Is it possible to stage schizophrenia? A systematic review

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INTRODUCTION: A staging model is a clinical tool used to define the development of a disease over time. In schizophrenia, authors have proposed different theoretical staging models of increasing complexity. Therefore, the aims of our study were to provide an updated and critical view of the proposed clinical staging models for schizophrenia and to review the empirical data that support them.

METHODS: Systematic literature review following PRISMA guidelines. From the PubMed database and backward reference search, a total of 141 records were retrieved, but only 20 were selected according to the inclusion criteria: (a) available in English; (b) participants with schizophrenia ≥ 18 years; and (c) theoretical and empirical research studies intended to develop, validate, and/or improve staging models of schizophrenia.

RESULTS: Different clinical staging models for schizophrenia were identified, information about the proposed stages was tabulated and presented in the Results section (Tables 1, 2). Most of which include neuroimaging, functioning, and psychopathology, but only two models add objective biomarkers and none include patient point of view. However, few models have been psychometrically tested or used small samples and thus have been validated only partially. In addition, five studies proposed therapeutic interventions according to the stage of the disorder from a theoretical point of view.

DISCUSSION: In conclusion, it is possible to stage schizophrenia, but the models developed have several limitations. Empirical validation and inclusion of more specific biomarkers and measures of other life areas affected by schizophrenia could help in the development of more valid models.

Translational Psychiatry (2022) 12:197 ; https://doi.org/10.1038/s41398-022-01889-y

INTRODUCTION

A staging model is a clinical tool used to define the development of a disease over time [1] that allows for integration of clinical information together with biomarkers, comorbid disorders, and other relevant variables, thus promoting personalized interventions [2]. These models have acquired primary importance in different areas of medicine, such as oncology and cardiology.

Due to the lack of studies that treat psychotic and affective disorders as developmental diseases, Fava and Kellner [3] developed the first clinical staging model in psychiatry. Since then, there has been increasing interest in clinical staging models for severe mental disorders, especially for psychotic disorders, in order to distinguish earlier, nonspecific phases of illness from later and more severe features associated with chronic disease [4]. Staging models provide clinicians a selection of treatments adapted to the early stages of the disease to prevent progression and provide remission. Furthermore, they may offer a unitary framework and individualization of care, which minimize heterogeneity in clinical practice and improve patient prognosis [5, 6].

The first staging model for schizophrenia was developed in 1993 [3]. Since then, authors have proposed different theoretical staging models of increasing complexity. These models are based on different dimensions that are affected by the progression of the disorder. However, although different staging models have been proposed, there is no consensus, nor is there enough empirical evidence to support the use of these models in clinical practice. Furthermore, reviews on the topic have focused on the biological basis of the disease, neglecting its multidimensional nature [1, 6–9]. Therefore, taking a multidimensional perspective, the first aim of this systematic literature review is to provide a global updated and critical view of the clinical staging models proposed for schizophrenia. The second aim is to review the empirical data supporting these models, and ultimately, the biological and psychological interventions proposed according to the stages.

METHOD

The present systematic review follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10] (Supplementary Table 1). However, we did not prepare a protocol for this review, nor was it registered.

Search strategy

For this review, we conducted a systematic search in the PubMed database. In order to limit the results to the most relevant, the search strategy was: ("staging") AND ("schizophrenia"). We supplemented the database search by reviewing reference lists.
of articles meeting our inclusion criteria (backward reference search).

**Study selection**
The articles found were examined in order to select those that met the following inclusion criteria:

(a) Available in English.
(b) Participants with schizophrenia ≥18 years.
(c) Theoretical and empirical research studies intended to develop, validate, and/or improve staging models of schizophrenia (reviews were therefore excluded).

The database searches (completed July 20, 2021) returned 134 records (see Fig. 1 for full flowchart). One researcher (CMC) reviewed all record titles and abstracts. Then that researcher screened the full text of the articles for inclusion. If in doubt, two additional researchers were consulted (M.P.G.P., L.F.T.). After identifying 45 full-text reports, one report was not accessible (we tried to contact the authors but did not receive a response [11]), 26 were excluded because they were reviews (n = 13) or did not focus on a clinical staging model for schizophrenia (n = 13), and two articles were not available in English. Later, we searched for articles cited in any of the included studies and found seven articles potentially fulfilling the inclusion criteria. Three reports were excluded because they did not focus on a clinical staging model for schizophrenia; thus, four met the inclusion criteria. Therefore, of the identified records (n = 141), 20 reports on 17 studies constitute the final sample used in this review.

