Review Article

Psychotic spectrum disorders: Definitions, classifications, neural correlates and clinical profiles

Giulio Perrotta*

Psychologist sp.ing in Strategic Psychotherapy, Forensic Criminologist, Lawyer sp.ed SSPL, Researcher, Essayist, Italy

Abstract

The psychotic spectrum is the category that groups together a series of disorders linked to a symptomatology in which we witness the fragmentation of the plane of reality until it is completely broken. According to the DSM-V nosography, the disorders under examination are schizophrenia, delusional disorder, paranoid disorder, schizoid disorder, schizotypic disorder, schizoaffective disorder, brief psychotic disorder, psychotic break and catatonia. In this work, theoretical and practical profiles were analysed, paying attention to neurobiological content and therapeutic profiles, both psychotherapeutic and psychopharmacological. A note of disappointment has been made in the nosographic categorisation of dissociative disorders that currently would not be included in the psychotic spectrum disorders, although from the elements that emerged it would be interesting to revise them, precisely because of the clinical nature of the psychopathological category.

Contents of the manuscript

Definitions and general profiles

The term "psychosis", officially introduced by Ernst von Feuchtersleben in 1845, refers to all those psychopathological forms of psychopathology characterised by severe alteration of the person's psychic balance with impairment of reality examination, frequent absence or significant impairment of insight, and frequent presence of thought disorders (such as delusions and hallucinations) [1,2]. For this reason, there are different clinical articulations of psychotic disorders [3], precisely according to the symptoms described and whether or not they are:

a) "positive", i.e. characterized by expansion of perception and sensation (such as delusions and hallucinations);

b) "negative", i.e. characterised by introjection and hyporeactivity (such as autistic symptoms, catatonia and isolation);

c) ascribable to disorders of the "thought form", i.e.

alterations in the flow of ideas, mental organisational inconsistency and alterations in the associative links (such as paralogy, tangentiality, transverse responses and disconnected argumentative jumps);

d) attributable to disturbances of the "content of thought", i.e. the prevailing delusional ideation (such as delusions and interpretative cues);

e) ascribable to disturbances of "sense–perception", i.e. auditory hallucinations (imperative, commentary, denigrating or even teleological), visual, olfactory, tactile or taste hallucinations.

These symptoms may occur in the form of episodes or be concomitant with other types of syndromes, such as neurological diseases (such as epilepsy and dementia) [4–8], systemic diseases, both infectious and autoimmune (such as Systemic Erythematosus Eritematous Lupus, endocrinopathies, Porphyria, Wilson's Disease, Huntington's Disease, and neurological following trauma or neoplastic event), the uricemic condition, the state of toxicity resulting from the use of narcotics and alcohol, vitamin deficiencies

(such as B12 deficiency), but also psychopathological disorders related to anxiety [9], depression [10-11], bipolarity [12], dissociation [13,14] and personality disorders [15-17] which – for their nosographic classification – do not strictly relate to the psychotic category, although the opposite hypothesis could be taken into account in terms of dissociation [18].

The age of onset of psychosis is variable, precisely because it depends on the symptomatology under examination; on the severity of the morbid condition and on the prognosis (in relation also to other organic diseases); in the case of childhood psychosis, however, there may be abnormal behaviour already in the first year of life, but the average age range varies around 15-55 years, with a higher trend after 65 years for all the hypotheses linked to ageing and medical clinical conditions [3]. The aetiology of the disorder is, as for many medical conditions, multifactorial and largely unknown, but from a neurobiological point of view, psychotic symptomatology finds a correlation with organic alterations at various levels, or a marked genetic predisposition, or functional alteration of neurotransmitters such as dopamine, serotonin, glutamate, GABA, NMDA and endogenous peptides [19].

From a psychoanalytical point of view, on the other hand, psychoses are correlated with a break in the relationship of the Ego with external reality, due to the pressure of the Ex on the Ego. According to Sigmund Freud, the Ego gives in to the Ex and then partially recovers the construction of its own reality through delirium, recovering the objective relationship. According to psychoanalyst Melanie Klein, psychoses are linked to the fall into the schizoparanoid position of early childhood, while according to psychologist and analyst Carl Gustav Jung in psychoses there are unconscious autonomous complexes over the Ego complex, which is unable to maintain control over unconscious formations. According to Otto Kernberg, psychosis is distinguished from neurosis by the "spreading of identity" and the implementation of primitive defence mechanisms (primitive idealization, devaluation, splitting, projective identification, denial, omnipotence), which protect the individual from disintegration and fusion of self with the object, with regression in the face of interpretation. Another distinctive element is the loss of the perception of reality. In fact, unlike neurosis, the psychotic is unable to accept elements of the reality that surrounds him, and a different representation of it is created. From the point of view of existential psychology, Karl Jaspers speaks of psychotic experiences when these are experienced as incomprehensible to the subject because of the way in which they arise from psychic activity, causing the ontological conditions of existence (time, space, coexistence, planning) to decline. The social orientation of psychiatry also expresses an interpretation linked to the socio-environmental and relational context, which, as we have seen, is decisive for the integration of psychotic patients and their rehabilitation [2].

Psychopathological classifications with psychotic orientation and their neural correlates

Argumentative premise: The categories we will examine will follow the DSM-V's nosographic criteria [20].

Schizophrenia: On a scale of severity, "Schizophrenia" undoubtedly represents the most serious form of impairment of the reality plane that a subject can experience, as it represents the chronic psychosis par excellence, characterised by the persistence of symptoms of alteration of cognitive and perceptive functions, behaviour and affectivity, with a course of more than six months, and with strong maladaptation of the person, that is to say a severity such as to limit or compromise normal life activities [3].

The term was coined by the Swiss psychiatrist Eugen Bleuler in 1908 (describing the main symptoms as the 4-A: flattening of Affection, Autism, Reduced Association of Ideas and Ambivalence) and derives from the Greek σχίζω (schízō, 'I divide') and ΦPHN (phrén, 'brain'), i.e. 'splitting of the mind': it replaced that of 'Dementia praecox', formulated by Arnold Pick in 1891. The history of schizophrenia is complex and does not lend itself easily to a linear narrative. Descriptions of syndromes similar to schizophrenia rarely appear in historical documents prior to the 19th century, although tales of irrational, incomprehensible or uncontrolled behaviour are common. The first cases of schizophrenia reported in medical literature date back to 1797, thanks to the works of James Tilly Matthews and publications by Philippe Pinel in 1809. Early dementia was the term used in 1891 by Arnold Pick to classify a case of a psychotic disorder. In 1893 Emil Kraepelin introduced a distinction in the classification of mental disorders between early dementia and mood disorders (which included unipolar and bipolar depression). Kraepelin believed that early dementia was primarily a disease of the brain and in particular a form that differs from the others, such as Alzheimer's disease, which generally occurs at a later age. There are those who argue that the use of the term, in 1852, of démence précoce by the French doctor Bénédict Morel was the medical discovery of schizophrenia. However, this consideration does not take into account the fact that there is little data linking Morel's descriptive use of the term and the autonomous development of the concept of the disease called early dementia, which occurred at the end of the 19th century [21-26]. Despite the etymology of the term, however, schizophrenia does not in itself imply any "double personality" or "multiple personality disorder", a condition with which it is often mistakenly confused in common language and which is instead present in some dissociative syndromes; rather, the term indicates the "separation of mental functions" typical of the symptomatic presentation of the disease [27].

Worldwide, there are about 25 million patients with this diagnosis and it occurs 1.4 times more frequently in males than females and usually appears first in males. The peak onset age is between 20 and 28 years for males and between 26 and 32 years for females. The onset in paediatric age is much rarer, as is the onset in middle or old age [28-31].

With reference to aetiological profiles, a combination of genetic and environmental factors plays a fundamental role in the development of schizophrenia. Indeed, people with a family history of schizophrenia and suffering from transient psychosis have a 20 to 40% chance of receiving a diagnosis within a year. However, there are also specific hypotheses:

1) Genetic factors [32-39] Estimates of heredity vary due to the difficulty of separating the effects of genetics from those of the environment. The highest risk of developing schizophrenia is in the presence of a first-degree relative with the disease (6.5% probability). More than 40% of homozygous twins of patients with schizophrenia are also affected. Many genes are likely to be involved, each with small effects and unknown transmission and expression mechanisms. Many possible candidates have been proposed, including: a) specific copy number variations such as for the NOTCH4 gene and loci of hystonic proteins (there appears to be significant overlap between the genetics of schizophrenia and bipolar disorder); b) microdeletions in the 22q11 region are associated with a 30-fold higher than normal risk of developing schizophrenia; c) some GWAS studies have found a link between the 804A zinc finger protein and schizophrenia. Assuming a hereditary basis, a question from evolutionary psychology is why genes that increase the risk of psychosis have evolved, assuming that the condition would be maladaptive from an evolutionary point of view; one idea is that such genes are involved in the evolution of language and human nature is only a theoretical hypothesis.

2) Environmental factors [40-44]. These are factors that often act as adjuvants and never as the main cause of the onset of schizophrenia. Studies have shown that living in an urbanized environment, during childhood or adulthood, is related to a double risk of developing schizophrenia, even taking into account drug use, ethnic group and social group size. Other factors that play a very important role are social isolation and social hardship due to immigration, racial discrimination, family problems, unemployment, precarious housing conditions and family/ domestic violence.

3) Interfering factors from drug and alcohol use [45-52]. The direct correlation between the onset of schizophrenia (and other psychotic forms) and the use of amphetamines, cocaine and cannabis, in subjects with a genetic and clinical tendency, has been confirmed not as a trigger but as a competing factor. In particular, it has been noted that schizophrenia patients have a greater tendency to use nicotine than the general population.

