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Chapter

New Directions for Symptoms and Diagnosis in Schizophrenia

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Abstract

Schizophrenia represents one challenging mental disorder from all the psychotic spectrum, considered to be a major health problem worldwide and because of the characteristic symptoms, the diagnosis is associated with high levels of stigmatization. It is quite common that the first acute symptoms to occur in early adult life and cause severe distress not only to the patient in need but also to their families. The schizophrenia clinical picture is usually misunderstood by the general public and consists of positive symptoms, negative symptoms, disorganized speech or behavior during a specific amount of time. In order to establish an accurate diagnosis, it requires taking into consideration both international classification systems, Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and The International Classification of diseases (ICD-10), adding a fresh perspective to the newest chapter of ICD-11 called "Schizophrenia or other primary psychotic disorders", alongside with the diagnosis criteria, other new symptoms such as cognitive impairment emerge as an important feature of schizophrenia.

Keywords: Schizophrenia, positive symptoms, negative symptoms, classification systems, diagnosis

1. Introduction

A broad consensus points out that schizophrenia must be considered a complex mental disorder with an ongoing and rechanging hypothesis implying the possibility that diagnostic criteria could evolve during the course of new discoveries [1]. As we all know, most of the criteria characterizing schizophrenia are symptom-based, that usually rely on the psychiatrist's interpretation of what a patient defines as subjective experience, with no objective measures for a diagnostic test or even a biological marker, both of them could bring support in the clinical and treatment decision [2].

2. Defining schizophrenia from origins to the present

Regarding the terms melancholia or mania, the schizophrenia concept could be considered relatively recent from the mid-nineteenth century with the Morel cases as demence precoce and soon after appeared the Kraepelin integration under the name

of dementia praecox, a term that included several clinical forms such as dementia praecox simplex, depressive dementia praecox, circular dementia praecox, agitated dementia praecox, periodic dementia praecox, but he was reserved regarding pathognomonic symptoms in schizophrenia [3]. Analyzing the symptoms, Bleuler suggested that the distinction between mandatory basic symptoms and accessory symptoms such as delusion and hallucinations are considered in the present time more important for the nosological systems as positive symptoms. On the other hand, Bleuler's perspective supposed that the basic symptoms were the most important such as thought and speech derailment, volitional ambivalence, affective incongruence, and withdrawal from what means reality [4]. Passing time, Kurt Schneider developed a prototype diagnostic criterion for schizophrenia, called the first-rank symptoms that included audible thoughts, voices arguing, discussing, commenting about the patient, experiences of influence on the body, interference or thought withdrawal, thought broadcast, and delusional perception. All these symptoms had high specificity and were later included in the ICD-10 classification [5].

3. New trends, innovations and changes in the diagnosis of schizophrenia

The need for a common language for reporting disorders all around the world concluded in development of two classifications systems called The International Classification of Diseases (ICD) and The Diagnosis and Statistical Manual of Mental Disorders (DSM), which one has several interrelated versions and the second one includes just a single set of operational diagnostic criteria to be used [6]. The presence of two different criteria sets for the same diagnoses emphasizes that definitions and concepts for psychiatric disorders are somewhat provisional and arbitrary in continuous development. During several editions, major differences were identified between this two, as ICD 10th version acknowledges schizophrenia as a group of disorders while DSM-IV describes a more unitary view of the illness [7]. Despite the evolution or the differences between the classification systems establishing a diagnosis of schizophrenia it still remains to present day a restricted overview of a clinical picture, describing different courses and outcomes based on characteristic symptoms that need to be present in a cross-section of the clinical picture, that vary differentially in weight of the diagnostic significance, mentioned as at least one or two or more, the duration of symptoms is also important, and the longitudinal course pattern [8]. As mentioned earlier, ICD-10 included the Schneider first rank symptoms as attributed high importance to this fact, but considered enough four weeks to eliminate acute, assumed non-schizophrenic episodes that could be induced by substance abuse [9]. The DSM-IV requires a more confident duration of at least six months that includes the prodromal and residual symptoms, implying that DSM has a tendency of selecting more severe cases in comparison with the ICD. Also, DSM in the B criteria mentions the need for a significant social and occupational dysfunction as an important definition criterion, but different view in the ICD as being context-dependent the level of dysfunctionality [10]. There is hope that making a diagnosis of schizophrenia should permit identifying the syndrome with adequate differentiation between degrees of symptom expression in patients and quantify the severity of the associated impairments. Regarding the evolution classification systems, it is mentioned two extremes courses in which there is complete recovery or worse evolution to continuous, unremitting symptoms that lead to serious deterioration. On the other hand, a major percent of schizophrenic patients manifest an episodic course with relapses and

remissions, but it is worth mentioning a small percentage of those that recover very well [11]. The course pattern is not influenced by the symptoms, more important are the clinical onset, the duration of untreated psychosis, the comorbidity of substance abuse, and many else, but the characteristic symptoms tend to have predictive validity because just a small percentage of patients would be eventually reclassified into other mental illness categories cause as a clinical picture change [12].

Another perspective that needs to be mentioned is that of the choice between a categorical and a dimensional approach for the diagnosis of schizophrenia. The dimensional arrangement seems to have some difficulties, including an agreement on the number or nature of the dimension that needs to be established in order to be adequate for a clinically relevant variation, also there is not an empirically established grounded metric for the evaluation of severity or changes in psychotic disorders, and more important seems to be the complexity of dimensional concepts with different models in everyday clinical practice [13]. On the other hand, the categorical diagnosis represents an important tool for the clinicians, with precious information on the future relapse, recovery, risk of deterioration, and social disability, that play a role in the treatment decision with valuable data about similar patients in various communities. In this manner, the DSM-IV criteria for schizophrenia offers usefulness for predicting the outcome, because it implies some degree of chronicity, but considering schizophrenia on a spectrum may become more helpful in characterizing a syndrome with high heritability [14].

