Chapter

Clinical Staging in Schizophrenia Spectrum Disorders

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Abstract

The aim of this chapter is to summarize the state-of-the-art knowledge of clinical staging in schizophrenia spectrum disorders. Clinical staging has been introduced to psychiatry in the past two decades. Its primary goal is to divide the course of the disorder into recognizable stages based on seriousness, development and symptom characteristics in order to better predict prognosis and to adopt the most appropriate treatment strategies. The first staging model was developed in 1982. Since then several distinct concepts of clinical staging in psychiatry have emerged. To date, there is no clinical consensus regarding which staging model is the gold standard, nonetheless when merging them together an integrated staging concept arises. The integrated staging model of schizophrenia spectrum disorders is composed of four stages. The chapter will introduce the different staging models in a historical order as well as present the integrated staging model detailing the characteristics, timeline and dominating symptoms of each stage. Appropriate treatment strategies for the distinct stages will also be outlined.

Keywords: schizophrenia spectrum disorders, clinical staging

1. Introduction

Schizophrenia spectrum disorders (SSD) are a collection of psychotic disorders defined by abnormalities in one or more of the following symptom domains: hallucinations, delusions, disorganized thinking, catatonic behavior and negative symptoms [1]. The word 'spectrum' has been first added in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [1, 2], reflecting the notion that psychiatric disorders lie on a spectrum with no sharp boundaries between them [3, 4]. According to the DSM-V, SSD include schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychotic disorders due to another medical condition or substance/medication, and unspecified or specified schizophrenia spectrum and other psychotic disorders [1]. The prevalence rate for SSD is estimated to be 7 per 1000 [5], with higher rates in men than in women [6]. Currently, there are over 21 million people who are affected by this condition [7]. Diagnosis is made along a spectrum of symptoms and severity via clinical interviews as no confirmatory and diagnostic laboratory nor radiological tests are available [2]. Although schizophrenia represents only about one third of the SSD cases [8], it is the most researched disorder out of all [9].

Besides the internationally used diagnostic systems such as DSM or the International Classification of Diseases (ICD), there is another, complementary form of classifying psychiatric disorders called clinical staging [10]. First introduced in cardiology and oncology [11], clinical staging is different from the conventional diagnostic practices in a sense that it does not only define the extent of illness progression but also where a patient lies within the course of the disorder [10]. The basic assumptions of clinical staging are that (a) treatment in the early stages of the disorder is more efficient, (b) patients experience greater symptom severity in the later stages of the illness, and (c) the process of transferring to a later stage is connected with a typical clinical profile [12]. Although clinical staging as a model for classifying the development of disorders had been ignored in psychiatry in the past, several concepts have emerged in the past few decades [11]. The primary aim of clinical staging is promoting recovery in the early stages of psychiatric disorders as well as preventing progression to later stages [10]. Importantly, clinical stages of psychiatric disorders can be defined by many different aspects from symptom severity and persistence, through neurobiological changes, to the emotional processes that happen within the patient [10]. In this chapter, we aim to present, summarize and synthetize the clinical staging concepts of SSD through a systematic review.

2. Clinical staging concepts of schizophrenia spectrum disorders

The systematic review was conducted in November 2020 using the MEDLINE, EMBASE and Cochrane databases from 1999 with the following search terms: 'stage/staging', combined using the Boolean 'AND' operator with 'psychiatric disorder/schizophrenia/ psychosis/psychotic disorder'. Additionally, a manual search was also performed. Titles and abstracts were screened by one of the authors (Zs.D.) and relevant articles were independently assessed by two authors (A.B. and Zs.D.). English-language articles published in peer-reviewed journals describing complete staging models on SSD or psychiatric disorders, in general, were eligible to be included in the chapter (inclusion critera).

As a result of the systematic search, a total of 2045 articles were identified. After reviewing the abstracts to exclude those which clearly did not meet the above-mentioned criteria, 27 articles remained. Of these, 9 articles were included in the final review.

2.1 The Hoffman staging concept

Although most reviews do not count the staging model of schizophrenia proposed by Brian Hoffman in 1982, it can be considered to be the first attempt to divide the course of the disorder into recognizable stages [11, 13]. In his concept, Hoffman described the stages of schizophrenia based on the patient's reaction to his or her symptoms, beginning with anxiety (stage 1) and ending with acceptance (stage 5) (**Figure 1**) [13]. In the early phase of schizophrenia, before the first episode, the patient goes through considerable changes in their behavior and experience disturbance in thinking which can result in fear and anxiety or even anger [13]. Then, during the first episode of schizophrenia, the patient experiences a stage of denial (stage 2) where they no longer acknowledge that they have problem mainly due to excessive positive symptoms [13]. The third stage is about ambivalence, where the patients begin to have some insight into their disorder but might reject medication and go through multiple hospitalizations [13]. Before the final stage, acceptance (stage 5), there is a stage of depression (stage 4) where the

