoms
- Hallucinations
- Delusions
- Disorganization of thought and/or speech and behavior

Hallucinations are perceptions that occur without an actual external stimulus. They may involve all the senses, but the most common hallucinations in schizophrenia are the auditory ones, typically complex (voices). Schizophrenia presents among individuals' different types of auditory hallucinations, sometimes coexisting: dialoguing in third person about the patient, imperative, threatening, accusatory, and commenting voices. Frequently, auditory hallucinations and delusional beliefs influence each other and together contribute to an altered interpretation of reality: as an example, the patient hears voices insulting/threatening him/her and is thus led to believe that someone is pursuing him/her or reinforces the concomitant persecutory delusion.

Delusions are false beliefs that are held despite contrary evidence on which the patient has no insight, presenting with variable content.

Some of the most frequent contents of delusions, according to their content, in schizophrenia are

- *Persecutory*: It is the most common of the subtypes. Typical themes are that of being persecuted, controlled, poisoned, the object of a conspiracy, hindered in actions.
- *Influencing and control:* Delusions of thought control, insertion, withdrawal, and broadcasting have also been historically linked to the diagnosis of schizophrenia even if not exclusive. Patients may believe that their acts or bodily functions and mental activity are not under their voluntary control or ruled by individual physiology, but under the control and influence of other people or entities by means of instruments (radio waves or similar) or magical powers; these themes are usually referred to as delusions of passivity.
- *Reference*: Beliefs that random or neutral events are addressed to the subject in a special and meaningful way. Common ideas of reference include believing that occurrences on the television or radio (certain words said or songs played) are meant to deliver a special message to the subject.
- *Somatic and body transformation*: Patient believes he is going to be transformed in an animal or that some parts of his body are changing measure, consistency, or even constitution (i.e., "my bones are made of glass" or "I'm going to be transformed in a dog" or "my inner organs have been moved from their original position") frequently associated with somatic hallucinations. Other types of somatic delusions are that of infestation with parasites, body dysmorphic, and body odor.
- *Bizarre:* Ideas are clearly implausible, unusual, and hardly understandable (i.e., being an alien or a robot or having a microchip implanted in the brain to influence his/her thoughts).
- *Erotomania*: The patient believes another person, usually someone of higher status or famous, is in love with him/her.
- *Grandiose:* The patient believes he/she has great talent, special power, knowledge, a relationship with someone famous, or has made an important discovery. Grandiose delusions may have genealogical or religious content.

Among these, persecutory delusions and ideas of reference are the most frequently reported in schizophrenia, often co-occurring and determining suspiciousness and active social withdrawal.

Nevertheless, in response to the presence of all themes of delusions, patients have important affective involvement, especially during acute phases, and can appear depressed, anxious, irritable, litigious, or even aggressive. Acting delusion or in defense of the content of the delusion is frequent (i.e., aggression of the hypothetical prosecutor, stopping to eat for fear of poisoning by a family member, resuming suddenly a work, remaining barricaded himself at home, or leaving to escape from a threaten).

Disorganization is a key feature of patients with schizophrenia, potentially affecting thought, speech, and behavior, regardless of the severity of hallucinations or delusions. Thought disorganization is identified by the lessening or total loss of connections between ideas, affecting both behavior and communication. Disorganized behavior can be directly observed and may range from simple problems sustaining goal-directed self-care behaviors such as personal hygiene, to unpredictable and bizarre socially inappropriate outbursts.

Severely disorganized thought can result in inconsistent and disorganized speech that can lose its communicative finality. The most commonly observed forms of abnormal speech are tangentiality and circumstantiality, while more severe thought disorder includes derailment, neologisms, and word salad, which consists in a total lack of logical associations with words thrown together without any sensible meaning.

4.1.4.2 Negative Symptoms

Negative symptoms are core features of schizophrenia, conceptualized as an absence or diminution of normal processes and being also referred to as deficit symptoms. This group of symptoms identifies different declinations of the same psychopathological element, that is, disinterest/detachment from the outside world. Negative symptomatology progressively grows in importance and pervasiveness during the course of the disease, representing the main feature of the residual phase (when positive symptoms are strongly attenuated or absent). Symptoms can be divided into two main clusters: diminished expression, including alogia and affective flattening, and avolition, including apathy, anhedonia, and asociality. Negative symptoms are often correlated with a marked reduction of facial mimicry and gestures and frequently result in a loss of goal-oriented behaviors, personal interests, and libido. Decreases in personal care and a failure to comply with social conventions represent common aspects as well. Negative symptoms are independent from positive symptomatology, being very resistant to treatment and negatively affecting functional outcome.

Box 4.2: Negative Symptoms

- Apathy (absence of emotions)
- Abulia or avolition (lack of will/initiative)
- Alogia (poor content of speech, blocks, latency of response)
- Anhedonia (inability to experience pleasure)
- Affective flattening

4.1.4.3 Cognitive Deficit

Cognitive deficits represent, together with negative symptoms, the most critical dimension in schizophrenia treatment, determining high disability and being almost completely resistant to antipsychotic drugs. Cognitive impairment is often detectable before the onset of illness, is scarcely related to psychotic symptoms, and remains stable or worsens along the course of illness. The severity of cognitive impairment has been significantly linked to global functional outcome and patient's quality of life and is a main target of treatment. Among patients with schizophrenia, deficits are present in several cognitive domains, making it difficult to establish a clear pattern of specific deficits associated with the disorder. Patients typically perform one to two standard deviations below healthy controls on a broad range of neurocognitive measures, with the most prominent impairments observed in working memory, executive functions and processing speed. Neurocognitive functions represent part of the structuring elements of the complex cognitive domain of social cognition, also impaired in schizophrenia. Social cognition is a multifactorial construct that includes the abilities of individuals to understand themselves and others in the context of social interactions, such as empathy and theory of mind. Social cognitive abilities have been directly linked to quality of life, frequency and significance of interpersonal relationships, work attainments, and personal achievements. Language and communication are also altered in schizophrenia, with a strong impact on social, as well as global functioning. These deficits are detectable at different levels, encompassing the syntactic structure and higher-order domains involving the integration of context, such as figurative language comprehension.

Box 4.3: Impaired Cognitive Functions

- Executive functions
- Working memory
- Processing speed
- Selective and sustained attention
- Verbal fluency
- Verbal memory
- Psychomotor coordination

4.1.4.4 Catatonic Features

Catatonia refers to a syndrome characterized by alterations of movements and behavior. It has long been considered a core dimension of schizophrenia, also previously characterizing a clinical subtype. However, catatonic symptoms have been reported to occur in more than 10% of patients with acute psychiatric illnesses.

Box 4.4: Catatonic Syndrome
- Indifference to external stimuli, negativism
- Immobility, maintenance of forced postures (catatonic postures), and waxed flexibility (postures assumed by passive mobilization of patient's arts). This might be interrupted by sudden, bursting psychomotor agitation in some cases
- Automatic obedience
- Echolalia and echopraxia
- Stereotypes and mannerisms

4.1.4.5 Functional Impairment

Every aspect of schizophrenia symptomatology contributes to the impairment in patients' daily functioning, which hampers the achievement of an adequate quality of life. A certain degree of functional decline is often detectable before the acute onset of illness, persisting and gradually worsening also during periods of symptoms' remission. Patients with schizophrenia show impairments in several functional domains, including self-care activities, psychosocial, and work functioning. Functional deterioration determines a great social and financial burden on healthcare systems and society. Moreover, severe functional impairment is also associated with a higher risk of physical morbidities and, therefore, with reduced longevity.