4) Factors related to psychophysical development [53]. The presence in the mother of problems such as infection, hypoxia, stress and malnutrition during fetal development can cause a slight increase in the risk of developing schizophrenia in the unborn child during her lifetime. In fact, people born in winter in the northern hemisphere are more likely to be diagnosed with schizophrenia; this can be explained by increased rates of viral exposure in utero. However, the difference varies between about 5 and 8%.

5) Psychological factors [54-64]. Many psychological mechanisms have been held responsible for the development of schizophrenia, such as psychological trauma and child attachment disorders. Various cognitive bias have been identified in patients diagnosed with schizophrenia or in individuals at risk, especially when they are under stress or in confused situations. Some cognitive functions may also reflect global neurocognitive deficits, such as memory loss, while others may be related to particular problems and experiences.

Although not always apparent, however, some results from recent studies indicate that many individuals diagnosed with schizophrenia are emotionally sensitive, particularly to stressful or negative stimuli, and that such sensitivity may cause greater vulnerability to symptoms or illness. Other data suggest that the themes of delusions and psychotic experiences may reflect the emotional causes of the illness and that the way a person interprets such experiences may influence the symptomatology, not surprisingly the use of "safety behaviours" to avoid imaginary threats may contribute to the chronicity of delusions.

6) Neurobiological factors [65-71]. Studies using neuropsychological tests and brain imaging technologies, such as MRI and PET, have shown that differences seem to occur more commonly in the frontal lobes, hippocampus and temporal lobes. A reduction in brain volume, lower than in Alzheimer's disease, has been reported in areas of the frontal cortex and temporal lobes. It is unclear whether these volume changes are progressive or pre-existing at the onset of the disease. These differences are linked to neurocognitive deficits often associated with schizophrenia. Since the neural circuits are altered, it has been alternatively proposed that schizophrenia can be regarded as a set of neurological developmental disorders. Particular attention has been paid to dopamine function in the mesolimbic pathway of the brain. This attention is largely the result of the accidental discovery that phenothiazine drugs, which block dopamine function, can reduce psychotic symptoms. This is also supported by the fact that amphetamines, which trigger the release of dopamine, can exacerbate psychotic symptoms in schizophrenia. The hypothesis that dopamine can influence the development of schizophrenia suggests that excessive activation of D2 receptors is the cause of the positive symptoms of the disease. Although the role of all antipsychotics in blocking D2 receptors has been considered correct for over 20 years, this was not demonstrated until the mid-1990s thanks to studies with PET and SPECT. The dopamine hypothesis, however, appears to be a reductive interpretation to date, not least because the more recent antipsychotic drugs (atypical antipsychotic drugs), which may be as effective as older drugs (typical antipsychotic drugs), also act on serotonin transmission and may have a slightly reduced effect on dopamine blockade. Research also focuses on the role of glutamate, a neurotransmitter, and the reduced function of the glutamate NMDA receptor found in schizophrenia, largely due to abnormally low levels of glutamate receptors in the brains of patients diagnosed with schizophrenia after death. It has also been found that glutamate-blocking drugs, such as phencyclidine and ketamine, can mimic the symptoms and cognitive problems associated with the condition. Several attempts have therefore been made to try to explain the link between altered brain function and schizophrenia: one of the most common hypothesis concerns the role of dopamine: the malfunction of dopaminergic neurons could be the cause of misinterpretations by the mind leading to the development of psychosis.

7) "Folic acid" hypothesis [72-82]. Among the hypotheses of the physiopathological causes of schizophrenia there is

a deficit and/or altered function of folic acid that involves: alterations in DNA methylation; abnormalities in glutaminergic transmission, alterations in mitochondrial function, folate deficit, maternal hyperhomocysteinemia. Recent research indicates a correlation between the increase in IL-6 and TNF-α with pathological homocysteine levels due to the C677>T gene mutation of the MTHFR enzyme. A study correlates the appearance of schizophrenic symptoms with a deficit in the activity of glutamate carboxypeptidase II (GCPII), a key enzyme for the absorption of folic acid. Finally, another research group relates the negative symptoms of schizophrenia to a folic acid deficiency due to the deficiency of the enzyme MTHFR.

In relation to clinical signs, since 2013, the patient suffering from schizophrenia presents a very clear and distinct picture from other forms; however, this was not the case in the past. In the 20th century, psychiatrist Kurt Schneider listed the forms of psychotic symptoms that he believed distinguished schizophrenia from other psychotic disorders; these were called "first rank symptoms" or "Schneider's first rank symptoms" or "Schneider's". They include delusions of being controlled by an external force, the belief that thoughts are inserted or eliminated from one's conscious mind, the belief that one's thoughts are transmitted by other people and hearing hallucinatory voices commenting on one's thoughts or actions or experiencing a conversation with other hallucinated voices. A review of the diagnostic studies conducted between 1970 and 2005 did not confirm or refute Schneider's findings, however, it suggested that top-ranking symptoms should be de-emphasized in future reviews of diagnostic methods. The more traditional classification instead considers four main forms of schizophrenia: a) "catatonic schizophrenia"; b) "ebephrenic (or juvenile) schizophrenia"; c) "paranoid schizophrenia"; d) "typical schizophrenia". The DSM criterion, on the other hand, from 2013, with reference to schizophrenia, no longer distinguishes it in subtypes but adheres to the idea of the "spectrum of schizophrenia". Separate categories in the spectrum are: delusional disorder, schizophreniform disorder, schizoaffective disorder, schizotypic personality disorder, short psychotic disorder and substance/pharmaceutical-induced psychotic disorder [3,83,84].

From DSM-V, the evaluation criteria are as follows [3]

A) Two or more of the following symptoms, present for a significant part of time during the period of one month. At least one of these symptoms must be:

1. Delusions;

2. Hallucinations;

3. Disorganised speech (derailment or inconsistency);

4. Coarsely disorganised or catatonic behaviour;

5. Negative symptoms (decreased expression/emotions, or abulia).

B) For a significant amount of time since the onset of the disorder, the level of functioning in one or more of the main areas, such as work, interpersonal relationships, or self-care is markedly below the level reached before the onset.

C) Continuous signs of the disorder persist for at least 6 months. This 6-month period must include at least 1 month of symptoms meeting criterion A, and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, signs of the disorder may only be shown by negative symptoms or by two or more symptoms listed in criterion A in an attenuated form (extravagant beliefs, unusual perceptual experiences).

D) Schizoaffective disorder and depressive or bipolar disorder with psychotic characteristics have been excluded because:

1. no major depressive or manic episodes occurred during the active phase of the symptoms; or

2. if episodes of mood alteration occurred during the active phase, they occurred for a minority of the total duration of the active and residual periods of the disease.

E) The disorder is not attributable to the physiological effects of a substance or another medical condition.

F) If there is a history of autism spectrum disorder or early childhood communication disorder, the additional diagnosis of schizophrenia will only be postulated if hallucinations or preeminent delusions are present for at least 1 month in addition to the other required symptoms of schizophrenia.

Please also specify

1) The following course indicators should only be used after one year of the duration of the disorder and if they do not contradict the diagnostic course criteria;

2) first episode, currently in acute episode;

3) first episode, currently in partial remission;

4) first episode, currently in complete remission;

5) multiple episodes, currently in acute episode;

6) multiple episodes, currently in partial remission;

7) multiple episodes, currently in complete remission;

8) with/without catatonia.

Psychotic symptoms can be present in many other mental disorders, however, including bipolar disorder, borderline personality disorder, drug intoxication and drug-induced psychosis. Delusions ("not bizarre") are also present in delusional disorder and social withdrawal in social phobia, avoidance personality disorder and schizotypical personality disorder. Schizophrenia is in comorbidity with Obsessive-Compulsive Disorder (OCD), much more often than could be explained by pure chance, although it can be difficult to distinguish obsessions that occur in OCD from delusions of schizophrenia. A small percentage of people who stop

taking benzodiazepines experience severe withdrawal syndrome, which can resemble schizophrenia and may later be misdiagnosed as such. A general medical and neurological examination may be necessary to rule out medical conditions that can rarely produce schizophrenia-like psychosis, such as metabolic disorders, systemic infections, syphilis, HIV infection, epilepsy or brain injury. Investigations are generally not repeated for recurrences, unless there is a specific medical indication or any undesirable effects due to antipsychotic drugs [85-87].

Delusional disorder

"Delusion" [88] (or incorrigible misconception) is a term used to refer to a disturbance in the content of thought, which can be present in various psychic illnesses, e.g. schizophrenia, depressive or manic episodes with psychotic symptoms, chronic delusional disorder (or paranoia). This is a misjudgement of reality that is not corrected by criticism or experience, as the decisions and behaviours that are adopted serve to self-confirm this pattern of thinking. Chronic forms of delirium, based on the rational and lucid elaboration of a system of erroneous beliefs, may be the only symptom of a psychic pathology, in this case in particular chronic delusional or paranoid disorder. The numerous forms of delirium can be classified from different points of view, for example according to the physiological cause, duration, or symptomatology. In its "hyperactive form", it manifests itself mainly as severe confusion and disorientation, develops with a relatively rapid onset and tends to fluctuate in intensity; in its "hypoactive form", it manifests itself with a sudden withdrawal from interaction with the outside world (things and people).