**Data extraction**
Data were extracted from the studies using the data extraction form (Tables 1, 2, 3) and were collected by one researcher (C.M.C.). If in doubt or in case of unclear information, a consensus was reached after discussion with two of the other authors (M.P.G.P. and L.F.T.).

To explain the models developed to date, we collected the following data:
- Report: authors and year.
- Clinical staging models: including phases of the proposed models and characteristics of the phases (neuroimaging, functioning, psychopathology, cognition, affective symptoms, and endophenotypic and biological markers, if applicable).
- Interventions: including psychological and pharmacological interventions theoretically proposed by authors for each phase.
- Validation of staging models: including the objective of the research, sample sizes, stages of the participants, and conclusions of the studies.

**RESULTS**

**Description of studies**
A total of 20 articles met the inclusion criteria for this systematic review as follows:
- Eight articles report a clinical staging model of schizophrenia (6 based on multidimensional domains and the other two based on a single domain).
- Seven articles validate any of these multidimensional models.
- Three articles validate and/or improve these models.
- And finally, two articles propose interventions for prodromal phases of schizophrenia from a theoretical point of view.

To clearly and transparently present our results, we created three tables (Tables 1, 2, and 3) and a figure (Fig. 2) that summarize and complete the information provided in this section.

**General staging models for schizophrenia**
Fava and Kellner developed the first staging model for schizophrenia in 1993 [3]. They proposed a 5-stage model based on previous research findings on clinical progression of the mental disorder. In their model, the initial phases of the disease are differentiated according to patient functioning and psychopathological characteristics. For the later phases, only DSM-III-R criteria and length of illness are used. A few years later, with the aim of integrating later findings, Cosci and Fava [12] redefined the model, eliminating the subchronic phase, reducing the model to 4 phases (Table 1a).

In 2001, Lieberman et al. [13] developed a 4-phase model comprising clinical features and underlying pathophysiological process. Specifically, the authors used physical anomalies, changes in neuroanatomy, and cognitive and social deficits as indicators of disease progression. Furthermore, their model differs from the previous one in that it includes a first stage termed “Premorbid,” characterized by physical, cognitive, and coordination problems.

Focusing on the prodromal phase, Singh et al. [14] divided their 3-stage model into 2 subphases: a first period of non-diagnostic symptoms (P2). They describe unease as a concept similar to the “morbid unease” proposed by Copeland [15], where the symptom was definitely present, but not of a severity to reach a level of caseness. This model differentiates between the phases mainly according to clinical progression, so that the emergence of first psychotic symptoms (FPS) constitutes the second stage, and the development of symptoms leading to a definitive diagnosis constitutes the last stage. The Nottingham Onset Schedule (NOS) a short, guided interview to measure the onset of psychosis is based on this model.

Focusing on neuroanatomical changes based on previous cognitive and neuroimaging data, Agius et al. [7] proposed three stages: the prodrome, the first episode, and the chronic phase. These stages are based on the development of the disease and the progressive loss of gray matter, resulting in changes in patient cognition (Table 1a).