Functional outcome is mainly influenced by neurocognitive functions and social-cognitive skills such as empathy, theory of mind, and emotion recognition. Taken together, these deficits negatively affect social interactions, further impairing real-world functioning and patient's autonomy. Most of them are targeted by current rehabilitative programs in articulated designs addressed to all these components.

Notably, functional impairment is only marginally affected by positive symptomatology. Similarly to negative and cognitive symptomatology, antipsychotic pharmacological treatment is not yet clearly effective in improving functional outcome directly, but through the mediation of the reduction of positive symptoms.

4.1.4.6 Clinical Course

Schizophrenia is characterized by a chronic and progressive course of illness, with a relapsing/remitting pattern of acute exacerbations. Remissions are generally partial and incomplete, with the persistence of a certain degree of symptoms. Negative and cognitive symptoms tend to progress along the course of illness, increasing proportionally with the number of relapses and conditioning progressive functional impairment (educational and work performance) and social disability (social withdrawal). Nevertheless, most of primary cognitive and functional deterioration occurs during the early stages of the illness, typically within 3–5 years after symptom onset. Nowadays, with current treatment available, following these disruptive early stages, the illness stabilizes and, despite possible subsequent exacerbations,

there is generally no further significative illness-driven decline in cognition and, partially, in functioning. However, the magnitude of this deterioration appears to be at some degree related to the duration of untreated psychosis, as also evidenced by patients showing treatment resistance is characterized by worse longitudinal cognitive and functional outcome and the different course in the preneuroleptic era, almost invariably leading to a severe worsening. Indeed, on the one side, persistence of active positive symptoms has been associated with brain structural and functional decline and, on the other, limit patient's ecological daily cognitive training by leading to active social withdrawal. So a secondary (to nonfunctioning due to persistent positive symptoms and negative symptoms) worsening in cognition may be seen when illness is not under control. So, despite the poor correlation of cognitive and positive symptoms seen in current research, in clinical reality the control of positive symptoms and the reduction of re-exacerbations with continuous use of antipsychotics is fundamental and underlines the need to favor compliance to treatment.

The clinical course can be divided into three major "phases" even if the illness is a chronic one (four, if we consider prodromal phase).

Premorbid Phase

A substantial proportion of patients show a significant premorbid impairment detected in terms of cognitive functioning and poor social adjustment (varying degrees of nonspecific negative and cognitive symptoms) that frequently hamper the achievement of standard scholastic results. Deficits mainly affecting motor coordination, motor sequence, and sensory integration, named neurological soft signs, are also detectable in subjects who will later develop schizophrenia, even if mainly subtle.

Box 4.5: Neurological Soft Signs (NSS)

- Altered domains
- Motor coordination: diadochokinesia, finger-thumb opposition
- Sensory integration: gait, tandem gait, two-point discrimination
- Complex motor tasks: finger to nose test, fist edge-palm test (prono-supination task)
- Spatial motor task: right-left orientation, graphesthesia, stereognosis
- Primitive reflexes

Prodromal Phase

The onset of the disease is often preceded by a prodromal phase characterized by attenuated positive symptoms (subthreshold unusual ideas or perceptions), declining of functioning in terms of educational or work performance, and progressive social withdrawal with loss of interests. The subject experiences a reduction in the quality and quantity of social and affective relationships, appearing detached from life events. This phase is frequently accompanied by a sense of alienation of the

subject with respect to the surrounding environment, together with a great anguish and an internal feeling of disruption of psychic functions. This phenomenon, defined as *delusional mood,* is described as a terrifying experience in which the individual has the subjective perception that something indefinable and devastating is going to happen. Moreover, bizarre ideas, fatuous or perplexed expressions, and strange behaviors may be reported, such as inappropriate laughter, often secondary to unusual perceptions. *Delusional perceptions* (abnormal meanings attributed to real perceptions) or *delusional intuitions* (sudden and aberrant enlightenment) are also frequently described.

Acute Exacerbation

The first psychotic episode is generally recognized as the formal onset of the disease and usually occurs in late adolescence or early adulthood. It is characterized by the presence of delusions, hallucinations, and disorganization, also accompanied by behavioral problems like psychomotor agitation or acting related to the delusional and hallucinatory contents (a patient may stay weeks at home without going out with sunblinds down because he is scared by people observing him and prosecuting him). The first years of illness are often characterized by repeated episodes of acute psychosis, with variable duration of inter-episode remission or attenuation of positive symptoms. During these episodes, hospitalization is often required, aimed at clinical management and behavioral observation and control sometimes necessary for the behavioral consequences of severe delusional or hallucinatory or disorganization symptoms and the severe anguish the patient may show, and faster therapeutic optimization. Fewer episodes and lower severity are achieved with early and effective pharmacological treatment and its maintenance over time as prophylaxis. The lack of compliance with antipsychotic treatment is the main cause of relapses. Exacerbations can be triggered also by stress and substance abuse.

Chronic Phase

Throughout the course of illness, a phase of relative stability can be reached in which positive symptoms become less severe, while negative symptoms and cognitive deficits remain the more prominent features. In this phase, the functional impairment persists and should be addressed with specific rehabilitative intervention.

4.1.4.7 Diagnosis

At first, schizophrenia is generally diagnosed on the presence of positive symptoms (not necessarily continuous) and impaired functioning in the absence of significant mood symptoms, neurological illness, or substance use that can account for the psychotic symptoms. Despite the absence of reliable diagnostic tests, biomarkers, and pathognomonic symptoms, neuroimaging (to exclude organic causes in the differential diagnosis), diagnostic interviews, and cognitive testing are frequently used to support the clinical diagnosis based on symptoms.

The diagnosis of schizophrenia must be carefully evaluated due the aspecifical nature of most symptoms and symptoms combination in psychotic onsets of any kind (in particular care should be used to exclude the onset of a mood disorder or an acute psychosis driven by a substance abuse or a medical condition or a medication).

Nevertheless, the onset of a significant part of cases is insidious and not necessarily attributed to a mental illness due to the later presentation of positive symptoms and attenuates progressive losing of functioning and performance attributed to an adolescent "crisis."

Psychic examination and anamnestic collection are the main diagnostic tools for a correct clinical assessment. Anamnesis must be focused on specific issues, such as prodromal symptoms, family history, and specific risk factors (substance use/abuse). Another crucial aspect in evaluating patients is functional assessment: scholar/working functioning, social skills, personal autonomy, and daily functioning in the domestic/family environment.

The psychiatric interview allows the clinician to explore the current positive and negative symptomatology of the patient, and also to estimate the cognitive impairment.