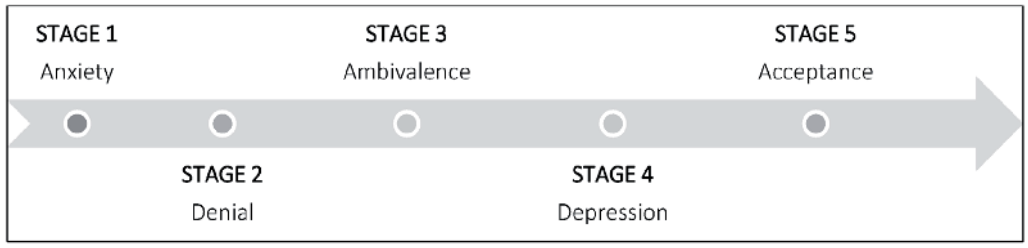

Figure 1.
The Hoffman staging concept.

patient realizes the seriousness of the disorder [13]. During this stage it is important to monitor the patient to prevent suicide and alter the medication doses accordingly [13]. Although this staging concept is different from the others, it recognizes the importance of taking into account the patient's emotional response to his or her symptoms and the progression of the disorder which is now considered vital in a modern, person-centered care [14].

2.2 The Fava and Kellner staging concept

The first staging model of schizophrenia is attributed to Fava and Kellner who proposed their concept in 1993 [11, 15]. According to their model, schizophrenia starts with a prodromal stage (stage 1), where mainly negative and affective symptoms are present with considerable deterioration in functioning (**Figure 2**) [15]. The second stage is the acute episode of schizophrenia, dominated by positive symptoms [15]. The residual or third stage is described by the absence of positive symptoms and increased presentation of negative symptoms (resembling to stage 1) [15]. Finally, the authors differentiate between subchronic (stage 4) and chronic (stage 5) phases based on the duration of the illness; if it persists more than 6 months but less than 2 years then it is stage 4, if it is present for more than 2 years then it is stage 5 [15]. Additionally, it is also emphasized that a "rollback phenomenon" can also occur where patients in stage 2 progress to stage 1 instead of stage 3 and achieve remission eventually [15].

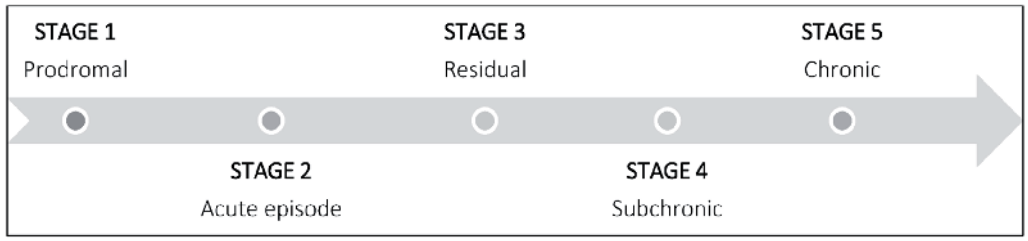

Figure 2.
The Fava & Kellner staging concept.

2.3 The staging concepts of Lieberman and Insel

According to Lieberman, schizophrenia is composed of three pathophysiologic phases described in four stages [11, 16]. The first is the neurodevelopmental or premorbid phase which begins in early adolescence or even sooner and is characterized by mild cognitive and social impairments (stage 1) (**Figure 3**) [16]. Then the second phase is the neuroplastic phase which can be further divided into prodromal, and onset and deterioration sub-phases and is referred to as stage 2 and 3 in the model,

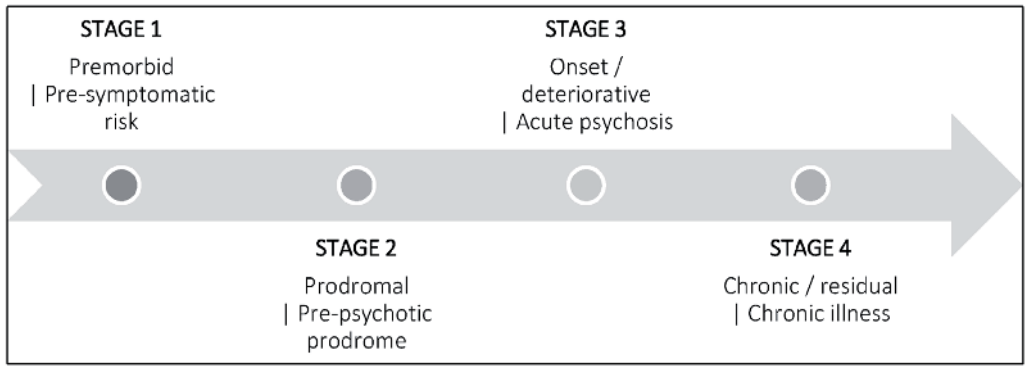

Figure 3.
The staging concepts of Lieberman and Insel.

accordingly [16]. Throughout the prodromal stage besides the above mentioned deficits, mild psychotic symptoms might be already present which lead to a full-blown psychosis during the onset (stage 3) [16]. The final pathophysiological phase is the neuroprogressive one, which is described as the chronic or residual stage characterized by considerable negative and cognitive symptoms as well as further psychotic episodes [16]. Lieberman recommends the use of antipsychotic medication only after the onset of the first psychotic episode [16]. Similarly, to Lieberman, 9 years later Insel also identified the same stages of schizophrenia albeit with slightly different names; pre-symptomatic risk (stage 1), pre-psychotic prodrome (stage 2), acute psychosis (stage 3) and chronic illness (stage 4) [17, 18]. In his staging concept, he also details the features, diagnosis, disability and intervention at each distinct stage [17].