In 2010, McGorry et al. [16] completed the development of a complex model reflecting the clinical and biological progression of the disease, where stages are not static categories and patients can return to previous phases. For the first time, this model includes, in addition to neuroimaging, functioning, and psychopathology, cognition, affective symptoms, and endophenotypic and biological markers. Regarding biomarkers, they proposed prepulse inhibition, P 50, smooth pursuit eye movements, olfactory dys-}
| Stage 0 | Premorbid phase | Mild physical abnormalities | Mild cognitive impairments | Social deficits | Neurodevelopmental abnormalities | Prediagnosis | Mild symptoms | No symptoms | Increased risk of psychotic or mood disorders |
|-------|----------------|-----------------------------|---------------------------|----------------|---------------------------------|--------------|---------------|------------|----------------------------------|
| Stage 1 | Prodromal phase | Affective and negative symptoms | Deterioration of functioning | Prodromal phase | Non-specific mood symptoms | Neuroplastic dysfunction | Prodromal phase | Loss of gray matter | Prodromal phase | Prodromal phase |
| Stage 1a | Prodromal phase (P1) Unease | Non-specific symptoms | Neurocognitive deficits/severe mood disorders | Functional changes | Distress disorder | History of developmental or learning disorder | GAF/SOFAS: 70–100 | QIDS: 0–11 | Reducions in total sleep |
| Stage 1b | Prodromal phase (P2) Non-diagnostic symptoms | Moderate symptoms | Moderate cognitive changes | Functional impairment (GAF 70) | Attenuated syndrome | GAF/SOFAS: 60–70 | QIDS: 11–20 | YMRS: 9 | Mild deficits in executive functioning | Emerging gray matter loss | Pro-inflammatory cytokine elevation (among others) |
| Stage 2 | First psychotic episode (DM-III-R) | First psychotic episode | First psychotic episode | First psychotic symptoms | First psychotic episode | First psychotic symptoms | Neurocognitive deficits | Functional impairment (GAF 30–50) | Discrete disorder | GAF/SOFAS: 40–60 | QIDS: 20 | YMRS: 15 | Moderate deficits in executive functions | Significant loss of gray matter | Pro-inflammatory cytokine elevation with tendency towards reduced markers of cell-mediated immunity (among others) |
| Stage 2a | Residual phase (DSM-III-R) | Residual phase | Chronic phase | Neurotoxicity, loss of cell processes and apoptosis | Diagnosis | Delusions, hallucinations, first rank symptoms, thought disorder or catatonic symptoms | Chronic phase | Cortical and subcortical brain areas affected | Recurrent/persistent disorder | GAF/SOFAS: 40 | Severe reductions in executive functions and/or social cognition | Reduction in hippocampal volume |
| Stage 2b | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase |
| Stage 3a | Partial remission from the first episode | Incomplete remission | Moderate level of functioning |
| Stage 3b | Remission | Severe reduction in functioning |
| Stage 3c | Multiple relapses | |
| Stage 4 | Subchronic phase (6–24 months) | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase | Chronic phase |
| Stage 4 | Chronic phase | Severe, persistent and unmitting illness | Chronic phase | Enlarged ventricles | Severe psychotic symptomatology | Highly impaired |
### (a) Staging models for schizophrenia

| Stage 5 | Chronic phase (>24 months) |
|---------|----------------------------|
| Functioning | Depressive symptoms |

| Stage 1 | Early stage (18–34 years of age) | First 3 years of evolution |
|---------|----------------------------------|---------------------------|
| Depressive symptoms | Excitement and hostility increase | Positive symptoms dominant |
| Negative, anxiety and depressive symptoms stable | 

| Stage 2 | Middle stage (35–44 years of age) | 3–12 years of evolution |
|---------|----------------------------------|-------------------------|
| Excitement and hostility dominant | Negative, anxiety, depressive symptoms, and neurocognitive deficit increase |
| Positive symptoms stable | 

| Stage 2a | 3–6 years of evolution |
|----------|------------------------|
| Positive symptoms tend to remit | Excitement and hostility increase |
| Negative, anxiety and depressive symptoms increase | 

| Stage 2b | 6–12 years of evolution |
|----------|------------------------|
| Excitement and hostility stable | Negative, anxiety and depressive symptoms increase |
| Positive symptoms stable | Neurocognitive deficit rise |

| Stage 3 | Advanced stage (≥45 years of age) | 12–25 years of evolution |
|---------|----------------------------------|-------------------------|
| Negative symptoms and neurocognitive deficit rise | Depressive and anxiety dominant |
| Depression and anxiety dominant | 

| Stage 3a | 12–18 years of evolution |
|----------|------------------------|
| Excitement and hostility dominant | Negative and positive symptoms increase |
| Neurocognitive deficits increase | 