As the new approval of the 11th Revision of the ICD appeared, it raises new questions regarding the status of nosology of mental illnesses, and what changes have been made to the diagnostic guidelines. The principles underlying the revision of ICD-11 include global applicability that refers to the cultural diversity of the new version of ICD-11 must incorporate, also scientific validity as it is established as a State-of-the-Art in terms of research and classification of mental pathologies and clinical utility by including the accuracy of descriptions, the ease of application, the time required for use and the need to select appropriate therapeutic and management decisions [15]. The ICD-11 includes a flexible, alphanumeric coding named BLOCK, and its use allows a larger diagnostic grouping, based on scientific evidence and clinical needs. The ICD-11 includes 28 chapters, with 6 chapters in addition to the old version of ICD-10. In the previous version of ICD-11, the number of groups was restricted by a decimal coding system, thus allowing a maximum of 10 pathological groups included, resulting in the loss of scientific relevance and clinical utility [16]. The organization of the ICD-10 reflects the original conceptualization of the Kraepelin Textbook of Psychiatry, but ICD-11 tries to order the diagnostic groups in chapter 06 called Mental, behavioral or neurodevelopmental disorders from a developmental perspective and brings them together diagnoses according to etiological, psychopathological, and phenomenological characteristics. Regarding the composition of the ICD-11 structure, the American Psychiatric Association also had a great influence, wanting to increase the concordance between ICD-11 and DSM-5 [17]. It is important to mention the main objectives for the DSM-5 diagnostic guide for Mental Disorders such as clinical utility, with its considerations being the facilitation of evaluation in the clinical routine, providing clarity in distinguishing the various psychiatric disorders, and only additionally, it provides research support for a better understanding of the cause and psycho-pathogenic pathways, also the organization reflects the process of development and evolution throughout life. Multiple comparative studies have reported positive evaluations by clinicians in terms of clinical utility, reliability, and diagnostic process quality for the ICD-11 system compared to ICD-10

[18]. In ICD-11 it has replaced the chapter from ICD 10—Schizophrenia, schizotypal disorders, and delusional disorders with—Schizophrenia or other primary psychotic disorders (BlockL1-6A2) and is the second chapter in the list of nosological classes, following chapter Neurodevelopmental disorders. Different from ICD-10 where it was preceded by Organic Mental Disorders and Substance Use Disorders. In ICD-11 the term Spectrum is not used, as in DSM-5 (Schizophrenia Spectrum Disorders and Other Psychotic Disorders) for class labeling. Research places many disturbances across a spectrum, namely very close illnesses that have in common symptoms, risk factors, neural substrate, and this spectrum concept actually accepts that the boundaries between the disturbances are much more flexible and vaguely defined [19].

Starting from the hypothesis that the diagnosis of Schizophrenia and the initiation of treatment is made relatively late, thus explaining the unfavorable evolution. It is proposed to introduce the diagnosis of Attenuated Psychosis in the DSM-5, thus providing the framework and support for clinicians in recognizing and monitoring psychotic symptoms from the earliest stages of manifestation with a desire to obtain a practice of rapid and early intervention [20]. It was proposed to introduce this construct in ICD-11, but it was abandoned, the reason was the increased prevalence in establishing the diagnosis of psychosis because there is a percentage of vulnerable individuals at risk but who will not develop criteria for a clear diagnosis of schizophrenia, attracting a high degree of stigma [21].

The term "primary" in the name chapter from the ICD-11 classification system, indicates that psychotic processes are the core feature of these disorders, in contrast to other mental disorders that may be associated with psychotic symptoms, but they occur as a result of other psychopathological mechanisms involved. It can be assumed that this term refers to the clinical construct that has no correspondence at the level of biological or genetic markers, and the actual cause remains still unknown even today [22].

Defining schizophrenia from origins to the present time includes mentioning that the construct of Schizophrenia in ICD-10 and DSM-IV-TR derives from the Kraepelin formulation of praecox dementia, with two distinct patterns of evolution, first one as Dementia praecox, the other one as Manic-depressive psychosis. Also, Bleuler considers a group of schizophrenia, having in common the split of mental functions (fundamental and accessory symptoms), in association with Schneider's first-order symptoms [23]. As we can conclude the current definition of Schizophrenia in ICD and DSM includes the chronicity of Kraepelin, the Bleuler negative symptoms, and Schneider's positive symptoms. But in ICD-11, the importance given to Schneider symptoms of the first rank is abandoned, although they remain unchanged, they are considered of the same importance as the rest of the positive symptoms. The consideration of this change stands because they are not being considered specific and pathognomonic, and the delimitation between bizarre and non-bizarre is difficult to estimate [24]. The impact of this change will be reduced, as a reflection of the prevalence of diagnosis, because most studies estimate that less than 5% of those diagnosed with Schizophrenia would have obtained it only in the presence of a single bizarre delusional idea [25]. Moreover, the distinction between delirium and phenomena of control or xenopathic influence on the self is kept, as considered core symptoms. An innovation brought by ICD-11 is the introduction in the description of the disorder of cognitive deficits, as characteristic symptoms of Schizophrenia, but with no clarifications to be provided regarding the issue of prodromal, active, or residual phases [26].

ICD-10 views Schizophrenia as a group of disorders, while DSM-IV describes it as a unitary condition, but in ICD-11-Schizophrenia is presented simpler, as the clinical

forms from the ICD-10 are abandoned, an aspect also found in DSM-5 due to the lack of clinical subtypes. The elimination of these subtypes was decided due to the belief that they offer a weak heterogeneity of the disorder, with low longitudinal stability, as the research does not confirm their predictive validity, and also, they do not exert influences on the therapeutic approach [27]. Studies show in their current clinical practice a reduced use of them, only the paranoid and undifferentiated subtype registered a more frequent use, as paranoid ideas are considered nonspecific, and can be found in affective episodes, delusional disorders, or dementia [28].

The past construct was considered inadequate to describe the evolutionary stages and psychopathological dimension of schizophrenia. For this reason, a set of dimensional ratings has been introduced, for a better description of the symptomatic manifestations, they can be applied only after the formulation of the diagnoses. It is considered of little importance to focus on the diagnostic categories when the dimensional classification is the one that focuses on the relevant aspects of the current clinical presentation, as well as the recovery [29]. Dimensional specifications of the evolution were also introduced, in order to emphasize the existence of different clinical-evolutionary profiles of a unique disorder. This draws attention to distinct profiles of the manifestation of the same disorder. Importance is given to the differentiation between the first episode of Schizophrenia, and subsequent, multiple episodes, in partial or complete remission, or on a continuous evolution, thus implying the need to establish a diagnosis as early as possible [30].