Among the specifications of the term delirium we can mention the following most important and frequent ones:

1) **Collapse delusion:** A transient condition that occurs frequently in acute illnesses, coinciding with the cessation of febrile states;

2) **Reference delusion:** The patient attributes a special meaning to objects, events or people close to him;

3) **Touch delusion:** It consists in the excessive mania of touching certain objects;

4) **Nihilistic delusion:** It is found in melancholic depressions, and is made up of an incoherent mass of negative ideas;

5) **Oneiric delusion:** It consists in a disturbance of the conscience that leads to emotions similar to those present in the oneiric phase (the conscience of the disturbed person enters a phase such that it is unable to distinguish reality from the oneiric profile of itself);

6) **Professional or occupational delusion:** It consists in recreating, on the patient's part, the usual conditions and places of work;

7) **Residual delusion:** Represented by the persistence of delusional representations at the level of thought, even after the perturbation has ceased;

8) **Interpretative delusion:** The subject interprets random facts as facts linked to him, feeling that he is the main actor or feeling indicated as a party in the case;

9) **Persecution delusion:** The patient believes he is the object of persecution (a situation often identified also with the term paranoia);

10) **Bizarre delusion:** The patient adheres to a system of totally implausible beliefs (in the culture of reference);

11) **Control delusion:** The patient is convinced that his thoughts or emotions are under the control of some external force;

12) **Insertion delusion:** Similar to the previous one; the patient is convinced that some of his thoughts are imposed on him by an external force;

13) **Erotomanic delusion:** The patient is convinced that a certain person (often a celebrity) is secretly in love with him;

14) **Jealousy delusion:** The patient has the unfounded and obsessive belief that he is betrayed by his partner. Among delusions, it is the most frequent;

15) **Delusion of grandeur (megalomania):** The patient has the conviction that he is extremely important, for example, that he has been chosen by God to carry out a mission of fundamental importance, or that he is the only holder of extraordinary knowledge or powers;

16) **Somatic delusion:** The patient is convinced that his body has something unusual, such as a rare disease, some kind of parasite or an unpleasant smell;

17) **Religious delusion:** The patient is convinced that religious forces (almost always belonging to his own religion) protect him from misfortune, or from a disease (real and existing);

18) **Identity delusion:** He who is affected believes he is another person, often important people such as Kings, Princes or Presidents.

Psychoanalysis explains certain forms of delirium such as the emergence at the level of conscious thought, in metaphorical and allegorical form, of unconscious content. This psychological mechanism is carried out without the subject's knowledge, so the answer is inherent not to the actual meaning of the unconscious emergence, but to its allegorical derivative that causes the delirious form that is found in the action of the subject that causes bewilderment in others who judge the behaviour as an act of madness. The delirium of persecution can be explained in terms of a conflict between the subject's ego, fixed in a narcissistic regressive phase, (and often megalomaniac) and the critical super ego, which the subject pathologically identifies with the others, through the mechanism of defence of the projection (thus feeling judged and opposed by the neighbour). This apparently inexplicable activity is an attempt of the subject to relate with reality giving

it a sense, even if questionable, we are in the presence of a schizophrenic language that cannot be understood [2,89].

Paranoid personality disorder

It is a personality disorder characterised by distrust and suspicion that leads to the interpretation of other people's motivations as malevolent for their own person or for the people the paranoid loves (children, parents, family members...). Individuals who mature this personality structure are dominated in a rigid and pervasive way by fixed thoughts of persecution, fears of being harmed, and the constant fear of being betrayed even by loved ones, without the intensity of such thoughts reaching delirious characters. The "examination of reality" remains, in fact, intact. According to the psychodynamic perspective, these personality characteristics are mainly attributable to a massive use of the projection defence mechanism, through which the characteristics considered bad belonging to one's own person are attributed, projected outside, on other people, or on the whole environment, which will thus be perceived as constantly hostile and dangerous for the survival of the individual. Paranoid Disorder is the result of a collection of behaviours, tendencies or personality characteristics that are mainly found in individuals who are then classified as suffering from Paranoid Disorder. We speak of "distrust and suspicion" towards others if there are four or more of the following characteristics: unrealistic suspicions of being exploited or damaged; unjustified doubts about the loyalty of friends; fear of trusting others; misunderstanding of other people's words, such as simple reprimands or other, to more threatening meanings prevalence of resentment towards others; unjustified feeling of being attacked or harmed, and tendency to react; unjustified fear of being betrayed by the spouse. There are also more serious illnesses, which present the typical paranoid symptoms, but are no longer part of the diagnosis of personality disorder. If the persecutory ideas have a delusional content, we then speak of paranoid psychosis or "lucid delirium" (paranoid schizophrenia). From the psychodynamic point of view, its collocation is well understood: the mechanism of projection is a strategy of defence of the ego considered primitive, i.e. used in a massive way in very early childhood. In adulthood, projection will be used in a more attenuated way (in common language, it is called paranoia), and tolerable for adaptation, which also presupposes the exercise of trust or, in Melanie Klein's words, gratitude. In individuals whose personality structure leads the Ego to employ a massive use of projection and other archaic defences as the main adaptation strategy, one has a picture of Paranoid Personality Disorder [90].

Schizoid personality disorder

In this personality disorder, the main trait is the lack of the desire for close relationships with other human beings, and the emotional "detachment" of the subject from people and the surrounding reality. The schizoid personality manifests closure in itself or a sense of distance, elusiveness or coldness. The person tends to isolation or has formal or superficial communicative relationships, does not appear interested in a deep bond with other people, avoids involvement in intimate relationships with other individuals, with the possible exception of first degree relatives. The schizoid subject, on clinical examination, shows a pervasive tendency to live emotionally in a rigidly separated "own world" of the external world of social relations, and his own idea of the self is affected by uncertainties. In some cases he manifests "coldness" on the outside with attitudes of rejection, discomfort, indifference or contempt (perhaps addressed to unrelated personalities), or other modes of closure, elusiveness, emotional block or detachment. The situations that trigger the schizoid response, i.e. the manifestation of symptoms, are generally those of an intimate nature with other people, such as expressions of affection or confrontation. The schizoid person is not able to express his/her emotional participation consistently and in a relationship context; in contexts where spontaneity, sympathy or affability is required, he/she appears rigid or clumsy. In superficial relationships and formal social situations – such as work and regular situations – the subject may appear normal. A typical characteristic feature of the schizoid personality is the absence or reduced ability to feel real pleasure or interest in any activity (anhedonia). In the individual experience of the schizoid patient prevails a sense of emptiness or lack of meaning, referring to his or her external existence: the subject is unable to derive pleasure from external reality, nor to perceive himself or herself as fully existing in the world. The schizoid subject often appears to be a person who tends to be insensitive to manifestations of emotional participation or judgements of others – e.g. encouragement, praise or criticism – i.e. he or she may appear to be a 'little influential' personality. Low fear in response to physical danger, or higher-than-normal tolerance of pain, can also be part of the picture. The introverted/schizoid subject often presents a rich and articulated imagination and intense emotional experience, concentrating many of his emotional energies on cultivating a 'fantastic' inner world. By evoking memories of events concerning his emotional life he somehow satisfies certain needs without actively participating in the real world. The schizoid response would be a profound defensive mechanism directed towards reality as such, unconsciously perceived as a source of danger or pain. The schizoid patient is clearly distinguished from the schizophrenic by the fact that the schizoid disorder does not affect the logical-cognitive abilities: the subject is fully aware of reality even though he or she does not participate emotionally. Psychosis, a state of mind whose persistence is a symptom of schizophrenia, is either absent in the schizoid or limited to short episodes characterised by strong tension. One can then speak of psychotic attacks – or schizophreniform disorder – as reactions of the schizoid to emotional stress. People with a schizoid disorder have little or no sex life, or are perceived as unfulfilling in an emotional sense: by indulging in purely idealistic fantasies, schizoids can also indefinitely postpone mature sexuality [4]. The schizoid individual is little attracted to building intense emotional relationships, and may show intolerance towards inter-personal intimacy. He may appear reluctant to talk about the intimate aspects of his own self or to know those of the self of other individuals. As follows, the diagnosis can only be made in adulthood, since the evolution of symptomatology is made at the transition from adolescence to maturity. The characteristics expressed by the

child's personality - such as shyness, aggressiveness - are mostly not reliable indicators of a future development of the disorder. As in the case of schizophrenia, also in the schizoid disorder it is often difficult to convince the individual of the existence of the disorder and the need for intervention, because if in the schizophrenic the mathematical logical processes are affected, and therefore he is not able to understand that there is a problem, in the schizoid instead, although he is a lucid subject, having a certain reluctance to open his self in front of others, the attempt to approach the subject can generate a strong closure or even a psychotic reaction. This is aggravated by the distorted image of his self that the subject may have built up over the years [91-93].