### (b) Staging models for schizophrenia

| Stage 1 | Fountoulakis et al. [20] |
|---------|-------------------------|
| PANSS domains: | First 3 years of evolution |
| Negative domain | Positive symptoms dominant |
| Depression-Anxiety | Excitement and hostility increase |
| Hostility-Aggression | 

| Stage 2 | Fountoulakis et al. [21] |
|---------|-------------------------|
| PANSS domains: | First 3 years of evolution |
| Negative domain | Positive symptoms |
| Positive domain | 

| Stage 2a | 3–6 years of evolution |
|----------|------------------------|
| Positive symptoms tend to remit | Excitement and hostility increase |
| Negative, anxiety and depressive symptoms increase | 

| Stage 2b | 6–12 years of evolution |
|----------|------------------------|
| Excitement and hostility stable | Negative, anxiety and depressive symptoms increase |
| Positive symptoms stable | Neurocognitive deficit rise |

| Stage 3 | 12–25 years of evolution |
|---------|-------------------------|
| Negative symptoms and neurocognitive deficit rise | Depressive and anxiety dominant |

| Stage 3a | 12–18 years of evolution |
|----------|------------------------|
| Excitement and hostility dominant | Negative and positive symptoms increase |
| Neurocognitive deficits increase | 

### Table 1. continued

#### (b) Staging models for schizophrenia

| Dragioti et al. (2016) | Fountoulakis et al. [20] | Fountoulakis et al. [21] |
|-----------------------|--------------------------|--------------------------|
| **Stage 3b**           | 18–25 years of evolution |                          |
| Negative symptoms and neurocognitive deficit dominant | Depression and anxiety dominant | Excitement and hostility decrease |
| Positive symptoms decrease |                          |                          |
| **Stage 4**            | 25–40 years of evolution |                          |
| Neurocognitive deficits increase | Neurocognitive impairments | |
| **Stage 4a**           | 25–40 years of evolution |                          |
| Negative symptoms increase | Neurocognitive impairment dominant | Depression and anxiety decrease |
| **Stage 4b**           | ≥ 40 years of evolution  |                          |
| Neurocognitive deficits dominant | Excitement and hostility increase | |

GAF Global Assessment of Functioning, SOFAS Social and Occupational Functioning Scale, QIDS Quick Inventory of Depressive Symptomatology, YMRS Young Mania Rating Scale.

Clinical validity of staging models of schizophrenia.

In recent years, the number of studies aiming to validate these models have increased. Specifically, we found 9 articles that try to validate the McGorry et al. [16] and Hickie et al. [17] models (see Table 2).

The McGorry et al. [16] model was validated for the first time by Berendsen et al. [22]. They designed a cross-sectional study with 258 acute ward patients, where patients were classified into stage 1 (less than 12 years of duration), stage 2 (12–25 years of duration), stage 3 (25–34 years of age), and stage 4 (≥ 35 years of age). They found that the McGorry et al. [16] model has acceptable construct validity between earlier and more recent studies and a high degree of inter-rater reliability.

Recently, different authors [19–21] have developed staging models of schizophrenia based on patient PANSS scores (Table 1a). These models have increased in importance due to the increasing number of new developments in the field of schizophrenia. The McGorry et al. [16] and Hickie et al. [17] models have increased in importance due to the increasing number of new developments in the field of schizophrenia.

Subsequently, Fountoulakis et al. [20] analyzed the predominant factors that explain more variance. Finally, the third stage is dominated by negative and affective symptoms. Therefore, in order to clarify the relationship between the symptoms in the stages according to PANSS domain and factor analysis, we performed an exploratory factor and discriminant function analysis (Table 1a).
schizophrenia outpatients. The results showed that, one year later, the majority of the patients were in the same stage and greater improvements occurred in more severe stages (Table 2). Recently, Berendsen et al. [24] developed a study whose results support the clinical validation of this staging model. Patients showed significant differences in the severity of negative, positive, and cognitive symptoms between stages. Furthermore, these authors propose dividing stage 2 based on duration of untreated psychosis (2a < 1 year; 2b ≥ 1 year), which is clinically important for the severity of negative symptoms.