2.4 The Singh staging concept

The staging concept by Singh and colleagues focuses predominantly on the chronology of psychosis onset [19]. Their model beings with the prodrome (stage 1), which is further divided into two parts; a period of unease (P1) and a period of non-diagnostic symptoms (P2) [19]. Then, the second stage is when the first psychotic symptoms appear, which refers to positive symptoms such as delusions and hallucinations [19]. Before receiving a definite diagnosis (stage 4), there is an intermediate stage where the symptoms build up, and there is already a diagnostic impression of schizophrenia (stage 3) [19]. Although this staging concept does not describe a complete model of SSD, its detailed description of the beginning of the disorder made it worthy of being included in this review (**Figure 4**).

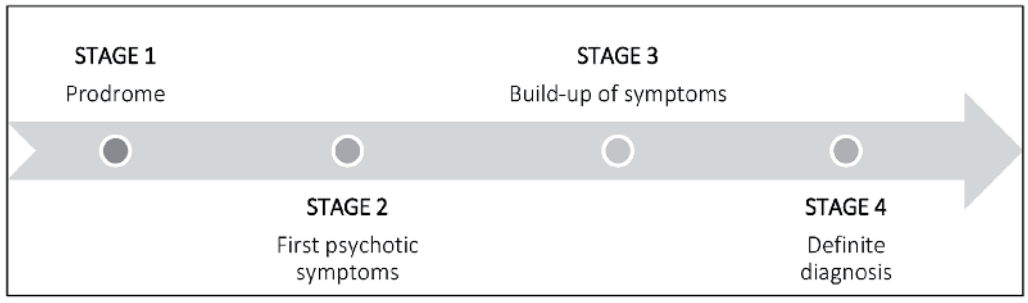

Figure 4.
The Singh staging concept.

2.5 The Agius staging concept

The simplest and probably most known concept of schizophrenia staging was described by Agius after about a decade of the Lieberman model [12]. Based on his research, the development of schizophrenia was divided into three distinct stages; the prodrome (stage 1), then the first episode (stage 2) and finally, the chronic phase (stage 3) (**Figure 5**) [12]. Although it was not included in the model as a separate stage, Agius also agrees on the fact that there is a premorbid phase before the prodrome [12]. It is also emphasized that the treatment of schizophrenia needs to be in accordance with the different stages of the disorder in order to achieve the desired outcomes [12].

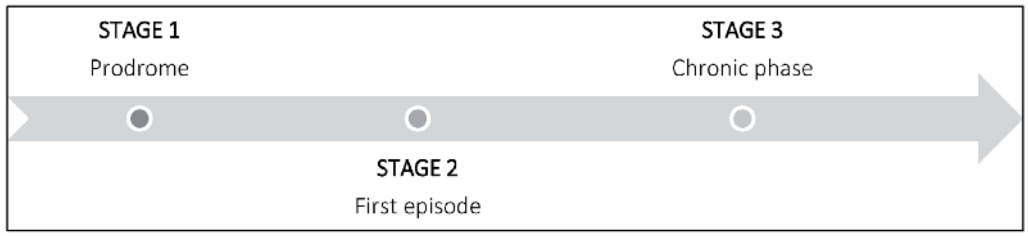

Figure 5.
The Agius staging concept.

2.6 The McGorry staging concept

One of the most developed and referenced [20–24] staging model of schizophrenia was proposed by McGorry and colleagues [10, 11]. This concept starts with stage 0, where the patient has no current symptoms yet, but an increased risk of psychotic disorder is present (**Figure 6**) [10]. Then, stage 1 (mild and moderate symptoms) is divided into two substages; 1a with mild and non-specific symptoms and 1b with subthreshold or moderate symptoms [10]. The first episode of psychosis defined to be at stage 2, followed by the three substages of stage 3 (incomplete remission and relapse(s)); incomplete remission (3a), relapse of psychotic disorder (3b) and multiple relapses (3c) [10]. Finally, stage 4 represents a persistent and severe illness [10]. Importantly, this staging concept can be applied not only to patients with SSD but also to patients with other severe mood disorders such as depression or bipolar disorder [10]. Besides the description of different stages, McGorry and colleagues also provided information regarding the potential interventions as well as indicative biological and endophenotypic markers to each stage in their framework [10].