Specific standardized rating scales are available to support clinicians in the assessment of the severity of symptoms and functional impairment. Concerning psychopathology, the Positive and Negative Syndrome Scale (PANSS) represents the gold standard for evaluation of schizophrenia, specifically investigating the presence and intensity of positive, negative, and general psychiatric symptomatology. PANSS is one of the most specific tools for schizophrenia. Concerning cognitive assessment, there are various well-validated and comprehensive neuropsychological batteries such as the Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) and the Brief Assessment of Cognition in Schizophrenia (BACS). These batteries assess domains of cognition that are typically impaired and strongly correlated with functional outcome in schizophrenia. The explored functions are working memory, attention/vigilance, verbal learning and memory, visual learning and memory, and executive functions (reasoning, problem-solving) and speed of processing. Frequently, the cognitive assessment also includes an evaluation of Intelligence Quotient, through the Wechsler Adult Intelligence Scale (WAIS).

Finally, different scales have been developed in order to assess functional status and quality of life as well, evaluating both patient's and clinician's point of view. In this context, the most frequently used scales are the Global Assessment of Functioning (GAF) scale, the Specific Level of Functioning (SLOF) scale, the Quality-of-Life Scale (QLS), and the University of California, San Diego (UCSD) Performance-Based Skills Assessment (UPSA). These scales allow the evaluation of real-life behavior, offering a good perspective on global daily functioning and also providing a reliable measure of well-being.

Box 4.6: DSM-5 Diagnostic Criteria

1. Presence of at least two of the following symptoms lasting at least 1 month:
   - Delusions
   - Hallucinations
   - Disorganized speech
   - Disorganized or catatonic behavior
   - Negative symptoms
2. Level of functioning in one or more areas (school, work, social relations, self-care) is markedly low compared to the level reached before onset. In childhood or adolescence, there is the inability to reach the expected level of interpersonal, educational, or work functioning.
3. Continuous signs of the disorder must be present for at least 6 months (prodromal symptoms, negative or cognitive symptoms or attenuated psychotic symptoms).
4. Exclusion of a mood disorder or schizoaffective disorder.
5. Symptoms are not caused by a substance or a medical condition.
6. If a diagnosis of autism spectrum disorder is present, adjunctive diagnosis of schizophrenia occurs only in the presence of criteria described above.

4.1.4.8 Differential Diagnosis

The following differential diagnoses need to be considered when hypothesizing a diagnosis of schizophrenia:

– *Brief psychotic disorder*, differentiated by the duration of an episode of at least 1 day but less than 1 month, and with eventual full return to premorbid level of functioning.
– *Schizophreniform disorder*, differentiated by duration of psychotic illness. Diagnostic criteria are basically the same as for schizophrenia, but the duration of the psychotic episode ranges between 1 and 6 months. If the diagnosis is made before recovery, it should be qualified as "provisional," or changed to Schizophrenia if duration of the episode will exceed 6 months.
– *Delusional disorder*, differentiated by the rare presence of other psychotic symptoms (disorganized speech or behavior, negative symptoms, and cognitive deficit), the later age of onset.
– *Bipolar disorder* with psychotic features, differentiated by the presence of manic/hypomanic features, usually characterized by grandiose or persecutory delusions and/or hallucinations, or depressive episodes with delusions and hallucinations, usually characterized by themes of guilt and ruin, cyclic pattern of manifestations with restoring of functioning to premorbid level in interepisode periods.
– *Depression with psychotic features*, differentiated by the presence of severe depressive symptoms and delusions/hallucinations with contents of guilty and ruin and return to basal functioning at the end of the episode.

– *Schizoaffective disorder*, differentiated by the presence of mood episodes overlying chronic psychotic symptoms which remain after the manic or depressive episode is closed, and better functional outcome.
– *Personality disorders* such as schizotypal, schizoid, and paranoid personality disorders.
– *Drug and medication-induced psychosis.*
– *Psychosis secondary to organic causes.*

4.1.4.9 Comorbidities

Frequently, comorbidity with substance or alcohol abuse occurs. For this reason, differential diagnosis with substance-induced psychotic disorder results sometimes challenging. Moreover, nicotine dependence or smoking is highly prevalent in patients with schizophrenia compared to the general population.

Schizophrenia is characterized by a decreased longevity, with a life expectancy about 20% lower than the general population (61 vs. 76 years). Increased mortality is due to both psychiatric and medical conditions. Indeed, on the one side, schizophrenia is associated with higher rates of suicide, in particular at onset, with one-third of individuals attempting suicide at least one time over the entire course of illness and 5% of patients actually dying. On the other side, people with schizophrenia show elevated metabolic risk factors and incidence of cardiovascular morbidity and related mortality, compared with the general population. Indeed, the presence of obesity in patients with schizophrenia is two times higher than in the general population. Metabolic disorders are a consequence of rapid weight gain leading to obesity, dyslipidemia, and glucose intolerance which may develop into type 2 diabetes. It is difficult to determine whether the high prevalence of metabolic disorders in this population is independent of antipsychotic treatment or is a consequence of medication, especially some atypical antipsychotics such as olanzapine and clozapine. Besides pharmacological treatment, a number of explanations have been proposed, such as unhealthy lifestyle and dietary habits (related to the dimensions of negative symptoms and disorganization) that facilitate the development of obesity among patients with schizophrenia, genetic predisposition to altered glucose and lipid metabolism, and alterations of the hypothalamic–pituitary–adrenal axis linked to hypercortisolemia. Moreover, a crucial factor that further worsens the severity of medical and metabolic comorbidities is the lower capacity of patients with schizophrenia to seek medical assistance and to implement lifestyle interventions. Together with social isolation and stigma, reduced help-seeking behavior leads to a systematic under-recognition and undertreatment of cardiovascular disease of people with schizophrenia within primary care, which might contribute to the substantial cardiovascular-related morbidity and premature mortality observed in this patient group.

Metabolic alterations do not only negatively affect physical health but can lead to a worse psychopathological outcome as well. Indeed, recent findings pointed out that metabolic syndrome is associated with greater cognitive impairment, and, thus, also with poorer longitudinal functional status and clinical outcome.

4.1.4.10 Prognosis

Although positive symptom remission is achieved in almost 50% of patients within 5 years following treatment initiation, schizophrenia can lead to severe long-term disability, negatively affecting quality of life of both patients and their families. However, as previously evidenced discussing neurobiological and clinical features of the disorder, high heterogeneity of longitudinal outcome and prognosis is observed among patients, according to the severity of their symptomatology. Indeed, while many patients with schizophrenia have a lifelong vulnerability to recurrent episodes of re-exacerbations, a large proportion will have few relapses and get a good functional recovery. When adequately treated with both pharmacological and rehabilitative interventions, patients can achieve even high levels of autonomy, although often needing formal or informal financial and daily living support. The best possible personal autonomy, restored relationships, and ability to get and maintain a work are the targets toward which to look at as "the" target when treating a patient affected by schizophrenia, but the results may be quite variable in response in relation to personal premorbid resources social-familiar support and quality of medical support from services. Nevertheless, more specific factors and illness presentation and course features have been individuated as potential predictor of longitudinal outcome. Among positive prognostic predictors are reported acute onset, good premorbid cognitive functioning, short duration of untreated psychosis, early treatment response, absence of substance abuse, later age of onset, and female gender. On the other side, high number of relapses, impaired premorbid adjustment, prominent negative symptomatology, poor insight and low adherence to antipsychotic treatment represent the stronger predictors of poor longitudinal outcome.