In addition to applying their clinical staging procedure to 209 young people, the objective of Hickie et al. [17] was to demonstrate the inter-rater reliability of their model. They thus compared the stages assigned by the original treating clinicians who used an initial protocol and by the independent research team that had access to the sample’s medical records. Their results show that inter-reliability can improve reliability. To determine whether participants changed stage in the stability (only 7% of the sample remained stable).

Berendsen et al. (2021) To examine differences in severity for dimensional symptoms of psychosis between stages. n = 291 Stage 2 = 62 Stage 3a = 9 Stage 3b = 127 Stage 2b = 75 Stage 4 = 18 Significant differences in the severity of symptoms only were found in stages 3c and 4 (hallucinations (H = 14.34, p = 0.006), negative symptoms (H = 19.67, p = 0.001), and cognitive deficits (H = 26.29, p < 0.001)).

Hickie et al. [17] To demonstrate the inter-rater reliability of the model. n = 209 Stage 1a = 21 Stage 1b = 112 Stage 2 = 53 The inter-rater reliability was acceptable (K = 0.72, p < 0.001).

Romanowska et al. [25] To assess neurocognition in a sample of patients in the first stages of schizophrenia. n = 243 Stage 0 = 41 Stage 1a = 52 Stage 1b = 108 Controls = 42 Patients in stage 1b presented significantly poorer cognitive performance (MATRICS Overall Composite F = 5.70, p < 0.001).

Addington et al. [26, 27] To identify sample that met different stages of risk for the development of a serious mental illness (SMI) based on a published clinical staging model. To determine whether participants allocated to the different stages were a good fit to the model. n = 243 Stage 0 = 41 Stage 1a = 52 Stage 1b = 108 Controls = 42 Patients in stage 1b had significantly more severe symptoms than participants in lower stages (Functioning (F = 77.10, p < 0.002), depressive symptoms (F = 30.10, p < 0.002), and prodromal psychotic symptoms (F = 37.30, p < 0.002)).

Addington et al. [28] To describe changes in participants over 12 months to understand the course of illness progression in its earliest stages. n = 243 Stage 0 = 41 Stage 1a = 53 Stage 1b = 107 Controls = 42 Follow-up at one year showed stability (only 7–9% of the participants changed stage in the follow-up).

**Table 2. Validation of the clinical staging models.**

| Study | Objective/Feasibility | Sample | Stages | Conclusions |
|-------|------------------------|--------|--------|-------------|
| McGorry et al. (2010) Berendsen et al. (2018) | To examine the construct validity of the staging model by measuring differences in severity of clinical profiles and therapeutic improvement between clinical stages. | n = 258 | Stage 2 = 48 Stage 3b = 100 Stage 3c = 81 Stage 4 = 29 | Only stages 3c and 4 showed adequate construct validity [significant differences were found for negative symptoms (F = 4.56, p < 0.010), number of psychotic episodes (F = 13.65, p < 0.010), and premorbid functioning (F = 7.33, p < 0.001) according to stages]. |
| Berendsen et al. (2019) | To determine the inter-rater reliability of the clinical staging. To investigate whether a short course can improve reliability. n = 114 (no training) | Stage 2 = 22 Stage 3a = 1 Stage 3b = 39 Stage 3c = 41 Stage 4 = 11 | The inter-rater reliability in clinical staging was better after training (ICC = 0.57 vs ICC = 0.75). |
| Godin et al. [18] | To classify patients according to the model. To use clinical, cognitive, and treatment variables to explore validity. To explore the stability of the model. n = 770 | Stage 2a = 89 Stage 2b = 272 Stage 3a = 241 Stage 3b = 112 Stage 4 = 56 | Follow-up at one year showed good stability (62% of the sample remained stable). |
| Berendensen et al. (2021) | To examine differences in severity for dimensional symptoms of psychosis between stages. n = 291 | Stage 2 = 62 Stage 3a = 9 Stage 3b = 127 Stage 2b = 75 Stage 4 = 18 | Significant differences in the severity of symptoms only were found in stages 3c and 4 (hallucinations (H = 14.34, p = 0.006), negative symptoms (H = 19.67, p = 0.001), and cognitive deficits (H = 26.29, p < 0.001)). |
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*ICC Intraclass Correlation Coefficient, K Kappa Statistics, MATRICS The Measurement and Treatment Research to Improve Cognition in Schizophrenia.*
flexibility. In 2018, Addington et al. [26] described a study whose aim was to develop and validate an algorithm using the Hickie et al. [17] model. One year later, Addington et al. [27] compared clinical and sociodemographic information on patients in the first stages of the model. They found that the participants in stage 0 were similar to healthy controls, so they proposed discriminate patients with SMI risk be assessed for resilience in comparison with healthy subjects [27]. Recently, they analyzed the changes in this sample one year later [28]. The results show that changes in stages 0 and 1a were minimal; however, participants in stage 1b had the greatest improvement.