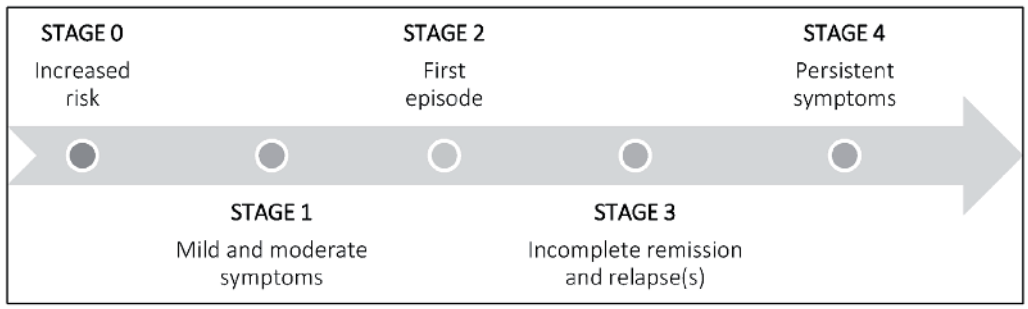

Figure 6.
The McGorry staging concept.

2.7 The Cosci staging concept

In 2013, Cosci and colleagues – similarly to this book chapter – aimed to summarize and integrate the staging models of schizophrenia, and other major psychiatric disorders through a systematic review and came up with a general staging concept that is composed of four stages (**Figure 7**) [11]. The model starts with a prodromal phase (stage 1) and follows the basic stages of psychiatric disorders in a longitudinal fashion with stage 2 being the acute manifestation, stage 3 the residual phase and stage 4 the chronic phase [11]. In contrast to McGorry [10] and Lieberman [16], the premorbid or increased risk phase was not included in this concept as they found no adequate support from the literature and argued that it has less clinical relevance as it can be only appraised retrospectively [11].

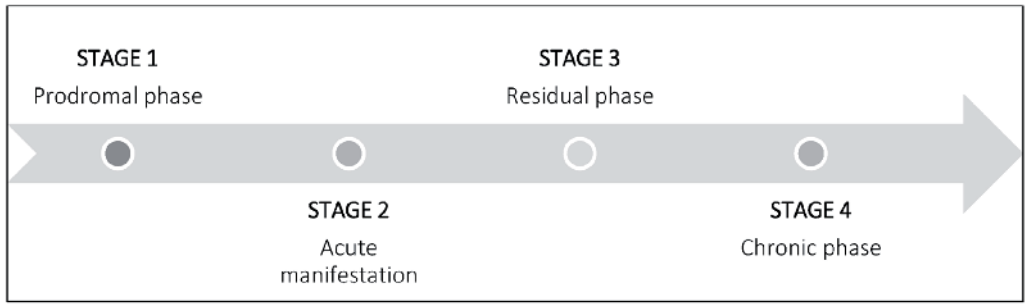

Figure 7.
The Cosci staging concept.

2.8 The Fountoulakis staging concept

A novel concept of clinical staging in schizophrenia was proposed by Fountoulakis and colleagues in 2019 using the Positive and Negative Syndrome Scale (PANSS) and the 5-factor model (a model based on the notion that schizophrenia is characterized by positive, negative, cognitive, affective and hostility symptoms) [25]. They aimed to develop a staging concept empirically through analyzing a very large sample (n = 2358) of stabilized schizophrenia patients with varying ages [25]. Based on the results, they identified 4 major stages of schizophrenia (**Figure 8**), starting with stage 1, dominated by positive symptoms. Besides describing the most influential symptom domain of each stage, they also provided a timeline of the disorder. According to this timeline, stage 1 lasts about 3 years on average [25]. In this first stage, excitement and hostility symptoms were found to increase over time and becoming the leading symptom group of stage 2, that lasts

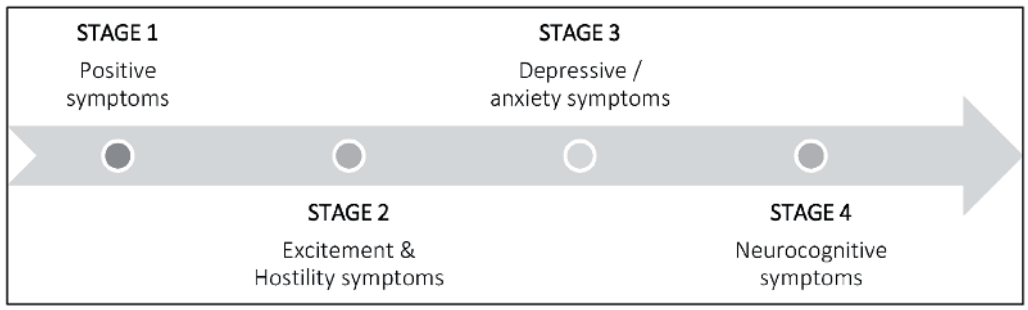

Figure 8.
The Fountoulakis staging concept.