4.1.5 Treatment

Treatment should address all the dimensions of the disease, therefore including positive, negative, and cognitive symptoms. Despite pharmacologic advances, the treatment of schizophrenia remains a challenge, and poor or suboptimal outcomes are still frequently observed. Ultimate treatment goals are remission and functional recovery. In order to achieve these targets, antipsychotic pharmacotherapy should always be integrated with cognitive-behavioral, social, and neurocognitive rehabilitative interventions. Pharmacological guidelines are treatment benchmarks. However, for each patient, it is necessary to adopt a personalized therapeutic approach taking into account current symptoms, comorbid conditions, past therapeutic response, adverse effects, and environmental influencing factors that could affect compliance.

The first and mandatory therapeutic approach for schizophrenia is pharmacological, based on antipsychotic therapy, aimed to reduce acute psychotic symptoms such as hallucinations and delusions and possibly induce remission (see Box 4.7). Although large-scale and meta-analytic studies indicate a similar efficacy of the first- (typical) and second-generation (atypical) antipsychotics during acute phases

of the disease, the advantage of a lower rate of extrapyramidal side effects may favor the second-generation antipsychotics for the need of chronic treatments.

Anyway, antipsychotic response is individual, and the results of effectiveness found in randomized controlled studies and meta-analyses do not necessary apply to the individual; antipsychotic response is now considered to have high interindividual variability and a high concordance of response in the same individual across time, i.e., after drug withdrawal due to noncompliance. There is no "winner" drug on average, but the winner drug for that patient. Resistant schizophrenia is a clear example: a rigid assessment of this response phenotype through sequential treatment with typical and possibly more than one atypical antipsychotic treatment leads to indication to clozapine, indicated specifically for resistant patients, with rates of response up to 70% in comparison with no response to the previously tried treatments.

Sometimes, especially after years of treatment, a good response may decay and a change in antipsychotic required to maintain stability, or a resistance may develop, leading to the indication to clozapine.

Different antipsychotics may fit the neurobiology of each subject, and this is the major advantage for clinical efficacy of having nowadays a wide number of available antipsychotics, including the old ones: the higher number allows to treat at the best a higher number of patients in comparison to the time where only neuroleptics (strongly homogeneous in the main pharmacodynamic profile, with shared high affinity to D2 receptors prevailing at clinically used dose over the other, minor properties) were available.

Especially during the acute phase, concomitant treatment, addressing specific symptoms such as insomnia and/or agitation, is often indicated. Benzodiazepines are typically the first choice for this purpose.

After the onset phase, with a diagnosis clearly confirmed, antipsychotic treatment should be continued throughout the course of the disease. This is crucial to prevent relapses and maintain clinical stabilization, which, in turn, is important to improve social withdrawal and functional impairment and to make possible rehabilitation. Indeed, a good response to antipsychotics, together with rehabilitative interventions, allows the recovery of functional capacities and the improvement of quality of life.

The discontinuation of antipsychotic therapy during stable phases of the illness is associated with poorer cognitive and functional outcomes, higher rates of relapse, and incomplete inter-episodic remission (persistence of residual symptoms). If the patient shows poor compliance to pharmacological treatment, antipsychotics can be administered intramuscularly once or twice a month, and, recently even every 3 months (depending on of the pharmacokinetic properties) as long-acting injectable (LAI) formulations in order to avoid the risk of self-discontinuation.

During antipsychotic treatment, a primary goal is to limit side effects to improve compliance and thus to prevent relapses. Prompt detection and treatment of adverse effects of antipsychotics are crucial in the overall management of schizophrenia. Side effects may undermine treatment adherence and affect functional capacity, subjective well-being, quality of life, and life expectancy. The adverse effects that should be regularly monitored include sedation, sexual and reproductive system

dysfunctions, extrapyramidal symptoms, weight change, alterations in blood pressure, lipid profile, and fasting blood glucose levels. Recent data have shown that the assessment of potentially problematic adverse effects, particularly metabolic, such as increases in glucose and lipid levels, is still suboptimal in clinical practice and need to be significantly implemented.

Concerning cognitive symptoms, antipsychotic agents have no or minimal effects on neuropsychological performance, and despite extensive economical and research efforts, to date, no effective newly developed procognitive drugs are available yet. On the other hand, different nonpharmacological rehabilitative approaches showed promising results and are starting to be routinely implemented in clinical practice. Among these, cognitive remediation techniques were proved effective to the point that they are currently considered the best treatment option, being able to induce significant changes not only at the behavioral but also at the biological level, leading to a global improvement in neural system dysfunction. However, cognitive remediation has been shown to be strongly effective when delivered together with cognitive-behavioral and social skills rehabilitation, leading to persisting cognitive improvements. However, it is important to remind that a requirement for a good outcome of rehabilitative interventions is the presence of clinical stabilization, particularly concerning positive symptomatology. Response to pharmacological treatment is thus a necessary requirement for rehabilitation.

Although schizophrenia was long considered a disease characterized by progressive clinical and functional deterioration, nowadays the goal of treatment is not just remission, but also recovery (see Box 4.7). Evidence supports the idea that the course of the illness is not inevitably deteriorating and that functional recovery can be achieved.

Box 4.7: Remission and Recovery

Remission

Remission in schizophrenia, as for other chronic psychiatric and nonpsychiatric illnesses with relapsing and remitting courses, does not require symptoms to be completely absent and can be associated with some residual symptomatology.

Remission has been defined as "a state in which patients experience an improvement in core symptoms to the extent that any remaining symptoms are of such low intensity that they no longer interfere significantly with behavior and are below the threshold typically utilized in justifying an initial diagnosis of schizophrenia."

A univocal definition of remission for schizophrenia is lacking. The Remission in Schizophrenia Working Group (RSWG) developed a consensus definition of symptomatic remission that consists of two elements: a severity criterion covering the core symptoms of schizophrenia (low scores on eight diagnostically relevant symptoms in the PANSS) coupled with a time criterion (symptom severity criteria should be achieved for a minimum period of

6 months). Symptomatic remission is a challenging but achievable objective for a significant proportion of patients with schizophrenia, given the ongoing efforts to better understand the condition and the ongoing search for better treatments.

Symptomatic remission of positive symptoms does not necessarily mean that the patient is functioning well, because other illness components may persist, leading to functional impairment.

Recovery

Remission is a necessary, but not sufficient, step toward recovery, which is a longer-term and more complex goal to achieve. Recovery is less precisely defined than remission. In general, recovery can be defined as sustained symptom remission, accompanied by functional rehabilitation (e.g., cognitive, social, and vocational) and reduced use of medical health services. It is generally assumed that recovery comprises both objective and subjective components: the objective domain refers to clinical outcomes which are evaluated through operationally defined criteria; the subjective domain refers to the process of positive changes in an individual's subjective experience of themselves as human beings. Not all patients with schizophrenia can achieve recovery. In literature, the lack of consensus on its definition gives rise to heterogeneous data, with the percentage of patients with schizophrenia achieving recovery varying from 13.5 to 50%. Recovery may be influenced by multiple factors such as adherence and response to treatment, support from family and society, adjustment coping, and reappraisal. Factors that have negative effects on recovery are higher levels of cognitive deficits and negative symptoms, stigmatization (both self-stigma and social stigma), poor service engagement, side effects of medications, and lack of self-awareness.