Potential interventions according to clinical stages
In addition, to design a staging model for schizophrenia, some authors have proposed personalized interventions according to the stage of the disorder. These treatments could help prevent progression of the disorder and improve the patient’s prognosis (Table 3, Fig. 2).

In the premorbid phase, Lieberman et al. [13] proposed that gene therapy could be a potential treatment. In this sense, although recent results from Copy Number Variants (CNV) [29, 30] and Polygenic Risk Score (PRS) [31, 32] support the contribution of genetics to both schizophrenia and the transition from the ultra-high-risk state to psychosis, there is still no consensus on its clinical use. On the other hand, Cornblatt [33] analyzed preliminary findings from the Hillside Recognition and Prevention (RAP) program. In this program, patients were classified into four groups according to the severity of the symptoms. The first group with premorbid symptoms—the clinical high risk (CHR) group—received psychotherapy only, as in the early stages it is advisable to use less invasive treatment than at later stages. Finally, the worldwide effort made by the International Early Psychosis Association (IEPA) merits special attention. The IEPA was created in 1998 (currently called IEPA Early Intervention in Mental Health), with the aim of increasing knowledge related to the early phases of psychiatric disorders, their causes, and possible prevention strategies [34]. It has promoted the creation of early intervention units in different countries [35] and constitutes an international network that facilitates communication and collaboration among mental health professionals around the world [34].

For stage 1, antipsychotics have been proposed by different authors [6, 13, 33]. Cornblatt [33] and Carrion et al. [36] also found that treatment with antidepressants may be effective at reducing nonspecific symptom progression. Furthermore, environmental factors such as substance abuse and stress, associated with the onset of the disorder, are therapeutic targets [13, 16]. The authors have proposed psychological interventions such as cognitive, supportive, and the cognitive behavioral therapy (CBT) that can buffer risk and reduce progression to psychotic symptoms [16].

In stage 2, where clear psychotic symptoms are present and functioning is affected, pharmacological and psychosocial treatments are useful in order to stimulate functional and clinical recovery. Different authors have reported that atypical antipsychotics have shown better tolerability and can be more useful in these early stages [16]. Family is essential in providing care and support for the patients. These have been associated with fewer relapses, so the inclusion of family support therapies can be used to improve the patient’s prognosis [7, 16].

In later stages, medication adjustment and more aggressive treatments are chosen [7, 13, 16]. However, psychosocial interventions are still necessary as they can help prevent the risk of future relapses and the development of disability [7, 16].

DISCUSSION
We did a systematic review of staging models for schizophrenia. Over the years, more comprehensive general theoretical models have been developed and studies trying to validate these models have been performed. Over time, models have been improved by including biomarkers in addition to clinical, cognitive, and functional variables, giving them the true characteristic of staging models with objective data. However, to date there are still few models that include objective variables e.g., biomarkers, diagnosed physical comorbidities, or subjective self-reported variables, such as quality of life.