Schizotypical personality disorder

It is a personality disorder characterized by a tendency towards social isolation, an eccentric, typically vague or metaphorical style of communication and thinking, strange behavioural patterns, and unusual ideas or beliefs, usually involving "magic" thinking, unusual perceptions, mild paranoid ideation, and other minor manifestations. It is sometimes referred to as "schizotypy", although this is a slightly different nosographic entity, i.e., a psychic theory concerning pathologies of the schizophrenic spectrum but less severe than true schizophrenia, unlike schizotypic disorder which is a personality disorder, although often schizotypy (a word derived from schizophrenia and which refers to having a "split personality" as well as a contraction of "schizophrenic phenotype") - i.e. strangeness and eccentricity without the presence of real psychosis and with maintenance of insight (self-awareness of one's condition) - is often described as the typical characteristic of the disorder. Schizotypic patients have individualised or unconventional belief systems, for example they believe in "powers" or supernatural perceptions or phenomena. The typical thinking of these subjects is called "tangential", i.e. allusive and dispersive. It happens that sometimes they seem to be "brooding" about themselves. The subject has a peculiar way of dressing and presenting himself, sometimes scruffy, however always original, sometimes he can speak alone in a low voice in public, repeating his thoughts, or gesticulate lightly and without external reason. Patients suffering from this disorder have a high comorbidity with other personality disorders. This may be partly due to the fact that the criteria described in the DSM-5 and previous DSMs include parameters that are also in common with other disorders, creating areas of overlap. The other personality disorders that at first glance share some traits with the schizotypical disorder are: the schizoid disorder (also cluster A), as regards the subject's tendency to isolate himself from others and the possible presence of anhedonia towards many areas, except specific interests; the avoidant disorder (cluster C), which also presents symptoms of anxiety and worries - over which the subject has no control - linked to interactions with others, from which the patient tends to isolate himself; the borderline personality disorder (cluster B), due to unstable emotionality (rapidly fluctuating mood) and fear of social and personal rejection, with possible sporadic psychotic symptoms such as derealization and depersonalization, anger, apathy, sudden

mania or melancholy, and dissociation; as in covert narcissism (cluster B), the patient feels unique and particular, not understood by others, devalued; finally, fixed ideas, which are the main feature of the paranoid personality disorder (cluster A): obviously there is no clear and precise boundary between simply "strange" ideas and paranoid fixed ideas, although they are two different and recognisable styles. However, these patients are usually inhibited or blocked in social and personal relationships, or face them in an atypical way (having a lot of difficulty in coping or adapting strategies), thus appearing strange in the eyes of unfamiliar people and thus feeding a closed circle of mutual distrust. Sometimes, in the case of an uncertain diagnosis, schizotypical traits, or cluster A traits (eccentricity, paranoia, isolation) are mentioned. The schizotypic therefore presents the so-called "paranoid ideation", but without reaching the extremes of the true paranoid, and tends to attribute more negative characteristics to other individuals (a condition that is also possible in the avoider), instead of devaluing himself as in the avoider disorder, and does not often perceive his inadequacy, projecting it on others (worrying about possible damages that they could do to him: for example cheating him, using him, defaming him, acting "magically" against him, infecting him with diseases or causing him legal problems); in the avoider and the schizoid there are no distortions of thought and evident eccentricity, but only social isolation (out of fear in the former, out of disinterest in the latter). The perception of reality of the schizotypic patient is not seriously altered as in psychosis and delusional disorder, the examination of reality is not completely compromised and thinking, even if it appears rambling or strange in style, is not as disorganised as that of schizophrenics. He therefore maintains a certain functioning, albeit to the limit, as is typical of many personality disorders. Despite the subject's tendency to close in on himself, brooding with thought, and to isolate himself by showing closure and moderate anxiety, fixed ideas have, as we have said, a milder form than paranoid ones, being less hostile towards the outside, even though they can become so under conditions of strong stress. Finally, a family and statistical correlation between schizotypical disorder and schizophrenia has been demonstrated. A percentage - around 12% - of these schizotypical patients who also have close relatives of schizophrenia develop schizophrenia or delusional disorder themselves, but usually in a less severe form than their family, and from which they often recover. It is very common for schizotypics or those with schizotypic personality traits to develop depressive disorder, anxiety disorders, other mood disorders such as bipolar disorder, obsessive-compulsive disorder with poor insight (low awareness of the falsehood of obsessions and/or low resistance to compulsions) and related obsessive-compulsive spectrum disorders (delusional dysmorphophobia), hypochondria and delusional fear of germs and contagion, impulse control disorder, substance use disorder, uncontrolled eating disorder and trichotillomania), somatoform disorder, which focus on or derive from the characteristics of schizotypical disorder (social isolation, bizarre beliefs, fixed ideas) [94-96].

The disorder already develops in childhood or pre-adolescence; in addition to a biological origin with predisposing

characteristics (sometimes detectable physical abnormalities of the cerebral cortex, temporal lobe, biochemical differences in CSF and neurotransmitter dysfunctions) and genetic familiarity with mental illnesses of the schizophrenic spectrum (schizophrenia), schizoaffective disorder) or psychotic disorder in general (bipolar disorder, delusional disorder, psychotic depression, psychoneurosis, substance psychosis, brain injury or brain disease), it is thought that it can also influence the growth environment on the development of the disorder during the patient's youth. Many have experienced a traumatic event (even from their point of view) in early childhood (e.g. physical or emotional abuse; early separation from a loved one resulting from abandonment, prolonged absence or bereavement; a serious health problem), or have grown up in contact with close relatives with mental problems, incorrect parenting style or in dysfunctional families [97].

For the DSM-V [3], the diagnostic criteria are : A) A pervasive pattern of social deficits and interpersonal communication, which implies a state of discomfort of the subject in close interpersonal relationships, and a reduced capacity in them. The subject's difficulty also concerns cognitive (or perceptive) distortions and eccentricity of behaviour. This picture begins to appear in early adulthood (otherwise it is another pathology). It occurs in several contexts and is characterised by at least five of the following symptoms:

a) reference ideas: belief that coincidences and random external events have a particular and unusual meaning specific to themselves (recurring ideas that are not fixed ideas);

b) unusual beliefs or style of "magic thinking" (possible comorbidity with obsessive-compulsive disorder), such as to influence behaviour and not related to the norms and beliefs of the cultural substratum (superstition, clairvoyance, telepathy, sixth sense, bizarre fantasies);

c) unusual perceptive experiences (illusions, auditory or visual, such as believing to see people - a pervasive form of normal pareidolia, believing to "feel" the presence of absent people, or in moments of emotional distress, may sometimes suffer from transient psychotic episodes with delusions, paranoia or dissociation, splitting, rarely real hallucinations but still short and low frequency);

d) expressive style with obscure verbal content (vague, circumstantial or "tangential", metaphorical, too elaborate or stereotyped);

e) suspiciousness or paranoid ideation;

f) reduced, rigid and restrained affectivity or inappropriate to contexts;

g) strange, eccentric behaviour or appearance;

h) absence of close friends or confidants other than first degree relatives;

i) excessive social anxiety, which does not diminish by becoming familiar with the person and, unlike avoidance, tends to be associated with fears of paranoid structure and not with negative judgments about oneself.

B) Symptoms do not appear in conjunction with schizophrenia, nor with a psychotic mood disorder, nor with other psychotic disorders or developmental disorders.

Theodore Millon [3] proposed two types of schizotypy, although they could coexist. In fact, any individual with a schizotypical personality disorder may exhibit one of the following subtypes differently (note that Millon claims that pure variant personality is rare, but rather a mixture of a major variant with one or more minor variants is often likely):

a) "insipid", i.e. excessively passive and detached, with traits of extraneousness and non-being; openly grey, lazy, inexpressive; internally insipid, sterile, indifferent and insensitive; "dark", vague and tangential thoughts;

b) "fearful", i.e. excessively active and detached, with traits of strong suspicion, excessive sensitivity, alienation and disqualification of one's own emotions and feelings.

Schizoaffective personality disorder

The schizoaffective disorder, first described by Kirby in 1913 and taken up by Hock in 1921 and Kasanin in 1933 with the final definition, is characterised by being a condition in which a subject suffers from a whole series of symptoms related to schizophrenia in combination with a group of symptoms specific to mood-related illnesses, such as mania or depression. In the first case, these are mainly symptoms such as delusions or hallucinations. In most cases this type of problem is detected with considerable difficulty, just like all other mental illnesses. Schizoaffective disorder, in fact, can be considered as a sort of mixed condition between symptoms belonging to various mental illnesses. If it is not treated adequately, this type of disorder can lead to a significant reduction in the patient's quality of everyday life. Often, the patient tends to isolate himself or herself from all those closest to him or her and presents numerous social and integration problems. The proposed treatment can certainly improve symptom control and, at the same time, promote a better quality of life [98].

The criteria of DSM-5 [3] for this diagnosis are

A) An uninterrupted period of illness during which an episode of the major mood (major depressive or manic) is present in conjunction with criterion A of schizophrenia.

B) Delusions and hallucinations for 2 weeks or more in the absence of a major mood episode (depressive or manic) during the duration of the illness.

C) Symptoms that meet the criteria for a major mood episode are present for most of the total duration of the active and residual periods of the illness.

D) The disorder is not attributable to the effects of a substance or other medical condition.

Specify whether

1) Bipolar type;

2) Depressive type;

3) With/without catatonia.

Brief psychotic distortion

This disorder consists of delusions, hallucinations or other psychotic symptoms (such as disorganised speech and macroscopically disorganised or catatonic behaviour) that last at least 1 day but less than 1 month, with subsequent return to normal pre-morbid functioning. Pre-existing personality disorders, as well as certain clinical conditions (of an autoimmune and systemic nature) predispose to its onset. A major stressful event, such as grief, can trigger the disorder. A brief psychotic disorder, however, cannot be diagnosed if the symptoms are better attributable to a mood disorder with psychotic manifestations, schizoaffective disorder, schizophrenia, organic disorder or the adverse effects of a (prescribed or illegal) substance [3].