4.1.5.1 Pharmacological Treatment

Pharmacological treatment is based on antipsychotics, both typical (first generation) and atypical (second generation), each of which shows unique and different receptor activity and affinity (see Chap. 11). It is recommended to use a single antipsychotic (preferably atypical) at the lowest effective dose. There is a time latency in response since initiation of antipsychotic, which is typically of 4–6 weeks. However, an early response can be observed during the second week of treatment. In case of lack of response and/or tolerability issues despite adequate doses, a switch to another antipsychotic is recommended. In case of treatment resistance, as reported above, clozapine is the only indicated and evidence-based drug for TRS. Augmentation strategies (adding a second antipsychotic drug) should be contemplated only in case of incomplete response to clozapine.

Treatment-Resistant Schizophrenia

Poor response to at least two antipsychotic drugs at adequate dosage and duration of treatment.

Antipsychotic treatment is chronic over time with the aim to prevent exacerbations. The drug to which the patient has clearly responded in the exacerbation must be continued, but doses used in maintenance phase tend to be lower to minimize side effects and overall drug exposure. For some antipsychotics with high interindividual plasma-level variability, like clozapine, periodical plasma level evaluation may improve efficacy and minimize side effects avoiding under- and over-dosing and letting compliance to be controlled definitely.

When assessing resistance, a crucial aspect is, in fact, is to exclude nonresponse due to impaired or absent compliance; as previously mentioned, low adherence to treatment is one of the stronger predictors of poor longitudinal outcome, leading to greater risk of relapse, hospitalization, and eventually suicide. Large-scale studies reported that almost 75% of patients discontinue antipsychotic medication within 18 months due to insufficient efficacy, intolerable side effects, or for other reasons. Key drivers of low compliance include lack of insight, attitude toward medication (frequently a premorbid feature related to the subject's psychology and cultural background), side effects, and substance abuse. Factors positively related to adherence are a good therapeutic relationship with physician and perception of benefits of medication that must be underlined and strengthened by clinicians, together with obtaining the lower possible rate and severity of side effects.

4.1.5.2 Noninvasive Neurostimulation Techniques

To date, transcranial direct current stimulation (TDCS) and transcranial magnetic stimulation (TMS) have low levels of evidence to be effective in improving poor pharmacological response in schizophrenia. Possible applications of these noninvasive brain stimulation concern reduction of cognitive, positive, and negative symptoms, depending on the targeted cortical area.

4.1.5.3 Electroconvulsive Therapy (ECT)

Data on ECT are limited; ECT may be useful in treating catatonic symptoms in schizophrenia and as adjunctive treatment in certain resistant patients unresponsive even to clozapine.

4.1.5.4 Psychiatric Rehabilitation

Remission of positive symptomatology can be achieved through pharmacological treatment. However, pharmacotherapy's effect on the negative-cognitive dimension is poor. Rehabilitation programs aim to improve impaired cognitive, emotional, and social skills through cognitive training programs, group activities, and individually targeted interventions. The theoretical goal is to allow the patient to have a role, relationship, and a work for self-sustainment.

Rehabilitative interventions have been developed to complement psychopharmacological treatments and aim to assist patients in attaining their highest level of functioning, the better degree of symptom control, and the greatest level of subjective life satisfaction. Indeed, antipsychotic treatment has only limited efficacy on cognitive impairment, insight, and social skills, whereas rehabilitation interventions

specifically target these aspects of the disease. Moreover, rehabilitation interventions also aim to promote the recovery process in its subjective component, by encouraging self-determination and active empowerment. According to literature, many rehabilitative programs have proven their effectiveness in favoring functional recovery.

Main rehabilitative programs include cognitive remediation therapy (see Box 4.8), social cognitive interventions, psychoeducational intervention concerning disease, cognitive-behavioral therapy, and social skills training.

Box 4.8: Cognitive Remediation Therapy (CRT)
CRT for schizophrenia is a behavioral training-based intervention that aims to enhance through exercise, pen and paper or computerized, several cognitive functions such as attention, memory, executive function, social cognition, or metacognition durably. The ultimate goal of CRT is to improve functioning, limiting the impact of cognitive impairment on everyday life and supporting the effects of concomitant cognitive-behavioral and social rehabilitation. Its efficacy has definitely been demonstrated in patients with schizophrenia.

4.1.5.5 Clinical Case

U. is a 43-year-old engineer who stopped working 15 years ago. He is not married and lives with his mother. He spends most of his time alone, inactive, and his functioning is limited to a few daily home tasks that the patient performs only if stimulated. He rarely leaves the house, and, if he does, he is always accompanied by his mother or brother.

U. came to the attention of the psychiatrist nearly 15 years ago when he had troubles at work. At the time he claimed to clearly hear the voices of his chief and colleagues insulting and speaking ill of him among themselves by reason of his incredible skills. One day, he ran away from the workplace thinking they wanted to kill him, and he went to the police station to report everything. Finally, the police officer called the psychiatrist.

Nowadays, these contents of thought, despite being referred to the past, are pointed out with less emotional participation through a digressive and sometimes illogical speech. Despite suspiciousness is inferred by his glances, U. trusts his psychiatrist, probably because he knows him for a long time. During interviews with him, sometimes he described a sort of "psychological violence" and "mental dialogues" with deceased relatives. In the last period, U. has become very religious, often feeling very close to god and believing in a sort of interconnection with Him. Sometimes he gets frustrated, and irritability emerges relatively to his performance difficulties: since the onset of the disease, he was no longer able to work. Moreover, difficulties in maintaining concentration and attention are frequently reported. U. is indeed often distracted, as if he is listening to something/someone.

4.2 Other Psychotic Disorders

The spectrum of psychotic disorders includes different conditions, both primary and associated with substance use or medical pathologies. They show similarities to schizophrenia in clinical manifestation and only partially share etiopathogenetic mechanisms and risk factors. According to DSM-5, these disorders are defined by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms. Each of them exhibits different combinations of symptoms and deficits. We will summarize the main clinical features, differential diagnoses, and treatment indications for delusional disorder, schizoaffective disorder, brief psychotic disorder, and substance-induced psychotic disorder.

4.2.1 Delusional Disorder

4.2.1.1 Definition

Delusional disorder, or paranoid disorder in the previous nomenclature, is usually a chronic condition mainly characterized by the presence of one or more delusions related in themes to the main delusional idea, typically in the absence of other psychotic features. In addition, globally, functioning is relatively preserved without evolution to defective states.

4.2.1.2 Epidemiology

Delusional disorder is less frequent than other conditions, such as schizophrenia and mood disorders, and its lifetime prevalence in the general population is estimated at around 0.02%, without gender predominance. The relatively low prevalence may be in part due to underreporting. People with delusional disorder may not seek mental health help unless taken to attention by family or friends, because of their poor/absent insight of illness, but they may maintain a good general functioning.

It has a later age of onset as compared to schizophrenia. The mean age of onset is about 40 years, but it can occur at any age in life. Despite this, the appearance of delusions in patients older than 60 years is more likely attributable to an organic condition, such as dementia.

