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Review

ASSESSING THE TRAJECTORY OF SCHIZOPHRENIA EFFECTIVELY IN ORDER TO TREAT EFFECTIVELY

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SUMMARY

Introduction: *Schizophrenia is a complex psychiatric disorder characterized by heterogeneous symptom trajectories that significantly impact patient outcomes. We believe that the study of the trajectories of Schizophrenia is useful in assessing treatment options and outcomes. While the Positive and Negative Syndrome scale is usually used on one occasion to measure symptoms at a single time, if measured repeatedly , the PANSS is also useful in measuring trajectories. In order to illustrate and promote this serial use, we have reviewed papers which describe the delineation of Trajectories of Symptoms in Schizophrenia based on PANSS scores. This review integrates findings from longitudinal studies focusing on the trajectories of positive symptoms, negative symptoms, the relation between positive and negative symptoms and cognition, soft neurological signs, and treatment response in schizophrenia.*

Methods: *Studies were identified from the PUBMED database .Studies included in this review employed diverse methodologies such as trajectory analyses, longitudinal assessments, and clinical trials. Data were extracted from a range of patient cohorts, including those with first-episode psychosis and chronic schizophrenia.*

Results: *Longitudinal studies consistently demonstrate variability in the trajectories of positive symptoms, with most patients experiencing early stable remission, though a subgroup exhibits persistent or fluctuating symptomatology. Negative symptoms, on the other hand, often show poor improvement over time, correlating with impaired social and neurocognitive functioning. Cognitive deficits also vary, with some domains showing improvement while others, such as logical memory, deteriorate in certain patient subgroups. The relationship between positive and negative symptom trajectories highlights their complex relationship, influencing overall functioning and treatment outcomes. Antipsychotic medications demonstrate varied responses across patient cohorts, with distinct trajectory patterns observed based on medication type and patient-specific factors such as co-morbid substance abuse and duration of untreated psychosis.*

Conclusion: *Understanding the longitudinal trajectories of symptoms in schizophrenia is crucial for optimizing therapeutic strategies and improving patient outcomes. Personalised interventions tailored to individual symptom profiles and early clinical responses are recommended to enhance treatment efficacy and promote recovery. The PANSS scale can be used to delineate Trajectories of various symptom Groups in Schizophrenia.*

Key words: *schizophrenia - PANSS scale - trajectories - positive symptoms - negative symptoms - cognition - treatment modalities - outcome measurement*

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INTRODUCTION

Thirteen years ago we had described the progress of the illness in a patient with Schizophrenia as developing through a series of stages, starting with the prodrome of the disease, followed by the first episode of psychosis, and then proceeding through recurrent episodes, which can be separated by periods of normality or near normality, to the phase of chronic illness (Agius 2023, 2010). We described each of these phases of the illness as stages of the illness, and we have argued that these stages are underpinned by observable progressive loss of grey matter in the brain which can be observed by MRI images of the brain (Agius 2023, 2010).

While the above is true, it is also true that there is extreme variability, or heterogenicity in symptom presentation between individual patients, and this suggests that individuals diagnosed with a first-episode psychosis may encompass different sub-populations with potentially different illness courses and, hence, different treatment needs (Amoretti 2021). Equally, there is marked variability, or heterogenicity in the outcome, both if psychotic illness were to be untreated and in the response of individual patients to treatment with antipsychotic drugs (Abdin 2017, Rammou 2019). The studying of the longitudinal progress of the illness therefore becomes important.

The longitudinal progress of the illness over time from one stage of illness to the next is referred to as the trajectory of the illness.

The trajectory of the illness is important because not all patients with psychotic illness necessarily progress inevitably from prodrome to chronic illness. Often, the illness might stop at the prodrome, or after the first episode, or after a series of episodes and only a proportion of patients will progress to chronic schizophrenia.

While it might be that in some cases, the natural course of the illness might be that the illness might stop and return to normality after a period of what appears to be the prodrome of a psychotic episode, or after a first full episode of psychosis, in other cases the illness might, over time, progress on to a case of chronic schizophrenia.