about 9 years on average [25]. Throughout the first two stages, negative and depression/ anxiety symptoms were stable and started to increase steadily around the end of stage 2 [25]. Importantly, the second stage was further divided into 2 substages: stage 2a and 2b [25]. The latter lasts about 6 years and is described by the rise of negative, depressive and cognitive symptoms. During stage 3, which lasted 13 years on average, the most dominant symptoms were the depressive ones [25]. In the first phase of stage 3 (3a), hostility symptoms were found to decline, while negative and cognitive symptoms were increasing [25]. Then, in the second part of stage 3 (3b), positive and hostility symptoms almost disappeared [25]. Finally, the fourth stage was found to be characterized by cognitive symptoms, and according to their timeline, it begins 25 years after the first episode on average [25]. Similarly to the previous stages, stage 4 is also divided into 4a and 4b substages; 4a lasts about 15 years on average and is described by the robust increase of negative and cognitive symptoms, while 4b starts about 40 years after the first onset and is found to be dominated by mainly the neurocognitive deficits that the patients experience [25].

2.9 Similarities and differences between the historical staging concepts

A summary of the reviewed historical staging models of SSD is presented in **Table 1**. Interestingly, only about half of the staging concepts begin with a premorbid phase (Singh starts with prodrome which has a sub-stage, P1, that can be regarded as a premorbid phase), and except Fountoulakis and colleagues, all models have a prodromal phase. Importantly, the acute and chronic phase is present in all models (the Singh staging concept is not counted here, as it focused on the beginning of the disorder), while only again about half of the models included a residual or subchronic phase. In terms of the underlying pathophysiological changes of SSD in relation to the different stages, evidence from brain imaging studies provide support for the general notion that abnormalities are more prevalent in later stages than in earlier ones, these abnormalities are progressively worsening while patients advance from an earlier to a later stage and finally, supportive treatments such as essential fatty acid supplementation are more effective in the beginning of the disorder [26, 27]. Nonetheless, it is challenging to validate one particular model via pathophysiological changes described by brain abnormalities or other biomarkers as there is considerable heterogeneity in the clinical and pathophysiological picture of SSDs [27]. For instance, the size of the ventricles does not necessarily correlate with the severity or progression of symptoms nor signposts the patient's response to treatment [27].

	Premorbid phase	**Prodromal phase**	**Acute phase**	**Residual phase**	**Chronic phase**
Hoffman	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
	Anxiety	Denial	Ambivalence	Depression	Acceptance
Fava & Kellner		Stage 1	Stage 2	Stage 3–4	Stage 5
		Prodromal	Acute episode	Residual & Subchronic	Chronic
Lieberman	Stage 1	Stage 2	Stage 3		Stage 4
	Premorbid	Prodromal	Onset / deteriorative		Chronic / residual
Insel	Stage 1	Stage 2	Stage 3		Stage 4
	Pre-symptomatic risk	Pre-psychotic prodrome	Acute psychosis		Chronic illness

	Premorbid phase	Prodromal phase	Acute phase	Residual phase	Chronic phase
Singh	Stage 1 (P1)	Stage 1 (P2)	Stage 2–4		
	Prodrome	Prodrome	First psychotic symptoms & Build-up of symptoms & Definite diagnosis		
Agius		Stage 1	Stage 2		Stage 3
		Prodrome	First episode		Chronic phase
McGorry	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	Increased risk	Mild and moderate symptoms	First episode	Incomplete remission and relapse(s)	Persistent symptoms
Cosci		Stage 1	Stage 2	Stage 3	Stage 4
		Prodromal phase	Acute manifestation	Residual phase	Chronic phase
Fountoulakis			Stage 1–2	Stage 3	Stage 4
			Positive, excitement & hostility symptoms	Depressive & anxiety symptoms	Neuro-cognitive symptoms

Table 1.
Summary of the reviewed staging concepts.

3. The integrated staging model of schizophrenia spectrum disorders

Although the reviewed historical staging concepts of SSD are slightly different from one another, they can easily be integrated into one coherent model. To start with, there is one clinical stage that is present in all concepts: the first episode of psychosis. This acute phase can be interpreted as a milestone that divides the course of the disorder into a *before* and an *after* phase and so can be set as the first stage of the disorder. It is also the stage where the patient is most likely to be recognized and treated for the first time.

Most, but not all clinical staging concepts deal with the *before* phase, officially called the prodrome, since it is often determined retrospectively and is highly debated from the perspective of treatment [11]. Nonetheless, evidence is emerging regarding early interventions and it might become more and more relevant in the future [28]. Hence, in the integrated staging model, the prodromal phase is regarded as stage 0, representing its importance but debated nature. In many of the reviewed staging models, prodrome was further divided into substages, i.e. increased risk or pre-morbid phase, and mild symptoms or prodromal phase [10, 16, 17]. Although these substages might be important in the development of SSD, recognizing them may be even more challenging and unnaturalistic in real-life settings [11, 28, 29]. Thus, in the integrated model, this stage is not subdivided further.