4.2.1.3 Clinical Presentation

The clinical picture is mainly characterized by the presence of one, less commonly more, but related, delusion. According to DSM-5 criteria, to be diagnosed, the delusion must persist for at least over a month, but it is typically a chronic disorder. The delusion is usually systematized and pervasive and revolves around one main topic. The patient displays high emotional involvement and behaves according to the delusional idea. Although the disorder may manifest with any type of delusional content, typically the contents are plausible and believable, while bizarre delusions are rarer in this condition than in schizophrenia. Delusional disorder, differently from schizophrenia, does not globally compromise psychic functions, nor lead to

functional impairment. Moreover, insight is generally absent only in the field of events and experiences related the delusional idea.

In addition to delusions, hallucinations may rarely be present, but they are not prominent and are closely related to delusional content.

Mood may be altered secondary to and congruent with delusional content. For example, a patient with paranoid delusion may be depressed and anxious due to the preoccupation of being injured or betrayed by a friend or a spouse.

In delusional disorder, general behavior is not much altered, and global functioning is relatively preserved. However, patients may engage in abnormal behaviors related to the delusional idea that can result in occupational, marital, and social difficulties, and, not infrequently, legal problems.

The course of delusional disorder, although chronic, is usually better than that of schizophrenia. A remission period is achievable, but, even in the attenuation or absence of active delusions, the insight on previous ones remains poor or absent.

Box 4.9: DSM-5 Diagnostic Criteria of Delusional Disorder

1. One (or more) delusion lasting 1 month or longer.
2. Diagnostic criterion 1 of schizophrenia has never been met.
3. Hallucinations, if present, are not prominent and related to the delusional theme.
4. Functioning is not markedly impaired, and behavior is not bizarre.
5. Symptoms are not caused by substances or a medical condition.

4.2.1.4 Main Differential Diagnoses

- *Schizophrenia:* It can be differentiated from delusional disorder by the simultaneous presence of other psychotic symptoms (disorganized speech or behavior, negative symptoms, and cognitive deficit), the earlier age of onset, the substantial functional impairment, the worse course of illness.
- *Depressive and bipolar disorders and schizoaffective disorder*: In delusional disorder, mood alteration, if present, is not prominent but secondary to delusional content. If delusions occur exclusively during mood episodes, the diagnosis should be a depressive or bipolar episode with psychotic features. Nevertheless, a comorbidity between delusional disorder and a mood disorder in comorbidity should be considered.
- *Delirium, major neurocognitive disorder, psychotic disorder due to another medical condition, and substance/medication-induced psychotic disorder:* Delusions may occur in all these disorders, and the distinction should be made considering the coexistence of other symptoms, the age of onset, the course, and the presence of comorbidities. Delirium is characterized by abnormalities in consciousness, which is instead clear in delusional disorder. Psychotic disorder due to medical condition or medication induced can be considered in older patients, affected by other medical diseases and/or treated for them. Imaging or laboratory tests should be performed to rule out any organic cause.

– *Illness anxiety disorder:* In this disorder, the patient is worried about a physical illness, but his/her concerns, differently from delusional disorder somatic type, can be at least transiently reassured by medical exams. Also, some people with delusional disorder of this type may seek multiple medical assessments, but with their delusional idea not changing in front of clear evidence.
– *Body dysmorphic disorder* previously known as *dysmorphophobia*: This disorder is characterized by excessive concern about the appearance of one's body, often associated with behavioral abnormalities such as requests of medical procedures (i.e., plastic surgery). At onset, ideas that these patients have about their bodies are not delusional, but only extremely overvalued. Insight varies, although it is mostly poor. Onset is usually earlier than delusional disorder, tending to begin during the first decades of life. However, over time these preoccupations can develop a delusional quality, with almost 50% meeting criteria for a delusional disorder (somatic type).

4.2.1.5 Treatment

Antipsychotic medications are considered the mainstay of treatment, and FGAs appear to be slightly superior to SGAs. However, SGAs are more frequently used due to their more acceptable side effect profiles. A positive response to antipsychotic treatment occurs in nearly 50% of the cases. Due to the chronic course of the disorder, treatment should be continued indefinitely.

However, the treatment of delusional disorder is particularly challenging due to the patients' lack of insight and hypersensitivity to side effects, compared to patients with schizophrenia, both undermining adherence to the treatment regimen.

4.2.1.6 Clinical Case

P. is a 40-year-old history teacher. She has been married for many years. P. came to psychiatric attention as her husband brought her to the emergency room because she has completely refused to eat for 2 days. About 5 months ago, she started complaining of heartburn and digestive difficulties, only partially improved after a pharmacological treatment prescribed by her general practitioner. Since then, her husband says he noticed a change. P. is often silent, detached, and sometimes grumpy toward him. She appears worried, restless, and struggles to fall asleep. She spends a lot of time away from home, often stays at work late for overtime, and is evasive when he asks for explanations. Although she has always been careful about her physical fitness, she is described by her husband as a "good eater." However, for the last few months, she has been complaining of loss of appetite and has been eating irregularly. In fact, she eats mainly packaged foods, refusing anything cooked by her husband, and drinks only bottled water that she buys herself. In the last month, she has lost about 5 kg.

At the interview with the doctor, P. asks her husband not to attend. She appears suspicious and in a state of alertness. At first, she is not very talkative, but gradually she expresses her anxiety about the certainty that her husband wants to "get rid of her." She says that 4 months ago, she found out that her husband had an extramarital

affair with the neighbor. She reports that, at first, she noticed strange coincidences and then she became certain when her husband turned on the radio while the song "Arsenic" was playing. It was precisely in those days that the gastric problems started, according to her.

P. denies having ever heard voices or unusual noises. After her initial hesitation, her speech is fluid and coherent, and her mood appears depressed in consequence of the delusional beliefs.

4.2.2 Schizoaffective Disorder

4.2.2.1 Definition

As suggested by its denomination, schizoaffective disorder (SAD) is a disorder whose hallmark is the presence of affective symptoms, either depressive or manic, co-occurring with characteristic symptoms of schizophrenia, such as hallucinations and/or delusions. Researchers debate whether the diagnosis of SAD represents a comorbidity of schizophrenia and a mood disorder or rather actually exists as the mid-point on a continuum between schizophrenia and bipolar disorder. Indeed, since it was first defined in literature, its actual clinical distinction and validity as an independent nosological category have been largely discussed with conflicting points of view, leading to a large number of misdiagnosis.

4.2.2.2 Epidemiology

SAD has a lifetime prevalence of 0.3%, about one-third less common than schizophrenia.

The depressive subtype is more frequent in females (2:1), whereas no significant sex-related differences are reported for the bipolar subtype.

Similarly to schizophrenia, the onset of SAD is typically in early adulthood, although possible at any age, and later for women. The depressive subtype of SAD seems to be more frequent in the elderly, whereas the bipolar subtype seems to prevail in young people.

The risk for SAD is increased among individuals who have a first-degree relative with schizophrenia, bipolar disorder, or SAD.

4.2.2.3 Clinical Presentation

DSM-5 diagnostic criteria for SAD require the occurrence of an uninterrupted period of illness in which the characteristic symptoms of schizophrenia (criterion A for schizophrenia) are present simultaneously with affective symptoms meeting the criteria for a major mood episode, either depressive or manic. Moreover, in order to distinguish a SAD from a mood disorder with psychotic features, more than 2 weeks of psychotic symptoms in the absence of symptoms of a major mood episode are required. Lastly, affective symptoms need to be present for a significant period during active or remission psychotic phases of illness, in order to differentiate SAD from schizophrenia.