Since in most situations when psychotic illness is being diagnosed and treated, MRI scanning is not available, and the illness is evaluated on clinical grounds alone, then it becomes necessary to have very careful clinical evaluation of the illness, based on both the present clinical symptoms and signs and the past history of the patient from the beginning of the illness in order to be able to describe the stage of illness at which the patient is at presently and the trajectory by which the illness has developed to the present point. Thus, during the history taking process, the 'staging' of the illness and the describing of the 'trajectory' of the illness are two important and complementary processes in the describing of the particular patient with schizophrenia.

The importance of the staging of the illness and the establishing of the trajectory of the illness is twofold from a clinical point of view.

This is because, on the one hand, different types of treatment are appropriate to the different stages of the illness, and even the aims of treatment are different in each stage of illness, while on the other hand, the use of the appropriate treatment for the appropriate stage of illness will influence the course of the illness, and therefore 'the trajectory', and is indeed intended to do so by either causing the progress of the illness to stop, or even reverse to normality, or at least to slow down, so that relatively good functioning is maintained for longer. Thus treatment itself will influence the course of the "trajectory of illness".

Therefore, the assessment of patients with psychotic illness in order to evaluate the stage of the illness and to delineate the trajectory of the illness requires a high level of clinical assessment skills.

The Positive and Negative Syndrome Scale (PANSS) (Kay 1987) serves as an essential instrument for documenting and evaluating the symptoms of schizophrenia at any point in time during patient assessments. This scale is designed to measure both positive symptoms such as hallucinations, delusions, illogical changes in behaviour or thoughts, hyperactivity, and thought disorders, as well as negative symptoms, which include apathy, lethargy, and withdrawal from social events or settings. By administering the PANSS repeatedly, healthcare professionals can effectively trace the trajectory of these symptoms, allowing for a detailed understanding of the patient's condition over time. This capability is crucial for developing tailored treatment plans and adjusting therapeutic interventions based on the patient's evolving symptom profile. To substantiate the feasibility and effectiveness of using PANSS in this longitudinal manner, a review of recent literature has been conducted. This review will focus on studies that have employed PANSS to monitor the progression of schizophrenia symptoms, illustrating its application in clinical practice.

EARLY STUDIES

As early as 2002, Kupper and Tschacher (2002) studied 46 schizophrenia spectrum patients by daily observation during an average treatment period of 104 days. They identified five factors whose trajectories could be measured (Kupper 2002). These were (1) overall level of positive symptoms, (2) duration of nonspecific response, (3) slope of response in all symptom domains, (4) enduring negative symptoms, and (5) duration of response of psychotic symptoms (Kupper 2002). They reported that In general, patients with schizophrenia or schizoaffective disorder tended typically to have more marked enduring negative symptoms, tended towards a lower level of positive symptoms and showed a less prominent response to treatment, when compared to other patients with other forms of psychosis (Kupper 2002). These observations validated the concept of studying trajectories of positive and negative symptoms in schizophrenia (Kupper 2002).

Potkin et al. (2011) attempted to study the trajectories of psychotic illness when treated by placebo, or in other words the 'natural ' trajectory of acute psychotic illness over six weeks and another over a year (Potkin 2011). These placebo response trajectories were contrasted with two 6-week schizophrenia studies (Potkin 2011). While the placebo response trajectory analysis showed 58% had gradual improvement in the PANSS negative subscale score ($p<0.05$), fewer dropouts ($p<0.05$) and improvement in abnormal movements, this contrasted with 3 other trajectory groups which showed worsening on these measures, and the trajectory analyses showed a worsening of symptoms based on PANSS total score in the 1-year trial (+15.5, SEM 2.6) (Potkin 2011). In the 6-week short term trials, some gradual improvement of symptoms (-14.0, SEM 1.6) was also noted in 67% (n=114) of patients (Potkin 2011). It was commented that the results indicated that substantial heterogeneity in placebo response occurs in both the short-term and the long-term trials (Potkin 2011). It was admitted that in fact, almost all the subjects treated with placebo (98%) whose symptoms were improved had been treated with conventional antipsychotics just prior to the commencement of placebo treatment (Potkin 2011). It was said that the placebo response trajectories appeared to depend on which efficacy measure of symptom reduction was chosen, which prior antipsychotic had been used, as well as the trial duration (Potkin 2011). We report this study, because placebo response in clinical trials is the closest that one can observe to the 'natural ' trajectory of psychotic illness, although Potkin has shown that in fact there have been interference such as prior treatment with antipsychotics with the development of the illness in these patients (Potkin 2011). The most important finding in this study is the heterogenicity of the trajectory of illness and that there is a worsening of symptoms at the one year point if no antipsychotic medication is given (Potkin 2011).