4. Old and new symptoms in Schizophrenia

Along with the diagnosis criteria, both DSM-5 and ICD-11 have introduced a symptom specifier which replaced the subtypes of schizophrenia in the case of ICD. The specifier records information on the presence or absence of symptoms, their longitudinal course, response to treatment, and prognosis for the disorder [31]. The specifier must be constantly assessed throughout the course of the disease, and it determines the severity of clinical manifestations between patients and in the same patient at different episodes. For ICD-11 the specifier categories include positive, negative, depressive, manic, psychomotor, and cognitive deficits while DSM-5 splits positive symptoms and consider individually hallucinations, delusions, and disorganized course.

Positive symptoms were always the most evident features of schizophrenia and contributed highly to the stigma associated with illness. Positive symptoms include a wide palette of delusions, hallucinations that can involve one or several sensory receptors, disorganized thinking, passivity experiences, and altered behavior.

4.1 Delusions

Delusions are defined as false ideas or beliefs that cannot be attributed to the patient's educational, social, or cultural background, that are not amenable to logic, and of which the patient is strongly convinced. Delusions have been divided into primary and secondary delusions. Primary delusions, which are more characteristic of schizophrenia, do not occur in response to other psychiatric symptoms such as hallucinations. Secondary delusions are subsequent to other psychopathology (e.g. hallucinations or mood disorder) and are thus understandable in circumstances of the person's background culture, or emotional state [32]. Delusions in schizophrenia vary

in content (e.g. persecutory, grandiose, religious, self-referential) and may present as monothematic or polythematic; they can be correlated with hallucinations and can severely impact other mental aspects of the individual (e.g. mood, behavior). Other characteristics such as levels of conviction, preoccupation (subjugation of behavior), and distress should be considered when examining delusions. These features are also key aspects that can help distinguish between an over-valued belief and a delusional one. Studies show that 70% of patients experience persecutory delusions and 67% experience self-referential delusions [33]. Delusions have different degrees of organization. Some delusions are simple, whereas others are very complex and involve many people or organizations. Some delusions have a stable time course and may last for many years, while others are present for a short time. Studies suggest that certain factors such as single life, older age, delusions of being controlled, delusional behavior, and higher levels of psychopathology and functional impairment are associated with the persistence of delusional thinking [34].

4.2 Hallucinations

Hallucinations are defined as percepts, experienced by a person, in the absence of an appropriate stimulus from the outside world. In patients with schizophrenia auditory hallucinations are by far the most common, followed by visual hallucinations, and then by tactile and olfactory or gustatory hallucinations [35]. Hallucinations can involve one or more receptors and can occur unilaterally or bilaterally. They may be simple or complex and may have a laudatory, hostile, or imperative character. Studies suggest that the prevalence of hallucinations in multiple sensory modalities seems to be the most frequent perceptual symptom of patients diagnosed with a schizophrenia spectrum disorder. The same data showed that hallucinations experienced in a single sensory modality (especially auditory ones) increase the risk for the occurrence of more sensory perception disturbances [36].

Auditory hallucinations (AHs) are defined as experiences without an external stimulus with individuals perceiving voices distinct from their own thoughts, whether the voices are familiar or not. They are considered a main positive symptom of schizophrenia [37]. AHs are found with a lifetime prevalence rate of 60−80% in schizophrenia spectrum disorders [38] and a 1-year prevalence rate of 50−70% in schizophrenia specifically [39]. AHs may have a severe negative impact on one's mental health, for instance, increasing depressive symptoms and leading to suicidal ideation or attempt [36, 40].

Visual hallucinations are the second most common type of perception disturbances in schizophrenia with an estimated mean prevalence of 27% [39]. Visual hallucinations are not the only form of perceptual anomaly encountered in schizophrenia. Studies pointed out that over 60% of schizophrenic patients experience visual distortions involving changes in clarity, form, brightness, color, motion, or persistence of visual stimuli [41–44]. It has also been reported that visual imagery is increased in people with schizophrenia [45]. The presence of VH in psychosis has often been linked to a more severe psychopathological profile. In schizophrenia VHs typically co-occur in association with other hallucinations and other sensory modalities [46]. Studies reported that co-occurring visual and auditory hallucinations occur in up to 84% of individuals with schizophrenia [39].

Tactile and somatic hallucinations are the third most common type of perceptual disturbances presented in schizophrenia with a prevalence ranging from 4 to 25% across studies [46]. Tactile and somatic hallucinations are classified as bodily

hallucinations, a term that also includes a wide group of corporeal sensations such as sexual hallucinations, coenesthesiopathies, proprioceptive hallucinations, kinesthetic hallucinations, vestibular hallucinations, hallucinated pain, and thermal hallucinations [47]. Tactile hallucinations are also called haptic hallucinations and are defined as sensations of touch in the absence of a stimulus from the outside world. They can present as an apparent touch to the skin, a sting, a hand on one's shoulder, or a blow to the face. From a pathophysiological perspective, they are associated with activity in sensory cortical areas subserving the skin and subcutaneous tissues. Somatic hallucinations are defined as bodily sensations experienced inside the body, in the absence of an objectifiable source or cause [48]. Although the data on this type of hallucination is scarce, studies have suggested a correlation between tactile hallucinations and longer duration and severity of the illness [46, 49]. Sexual hallucinations, as a subtype of tactile and somatic hallucinations, are probably the most neglected types of hallucination. This may be due to several reasons involving the clinician who might not ask for information on perceptual disturbances that fall outside the five basic sensory modalities (i.e. olfaction, taste, vision, audition, and touch) and the patients suffering from sexual hallucinations who might be ashamed to talk about these phenomena [47].

Olfactory (OHs) and gustatory hallucinations are frequently associated, and they represent other types of hallucinations in schizophrenic patients. The prevalence of olfactory hallucinations ranges from 15% to 27%, while for gustatory hallucinations the prevalence is estimated from 4% to 14% [48]. Both types of hallucinations can occur as negative or positive ones. The most common negative olfactory hallucinations include odors of blood, smoke, burnt rubber, or feces while positive odors are fruity and perfume-like [50]. Sociocultural factors may modulate the self-reporting and/or detection of OHs and hallucinations in other modalities. Referential/control delusions promote the generation and/or maintenance of OHs independent of factors shared with other hallucinations. OHs and hallucinations of taste, touch, and bodily sensation frequently co-occur [51]. Studies focusing on OHs found no relationship between disease severity measures and type or frequency of OHs but reported significant relationships between frequency of OHs and severity of tactile hallucinations. Although the predominance of negative OHs was noted, there were also many reports of positive OHs [50].