DSM-5 separates bipolar and depressive subtypes: in bipolar type, at least a manic episode has occurred in the lifetime, whereas in depressive type only major depressive episodes have occurred.

Great heterogeneity characterizes clinical presentations of subject with SAD: some experience predominantly mood symptoms, other mainly psychotic symptoms. Psychotic symptoms usually occur before the onset of a prominent major mood episode, persisting after its remission. Similar to bipolar disorder, major mood episodes are recurrent, with variable durations typically longer in the depressive subtype.

Patients with SAD exhibit higher suicidal risk and higher rates of hospitalization and substance abuse than patients with schizophrenia or mood disorders.

Most patients with SAD tend to have a nondeteriorating course of illness, with an intermediate prognosis between schizophrenia and bipolar disorder. However, approximately 20–30% of patients show a deteriorating course with persistent psychotic symptoms, closely resembling longitudinal clinical course and deteriorating functional outcome of schizophrenia.

Predictors of poor outcome in SAD include poor premorbid functioning, insidious onset, absence of a precipitating factor, predominance of psychotic symptoms, early age at onset, poor inter-episode remission, SAD depressive subtype, and a family history of schizophrenia.

Box 4.10: DSM-5 Diagnostic Criteria of Schizoaffective Disorder

1. Diagnostic criterion 1 of schizophrenia + concomitant diagnosis of major depressive episode or manic episode.
2. Along the course of the illness, delusions or hallucinations, lasting at least 2 weeks, are present without the concomitant diagnosis of a depressive or manic episode.
3. Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the illness.
4. Symptoms are not caused by substances or medical conditions.

4.2.2.4 Differential Diagnosis

– *Bipolar and major depressive disorder:* The presence of psychotic symptoms out of a mood episode is crucial to distinguish SAD from a mood disorder with psychotic features. Patients with a mood disorder only experience psychotic features during a manic or depressive episode, whereas patients with SAD have psychotic symptoms during and out of mood episodes.
– *Schizophrenia:* Depressive symptoms may occur in schizophrenia, especially during the prodromal or residual phases, but they are less well characterized and often associated with negative symptoms. In patients with SAD, mood symptoms are prominent, whereas once the psychotic symptoms predominate for most of the course of illness, the diagnosis leans toward schizophrenia. In SAD,

global functioning is usually less impaired than in schizophrenia (and impairment is not a defining criterion in contrast to schizophrenia).
- *Delusional disorder:* Mood alterations, especially depression, commonly develop during its course. However, such presentations do not meet the criteria for SAD because the psychotic symptoms in delusional disorder are mainly delusions (they do not meet Criterion A for schizophrenia).
- *General medical and substance-induced conditions, delirium, and major neurocognitive disorder:* They may present with psychotic and mood symptoms, even combined. These conditions can be distinguished from SAD thanks to evidence from the clinical history, physical examination, laboratory findings, and any other investigations that the symptoms are pathophysiologically a consequence of these conditions.

4.2.2.5 Treatment

As for schizophrenia and bipolar disorder, long-term complex pharmacological therapies are required, targeting both psychotic and affective symptoms. Antipsychotics, mood stabilizers (lithium, anticonvulsants), and antidepressants are commonly used in combination, according to patient's stage of illness.

Since most patients present with prominent psychotic symptoms over time, treatment usually requires chronic treatment with antipsychotics. The SAD subtype may guide the choice of the add-on therapy. Mood stabilizers are indicated in patients with the bipolar subtype, whereas antidepressants in those with the depressive subtype, at least during the episodes. Patients with SAD tend to respond to lithium worse than patients with bipolar disorder, but atypical antipsychotics have shown mood-stabilizing properties in these patients and are thus often prescribed also for this purpose.

Similarly to other disorders, treatment resistance may occur in a minority of patients that can be thus prescribed with clozapine as second-level pharmacological treatment.

4.2.3 Substance-Induced Psychotic Disorder

4.2.3.1 Definition

Substance-induced psychotic disorders (SIPD) are brief psychotic syndromes occurring during or soon after the use of a substance or its withdrawal. This condition may persist for days or weeks after substance intoxication has resolved, or even longer if patients continue using the substance (see also Chap. 9).

4.2.3.2 Epidemiology

Although it is difficult to precisely evaluate the prevalence of these disorders, as they may be transient and patients may not seek medical help, SIPDs are common disorders with estimates of incidence ranging from 1.52 to 6.53 per 100,000 person-years. Up to 25% of first-episode psychosis is represented by SIPDs, and approximately 25% of these can progress to schizophrenia.

4.2.3.3 Clinical Presentation

Many substances with psychotomimetic properties are known to cause (or exacerbate) psychotic reactions resembling a primary psychotic disorder. The psychotogenic effect of these substances is related to their specific activities in different brain circuits (see Chap. 9).

The clinical presentation of an individual diagnosed with SIPD is quite similar to those presenting psychosis in the absence of substance use. It may include psychotic symptoms, such as delusions, hallucinations, disorganized thinking, grossly disorganized behavior, psychomotor disturbances (excitement or stupor), and an abnormal affect, which may range from intense fear to ecstasy. However, substance-induced psychotic symptoms are usually short-lived, remitting after sustained abstinence.

The risk of developing psychotic symptoms can vary according to the substance of abuse, the frequency and duration of abuse, and individual vulnerability to develop psychosis. Virtually all substances of abuse may induce acute psychotic syndromes, although cannabis, cocaine, amphetamines, and hallucinogens are associated with a greater risk for psychosis. Moreover, for some substances, in particular cannabis, there is a dose–response relationship, with psychosis occurring especially in those individuals who have been using high doses and over a lengthy period.

Cannabis use can cause a range of psychotic symptoms of variable severity, from acute short-term symptoms, related to intoxication, to severe and persistent symptoms leading to a diagnosis of cannabis-induced psychotic disorder (CIPD). Cannabis-induced toxic psychosis is characterized by mild alteration of consciousness, thought disorganization, hallucinations, distortion of time perception, and "dream-like" euphoria, usually resolving within a week. Absence of confusion and derealization distinguish cannabis-induced functional psychosis, associated with heavy and long-lasting THC assumption, clinically resembling an acute episode of schizophrenia and showing a rapid and good response to antipsychotic medications. If symptoms persist after discontinuation, functional psychosis can progress to a cannabis-induced chronic psychosis, hardly distinguishable form a chronic schizophrenia triggered by cannabis use and requiring long-term treatment.

The diagnosis of SIPD is not stable over time: a significant proportion of people with substance-induced psychosis later have a transition to a diagnosis of a schizophrenia-spectrum disorder or, less frequently, bipolar disorder, usually within the first 3–5 years after substance-induced psychosis.

Cannabis-induced psychosis and amphetamine-induced psychosis are associated with the highest risk for transition. Among cannabinoids, high-potency cannabis and synthetic cannabinoids carry the greatest risk of psychosis. Young age is associated with a higher risk of conversion to schizophrenia, with the highest risk in the range of 16–25 years.