Psychotic collapse or slippage

A "psychotic break-down" or "psychotic break-down" is a circumscribed and identifiable event in the history of a person who often precedes the chronicisation of a real psychotic disorder. More often than not, events of a traumatic nature have been described as serious violations of personal dignity and the integrity of the body, which in a psychic structure considered "theory of predisposition to pre-psychotic psychosis" causes a definitive psychic collapse typical of psychosis, leading to a withdrawal of emotional investments and the most common psychic activities from the environment. Other times the psychotic collapse is associated with a highly stressful event or period which, having reached an excessive accumulation, tests the individual to the point of triggering a psychotic crisis that can remain in chronic disorder. Also in this case the event is added to a weakened, "predisposed" structure. According to some research carried out on hallucinogenic substances (Gregory Bateson's well-known ones on himself with LSD), this kind of drug is able to reproduce some of the most common forms of delusions and hallucinations found in psychosis, while maintaining the awareness of the influence of the substance intact, without precipitating the user into total detachment from reality in the long term. However, it may happen that, in individuals "predisposed" to various forms of psychosis (the constitutional or environmental nature of this type of disorder has always been the subject of discussion), the use of hallucinogenic substances may favour a psychotic break-down [3].

Catatonic disorder

Catatonia" [3,99], first described by Kahlbaum in 1874 and later included among the clinical forms of dementia praecox by Kraepelin, is a complex neuropsychiatric syndrome characterised by a cluster of psychomotor signs and symptoms that develop in the context of numerous pathological conditions, not only psychiatric, but also neurological, toxic, endocrinological and infectious. It is traced back to a form of schizophrenia, characterised by motor alterations, negativism, fixed posture and/or stereotyped movements, echolalia and ecopraxia. The patient takes on the appearance of a statue, with immobility, inexpressiveness, inaccessibility. This inactivity, however, is only apparent, as it is instead sustained by an intense commitment of negativist opposition, which can range from muscle tension to mutism and refusal to feed. The phenomena of catalepsy are also frequent. All these signs define the picture of catatonic amazement, which can be abruptly interrupted by paroxysmal accesses: it is a sort of motor discharges that range from verbal crises to accesses of fury, often of an aggressive nature and the so-called catatonic agitation, a state of explosive turbulence, often of extreme violence. There is also the categorisation of catatonia as a consequence of an organic pathology, such as subarachnoid haemorrhage, multiple sclerosis, hydrocephalus, Parkinson's disease and others. The modes of manifestation of catatonia vary. The most characteristic symptoms are plastic rigidity, akinesia, stupor, mannerisms, mutacism, automatic repetition of words (echolalia) or sentences repeated continuously ("broken disc"). In some cases the immobility is suddenly interrupted by strong tremors, agitations and sometimes by escapes.

The clinical picture is therefore dominated by 3 or more of the following symptoms:

1) stupor, i.e. no psychomotor activity, but responds to basic stimuli (such as pain);

2) catalepsy, i.e. stiffness of the extremities and reduced sensitivity to pain;

3) waxy flexibility, i.e. a characteristic aspect of catatonia;

4) mutism, i.e. inability to communicate through voice and speech;

5) negativism;

6) fixed posture;

7) mannerism, i.e. excessive and overloaded use of expressive means, i.e. hasty and unnatural mimicry, behaviour and language;

8) stereotyping, i.e. repetition of an unchanged and constant sequence of one or more behaviours;

9) agitation, not influenced by external stimuli;

10) presence of Grimace, that is strange and abnormal facial expressions not correlated to the current experience;

11) echolalia, that is imitation of other people's speech;

12) ecopraxia, that is imitation of other people's movements.

Based on specific movement disorders and other clinical features, Fink and Taylor have described three main forms of catatonia which, in order of incidence, are:

a) inhibited catatonia (or Kahlbaum syndrome), characterised by mutacism, rigidity, negativism and posturing, in the absence of impairment of the state of consciousness. The response to noises and stimuli is diminished, as well as speech and spontaneous movements. In the most serious cases, the patient stops feeding, and there is stupor and incontinence;

b) malignant catatonia (CM, also known as lethal catatonia, with its iatrogenic variant, neuroleptic malignant syndrome, SMN), complicated by fever, severe alterations in the autonomic nervous system, delirium and muscular rigidity. The syndrome often has an ominous course with a rapid progression, usually a few days;

c) excited catatonia (Bell's Mania or Delirious Mania), characterised by severe motor hyperactivity, incessant and aphinalistic, stereotypes, impulsiveness, aggression, agitation. In the most serious cases it is complicated by delirium, with disorientation and inconsistency of speech.

In the differential diagnosis of catatonia, the following should be taken into consideration

a) Hyperkinetic syndromes induced by antipsychotics such as acute dystonia (causing abnormal postures and repetitive movements), tardive dyskinesia (repetitive movements most frequently affecting the oral-lingual district) and akathisia. Gilles de la Tourette's syndrome and obsessive-compulsive disorder can also manifest themselves with hyperkinetic motor disturbances similar to catatonia. Catatonic-like manifestations can also be induced by hypocalcaemia, tetanus, strychnine intoxication and rabies;

b) Hypokinetic syndromes induced by the use of antipsychotics such as iatrogenic parkinsonisms. However, they do not benefit from the lorazepam test but are attenuated and resolved by the administration of anticholinergics;

c) The 'stiff man' syndrome: in this case it can be particularly difficult to distinguish catatonia from this pathology with probable autoimmune genesis, characterised by rigidity, hypokinesia, altered levels of consciousness and instability of the autonomic nervous system; however, there is generally a fixed deformity of the spinal column and there are antibodies to decarboxylase acid antiglutamate (GAD-Ab) absent in catatonia; in addition, typical catatonic signs such as mutism and posturing are absent;

d) 'Locked-in' syndrome, a condition associated with ventral bridge and cerebellar peduncle lesions characterised by mutacism and immobility with preservation of the vertical eye movement through which patients attempt to communicate with their surroundings;

e) Malignant hyperthermia, a rare hereditary disease with autosomal dominant transmission, characterised by instability of the autonomic nervous system, hyperthermia and rigidity, which may occur during surgery in relation to the use of halogenated gases and neuromuscular blocker catatonia (such as succinylcholine), which is diagnosed by muscle biopsy;

f) Non-catatonic stupor: which may occur in relation to head trauma or anoxia;

g) Encephalopathy, which occurs in the context of a somatic disease and may be reversible with the treatment of the underlying condition;

h) Stroke: in which both anamnestic positivity for cerebrovascular disease and suggestive neuroradiological signs, as well as focal neurological signs, are found;

i) A state of non-convulsive epileptic disease, which can occur with stupor and responds to benzodiazepines, but the diagnosis is confirmed by typical EEG-graphic findings;

l) Autism: with a chronic course with onset in childhood;

m) Elective mutism: the patient, however vigilant, selectively refuses to talk to certain individuals: it is usually accompanied by personality disorders and/or pre-existing stressors (other signs of catatonia are missing);

n) Dementia: in the late stages it can lead to mutism, negativism, sitophobia and hypokinesia;

o) Parkinson's disease: in the terminal stages it can complicate with immobility, rigidity, mutism as well as greater depression, which in turn is a possible cause of catatonia. The Parkinsonian patient, however, presents resting tremor, postural instability and a positive response to levodopa (while the bizarre postures typical of catatonia are usually absent).

Bipolar disorder. Reasons for exclusion

Bipolarity is characterised by a more or less constant oscillatory alternation or with the prevalence of one of the de polarities (depressive or manic); therefore, it is a disturbance of mood alteration. In the past, although it was a syndrome identified with the label of "manic-depressive psychosis", today it is universally classified separately from the psychotic spectrum, precisely because of its nosographic characteristics, although certain symptoms may be common (suicidal tendency [100], hallucinations and delusions, during severe depressive and/or manic episodes).

Dissociative disorders. Reasons for potential inclusion

Dissociative disorders are excluded from the psychotic spectrum, according to the nosographic categorisation of the DSM-V; however, the need to criticise such a decision emerges here for the following reasons:

a) Symptomatology describes a discontinuity in the normal integration of consciousness, with dysfunctional alterations of different cognitive functions, such as to represent

an aberration in function and structure of the reality plane of the representative personality.

b) In the symptomatology described in these disorders the presence of psychotic traits is massive.

c) The psychic organization of the dissociative patient uses massive defense mechanisms of psychotic area.

d) In pharmacological therapy, although psychotherapeutic treatment is preferable, the use of antipsychotics (in addition to SSRI antidepressants and mood stabilisers) is envisaged (especially low-dose atypical antipsychotics such as levopraid, olanzapine and risperidone), especially in the hypothesis of chronic disorders and multiple personality, to successfully treat hyperactivation, disorganisation of thought, intrusive post-traumatic symptoms, as well as chronic anxiety, insomnia and irritability.

For these reasons, the writer suggests a different classification of this psychopathological category [18].

Clinical treatments

The best clinical treatment in psychotically oriented psychopathologies is always the integrated one, between psychotherapy (cognitive-behavioural, family, bodily and/ or strategic, which favours the early recognition of the symptomatology, in terms of consciousness, knowledge and awareness) [101-104] and psychopharmacology, bearing in mind that the preventive profile with respect to the onset of the disease can only be oriented towards avoiding the use of drugs and alcohol, and in the hope of an evolution of growth far from psychological trauma and destabilising events.