Multimodal hallucinations may be defined as anomalous perceptions occurring in two or more sensory systems, concurrently or serially in time, not necessarily sharing a single source, origin, or thematic content [52]. Recent evidence suggests that multimodal hallucinations are more common than previously recognized and have a greater negative impact than unimodal hallucinations. For example, recent evidence shows that 36–81% of patients with schizophrenia spectrum disorders experience multimodal hallucination [53]. When compared to unimodal experiences, multimodal hallucinations in clinical samples have been associated with increased levels of distress, negative affect, illness severity, and traumatic events [54, 55]. Research showed that patients with late-onset schizophrenia are considered to complain more of visual, tactile, and olfactory hallucinations, third-person running commentary, and accusatory or abusive auditory hallucinations, than early-onset patients [56]. Regarding accompanying symptoms, all types of hallucinations seem to be associated with other clinical features. Thus, the study of Melvin et al. [57] reported clusters of emotional feelings associated with hallucinations which by order of frequency could be described as fear and anxiety; despair and powerlessness; abused and threat; frustration and anger; loneliness; stress and distress and worry. The same research

highlighted co-occurring bodily feelings such as tension, pressure, agitation, chills, heaviness, and dizziness, across hallucination types identifiable, localized, specific, and communicable. The most involved body areas included the head and shoulders followed by the chest, abdomen, and legs and these corporeal sensations arose across hallucination types.

Few studies focused on the trajectories of hallucinations over the years. Ten years follow-up of auditory hallucinations in schizophrenia yield several important clinical implications. The results of the study suggested that the majority of patients with schizophrenia improve on auditory hallucinations during the first ten years with most patients improving within the first year. Another finding established a relationship between the presence of an alcohol abuse disorder and a longer DUP at treatment initiation and a worse course of auditory hallucinations over time [58]. Another study that included a 20 year follow-up period reported a decrease in both auditory and visual hallucinations over time with auditory hallucinations being more common than visual hallucinations, especially during the early years and throughout the course of the illness [59]. Within the study population, olfactory hallucination occurred at a low rate in schizophrenia patients during the 20-year follow-up, ranging from 0 to 11%. In terms of recovery prediction, auditory hallucinations were associated with being less likely to have a recovery over the next 20 years. The same authors pointed out that 44% of schizophrenia patients showed frequent or chronic hallucinations over the 20-year course of the study. The early presence of hallucinations predicted the lack of a future period of recovery in all patients, and increased hallucinatory activity was associated with reduced work attainment in all patients [60].

4.3 Disorganization

Another important factor that has received increasing attention in schizophrenia is disorganization with both disorganized thinking and behavior representing diagnosis criteria. The disorganization dimension was firstly introduced by Liddle [61] who identified inappropriate effect, poverty of content of speech, and formal thought disorder as component items using clinical assessment scales. Over time, research confirmed disorganization as a separate symptom dimension with respect to the positive one, with distinct associations with the course and outcome of schizophrenia [62, 63]. The Positive and Negative Syndrome Scale [PANSS] factorial analyses have identified different items, such as "conceptual disorganization", "difficulty in abstract thinking", "poor attention", "disorientation", "mannerism and posturing" and "stereotyped thinking", as component items of the disorganization dimension [64, 65]. Disorganization symptoms are found to be inversely associated with long-term functioning. Several studies showed a strong inverse correlation between disorganization and social functions emphasizing that the more symptomatic the patients are, the greater the difficulties in real-world functioning and performance [66, 67]. A large study investigating the role of illness-related factors on the global functioning in patients with schizophrenia observed a key role in the illness-related variables' disorganization. Defining the structure of the Positive and Negative Syndrome Scale (PANSS) disorganization dimension according to the consensus 5-factor solution proposed by Wallwork et al. [68] the results of the analysis pointed to an overlap that cannot be underestimated for the items "difficulties in abstract thinking" and "poor attention" with neurocognitive impairment. The authors also underlined those positive symptoms and disorganization proved to have significant direct and indirect effects on real-life functioning [69]. Ventura et al. [70] hypothesized that the close

link between disorganization and functional outcomes may be due to the impact of disorganization symptoms on communication and social interactions, as well as to the lack of compensatory mechanisms. Moreover, it has been suggested that symptoms such as incoherent thinking and speech can "mask" delusions and hallucinations. Other disorganization symptoms such as conceptual disorganization, loose associations, disrupted goal-directed sequencing, and circumstantiality, were found to have direct implications for community activities [69]. Disorganization dimension is also in relationship with neurocognitive functioning and studies observed that disorganization had a stronger impact on neurocognition than positive or negative symptoms [71–73]. In their meta-analysis, Ventura et al. [70] reported that disorganization was related to all domains of neurocognitive functioning including speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning, and problem-solving and social cognition). Specific items on PANSS such as "Conceptual disorganization" (P2) were reported as the item that correlated more than others with neurocognitive dysfunction. For the component item "Difficulty in abstract thinking" (N5) only a moderate association with the neurocognitive composite score was found [74]. Findings showed that patients experiencing first episode of schizophrenia (FES) have relevant levels of disorganized symptoms. Disorganization seems to show greater psychopathological affinities with negative symptoms than with positive symptoms with a putative potentiating detrimental effect on daily functioning and social interaction. Authors pointed out that evidence of significant baseline correlations between disorganization and other PANSS domains suggests that it may be an early clinical feature of general severity in FES psychopathology [75]. Disorganization criteria seem to play a role key also in the cases of treatment resistant schizophrenia. A recent study identified a higher severity of conceptual disorganization difficulty in abstract thinking and unusual thought content items within PANSS to be predictive of treatment resistance to schizophrenia [76]. Although the disorganized dimension is the least studied when compared to the positive and negative dimensions of the PANSS, there is consistent evidence for the clinical impact of disorganization and its correlates in neurocognition, genetics, and neuroimaging [77].