Alcohol-induced psychosis/hallucinosis is a rare condition characterized by acute onset of auditory hallucinations (characteristically in the form of derogatory voices), often associated with persecutory delusions. These symptoms usually occur in clear consciousness and absence of thought process disorder in individuals with heavy alcohol consumption. These symptoms usually improve quickly, within a week, although they can become chronic due to ongoing

alcohol abuse. Alcohol-induced psychosis should be differentiated from psychotic symptoms that may occur in alcohol withdrawal delirium ("delirium tremens"), wherein hallucinations are more likely visual than auditory, and associated with alterations in consciousness, neurovegetative symptoms, and psychomotor agitation. Chronic use of alcohol can also more frequently determine a jealousy delusional disorder.

Box 4.11: DSM-5 Diagnostic Criteria of Substance-Induced Psychotic Disorder

1. Presence of delusions and/or hallucinations.
2. Symptoms of criterion 1 start during or soon after substance intoxication or withdrawal or after exposure to a medication.
3. The substance/medication is capable of inducing the symptoms observed.
4. The disturbance is not better explained by other psychotic disorders.
5. The disturbance does not occur exclusively during a delirium.
6. The disturbance causes significant distress or functional impairment.

4.2.3.4 Differential Diagnosis

The differentiation of substance-induced psychotic disorder (SIPD) from primary psychotic disorder is particularly difficult.

Clinically, the most straightforward way to make an appropriated differential diagnosis is by assessing the temporal relationship between onset of psychosis and substance assumption.

According to DSM-5, the distinction should be based on the persistence of psychotic symptoms for a prolonged period (about 1 month) after the cessation of substance use. However, this criterion may be difficult to apply because patients may continue using the substance. Some clinical characteristics may assist differential diagnosis during the acute episode. Onset before substance use, personal/family history of other psychotic disorders, poor premorbid functioning, prevalence of auditory hallucinations, poor insight into symptoms, emotional detachment, and apathy suggest the presence of primary psychotic disorders rather than SPID. On the other side, some clinical features may help direct diagnosis to SIPD: a later age of onset, better insight into symptoms, prevalence of altered state of consciousness (confusion, disorientation), prevalence of visual or tactile hallucinations, fewer or less severe negative symptoms, higher levels of impulsivity, aggression and suicidal thoughts, overexcitement and excessive emotional involvement, and personal or family history of substance use disorders.

4.2.3.5 Treatment

Management of patients with SIPD is complex, requiring treatment of both psychosis and substance-related organic symptoms. Moreover, patients with SIPD are usually less compliant with treatment and have a generally poorer response to antipsychotic treatment.

Antipsychotic treatment is indicated to manage acute psychotic symptoms and agitation and may be discontinued after symptoms remission and with careful observation.

However, for individuals with persisting symptoms or who are not able to establish periods of abstinence, antipsychotic medications should be indicated as long-term treatment to prevent relapses. Moreover, pharmacotherapy should be accompanied by psychoeducational and psychosocial interventions targeting the substance use disorder (i.e., CBT). Some studies have suggested that treatment with atypical antipsychotic medications is also associated with decreased craving and substance use.

4.2.4 Brief Psychotic Disorder

4.2.4.1 Definition

Brief psychotic disorder (BPD) is an acute and transient psychotic syndrome that lasts at least 1 day but less than 1 month and is followed by complete remission, with possible future relapses. Severe psychological stressors may trigger BPD.

Over time, such clinical syndromes have been renamed as "bouffée délirante," "cycloid psychosis," "reactive psychosis," "emotional psychoses," or "atypical psychosis," in an attempt to differentiate them from other psychotic disorders.

4.2.4.2 Epidemiology

Reliable data on its incidence and prevalence are not available, but the disorder is considered uncommon, accounting for 4–10% of first-episode psychosis.

The average age of onset is the mid 20–30s, but onset can occur across all the lifespan.

BPD is more common in women (2:1), especially when related to a stressor. Moreover, it is more frequent in individuals with personality disorders, most commonly histrionic, narcissistic, paranoid, schizotypal, and borderline.

Studies reported a higher incidence of brief psychotic disorder in developing countries and in populations known to be under high stress, such as refugees, immigrants, earthquake victims, etc.

4.2.4.3 Clinical Presentation

According to DSM-5, diagnosis of BPD requires the presence of at one least positive psychotic symptom (delusions, hallucinations, or disorganized speech). Other than psychotic symptoms, there may be other symptoms such as labile mood, confusion, and impaired attention and memory, which are usually more common at the onset of brief psychotic disorder than at the onset of other chronic psychotic disorders. Occasionally, depressive symptoms may follow the resolution of the psychotic symptoms. BPD is also associated with an increased risk of suicidal behavior.

A BPD may occur in response to a traumatic or stressful life event, such as delivery, bereavement, as well as to large-scale tragedies environmental disaster, war, or pandemic, but also personal events with peculiar emotional impact for the subject.

Regardless of the objective entity of the traumatic event, the stressor usually has major significance and strong emotional impact for that subject.

Although during an acute episode the level of functioning results significantly impaired, the prognosis is generally very good with complete remission of symptoms and return to premorbid functioning, unlike other psychotic disorders. Some individuals, however, may experience relapses in their lifetime, especially in the setting of a stressful psychosocial milieu.

Furthermore, it is to note that patients with BPD have low diagnostic stability and a high transition rate (around 50%) to long-lasting psychiatric disorders, mainly schizophrenia or mood disorders.

Some positive prognostic indicators for the brief psychotic disorder are sudden disease onset, presence of stressful triggers, short duration of symptoms, good premorbid adjustment, no familiar history for psychosis.

Box 4.12: DSM-5 Diagnostic Criteria of Brief Psychotic Disorder

1. Presence of one (or more) of the following symptoms. At least one of these must be A, B, or C:
   (A) Delusions.
   (B) Hallucinations.ssss
   (C) Disorganized speech (e.g., derailment or incoherence).
   (D) Grossly disorganized or catatonic behavior.
2. The duration of symptoms is at least 1 day but less than 1 month.
3. The disturbance is not better explained by another psychotic or mood disorder, and it is not induced by substances or medical conditions.

4.2.4.4 Differential Diagnosis

It is essential to consider other possible conditions before determining a final diagnosis of brief psychotic disorder. Differential diagnoses include any disorder manifesting with psychotic symptoms: mood disorders with psychotic symptoms, schizophrenia-spectrum disorders, delusional disorder, substance-induced psychotic disorders, and psychotic symptoms secondary to medical conditions (i.e., delirium). Also, personality disorders should be taken into account, especially those included in cluster A (schizoid, schizotypal, and paranoid), often characterized by mild positive symptoms, and the borderline personality disorder, which frequently presents dissociative symptoms that need to be distinguished from actual hallucinations.

A diagnosis of brief psychotic disorder can only be made after the symptoms have remitted, as the symptomatology may otherwise be an early manifestation of another disorder with a psychotic component.

4.2.4.5 Treatment

Due to the limited evidence on the treatment of brief psychotic disorder, current treatment recommendations are based on antipsychotic pharmacological interventions known to be effective in other psychotic disorders. Indeed, the treatment of

brief psychotic disorder is similar to the treatment of an acute exacerbation of schizophrenia and consists of the use of two main classes of drugs, which are antipsychotics and benzodiazepines. Although BPD usually shows a complete resolution of symptoms within 1 month after onset, maintenance treatment with antipsychotics for some months after symptoms remission is indicated.

Further Reading

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