1) Compared to the psychopharmacological profile it is interesting to focus on the following data:

2) The primary treatment of "schizophrenia" [105-114] involves the use of antipsychotic drugs, often in combination with psychological and social support. Hospitalization may be necessary only for serious episodes and may be decided voluntarily or, if legislation permits, against the patient's will. Long-term hospitalization is rare, and support therapies include reception centres, routine visits by health professionals dedicated to the mental health of the community, employment support and the creation of support groups. Evidence suggests that regular exercise has a positive effect on the physical and mental health of people with schizophrenia. Therapies of the past, such as electroconvulsive therapy and insulin therapy, have never yielded appreciable results and are no longer used, having now replaced such practices with the use of psychotropic drugs. First-line psychiatric treatment for schizophrenia is the use of antipsychotic drugs that can reduce the positive symptoms of psychosis in about 7-14 days. Antipsychotics, however, fail to significantly improve negative symptoms and cognitive dysfunction. Long-term use reduces the risk of relapse. The choice of which antipsychotic to use is based on the assessment of benefits, risks and costs. One can discern which class of antipsychotic is best, differentiating between typical or atypical. Both have the same frequency

of relapses when used at low doses. Clozapine is an effective drug for those who respond little to other preparations, but has a potentially serious side effect: agranulocytosis (low white blood cell count) in 1-4% of cases. Typical antipsychotics have side effects more often affecting the extrapyramidal system, while atypicals are associated with a higher risk of developing obesity, diabetes and metabolic syndrome. Some atypicals, such as quetiapine and risperidone are associated with a higher risk of death than the typical antipsychotic perfenazine, while clozapine is associated with the lowest risk of death of all. It is unclear whether more recent antipsychotics reduce the chances of developing neuroleptic malignant syndrome, a rare but very serious neurological disease. For individuals who are unwilling or unable to take medication regularly, preparations of long-acting antipsychotics may be used to achieve symptom control. They reduce the risk of recurrence to a greater extent than drugs taken orally. If this is used in combination with psychosocial interventions, it can improve long-term adherence to treatment. Among the supportive drug therapies, recent scientific work confirms a role for folic acid intake as a key precursor to the synthesis of the main chemical mediators of psychiatric pathology; as well as a modulator of abnormalities in glutaminergic transmission, and in the frequent alterations in mitochondrial function present during schizophrenia. Finally, it is notoriously used for the correction of folate deficits present during schizophrenia. Acetylcysteine has also been tested with promising preliminary results. Sarcosine (an amino acid derivative) and Tofisopam (an atypical benzodiazepine), on the other hand, have shown a positive effect on the symptoms of the disease, particularly the negative ones, in several studies. Other studies have investigated the usefulness of compounds classified as supplements, e.g. high doses of N-Acetyl Cysteine have shown several beneficial effects, although future studies will be necessary to further clarify their efficacy in disorders of the disease spectrum and effects on cognition.

3) The treatment of "delusion" and "paranoia" [3] is generally compensatory. The delusional disorder generally does not lead to serious deterioration or change in personality, but delusional concerns may gradually worsen, which is more pronounced in the paranoid disorder. Most patients may continue to work as long as their work does not involve aspects related to their hallucinations. Treatment aims to establish a good doctor-patient relationship and to manage complications. Substantial lack of insight is a challenge to treatment and only if patients are assessed as dangerous, hospitalization may be necessary. Among other things, there is insufficient data to support the use of any particular drug, although anxiolytics combined with antipsychotics can sometimes eliminate symptoms in acute and chronic phases; the best choice is psychotherapy, shifting the patient's main area of concern from delusional to a more constructive and rewarding one, making it a difficult but reasonable long-term treatment goal.

4) The treatment of "schizoid" [3] is generally combined, with a pharmacological prevalence oriented on SSRI antidepressants and low-dose neuroleptics.

5) The treatment of "schizotypic" and "schizoaffective"

[3,115] is the use of typical antipsychotics, such as haloperidol, and atypicals such as risperidone, quetiapine, aripiprazole and olanzapine (to be used with caution in patients subject to hypersensitivity linked to dopamine decrease), but also of anticonvulsants (such as sodium valproate) and SSRIs (especially if there is comorbidity with obsessive-compulsive disorder or depression or bipolar disorder) is considered a fairly effective treatment, together with cognitive-behavioural psychotherapy as a support. The schizotypical and schizoaffective patient must also avoid the use of certain types of synthetic drugs such as methamphetamine during life, which have been shown to significantly increase the risk of developing psychosis in these subjects.

6) The treatment of the patient with "short psychotic episode" [3] is similar to the treatment of an acute exacerbation of schizophrenia, but short-term monitoring and treatment with antipsychotics may be necessary.

7) Treatment of the "catatonic" patient [99] is similar to treatment of acute exacerbation of schizophrenia, but short-term monitoring and treatment with antipsychotics may be necessary. Failure to recognise the syndrome resulting in delay in therapeutic intervention is inevitably reflected in prolonged immobilization, enticement, malnutrition and puts the patient at an unjustified risk of serious internalistic complications (hydroelectrolytic disorders, pressure ulcers, rhabdomyolysis and acute renal failure, thrombus-embolic disorders, acute urinary retention, systemic infections, ab ingestis pneumonia) which are potentially fatal. In addition, if the first catatonic symptoms and/or signs are not correctly detected and diagnosed, the clinical picture may be further aggravated by the administration of antipsychotic drugs (commonly used in the treatment of mood disorders or concomitant psychosis), often responsible for evolution into lethal or "malignant" forms. Although different therapeutic approaches have been tried in the past, the current treatment of catatonia is based on the use of benzodiazepine molecules and ECT. Amobarbital was the first therapeutic treatment to be proven effective, but over time barbiturates have been replaced by benzodiazepines, which are currently the cornerstone of catatonic drug therapy. When the pharmacological treatment fails, a cycle of ECT must be started.

Conclusions

The psychotic spectrum is the category that groups together a series of disorders linked to a symptomatology in which we witness the fragmentation of the plane of reality until it is completely broken. According to the DSM-V nosography, the disorders under examination are schizophrenia, delusional disorder, paranoid disorder, schizoid disorder, schizotypic disorder, schizoaffective disorder, short psychotic disorder, psychotic break and catatonia. In this work, theoretical and practical profiles were analysed, paying attention to neurobiological content and therapeutic profiles, both psychotherapeutic and psychopharmacological. A note of disappointment was made in the nosographic categorisation of dissociative disorders that currently would not be included in

the psychotic spectrum disorders, although from the elements that emerged it would be interesting to review them in this way.

References

1. Perrotta G (2019) Psicologia generale. Luxco Ed., 1st ed.
2. Perrotta G (2019) Psicologia dinamica. Luxco Ed., 1th ed.
3. Perrotta G (2019) Psicologia clinica. Luxco Ed., 1th ed.
4. Perrotta G (2019) Alzheimer's disease: definition, contexts, neural correlates, strategies and clinical approaches. J Aging Stud Ther 1. **Link:** https://bit.ly/2KMINeK
5. Perrotta G (2019) Parkinson's disorder: definition, contexts, neural correlates, strategies and clinical approaches. J Neurosci Neurol Surg 4.
6. Perrotta G (2020) General overview of "human dementia diseases": definitions, classifications, neurobiological profiles and clinical treatments. Journal of Gerontology & Geriatrics Studies 6.
7. Perrotta G (2020) Epilepsy: from pediatric to adulthood. Definition, classifications, neurobiological profiles and clinical treatments. J Neurol Neurol Sci Disord 6: 014-029. **Link:** https://bit.ly/2L0GC7d
8. Perrotta G (2020) The pharmacological treatment of epileptic seizures in children and adults: introduction, clinical contexts, psychopharmacological profiles and prospects in the neurogenetic field. Journal of Neuroscience and Neurological Surgery 6: 8. **Link:** https://bit.ly/34QPtzv
9. Perrotta G (2019) Anxiety disorders: definitions, contexts, neural correlates and strategic therapy. J Neur Neurosci 6: 046. **Link:** https://bit.ly/2WSmiaT
10. Perrotta G (2019) Depressive disorders: Definitions, contexts, differential diagnosis, neural correlates and clinical strategies. Arch Depress Anxiety 5: 009-033. **Link:** https://bit.ly/2KADvDm
11. Perrotta G (2019) Panic disorder: definitions, contexts, neural correlates and clinical strategies. Current Trends in Clinical & Medical Sciences 1. **Link:** https://bit.ly/38IG6D5.
12. Perrotta G (2019) Bipolar disorder: definition, differential diagnosis, clinical contexts and therapeutic approaches. J Neuroscience and Neurological Surgery 5. **Link:** https://bit.ly/34SoC67
13. Perrotta G (2019) Delusions, paranoia and hallucinations: definitions, differences, clinical contexts and therapeutic approaches. Cientific Journal of Neurology (CJNE) 1: 22-28.
14. Perrotta G (2019) The reality plan and the subjective construction of one's perception: the strategic theoretical model among sensations, perceptions, defence mechanisms, needs, personal constructs, beliefs system, social influences and systematic errors. J Clinical Research and Reports 1. **Link: Link:** https://bit.ly/3b34baH
15. Perrotta G (2020) The concept of altered perception in "body dysmorphic disorder": the subtle border between the abuse of selfies in social networks and cosmetic surgery, between socially accepted dysfunctionality and the pathological condition. J Neurol Neurol Sci Disord 6: 001-007. **Link:** https://bit.ly/3rAQc1j
16. Perrotta G (2020) Narcissism and psychopathological profiles: definitions, clinical contexts, neurobiological aspects and clinical treatments. J Clin Cases Rep 4: 12-25. **Link:** https://bit.ly/2KCwxOa
17. Perrotta G (2020) Borderline Personality Disorder: definition, differential diagnosis, clinical contexts and therapeutic approaches. Ann Psychiatry Treatm 4: 043-056. **Link:** https://bit.ly/3hx2B1N
18. Perrotta G (2020) Perrotta Integrative Clinical Interview (PICI-1). LK ed.