Disorganized behavior and deficits in adaptive goal-directed behavior contribute to disability in schizophrenia [78]. Behavioral abnormalities may include context-inappropriate commission errors that may appear bizarre and out of place [79]. Similar to the explanation for the disorganized speech in schizophrenia, behavioral disorganization may be a manifestation of an underlying abnormality of the neural activity supporting a specific type of conceptual knowledge encoding goal-related requirements of behavioral actions. Execution and comprehension of behavior may share neural systems subserving real-world knowledge and particularly more complex, non-routine tasks, such planning may depend on a neural system [80–83]. Several psychopathology-based models tried to provide an integrative theoretical approach to the study of goal-directed behaviors. An initial bidimensional model proposed by Frith, [84] which is based on the distinction between positive and negative symptoms of schizophrenia, represents the most useful framework for the clinical, theoretical, and epistemological study of goal-directed actions. According to Frith, there are two main paths of action: those produced in response to environmental stimuli and those driven by a goal and a willed intention to act. The model proposes that impairments in these two paths may differ according to the dominant symptoms in people with schizophrenia. When negative symptoms are dominant, people with schizophrenia may have trouble connecting their goals and plans with the intention to act, thus leading to a failure of self-initiated actions. Instead, when positive symptoms

are dominant, stimulus-driven actions are disinhibited, leading to abnormal or perseverative behaviors. The Hardy-Baylé model [85] suggests that disorganized symptoms may be specifically linked to impairments in contextual processing leading to impaired social behaviors. A common impairment in goal-directed behaviors in people with schizophrenia is a deficit in the perception and contextual integration of others' actions with a tendency to perceive specific events rather than units of inter-connected behaviors relevant to the achievement of a goal, deficits that are associated with more severe disorganized symptoms [86, 87].

4.4 Passivity symptoms

Passivity experiences are hallmark symptoms of schizophrenia. They are characterized by the belief that one's thoughts or actions are influenced or controlled by an external agent. From this point of view, psychotic passivity experiences can be generally understood as a failure of the causal association between internal representations of action programs and the perception of external changes resulting from those actions [88]. Recent psychopathological models underlined the perceptual features of passivity experiences. These models suggest that passivity experiences in schizophrenia generally arise from dysfunctional processing of sensory perceptions resulting from own actions [89–91]. In accordance with this model, the action monitoring approach might provide a pathophysiological model of the self-monitoring failure involved not only in passivity experiences but also in other schizophrenic symptoms like, for example, auditory hallucinations which are possibly linked to defective monitoring of speech production [88, 92]. The feeling of control over own actions and their consequences, also known as the sense of agency, is thought to comprise multiple inter-related elements [93]. One element, self-agency, is the subjective awareness that one has initiated and executed one's actions, while other-agency is the representation of events caused by another person or agent [94]. Research pointed out that individuals with schizophrenia and passivity symptoms make many errors on motor tasks that measure agency when reporting the agent of their actions [88, 91]. These agency errors are thought to be caused by abnormal internal timing processes in schizophrenia [95]. Timing mechanisms are the neurological and neuropsychological processes that dictate the internal experience of the flow of time and play a key role in the coordination of neural circuits and events [96, 97]. Normal internal timing has an important role in the coordination of action elements and correct agency attributions [98]. Patients with schizophrenia and passivity symptoms have impaired timing and a broader perceptual binding window for sensory events when making action decisions, resulting in altered sensitivity to temporal incongruence. Along with internal timing problems that contribute to excessive associability with external sensory stimuli studies show that passivity symptoms are linked to deficits in body representations encompassing body image and body schema and changes in the sense of agency [99, 100].

4.5 Negative symptoms

Negative symptoms are defined as a weakening or absence of normal behaviors and functions related to motivation and interest, or verbal/emotional expression. The negative symptom domain consists of five key constructs: blunted affect, alogia (reduction in quantity of words spoken), avolition (reduced goal-directed activity due to decreased motivation), asociality, and anhedonia (reduced experience of

pleasure). Negative symptoms are common in schizophrenia and can occur at any point in the course of illness, although they are reported as the most common first symptom of schizophrenia [101]. Their prevalence in first-episode psychosis is high, 50–90% and 20–40% of schizophrenia patients have persisting negative symptoms [102]. Studies show that the majority of the patients diagnosed with schizophrenia spectrum disorders have at least one negative symptom while 41% of the patients present at least two negative symptoms [103]. In a 15-year prospective study of patients with schizophrenia, schizoaffective and affective disorders, the prevalence of negative symptoms was found to be as high as 75% for the first diagnosis category [104]. Moreover, negative symptoms along with other nonspecific clinical symptoms, such as depression, anxiety symptoms, social isolation, and school/occupational failure are often present during the prodromal phase of schizophrenia [105]. In a retrospective study assessing the onset of schizophrenia, negative symptoms were observed in 95% of patients seeking psychiatric assistance. Furthermore, in the pre-symptomatic phase of the disease, 32.7% of the subjects demonstrated social withdrawal with increasing self-isolation, 25.8% developed asthenoneurotic and asthenodepressive symptoms, and only 7% showed apatho-abulic manifestation [106]. The term negative symptom is a general, descriptive term that does not involve considerations about the symptom cause, longitudinal stability, or duration. Contrarily, primary and secondary negative symptoms refer to distinct subgroups of negative symptoms differing in their cause, longitudinal stability, or duration and differentiated through longitudinal observation. Primary and enduring negative symptoms refer to the symptoms that are intrinsic to schizophrenia, while secondary negative symptoms refer to negative symptoms occurring in association with, or presumably caused by, positive symptoms, affective symptoms, medication side effects, environmental factors, or other treatment- and illness-related aspects. The term deficit symptoms are used to refer to those negative symptoms that are present as enduring symptoms, present during and between episodes of positive symptom exacerbation, and observable regardless of the patient's medication status; they are caused by a specific disease process that is separate from the genetic and neurobiological factors that contribute to nondeficit schizophrenia [107, 108]. The deficit syndrome appears to remain stable throughout the course of illness, occurring in approximately 15% of patients experiencing the first episode of schizophrenia and in 15–20% of all cases of schizophrenia [109, 110]. In contrast to all other variants of the disease, patients with deficit schizophrenia consistently demonstrate the worst therapeutic and social prognosis [111]. Several studies confirmed a two-factor structure of negative symptoms (motivational-volitional and emotional-expressive disorders) which seems to be supported by the trajectory of their development in the course of the disease, including their long-term stability and relationship with functional outcomes [112, 113]. This classification may be explained by possible different neurophysiological and neurochemical mechanisms [114]. The severity of negative symptoms in schizophrenia has been linked to worse functional outcomes in areas such as occupational and academic performance, household integration, social functioning, and quality of life [115]. Also, a relationship between specific negative symptoms and impaired functioning has been outlined. Thus, avolition has been proposed as a key negative symptom construct related to functional deterioration while loss of motivation is thought to be associated with changes in social behaviors [101, 115]. Although the distinction between primary and secondary negative symptoms is important, managing negative symptoms and differentiating between the two categories of symptoms in schizophrenia is a major challenge for psychiatric services [116].