Jager et al. followed 268 patients with schizophrenia over two years (Jager 2014). Two trajectories were identified; a group with amelioration in all PANSS subscales (60%) and a group with stable positive/negative and deteriorating general psychopathology symptoms (40%) (Jager 2014). Global functioning (GAF score), gender, age, living situation and involuntary admission predicted which course trajectory group the patients would be placed in (Jager 2014). The results underline the heterogeneous course of the illness, which ranged from amelioration to deterioration over a 2-year period (Jager 2014).

COMPARING TRAJECTORIES FOR POSITIVE SYMPTOMS TO TRAJECTORIES FOR NEGATIVE SYMPTOMS

It is only relatively recently that it has been possible to describe how there may be different trajectories for different groups of symptoms. In particular, Trajectories for Positive Symptoms, for Negative Symptoms, for Cognition, and for Soft Neurological signs have been described.

In each of these groups of symptoms, there are some patients which have more positive outcomes, and patients who have more negative outcomes.

One such study, by Abdin et al. (2017) is based on the data base of the Singapore early intervention service. It attempted to describe the trajectories of symptom severity in first episode psychosis and their impact on functioning over a 2-year follow-up period (Abdin 2017). By Abdin et al's study aimed to identify discrete trajectories of positive, negative and general psychopathological symptoms as well as general functioning (Abdin 2017). By Abdin et al's study also aimed to determine predictors of the identified symptom trajectories and subsequently to investigate the relationship between the symptom trajectories and the functioning trajectories (Abdin 2017). It should be clarified that, because of the diagnostic instability in patients which experience psychosis for the first time, the term ' first episode psychosis' is used in this study rather than 'schizophrenia'.

POSITIVE SYMPTOMS

In a study from the OPUS trial, Austin (2015) studied the trajectories of response to treatment in 496 patients with first episode psychosis, who were studied over ten years (Austin 2015). In this study, (Austin 2015) five distinct trajectories were identified for positive symptoms; (1) good response (to treatment) - 47%, (2) delayed response - 12%, (3) relapse - 15%, (4) non-response - 13% and (5) episodic response - 13% (Austin 2015). It was found that longer duration of untreated psychosis (OR 1.27-1.47, $p<0.05$) and substance abuse (OR 3.47-5.90, $p<0.01$) were associated with poorer positive symptom trajectories, that is, higher levels of psychotic symptoms in this trajectory (Austin 2015). In this study, Positive symptoms showed a general pattern of reduction and stabilization over time (Austin 2015). In this study, a proportion of people displayed significant changes in symptoms several years after diagnosis (Austin 2015).

To have a longer duration of study, Goghari et al. (2013) studied 150 young patients, including 51 patients with schizophrenia, 25 patients with schizoaffective disorder, 25 patients with bipolar disorder with psychosis, and 49 patients with unipolar depression and hallucinations over 20 years. The results showed that frequent or persistent hallucinatory activity over the 20-year period was a feature of 40-45% of the schizophrenia patients (Goghari 2013). It was shown that the early presence of hallucinations predicted the lack of future periods of recovery in all patients (Goghari 2013). Furthermore, increased hallucinatory activity was shown to be associated with reduced work attainment in all the patients (Goghari 2013).