Similarly, to the *before* phase, there are slight differences between the historical staging concepts in terms of what happens *after* the first onset of psychotic symptoms. Some argue that there is only one stage after the acute manifestation

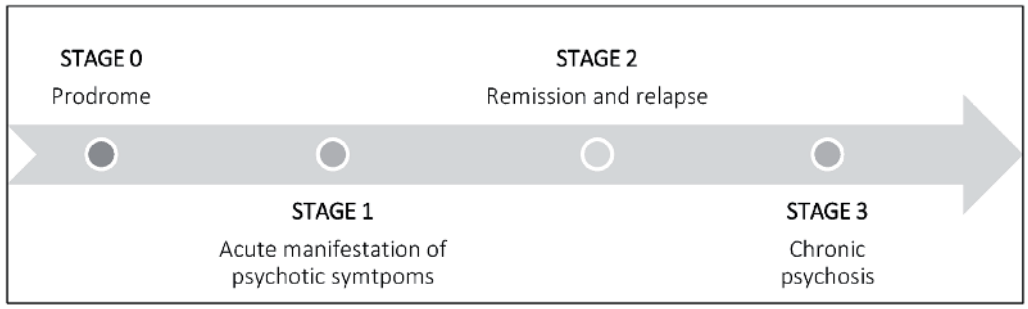

Figure 9.
The intergraded staging model of schizophrenia spectrum disorders.

of symptoms [12, 16, 17] while others define three or even more distinct stages [13, 15, 25]. The most influential models opt however for two subsequent stages [10, 11, 19]; a residual or pre-chronic stage characterized by incomplete remission, relapses as well as depressive symptoms, and a chronic stage with persistent symptoms dominated by neurocognitive deficits. In the integrated staging model these phases represent stage 2 (remission and relapse) and 3 (chronic psychosis), respectively (**Figure 9**).

3.1 The prodrome (stage 0)

In the integrated staging model of SSD, stage 0 is called the prodrome. This is a period of the disorder when some mild or even moderate symptoms are present, however there is no sign of full-blown psychosis yet [10]. Given the fact that this phase is just preceding the first onset of psychotic symptoms, the prodrome is a retrospective concept that can be mainly recognized and defined afterwards [28, 29]. In terms of timeline, the prodrome can last from weeks to even years, but most typically, its duration is about a year [28].

During the prodrome, the patient goes through considerable changes in their behavior and might start to experience disturbance in thinking which in turn results in anxiety or even anger [13]. The symptoms present during this time are heterogenous; mostly negative symptoms such as anhedonia, asociality or amotivation along with changes in perception, mood, beliefs and cognition [29, 30]. In terms of neurobiological changes, there are signs of abnormal dopamine synthesis, prefrontal cortex (PFC) dysfunctions and gray matter volume reductions in several brain regions including the PFC, hippocampal gyrus and lateral temporal lobe [31–34].

Given the notion that the earlier the treatment is received, the better the prognosis of SSD, there is considerable interest in starting pharmacological interventions during the prodrome [28, 29]. However, the main problem with this concept is the potential number of false positives, those individuals who, despite having symptoms and distress, will not develop psychosis after the prodromal period [29]. Thus, many argue that prescribing antipsychotic medication to these individuals is highly questionable from an ethical perspective, claiming that even the newest antipsychotic medications are not without side effects, might induce cognitive harm and can stigmatize the patient for life [28, 29, 35].

To overcome the barrier of treating individuals in the prodrome while also excluding the false positives, there are tendencies of developing new criteria that can accurately detect patients who are in an 'ultra-high risk' (UHR) mental state and hence are most likely to develop psychosis and benefit from pharmacological treatment too [29, 36]. An example of such criteria is the Personal Assessment and Crisis Evaluation (PACE), which defines someone at UHR of psychosis if they

have one or more of the following diagnosis; "(a) attenuated psychotic symptoms, (b) brief limited intermittent psychotic symptoms, (c) a significant decrease in functioning (maintained for at least a month) with either schizotypal personality disorder or a first-degree relative with psychotic disorder" [28, 36, 37].

The aims of early intervention in the UHR group are threefold: first, to alleviate the symptoms that the patient experiences; second, to decrease the risk of transitioning to a first episode of psychosis; and third, to reduce the time before starting an antipsychotic treatment after the onset of psychosis [36]. To date, there are only a few pharmacological trials with antipsychotic medication in this patient group, both indicating a tendency for a decreased rate of conversion to psychosis after one year [38, 39]. Nonetheless, more research is required to understand the risks and benefits of pharmacological treatment during the UHR period. Meanwhile, according to current guidelines the use of antipsychotic medication during the prodrome is only recommended in case of the more complex cases [40, 41], while the recommended interventions are family psychoeducation, individual or group cognitive behavior therapy, active substance use reduction and neuroprotective agents such as omega-3 [10].