4.6 Psychomotor disturbances

The most common psychomotor disturbances encountered in schizophrenia are catatonic restlessness or agitation, posturing, waxy flexibility, negativism, mutism, or stupor [117]. Catatonia is a clinical syndrome characterized by the presence of multiple psychomotor disturbances. Catatonic phenomena comprise more than 40 affective, behavioral, and motor symptoms (e.g. stupor, mutism, waxy flexibility, rigidity, posturing, mannerism, negativism, and stereotypy) [118, 119]. The syndrome may present in two different subtypes: hypokinetic or retarded catatonia and hyperkinetic or excited catatonia. The hypokinetic type is associated with signs reflecting a paucity of movement, including immobility, staring, mutism, rigidity, and reduced oral intake, along with more bizarre features such as posturing, grimacing, negativism, waxy flexibility, echolalia or echopraxia, stereotypy and verbigeration [120]. Excited catatonia, on the other hand, is characterized by severe psychomotor agitation potentially leading to life-threatening complications such as hyperthermia, altered consciousness, and autonomic dysfunction [121]. Research reported a prevalence of catatonia in schizophrenia of 9.8% [122]. The outbreak of catatonia is usually acute, in a matter of hours or days, resulting in frequent use of the emergency departments and hospitalisation. However, in schizophrenia, the syndrome may have a subacute onset and a tendency to become chronic [123].

Mutism is an inability or unwillingness to speak, resulting in an absent or marked lack of verbal output. Similar to other symptoms within psychomotor disturbances, mutism rarely occurs as a single feature. It is commonly seen in association with disturbances in behavior, thought processes, affect, or level of consciousness [124]. Data from literature suggest that mutism in schizophrenia can be a consequence of positive symptoms (i.e. secondary to other psychotic symptoms like delusions and hallucinations, e.g., due to hallucinations commanding the patient to not speak) or part of disorganized behavior (i.e. as an extreme form of alogia). Mutism might develop in a patient, even involuntarily, to mitigate the distress caused by paranoid delusions or hallucinations or to disguise the illness and reduce the associated stigma [125]. A recent report suggests that religion and the psychological uses of silence appear to play a part in the occurrence of the symptom of mutism [126].

4.7 Psychomotor slowing

Psychomotor slowing (hypokinesia) is defined as a reduction in the initiation, amount, or speed of movement, slowness in planning and execution of motor tasks, and as a decrease in the total quantity of activities. This slowing in actions co-occurs with other motor symptoms such as spontaneous involuntary movements (e.g. dyskinesias) and is a core feature of the disorder that is present across the different stages of schizophrenia (i.e. prodromal, first episode, chronic stage) [127–129]. Psychomotor planning present in the early stages of schizophrenia involves deficient planning in motor sequences but intact motor action [130]. Patients diagnosed with schizophrenia can be observed to have longer thinking latencies and to be slowed in their responses or in their movements. In more severely affected patients, movements can be extremely slow, and psychomotor activity is sometimes reduced to the bare minimum, affecting their social-communicative interactions and daily-life activities. Both gross and fine motor performances have been reported to be affected [131]. The current state of knowledge suggests that psychomotor slowing in schizophrenia is related to a disturbance in cortico-subcortical interaction within the motor loop

compensated by premotor cortical activity [132]. Hypokinesia is frequently correlated with negative symptoms (avolition) and with parkinsonian signs [133]. Evidence suggests that psychomotor slowing is present in unaffected first-degree relatives and twins of patients and that it is associated with both symptoms and relevant structural and functional abnormalities across the schizophrenia spectrum, indicating that this feature may be a key endophenotype for schizophrenia. General psychomotor slowing in psychosis was found to become progressively worse from the prodromal stage to chronic schizophrenia [134]. Studies showed that hypokinesia is a prognostic factor for poor social, functional, and clinical outcomes [131].

4.8 Affective symptoms

In addition to positive, negative, and disorganization, patients with schizophrenia often exhibit affective symptoms, including depression and anxiety. Affective symptoms in schizophrenia can be particularly disturbing for the patients increasing the risk of suicide and diminishing quality of life [135]. Because of the frequent overlap between the negative symptoms and affective symptoms, it can be often difficult to distinguish between the two domains, especially when it comes to depressive symptoms. Studies pointed out that depressive symptoms may be present in as many as 80% of patients with schizophrenia while symptoms of mania are reported in as many as 20% of individuals with schizophrenia [136]. Despite this fact, only 10–30% of patients with schizophrenia spectrum disorders meet criteria for the schizoaffective disorder [137], with a significant proportion of patients meeting diagnostic criteria for both schizophrenia and mood disorders. A recent meta-analysis reported a prevalence of 28.6% for comorbid depression in schizophrenia [138]. In addition to patients who meet criteria for major depression, there are also a significant number of patients with schizophrenia who experience subsyndromal depressive symptoms. A study including a large, multicenter sample of older adults with schizophrenia spectrum disorder found that 78.1% of older adults had either subsyndromal or syndromal depressive symptoms with a higher prevalence of subsyndromal depressive in individuals with an onset of schizophrenia spectrum disorder before 40 years of age than in those with an age at onset between 40 and 60 years [139]. The most prevalent depressive symptoms reported in individuals with schizophrenia were depressed mood, morning depression, diminished work and activities, guilt, anergia, psychological anxiety, observed depression, initial insomnia, and hopelessness [140]. Up-to-date literature highlighted that comorbid depressive symptoms are present in all phases of schizophrenia [141] and they correlated with a higher risk of suicide [142, 143], worse psychosocial functioning [144], and poorer quality of life [145].

4.9 Cognitive symptoms

Although cognitive impairment is not among the diagnostic criteria in schizophrenia it is considered to be a core feature of schizophrenia. Deficits are moderate to severe across several domains, including attention, working memory, verbal learning and memory, executive functions, and social cognition. These deficits pre-date the onset of frank psychosis and are stable throughout the course of the illness in most patients [146]. The presence of cognitive deficits observed from the first episode of the illness suggests they are not due to exposure to neuroleptic medication [147]. Results from studies assessing the longitudinal changes in cognition for patients with schizophrenia support the presence of a cognitive decline that progresses after the psychosis onset.