Goghari and Harrow carried out another study (Goghari 2016), including auditory, visual, and olfactory hallucinations over 20 years in 150 young patients, namely 51 with schizophrenia, 25 with schizoaffective disorder, 28 with bipolar disorder with hallucinations, and 79 unipolar depression with hallucinations (Goghari 2016). At the initial hospitalization, the schizophrenia and schizoaffective patients had a greater rate of auditory and visual hallucinations than the bipolar and depression patients (Goghari 2016). However, over the longitudinal trajectory of their illness, a greater percentage of schizophrenia patients had auditory and visual hallucinations than schizoaffective, bipolar and depression patients (Goghari 2016). It was found that visual hallucinations differentiated the groups to a greater degree over the 20 year course than did auditory hallucinations (Goghari 2016).

In Abdin et al's study Two distinct trajectories were described for positive symptoms (Abdin 2017). These were (1) early response to treatment trajectory and (2) stable trajectory and delayed response trajectory (Abdin 2017).

In a study of 373 participants in the OPUS trial, (Starzer 2023) five trajectories of positive symptoms were identified: (1) early continuous remission (50.9% of the sample), (2) stable improvement (18.0%), (3) intermittent symptoms (10.2%), (4) relapse with moderate symptoms (11.9%), and (5) continuous severe symptoms (9.1%). (Starzer 2023) Substance use disorder, (odds ratio, OR: 2.83, 95% CI: 1.09-7.38, $p=0.033$), longer duration of untreated psychosis, (OR: 1.02, 95% CI: 1.00-1.03, $p=0.007$) and higher level of negative symptoms (OR: 1.60, 95% CI: 1.07-2.39, $p=0.021$) were predictors of the relapse with moderate symptoms trajectory (Starzer 2023), while only longer duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, $p=0.030$) predicted membership to the continuous severe symptoms trajectory (Starzer 2023).

In another study by Habtewold of 1119 patients, the patients also had either a decreasing, increasing, or relapsing symptoms course for positive symptoms (Habtewold 2023).

Auditory hallucinations are a key diagnostic feature of schizophrenia and are one of the most frequent and debilitating of the positive psychotic symptoms (Köhler-Forsberg 2022). To study this symptom in particular, 496 patients with a first schizophrenia-spectrum disorder were taken from the OPUS study cohort and assessed at baseline and after one, two, five, and ten years for auditory hallucinations, scoring from 0 ("None") to 5 ("Severe: Voices occur often every day") (Köhler-Forsberg 2022).Three trajectories of auditory hallucinations were identified (Köhler-Forsberg 2022). (1) The Low-Decreasing trajectory (77%) had the lowest mean score at baseline (mean score = 2.1). In this trajectory, the score improved within the first year (mean score = 0.5) and stayed low (mean score = 0 after ten years) (Köhler-Forsberg 2022). (2) The High-Fluctuating trajectory (10%) improved during the first two years from a mean score of 3.0 to 1.0, but increased after five and ten years (mean score = 2.4) (Köhler-Forsberg 2022). (3) The High-Increasing trajectory (13%) started at a high level (mean score = 3.5), improved a little after one year (mean score = 3.0), but then increased to a mean score of 4.8 after ten years (Köhler-Forsberg 2022).

For auditory hallucinations, alcohol misuse and longer duration of untreated psychosis were associated with increased odds of being in the High-Increasing compared to the Low-Decreasing trajectory (Köhler-Forsberg 2022).

NEGATIVE SYMPTOMS

Negative symptoms have been associated with poor outcome and remain difficult to treat in patients with psychosis (Rammou 2017). The negative symptoms of schizophrenia include volitional (motivational) impairment manifesting as avolition, anhedonia, social withdrawal, and emotional disorders such as alogia and affective flattening (Mosolov 2022). Negative symptoms make worse the patients' quality of life and functioning (Mosolov 2022).

Trajectories of Negative symptoms have been the focus of much study in recent years.

In a study from the OPUS trial, Austin (Austin 2015) studied the trajectories of response to treatment in 496 patients with first episode psychosis, who were studied over ten years. Poor social functioning (OR 1.34-5.55, $p<0.05$), disorganized symptoms (OR 2.01-2.38, $p<0.05$) and schizophrenia diagnosis (OR 5.70-8.86, $p<0.05$) were associated with poorer negative symptom trajectories, that is, higher levels of negative symptoms in this trajectory (Austin 2015). Negative symptoms typically showed less variation (when compared to positive symptoms) over the ten years of the study (Austin 2015).