19. Kandel J (2017) Principi di Neuroscienze, Ambrosiana, Milano.

20. APA (2013) DSM-V, Washington.

21. Yuhas D (2013) Throughout History. Defining Schizophrenia Has Remained a Challenge. Scientific American Mind. **Link:** https://bit.ly/3nXM6OG

22. Heinrichs RW (2003) Historical origins of schizophrenia: two early madmen and their illness. Journal of the History of the Behavioral Sciences 39: 349-363. **Link:** https://bit.ly/2MnPjJx

23. Noll R (2011) American Madness: The Rise and Fall of Dementia Praecox. Cambridge, MA, Harvard University Press.

24. Noll R (2012) Whole Body Madness. Psychiatric Times 29: 13-14. **Link:** https://bit.ly/2L9wJnG

25. Hansen RA, Atchison B (2000) Conditions in occupational therapy: effect on occupational performance. Hagerstown. MD, Lippincott Williams & Wilkins. **Link:** https://bit.ly/34XEunO

26. Berrios GE, Luque R, Villagran J (2003) Schizophrenia: a conceptual history. Rev Int Psycol Ter Psycol 3: 111–140. **Link:** https://bit.ly/3rCH1Od

27. Picchioni MM, Murray RM (2007) Schizophrenia. BMJ 335: 91-95. **Link:** https://bit.ly/3pyKRWH

28. Kumra S, Shaw M, Merka P, Nakayama E, Augustin R (2001) Childhood-onset schizophrenia: research update. Can J Psychiatry 46: 923-930. **Link:** https://bit.ly/34XrLBE

29. Hassett A (2005) Psychosis in the Elderly. London: Taylor and Francis 6.

30. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, et al. (1992) Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychol Med Monogr Suppl 20: 1-97. **Link:** https://bit.ly/2L7Usom

31. Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, et al. (2006) Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. Arch Gen Psychiatry 63: 250-258. **Link:** https://bit.ly/3pvKGeC

32. O'Donovan MC, Williams NM, Owen MJ (2003) Recent advances in the genetics of schizophrenia. Hum Mol Genet 12: R125-R133. **Link:** https://bit.ly/2WWbPLo

33. McLaren JA, Silins E, Hutchinson D, Mattick RP, Hall W (2010) Assessing evidence for a causal link between cannabis and psychosis: a review of cohort studies. Int J Drug Policy 21: 10-19. **Link:** https://bit.ly/3hzEnUz

34. O'Donovan MC, Craddock NJ, Owen MJ (2009) Genetics of psychosis; insights from views across the genome. Hum Genet 126: 3-12. **Link:** https://bit.ly/3aSeFcN

35. Craddock N, Owen MJ (2010) The Kraepelinian dichotomy - going, going. But still not gone. British Journal of Psychiatry 196: 92–95. **Link:** https://bit.ly/34XfSvI

36. Bassett AS, Chow EW, AbdelMalik P, Gheorghiu M, Husted J, Weksberg R (2003) The schizophrenia phenotype in 22q11 deletion syndrome. Am J Psychiatry 160: 1580-1586. **Link:** https://bit.ly/3hu0nA8

37. Horowitz A, Shifman S, Rivlin N, Pisante A, Darvasi A (2005) A survey of the 22q11 microdeletion in a large cohort of schizophrenia patients. Schizophr Res 73: 263-267. **Link:** https://bit.ly/2L9xCN2

38. Crow TJ (2008) The 'big bang' theory of the origin of psychosis and the faculty of language. Schizophr Res 102: 31-52. **Link:** https://bit.ly/3aWiSfy

39. Mueser KT, Jeste DV (2008) Clinical Handbook of Schizophrenia, New York, Guilford Press 22-23. **Link:** https://bit.ly/37ZV2gN

40. Jim van Os (2004) Does the urban environment cause psychosis?. British Journal of Psychiatry 184: 287-288.

41. Selten JP, Cantor-Graae E, Kahn RS (2007) Migration and schizophrenia. Current Opinion in Psychiatry 20: 111–115. **Link:** https://bit.ly/38S39ey

42. Perrotta G (2020) Psychological trauma: definition, clinical contexts, neural correlations and therapeutic approaches. Curr Res Psychiatry Brain Disord: CRPBD-100006. **Link:** https://bit.ly/37UD3bz

43. Perrotta G (2020) Neonatal and infantile abuse in a family setting, Journal of Pediatrics and Child Health. Open J Pediatr Child Health 5: 034-042. **Link:** https://bit.ly/2KApVQo

44. Perrotta G (2020) Dysfunctional attachment and psychopathological outcomes in childhood and adulthood. Open J Trauma 4: 012-021. **Link:** https://bit.ly/2Mi2ThB

45. Larson M (2006) Alcohol-Related Psychosis. eMedicine, WebMD.

46. Gregg L, Barrowclough C, Haddock G (2007) Reasons for increased substance use in psychosis. Clin Psychol Rev 27: 494-510. **Link:** https://bit.ly/38MlGsN

47. Large M, Sharma S, Compton MT, Slade T, Nielssen O (2011) Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen Psychiatry 68: 555-561. **Link:** https://bit.ly/381xGYr

48. Leweke FM, Koethe D (2008) Cannabis and psychiatric disorders: it is not only addiction. Addict Biol 13: 264-275. **Link:** https://bit.ly/2X0G97I

49. Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, et al. (2007) Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 370: 319-328. **Link:** https://bit.ly/34VhAgS

50. Sewell, Ranganathan, M, D'Souza, DC (2009) Cannabinoids and psychosis. International Review of Psychiatry 21: 152–162. **Link:** https://bit.ly/3pCZYhE

51. Henquet C, Forti M, Morrison P, Kuepper R, Murray RM (2008) Gene-Environment Interplay Between Cannabis and Psychosis. Schizophr Bull 34: 1111-1121. **Link:** https://bit.ly/2JBhp30

52. Sagud M, Mihaljević-Peles A, Mück-Seler D, Pivac N, Vuksan-Cusa B, et al. (2009) Smoking and schizophrenia. Psychiatr Danubina 21: 371-375. **Link:** https://bit.ly/3n2joLk

53. Yolken R (2004) Viruses and schizophrenia: a focus on herpes simplex virus. Herpes 11: 83A-88A. **Link:** https://bit.ly/2X0rdXn

54. Broome MR, Woolley JB, Tabraham P, Johns LC, Bramon E, et al. (2005) What causes the onset of psychosis?. Schizophr Res 79: 23-34. **Link:** https://bit.ly/3aVScLZ

55. Bentall RP, Fernyhough C, Morrison AP, Lewis S, Corcoran R (2007) Prospects for a cognitive-developmental account of psychotic experiences. Br J Clin Psychol 46: 155-173. **Link:** https://bit.ly/3o2fu6D

56. Kurtz MM (2005) Neurocognitive impairment across the lifespan in schizophrenia: an update. Schizophr Res 74: 15-26. **Link:** https://bit.ly/2X0fBn3

57. Cohen AS, Docherty NM (2004) Affective reactivity of speech and emotional experience in patients with schizophrenia. Schizophr Res 69: 7-14. **Link:** https://bit.ly/3aUY7kd

58. Horan WP, Blanchard JJ (2007) Emotional responses to psychosocial stress in schizophrenia: the role of individual differences in affective traits and coping. Schizophr Res 60: 271-283. **Link:** https://bit.ly/2Mdv6WC

59. Smith B, Fowler DG, Freeman D, Bebbington P, Bashforth H, et al. (2006) Emotion and psychosis: links between depression, self-esteem, negative schematic beliefs and delusions and hallucinations. Schizophr Res 86: 181-188. **Link:** https://bit.ly/2KO0n28

60. Beck AT (2004) A Cognitive Model of Schizophrenia. Journal of Cognitive Psychotherapy 18: 281-288. **Link:** https://bit.ly/38MpxpL

61. Bell V, Halligan PW, Ellis HD (2006) Explaining delusions: a cognitive perspective. Trends Cogn Sci 10: 219-226. **Link:** https://bit.ly/2MnP6pN

62. Freeman D, Garety PA, Kuipers E, Fowler D, Bebbington PE, et al. (2007) Acting on persecutory delusions: the importance of safety seeking. Behav Res Ther 45: 89-99. **Link:** https://bit.ly/2KliZAK .

63. Kuipers E, Garety P, Fowler D, Freeman D, Dunn G, et al. (2006) Cognitive, emotional, and social processes in psychosis: refining cognitive behavioral therapy for persistent positive symptoms. Schizophr Bull 32: S24- S31. **Link:** https://bit.ly/3of0EJK

64. Perrotta G (2020) Human mechanisms of psychological defence: definition, historical and psychodynamic contexts, classifications and clinical profiles. Int J Neurorehabilitation Eng 7: 1. **Link:** https://bit.ly/2MlFTye

65. Kircher T, Thienel R (2006) Functional brain imaging of symptoms and cognition in schizophrenia. The Boundaries of Consciousness. 302.