3.2 The onset (stage 1)

The first stage of the integrated staging model of SSD starts with the acute manifestation of psychotic symptoms or in other words the onset of the first episode of psychosis. Throughout this stage of the disorder patients experience predominantly positive symptoms such as hallucinations, paranoia or delusions and are likely to be in denial of accepting that there is something wrong and that they need medical help [10, 13]. This denial often manifests in aggression or agitation and might as well result in the hospitalization of the patient [42]. Besides the dominating positive symptoms, negative symptoms such as alogia or asociality and hostility may also be present [16, 25].

Currently, there is no strong scientific evidence on the cut-off point for the end of the first episode, nonetheless, it is estimated to be within the first 2–5 years following the onset of the psychotic symptoms [43–45]. Indeed, Fountoulakis and colleagues found that the first stage of SSD lasts 3 years on average [25].

The main treatment goal during the first stage of SSD is to resolve psychotic symptoms and to increase the chances of the patients to returning to their normal life as effectively and expeditiously as possible [41]. To do so, antipsychotic medications are utilized [46], in most cases in the form of oral antipsychotics due to being less invasive and more accepted in the long run [47]. Many patients, however, might need long-acting, injectable antipsychotics in order to increase compliance [48], as several studies indicated that more than 40% of patients are nonadherent during the first 9 months of treatment, hence increasing their chance to relapse [49].

In addition to pharmacological treatment it is also important to provide further support to the patients and their caregivers via clinical psychologists, occupational therapists and social workers [10, 41]. The family or caregivers might need to attend psychoeducation or other therapy as well in order to ensure better coping [41].

After the first episode, there are multiple trajectories possible how the disorder can continue. According to the thumb rule described by Shepherd and colleagues, one third of the patients will go on remission and will not experience any more subsequent episode, the second third of the patients will experience one or more psychotic episodes (stage 2), while the third group of patients will experience multiple relapses and unremitting illness which will be later described as chronic disorder (stage 3) [50].

3.3 Remission and relapse (stage 2)

Between stage 1 and 3 is the most heterogenous phase of the disorder, the remission and relapse stage. During this period of SSD, patients first experience a temporary or incomplete remission from the first episode, but then there is a relapse or even multiple relapses of psychotic symptoms in the form of episodes [10]. If looking at the chain of events in a chronological order, before being in remission, the patient first responses to the treatment, which is usually determined by a certain amount of reduction in symptoms (between 20–50%) on a validated rating scale such as the Positive and Negative Syndrome Scale (PANSS) or the Clinical Global Impression (CGI) [51, 52]. Then the patient moves to remission, which, according to the Remission in Schizophrenia Working Group (RSWG), is an "increasingly achievable stage in the treatment of schizophrenia, serving to expand the current ceiling of patient progress beyond "stability" [53]. Although there are various criteria on how remission is defined, it essentially means a period of the disorder when symptoms are mild and/or there is no "active" psychosis [53]. When symptoms start to reappear after this mild or symptom-free period, and the patient is experiencing a worsening in functioning, we are talking about relapse [54, 55]. Nonetheless, as mentioned previously, a third of patients might not relapse rather achieve recovery [50], a state where the patient is able to function both socially and occupationally and has considerable symptomatic improvement [55, 56].

The second stage of SSD is hence quite various in terms of the type and severity of symptoms. Nonetheless, in most cases, the negative and depressive / anxiety-like symptoms [25] are highly dominant in-between relapses, affecting the patient's quality of life enormously [57]. Throughout a relapse the positive and hostility-related symptoms might particularly increase [25, 55].

According to Fountoulakis and colleagues, the duration of this second phase is around 9 years on average, followed by a 13 years-long period dominated by depressive symptoms [25], so an up to 10-year long period for the second stage is adapted.

The primary treatment goal during this stage is first to achieve complete remission and then to prevent relapse as well as to stabilize the patient mediated by specialist care services [10]. Given the high level of negative and depressive/ anxiety-like symptoms, the secondary aim should be to alleviate these, either by using a novel second-generation antipsychotic medication such as cariprazine and amisulpride or a combination of antipsychotic and antidepressant medication [58].

3.4 Chronic psychosis (stage 3)

The third and final stage of the integrated staging model is the chronic psychosis stage. Throughout this period of the SSD the symptoms are still severe, persistent or unremitting [12]. The patients might continue to experience numerous relapses while usually suffering mostly from negative, affective (depressive/ anxiety-like) and neurocognitive symptoms, with the latter increasingly becoming the most prominent symptom group of the disorder over time [12, 25]. Suicidal ideation might also be more common at this stage of the illness [59]. Nonetheless, patients usually develop some kind of acceptance and integrate the fact of the disorder into their life [13].

The chronic psychosis stage of SSD begins about 15–20 years after the first episode [25, 45]. Patients in this late stage are usually disabled at a certain degree and are likely to be unemployed or retired [45].