In Abdin et al's study, four distinct trajectories were described for negative and general psychopathology symptoms (Abdin 2017). These were (1) early response to treatment and stable trajectory, (2) early response and relapse trajectory, (3) slower response and no response trajectory and (4) delayed response trajectory (Abdin 2017).

In another study of 373 participants in the OPUS trial, (Starzer 2023) two trajectories of negative symptoms were identified: (1) symptom remission (51.0%) and (2) continuous symptoms (49.0%). Predictors of the continuous symptoms trajectory were male sex (OR: 3.03, 95% CI: 1.48-6.02, $p=0.002$) and longer duration of untreated psychosis (OR: 1.01, 95% CI: 1.00-1.02, $p=0.034$).

Phahladira et al. (2022) identified a two-factor structure for negative symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS) in schizophrenia, these were experiential and expressive groups of symptoms (Phahladira 2022). Their study was a longitudinal study of 106 minimally treated participants with a first episode of a schizophrenia spectrum disorder who received treatment with flupenthixol decanoate 2-weekly injections over two years (Phahladira 2022). Their study showed that there were experiential and expressive groups (referred to as subdomains in the paper) of negative symptoms, which were strongly correlated (Phahladira 2022). The treatment response trajectories for the two subdomains did not differ significantly (Phahladira 2022). They found significant main effects for disorganised symptoms and extrapyramidal symptoms were associated with the expressive subdomain, and disorganised symptoms and depressive symptoms were associated with the experiential subdomain (Phahladira 2022).Thus the two negative symptom subdomains are closely related, have similar premorbid correlates and respond similarly to antipsychotic treatment. Depression affects the experiential subdomain, whereas extrapyramidal symptoms affect the expressive subdomain (Phahladira 2022).

Chan et al. (2020) explored the 10-year trajectories and outcomes of negative symptoms in patients with first-episode schizophrenia-spectrum disorder in 214 patients (Chan 2020). Chan et al. identified three longitudinal clusters of negative symptoms and 15% of patients were in the relapsed group (Chan 2020). Chan et al. found that Male gender and duration of hospitalizations in year four were significant determinants of relapse negative symptoms (Chan 2020). Furthermore, Lower education level, higher year-one negative symptom score and more months of unemployment during the first 3 years predicted overall negative symptoms at 10-years (Chan 2020). Chan et al. found that Male gender was a predictor only for avolition and anhedonia while duration of untreated psychosis was only a predictor of anhedonia (Chan 2020). Chan et.al commented that these results highlighted the hetero-

geneity of longitudinal outcomes of negative symptoms and therefore the importance of personalized interventions for each patient (Chan 2020).

Leucht et al, in a recent study, found that a single trajectory best described the treatment response of patients with predominant negative symptoms (Leucht 2023). They commented that their results indicate that patients with predominant negative symptoms with over ten years of schizophrenia do respond rapidly to adequate treatment and follow a course of steady improvement (Leucht 2023).

One important negative symptom of Schizophrenia is Apathy. Lyngstad et al studied the trajectory of apathy in Schizophrenia in 198 first episode of psychosis patients compared to 198 healthy controls over a ten year period (Lyngstad 2020). In the healthy controls, mean apathy levels were low and stable (Lyngstad 2020). In the first episode of psychosis patients, apathy levels decreased significantly during the first year of treatment, followed by long-term stability (Lyngstad 2020). High individual levels of apathy at the beginning of the study were associated with higher apathy levels during the follow-up (Lyngstad 2020). It was found that Long Duration of untreated psychosis and high levels of depression at baseline predicted higher apathy levels at follow-up (Lyngstad 2020). The effect of Long Duration of untreated psychosis was persistent, while the effect of baseline depression decreased over time (Lyngstad 2020). At 10 years, apathy was statistically significantly associated with reduced functioning (Lyngstad 2020). It was commented that the early phase of the illness may be critical to the development of apathy in first episode of psychosis patients (Lyngstad 2020).