Biomarker research has confirmed that schizophrenia is a disease with chronic low-grade systemic inflammation [37–40], as well as cognitive impairment [41]. Although there are divergent results, different studies of inflammation seem to indicate a role of interleukins [42], specifically IL-6 and TNF-α, in clinical manifestations.
of the disease, and they are the most replicated in previous research [39]. Recent studies have also reported an association of IL-6 and TNF-α with negative symptoms [43]. For example, González-Blanco et al. [44] showed that interleukin IL-1β was associated with global symptomatology and IL-2 with anhedonia and avolition. The previous literature also reflects an association between schizophrenia and interleukins. A systematic review by Ribeiro-Santos, Teixeira and Vinicius [45] found that MCP-1 and IL-18 levels were associated with
cognitive impairments in schizophrenia. In addition, Lim et al. [32], Perkins et al. [46], and He et al. [47] reported PRS as a potential biomarker for early cognitive deficits or for the transition from the ultra-high-risk state to established psychosis.

The frequent physical comorbidities in these disorders, such as cardiovascular diseases, diabetes, metabolic syndrome, etc., even in first episode patients [48, 49], have not been taken into account in the reviewed models. The scientific literature has also indicated the significant effect that physical illness has on the treatment and outcome of schizophrenia [50]. Considering that people with schizophrenia have 15 years’ lower life expectancy due to their physical health [51] and in view of the negative effects these diseases have on cognition and functioning [52, 53], physical comorbidities should also be taken into account when developing staging models in future studies.

It is of note that none of the reviewed models include patient-reported outcomes. It would be interesting to introduce the patient's point of view into the stages. Obtaining information from patients themselves is of great value and should be considered complementary to the clinician's point of view. Negative symptoms of schizophrenia involve internal experience and, therefore, are more accessible and suitable for self-reporting [54]. Furthermore, it is well known that quality of life is a distal marker of the results of disease interventions, which can only be reported by the patient. Thus, the effect of the disorder and its treatments on the life of patients should be taken into account in the different stages of the models.

Regarding validation, it is encouraging to see that there are increasing numbers of empirical clinical studies concerned with establishing the validity and reliability of the proposed theoretical models. Unfortunately, such studies have included small samples or patients who are in specific stages of the models. In this sense, Berendsen et al. [23] point out that the problem is mainly in the early stages of the disease. Therefore, their results apply only to specific stages of schizophrenia spectrum disorders and not to the preclinical stages of disease; this is because these patients were not included in the study as they had not been admitted to the hospital. Patients in premorbid and prodromal phases are not seen in clinical and hospital settings, making it difficult to access them. Thus, further high-quality studies are needed to empirically validate all the phases of these theoretical models.

For the purpose of increasing the utility of clinical staging models in daily clinical practice, therapeutic strategies have been proposed based on the disease stage. Biological and/or psychological interventions could thus be adjusted depending on the stage of disease. In the early stages, milder treatments can be effective, avoiding side effects and complications associated with unnecessarily high-intensity interventions [55]. We have reviewed different interventions proposed for each stage that could represent an advance in standardizing clinical practice and implementing personalized medicine, thus providing each patient with the most appropriate treatment depending on his/her disease stage. However, further research would be needed to confirm these therapeutic proposals.

This review has some methodological limitations. First, a limited number of databases were searched, and some relevant studies may be missing. However, this database is the most powerful for clinical research. Second, the different study methods greatly hinder the comparability of the data. The samples used were diverse in nature (i.e., age, context, length of illness, etc.). Finally, we found few longitudinal studies that report how patients move through the model; studies with follow-up were minimal and with short follow-up periods. Despite these limitations, it should be pointed out that, on the one hand, there is little tradition of developing clinical staging models in psychiatry and, on the other hand, we followed the PRISMA guidelines. Therefore, although not every study has been included, the methodology has been rigorous. Furthermore, to our knowledge, this is the first systematic review that uses a multi-dimensional perspective to provide an update on the clinical staging models of schizophrenia and the biological or psychological interventions proposed for each stage.

In conclusion, with this review, we have demonstrated that is possible to stratify schizophrenia. Psychiatries have growing interest in clinical staging models for schizophrenia as evidenced by the increasing numbers of publications on the subject in recent years. However, these models would benefit from the inclusion of more specific and validated biomarkers and other measures of life areas affected by schizophrenia such as comorbidity with physical diseases and health-related quality of life. In addition, they need to be psychometrically tested before including them in daily clinical practice.

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