Treatment in the chronic disorder stage is similar to stage 2 treatment with a high emphasis on the prevention of further exacerbation of the illness and long-term stabilization alongside with augmentation strategies and other psychosocial therapies such as active social participation and/or vocational rehabilitation [10]. Preferred pharmacological treatments include clozapine and long-acting antipsychotic medications [12], although drugs addressing negative and cognitive symptoms (such as cariprazine and amisulpride) may also be of benefit [58].

3.5 Summary of the integrated staging model

The integrated staging model starts with the prodrome (stage 0), which is a period of the SSD where patients are already experiencing some changes in their behavior alongside mild negative and affective symptoms (**Figure 10**). Diagnosis is usually not yet received as the symptoms are too mild and unspecific to be certain about what causes them. This period can last from a few weeks to years. Pharmacological interventions throughout the prodrome are still researched, nonetheless psychosocial therapies are thought to be beneficial.

The first stage of the SSD according to the integrated staging model is the onset of the first episode of psychosis characterized by positive and hostility-like symptoms. This period can last between 2 and 5 years in average. Regarding treatment, the emphasis is on alleviating mostly positive symptoms and stabilizing the patient.

The second stage is the remission and relapse stage which is the most heterogenous phase of the disorder. Throughout this period some patients might experience one or multiple relapses, however about a third of the patients will stay in remission and may go to recovery. The dominating symptoms in-between episodes are the negative and affective ones. The remission and relapse stage last about ten years, between the 5th and 15-20th year of the illness. The primary goal of treatment during this stage is the prevention of relapses and achieving complete remission and recovery.

The final stage of SSD is the chronic psychosis stage dominated by increasing neurocognitive symptoms. Patients arriving to this late stage are likely to be suffering from disability and unemployment. Alongside the pharmacological treatments that aim to prevent the further exacerbation of illness there is an emphasis on psychosocial therapies to increase the everyday functioning of patients.

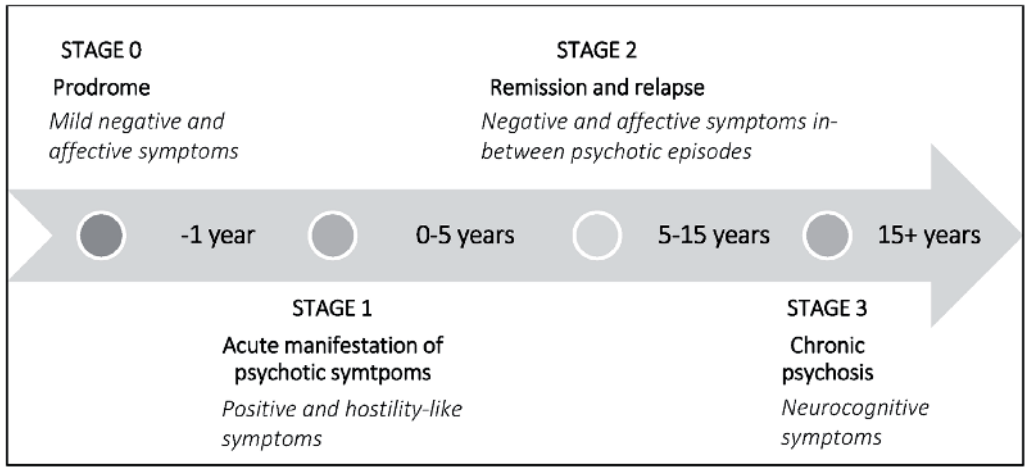

Figure 10.
The integrated staging model of schizophrenia spectrum disorders with timeline and symptom domains.

4. Conclusion

Clinical staging is a more refined form of diagnosis that provides information on how an illness progresses and where the patient lies within this progression [10]. It is based on the assumption that each stage can be described by a typical clinical profile with later stages being associated with greater symptom severity and that treating patients in the early stages of the disorder is more efficient [12]. The primary aim of introducing clinical staging into the field of psychiatry was to promote remission and recovery in the early stages of psychiatric disorders and hence to prevent patients to progress to later stages [10].

Since 1982, several staging concepts describing the course of psychiatric disorders have emerged. In this systematic review, we have identified and summarized 9 concepts that outline the clinical staging of schizophrenia spectrum disorders. Although there were some variations between the models, all identified the first episode of psychosis as a distinct stage that divides the course of the disorder into a *before* and *after* phase. Most of the variations in the concepts were due to the fact that there were disagreements in the number of stages before and after the first onset.

In order to unify the described concepts an integrated staging model of schizophrenia spectrum disorder has emerged that describes the course of SSD in four stages; the prodrome (stage 0), the onset (stage 1), remission and relapse (stage 2) and chronic psychosis (stage 3). The integrated model also provides timeline around when patients are likely to enter the next stage as well as what symptoms dominate and how to best treat them. Nonetheless, it is also important to note that not all patients will go through all stages and the primary goal of any treatment is to prevent patients to enter a later stage.

Conflict of interest

All authors are co-workers of Gedeon Richter Plc.

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