DIFFERENTIATION BETWEEN PRIMARY AND SECONDARY NEGATIVE SYMPTOMS

Negative symptoms make worse the patients' quality of life and functioning (Mosolov 2022). When making a diagnosis, it is important to differentiate between primary negative symptoms, which are seen as an integral dimension of schizophrenia, and secondary negative symptoms which occur as a result of positive symptoms, comorbid depression, side effects of antipsychotics, substance abuse, or social isolation (Mosolov 2022). If secondary negative symptoms overlap with primary negative symptoms, this may create a false clinical impression that the disease is worsening, with increase of deficit symptoms and disease progression, which may lead to the choice of an incorrect therapeutic strategy, with unnecessary increase in antipsychotic treatment (Mosolov 2022). It has been proposed that there are different longitudinal trajectories of primary and secondary negative symptoms in different schizophrenia stages, and that this should help in appropriate choice of treatment (Mosolov 2022).

RELATIONSHIP OF POSITIVE AND NEGATIVE SYMPTOMS TO COGNITION

Cognition and cognitive symptoms are a particularly important aspect of schizophrenia and tracing the trajectory of these symptoms is important, particularly in terms of developing approaches to cognitive remediation in order to hopefully improve prognosis (Shmukler 2015). It is beyond the scope of the present paper to discuss trajectories of cognition, but here we discuss the relationship between the trajectories of positive and negative symptoms and those of cognition in schizophrenia.

Thompson et al. (2013) compared trajectories (mean duration of 3.5years) of cognitive impairments in a sample of 201 community-dwelling schizophrenia (SCZ) patients (aged 40-100years) with 67 healthy comparison (HC) subjects (Thompson 2013). They wished to study the heterogeneity of clinical outcomes, as regards cognition, in older patients with schizophrenia (Thompson 2013). Three trajectories, here referred to as classes, were identified:

(1) Class 1 (85%of healthy controls and 50% of patients with schizophrenia) exhibited relatively high and stable trajectories of cognition, (2) Class 2 (15% of healthy controls and 40% of patients with schizophrenia) exhibited lower, modestly declining trajectories, and (3) Class 3 (10% of patients with schizophrenia) exhibited lower, more rapidly declining trajectories (Thompson 2013). Within the group of patients with schizophrenia, membership in Classes 2-3 (that is patients with modestly or rapidly declining Trajectories) was associated with worse negative symptoms and living in a care facility (Thompson 2013). Thompson commented that these results bridge the gap between schizophrenia studies demonstrating cognitive decline and those demonstrating stability (Thompson 2013). It is important that this heterogeneity in cognitive trajectories has important practical implications for design of appropriate interventions and appropriate case management of older patients with schizophrenia who show accelerated cognitive decline (Thompson 2013).

Another review by Gerretsen et al. (2014) studied older patients with schizophrenia, specifically in relation to impairment of insight. through the 62 studies included, they were able to show that insight impairment is associated with illness severity, premorbid intellectual function (i.e. IQ), executive function, and memory (Gerretsen 2014). Insight impairment improves modestly during midlife, worsening again in late life (Gerretsen 2014). Insight impairment tends to fluctuate with each episode of psychosis, probably due to worsening positive symptoms which improve with antipsychotic treatment (Gerretsen 2014). The relationship between insight impairment and cognitive dysfunction appears to attenuate with age, while the relationship with lower premorbid intellectual function remains preserved (Gerretsen 2014). The association between

impaired insight and negative symptoms remained unclear (Gerretsen 2014). The course of insight impairment follows a U-shaped curve, or trajectory, in which insight impairment is severe during the first episode of psychosis, modestly improves in midlife, and declines again in late life (Gerretsen 2014).

In a study of 373 participants in the OPUS trial, (Starzer 2023) trajectories displaying continuous positive and negative symptoms were linked to lower neurocognition, as measured by the Brief Assessment of Cognition in Schizophrenia (BACS) (z-score: -0.78, CI: -1.39 to -0.17, for continuous positive symptoms; z-score: -0.33, CI: -0.53 to -0.13, for continuous negative symptoms).