Thus, a recent study with 10 years of prospective follow-up of patients with first-episode psychosis found a progressive decline in IQ and in specific neurocognitive domains, such as verbal knowledge and memory in patients who were later diagnosed with schizophrenia [148]. Neurocognitive impairment in schizophrenia is also shown to be associated with neroanatomical alterations. A recent study demonstrated that cortical thickness in bilateral superior frontal and right transverse temporal regions correlates positively with cognitive performance (particularly attention/vigilance) suggesting that thickness in these regions is of specific importance for cognitive performance in schizophrenia, possibly reflecting compensatory processes [149]. The prevalence of cognitive impairments in patients with schizophrenia is high, with more than 80% of patients showing significant impairment [150]. Mascio et al. [151] reported a prevalence of 55% for one or more cognitive problems and a prevalence of 60% for at least one cognitive domain impairment in their large sample study. The cognitive dysfunctions within the research were also strongly correlated with several socio-demographic factors (gender, education, ethnicity, marital status, and employment) as well as adverse clinical outcomes.

Attention deficits are reported among most pervasive neurocognitive features and have a role in predicting functional outcomes. The components most studied in schizophrenia are selective attention and sustained attention. Attention operates to activate processes that enhance the processing of relevant signals, inhibits irrelevant signals in a way that strengthens resistance to interference and distractibility, and coordinates the realization of concurrent tasks by distributing processing resources. Decreased inhibition of interfering information seems to be a hallmark of cognitive disturbances in schizophrenia [152].

Memory is the cognitive area showing the most pronounced deficits with working memory and episodic memory appearing to be the most impaired. Working memory has been defined as the ability to transiently hold and manipulate information to guide goal-directed behavior. Its contents are constitutively updated, monitored, and manipulated in response to immediate processing demands [153]. Results from a large meta-analysis pointed to working memory deficits in task performance for patients with schizophrenia in all modalities examined showing that these deficits are robust across different tasks, modalities, and subject variables, though there appear to be more consistent and greater impairments in the visuospatial domain than other domains [154]. Similarly, another meta-analysis found statistically significant impairment across the domains of phonological, visuospatial, and central executive working memory, deficits which were not explained by discrepancies in current IQ between schizophrenia and control groups, duration of illness, or use of antipsychotic medications [155]. The working memory impairments appear to reflect alterations in the neural circuitry of the dorsolateral (DLPFC) prefrontal cortex [156]. Findings from multiple studies have clearly implicated pathology of the dorsolateral prefrontal cortex (DLPFC) as playing a central role in the pathophysiology of SZ, particularly with regard to key cognitive features such as deficits in working memory and cognitive control [157]. Working memory deficits, particularly in terms of impaired encoding and maintenance, are found in a disproportionate number of schizophrenia patients. Studies indicate that impaired working memory is a trait characteristic of schizophrenia and present from the prodrome to the chronic stages of the disorder. There is also evidence that working memory impairment is genetically transmitted and also present in unaffected relatives of schizophrenia probands at a higher rate than in the general population. All those factors lead to the assumption that working memory impairment is an excellent candidate for endophenotypic marker status in

terms of schizophrenia liability [158]. Episodic memory is a category of long-term memory defined as a record of a person's experience that includes temporally dated information and spatio-temporal relations [159]. Episodic memory is a cognitive area that is consistently impaired in schizophrenia from prodromal to chronic phases but is also found in first- and second-degree relatives of patients. Episodic memory impairment was linked to deficits in both encoding and retrieval processes [160]. Context processing in episodic memory reflects the ability to encode and retrieve relationships among event features, such as when, where, and with whom they occurred. Research suggested that disruptions in such processing may underlie the episodic memory impairments observed in schizophrenia [161, 162]. Magnetic resonance imaging studies revealed an apparent disruption in frontotemporal connectivity connected to episodic memory dysfunctions [163].

4.10 Executive functions

The term executive functions comprise a diverse set of cognitive capacities meant to guide, monitor, and control our actions and mental processes to meet particular goals in a purposeful manner. Executive functions may be defined as higher-order neurocognitive functions consisting of abilities to plan and structure goal-directed activity and problem-solving behavior in a strategic, flexible manner or as merely the ability to respond in an adaptive way to novel situations [164, 165]. These complex cognitive processes are crucial for many aspects of daily functioning, and their dysfunction plays a significant impact on academic, vocational, emotional, social, and adaptive functioning [166]. Impairment of executive functions is one of the most commonly observed deficits in schizophrenia through the various disease stages. Cognitive deficits in learning, memory, processing speed, and executive functioning are identified not only in chronic schizophrenia patients but also as early as the first episode of psychosis or even before the prodromal state [167–169]. The patients with the first psychotic episode show cognitive deficits across almost all cognitive domains, which are comparable to deficits displayed in the fully established disorder, and individuals at clinical high risk show intermittent degrees of deficits [170]. These deficits include impairment in tasks measuring conceptualization, planning, cognitive flexibility, verbal fluency, ability to solve complex problems, and working memory. The anatomical substrate associated with executive function alterations involve mostly the dorsolateral prefrontal cortex which is responsible for decision-making, and self-regulation of behavior [171]. Executive dysfunction in schizophrenia is an important clinical and social problem. Impairments in monitoring, attention shifting, planning, inhibition, rule generation, abstract thinking, and working memory, as well as the loss of skills required for the performance of complex tasks, can negatively impact patients' social and professional functioning as well as their quality of life [172].

Social cognition represents the cognitive capability to perceive, categorize and interpret social behavior of other people and concerns the various psychological processes that enable individuals to take advantage of being part of a social group. Social cognition is composed of multiple potential domains and multiple tasks can thus be used to measure it [173]. Several social cognitive subprocesses have been studied in individuals with schizophrenia, including face perception, voice perception, motor resonance, affect sharing, mentalizing, emotion experience, and emotion regulation [174]. While it is widely acknowledged that social cognition is a major determinant of functioning in schizophrenia with both direct and indirect effect, mediating

neurocognition, it is less clear which domain of social cognition most strongly affect outcomes [175]. Researchers have identified four main domains of social cognition in schizophrenia: social perception, emotion processing, theory-of-mind/mentalizing, and attributional bias. Social perception refers to identifying social cues and making accurate inferences about social roles, rules, context, and relationships. Emotion processing encompasses the ability to identify and understand emotions of others and to manage emotions of oneself. Theory of mind (ToM) is the ability to reason about mental states and understand intentions, dispositions, emotions, and beliefs of both oneself and others. Attributional style/bias indicates the way in which individuals infer the causes of particular social events [176]. Studies in the field of social cognition provided growing evidence that emotion processing, mentalizing, and social perception impairments are core features of schizophrenia that are present at a comparable level in recent-onset patients, not secondary to positive symptoms or medication effects, and relatively stable over the course of illness, and detectable at attenuated levels in unaffected biological relatives of patients and in prodromal phases of the illness [177].