66. Green MF (2006) Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry 67: 3-8. **Link:** https://bit.ly/2KGhSBC

67. Insel TR (2010) Rethinking schizophrenia. Nature 468: 187-193. **Link:** https://go.nature.com/3pCgnDg

68. Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, et al (1996) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci USA 93: 9235-9240. **Link:** https://bit.ly/3pyPuQz

69. Jones HM, Pilowsky LS (2002) Dopamine and antipsychotic drug action revisited. Br J Psychiatry 181: 271-275. **Link:** https://bit.ly/2L9ji7v

70. Konradi C, Heckers S (2003) Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment, Pharmacol Ther 97: 153-179. **Link:** https://bit.ly/3pD3xo2

71. Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA (2001) Effects of ketamine in normal and schizophrenic volunteers. Neuropsychopharmacology 25: 455-467. **Link:** https://bit.ly/3huGQ2F

72. Feng J, Fan G (2009) The role of DNA methylation in the central nervous system and neuropsychiatric disorders. Int Rev Neurobiol 89: 67-84. **Link:** https://bit.ly/3aXlHwD

73. Muntjewerff JW, Blom HJ (2005) Aberrant folate status in schizophrenic patients: what is the evidence?. Prog Neuropsychopharmacol Biol Psychiatry 29: 1133-1139. **Link:** https://bit.ly/2WZxoek

74. Fallgatter AJ, Ehlis AC, Herrmann MJ, Reif A, Hohoff C, et al. (2010) DTNBP1 (dysbindin) gene variants modulate prefrontal brain function in schizophrenic patients--support for the glutamate hypothesis of schizophrenias. Genes Brain Behav 9: 489-497. **Link:** https://bit.ly/3aS8eGB

75. Kiss T, Hoffmann WE, Hajós M (2011) Delta oscillation and short-term plasticity in the rat medial prefrontal cortex: modelling NMDA hypofunction of schizophrenia. Int J Neuropsychopharmacol 14: 29-42. **Link:** https://bit.ly/2JvW0bh

76. Rollins B, Martin MV, Sequeira PA, Moon EA, Morgan LZ, et al. (2009) Mitochondrial variants in schizophrenia, bipolar disorder, and major depressive disorder. PLoS One 4: e4913. **Link:** https://bit.ly/3b3QeZl

77. Ben-Shachar D (2009) The interplay between mitochondrial complex I, dopamine and Sp1 in schizophrenia. J Neural Transm 116: 1383-1396. **Link:** https://bit.ly/34WTFhe

78. Petronijević ND, Radonjić NV, Ivković MD, Marinković D, Piperski VD, et al. (2008) Plasma homocysteine levels in young male patients in the exacerbation and remission phase of schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 32: 1921-1926. **Link:** https://bit.ly/3o1aGy8

79. Zammit S, Lewis S, Gunnell D, Smith GD (2007) Schizophrenia and neural tube defects: comparisons from an epidemiological perspective. Schizophr Bull 33: 853-858. **Link:** https://bit.ly/2X0JyU2

80. García-Miss MR, Pérez-Mutul J, López-Canul B, Solís-Rodríguez F, Puga-Machado L, et al (2010) Folate, homocysteine, interleukin-6, and tumor necrosis factor alfa levels, but not the methylenetetrahydrofolate reductase C677T polymorphism, are risk factors for schizophrenia. J Psychiatr Res 44: 441-446. **Link:** https://bit.ly/38LcUeQ

81. Goff DC, Bottiglieri T, Arning E, Shih V, Freudenreich O, et al. (2004) Folate, homocysteine, and negative symptoms in schizophrenia. Am J Psychiatry 161: 1705-1708. **Link:** https://bit.ly/2JDcFtK

82. Roffman J, Weiss AP, Purcell S, Wong DH, Halsted CH, et al. (2008) Contribution of methylenetetrahydrofolate reductase (MTHFR) polymorphisms to negative symptoms in schizophrenia. Biol Psychiatry 63: 42-48. **Link:** https://bit.ly/3aQvEw2

83. Schneider J (1959) Clinical Psychopathology, 5ª ed, New York, Grune & Stratton. **Link:** https://bit.ly/2MdxgFl

84. Nordgaard J, Arnfred SM, Handest P, Parnas J (2008) The diagnostic status of first-rank symptoms. Schizophrenia Bulletin 34: 137-154. **Link:** https://bit.ly/3o6bgdW

85. Pope HG (1983) Distinguishing bipolar disorder from schizophrenia in clinical practice: guidelines and case reports. Hosp Community Psychiatry 34: 322-328. **Link:** https://bit.ly/3o4PQhn

86. Bottas A (2009) Comorbidity: Schizophrenia With Obsessive-Compulsive Disorder. Psychiatric Times 26. **Link:** https://bit.ly/37ZJ5I4

87. (2007) Gabbard's Treatments of Psychiatric Disorders. Fourth Edition (Treatments of Psychiatric Disorders). Am J Psychiatry 164: 1620-1621. **Link:** https://bit.ly/34ZQ4yR

88. Fagioli M (2011) Deliri e interpretazioni. in Left.

89. Gruhle HW (1952) Sul delirio. in Il sogno della farfalla 3.

90. Lingiardi V (2011) La personalità e i suoi disturbi. Il Saggiatore, Milano.

91. Lowen A (1982) Il Tradimento del Corpo, Roma, Edizioni Mediterranee.

92. Marchino L, Mizrahil M (2014) Il Corpo Non Mente, Segrate, Sperling e Kupfer. **Link:** https://bit.ly/3o3xTjo

93. Scardovelli M (2000) Subpersonalità e Crescita dell'Io, Roma, Borla. **Link:** https://bit.ly/34SHuSz

94. Meehl PE (1962) Schizotaxia, schizotypy, schizophrenia. American Psychologist 17: 827-838. **Link:** https://bit.ly/3n3jjaj

95. Siever LJ (1992) Schizophrenia spectrum disorders. Review of Psychiatry 11: 25-42.

96. Pulay AJ, Stinson FS, Dawson DA, Goldstein RB, Chou SP, et al. (2009) Prevalence, correlates, disability, and comorbidity of DSM-IV schizotypal personality disorder: results from the wave 2 national epidemiologic survey on alcohol and related conditions. Prim Care Companion J Clin Psychiatry 11: 53-67. **Link:** https://bit.ly/2WWBfJ9

97. Berenbaum H, Valera EM, Kerns JG (2003) Psychological Trauma and Schizotypal Symptoms. Schizophr Bull 29: 143-152. **Link:** https://bit.ly/381tR5y

98. Malaspina D, Owen MJ, Heckers S, Tandon R, Bustillo J, et al (2013) Schizoaffective disorder in the DSM-5. Schizophrenia Research 150: 21-25. **Link:** https://bit.ly/2MmRT2s

99. Callari A, Bartolommei N, Lattanzi L, Mauri M (2014) Clinical management of catatonic syndromes. Journal of Psychopathology 20: 144-152. **Link:**

100. Perrotta G (2020) Suicidal risk: definition, contexts, differential diagnosis, neural correlates and clinical strategies. J Neuroscience Neurological Surgery 6: 114. **Link:** https://bit.ly/3aMqcu5.

101. Perrotta G (2020) The strategic clinical model in psychotherapy: theoretical and practical profiles. J Addi Adol Behav 3: 5. **Link:** https://bit.ly/3rALHUG

102. Perrotta G (2020) Accepting "change" in psychotherapy: from consciousness to awareness. Journal of Addiction Research and Adolescent Behaviour 3.

103. Pharoah F, Mari J, Rathbone J, Wong W (2010) Family intervention for schizophrenia. Cochrane Database Syst Rev 12: CD000088. **Link:** https://bit.ly/3o4toou

104. Medalia A, Choi J (2009) Cognitive remediation in schizophrenia. Neuropsychol Rev 19: 353-364. **Link:** https://bit.ly/2WXpi5P

105. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, et al. (2012) Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 379: 2063-2071. **Link:** https://bit.ly/34WjoGD

106. Kane JM (2010) Pharmacologic treatment of schizophrenia. Dialogues Clin Neurosci 12: 345-357. **Link:** https://bit.ly/3aWvAeb

107. Hartling L, Abou-Setta AM, Dursun S, Mousavi SS, Pasichnyk D, et al. (2012) Antipsychotics in Adults With Schizophrenia: Comparative Effectiveness of First-Generation Versus Second-Generation Medications: A Systematic Review and Meta-analysis. Ann Intern Med 157: 498-511. **Link:** https://bit.ly/3rFY7dS

108. Essali A, Al-Haj Haasan N, Li C (2009) Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev 2009: CD000059. **Link:** https://bit.ly/2KFasyv

109. Chwastiak LA, Tek C (2009) The unchanging mortality gap for people with schizophrenia. Lancet 374: 590-592. **Link:** https://bit.ly/3o8Rf6Q

110. Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T (2004) Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psychiatry 65: 464-470. **Link:** https://bit.ly/38UEqqm .

111. McEvoy JP (2006) Risks versus benefits of different types of long-acting injectable antipsychotics. J Clin Psychiatry 67: 15-18. **Link:** https://bit.ly/3o1Tetz

112. Berk M, Malhi GS, Gray LJ, Dean OM (2013) The promise of N-acetylcysteine in neuropsychiatry. Trends Pharmacol Sci 34: 167-177. **Link:** https://bit.ly/3hx4Z8O

113. Magalhães PV, Dean OM, Bush AI, Copolov DL, Malhi GS, et al. (2013) A preliminary investigation on the efficacy of N-acetyl cysteine for mania or hypomania. Aust N Z J Psychiatry 47: 564-568. **Link:** https://bit.ly/3puJF6G

114. Strzelecki D, Podgórski M, Kałużyńska O, Stefańczyk L, Kotlicka-Antczak M, et al. (2015) Adding Sarcosine to Antipsychotic Treatment in Patients with Stable Schizophrenia Changes the Concentrations of Neuronal and Glial Metabolites in the Left Dorsolateral Prefrontal Cortex. Int J Mol Sci 16: 24475-24489. **Link:** https://bit.ly/37ZszaY

115. Chen CK, Lin SK, Sham PC, Ball D, Loh EW, et al. (2005) Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. Am J Med Genet B Neuropsychiatr Genet 136: 87-91. **Link:** https://bit.ly/3htFWnb