4.11 Other symptoms

In addition to the well-known symptoms criteria that characterized schizophrenia, there are often other symptoms that accompany psychotic episodes such as agitation, aggression, and hostility. Despite the fact that these symptoms seem alike they are considered conceptually different [178].

Agitation represents a state characterized by increased arousal with excessive motor and verbal activity, which seems very distressing to the patient. In the DSM-5, agitation is defined as a heightened motor activity linked with a feeling of inner tension [179].

On the other hand, aggression consists of an overt behavior with the intention of inflicting noxious stimulation, often with a destructive behavior, represented by verbal injuries, destroying objects, harming others, or directing aggression toward their self. Some patients that are agitated are not mandatory also aggressive, but the situation could escalate and from an agitated schizophrenic person, you could expect aggressive behavior [180]. Many studies, consider the terms violence and aggression to be the same, the difference is made only by the domains where they are used, as aggression usually appears in psychological studies or biomedical research, and violence is a term preferred by criminalists, sociologists, or police [181]. For schizophrenic patients, both of these symptoms, agitation and violent actions, represent the common reason for unvoluntary psychiatric hospitalizations, but from the population of individuals that have a diagnostic of Schizophrenia most of them are not violent, even more, they are likely to become victims than the cause of violent crimes [182]. Other studies compared the violence risk between schizophrenic patients and the general population, results found the risk to be elevated for persons with schizophrenia, actually two times higher, and an increase by nine times in patients associated with substance abuse comorbidity [183].

The last term mentioned as hostility, is a more complex symptom with a variety of meanings, including irritability, extreme suspiciously, demanding attitude, and refusal to cooperate. Specific hostility manifests during an acute phase of schizophrenia, it can be measured by the PANSS positive subscale and is usually associated with agitation [184].

4.11.1 Aggression/violence

From an interesting point of view, the link between psychotic schizophrenic patients and the symptom represented by violence is frequently discussed. There is a common question addressed to mental health clinicians regarding a patient's risk for future violence, the easement of which depends on many factors such as conditions of the evaluation, the period of time for which violent behavior is being predicted, and the most important factors would be the characteristical symptoms of schizophrenia [185]. Two of these symptoms include persecutory delusions and command auditory hallucinations, which were found in several studies as important predictors of violent behavior [186]. Nolan et al. conducted a study on schizophrenic patients with violent acts and found that more than 20% of assaults were attributed to the presence of positive symptoms [187]. More specific, false fixed beliefs of patients being followed, spied on, poisoned, threatened in some way, or the idea of losing control to an external force, such as the patient's mind being dominated by machines, or different power sources influencing him, these patients were 2 times higher at risk for engaging in aggressive actions, and even more likely predispose to violence when males were the gender evaluated [188]. In a recent study, Appelbaum et al. tried to analyze the relation between delusional content and aggression and found that the persecutory theme was significantly associated with the risk of taking action in response to the delusions [189]. Other studies pointed out, that there is an intermediate variable that links violence to delusions, and this symptom is anger that rises as a response to delusions, considered to be a key factor in this relationship [190]. The second symptom that studies referred to as being implied in the commitment of a violent act was the directive auditory hallucinations, experienced by almost half of the schizophrenic patients [191]. As a particularity, most of the command hallucinations are usually nonviolent, this is more important because researchers found out that patients are more prone to obey nonviolent commands than destructive and aggressive instructions [192]. On the other hand, a study conducted by McNeil et al. showed that from a group of 103 schizophrenic patients, a percentage of 33 reported they have had command auditory hallucinations containing instructions on how to harm people around them, but this phenomenon happened mostly during the preceding year, in general in the first years of disease evolution, and a percent of 22 of the evaluated patients actually complied with the orders given. Also, in this study authors agreed that the presence of command hallucinations, rise more than twice the risk of harming someone in the case their patients [193]. Other studies, achieved by completing a list of factors that are highly associated with the action of obeying the command hallucinations, and these include the coexistence of both delusions and auditory hallucinations, delusions that are tied to the hallucinations, that are congruent with the voices, the knowledge of the voice identity, believing that it is real, with superior power, or that it brings a benefit, not having resources in dealing with the voices, feeling out of control regarding this aspect, and the negative content of hallucinations [194–196]. In general conclusion, the majority of schizophrenic patients do not associate violent acts, but there are some data that found a greater number of total criminal convictions in patients with schizophrenia when they were matched with controls from the general population [197]. Also, patients with schizophrenia can't be characterized by the type of violence they committed; it is important to take into consideration multiple factors that have a role in this behavior [198].

4.11.2 Agitation

As mentioned earlier, agitation is a broad term, with high heterogeneity, considered more of a syndrome, with multiple causes, including Schizophrenia, defined by restlessness that can transform into excessive motor movements, often with no purpose, that has an unstable clinical course and is associated with sensible responses to internal or external stimuli [199]. The consequence of an agitation episode includes a breakthrough the therapeutic alliance, which usually is temporary and needs a fast intervention. The major risk of an agitation episode is the progression of it, which can lead to violence and also increase the hospital resources as the majority of agitated patients end up hospitalized [200]. A study estimated that 14% of an inpatients population of schizophrenia patients presented agitation, moreover the study found that approximatiely 20% of patients have episodes of agitation during their lifetime [201]. Besides the reactive agitation that can be directly connected to the content of the delusions, or triggered by the affective symptoms that accompany hallucinations, agitation in schizophrenia can appear in association with comorbid substance use or intoxication, environmental threats, or induced akathisia by the antipsychotic treatment [202]. A rare situation is the agitation of a schizophrenic patient with predominantly negative symptoms, the risk of agitation increases if the patient is noncompliant with treatment, is hospitalized many times, and presents positive symptoms [190].

Conflict of interest

The authors declare no conflict of interest.

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