Saleh et al. (2023) showed that Cognitive dysfunction and negative symptom severity account for distinct aspects of these behavioural changes and are independent of each other in treatment resistant schizophrenia, therefore suggesting the possibility of individualised treatment targeting these mechanisms to improve motivation (Saleh 2023).

Chan et al. (2023) studied 177 patients of age 25-55 with first episode psychosis explores the longitudinal changes and trajectories of cognitive functions in patients with adult-onset first-episode schizophrenia (FES) over four years and their relationships with the baseline subdomains of negative symptoms (Chan 2023). Two trajectories of cognitive functions were identified (Chan 2023). In these patients, longitudinal improvements were found in most cognitive functions except for logical memory (Chan 2023). Comparing the two trajectories of cognitive functions, one trajectory of patients had significant deterioration of logical memory while the other group had significant improvement (Chan 2023). In this study it was observed that patients with baseline diminished expression were associated with baseline and longitudinal changes of processing speed and verbal fluency while patients with diminished motivation were associated with baseline and longitudinal changes of processing speed (Chan 2023). Thus, in the study by Chan et al, adult-onset first episode psychosis patients had a homogeneous longitudinal improvement in most cognitive functions but not for logical memory, which suggests the unique nature of verbal memory (Chan 2023). The distinct relationship between baseline subdomains of negative symptoms with baseline and longitudinal cognitive functions suggests that there is a differential overlapping etiology between negative symptom subdomains and cognitive functions (Chan 2023).

TRAJECTORIES OF SOFT NEUROLOGICAL SIGNS IN SCHIZOPHRENIA

Schizophrenia patients exhibit subtle and non-localizing neurological abnormalities, referred to as neurological soft signs (Lui 2021). These Neurological soft signs are interesting to study because they vary along the course of schizophrenia (Lui 2021). As well as studying positive and negative symptoms, trajectories of Neurological soft signs have been studied using the abridged version of the Cambridge Neurological Inventory, at three points over five years (Lui 2021). It has been proposed, that neurological soft signs reflect the underlying neuropathology development in schizophrenia (Lui 2021, Bray 2009). In order to study the relationship between neurological soft signs and treatment resistance in first-episode schizophrenia patients, a longitudinal study was carried out on 52 first-episode schizophrenia patients over five years (Lui 2021). The trajectories of neurological soft signs in 29 treatment-responsive patients (with full symptomatic remission) and 23 treatment-resistant patients (who received clozapine) were compared (Lui 2021). Although the two schizophrenia groups had comparable neurological soft signs at baseline, the trajectories of neurological soft signs differed significantly (Lui 2021). Compared with the treatment-responsive patients, treatment-resistant schizophrenia patients had worsening of neurological soft signs over time (Lui 2021). Hence, it may be that progressive worsening of neurological soft signs in treatment-resistant schizophrenia patients may reflect the development of the underlying neuropathology of the illness (Lui 2021, Bray 2009).

RELATIONSHIP OF TRAJECTORIES OF POSITIVE AND NEGATIVE SYMPTOMS TO TRAJECTORIES OF FUNCTIONING

Additionally, the PANSS enables the description of trajectories of general patient functioning, which is frequently impaired in individuals with schizophrenia. This not only allows the tracking of the progression of positive and negative symptoms, but also the mapping out of the overall functioning and daily living capabilities of the patient. By comparing these trajectories, it becomes possible to gain a more comprehensive understanding of how fluctuations in symptom severity impact overall functioning and vice versa, thus facilitating more targeted and effective treatment strategies.

A study of the trajectory of general functioning was the Abdin study of 2017. Three distinct trajectories for functioning, that is (1) high functioning trajectory, (2) moderately stable functioning trajectory and (3) deterioration in functioning trajectory were identified in the Abdin et al. sample (Abdin 2017).

In the Abdin et al. sample, those in the delayed response trajectory for positive and negative symptoms, the early response and relapse for negative and general psychopathology symptoms and the slower response or no response trajectories for general psychopathology symptoms were significantly associated with higher odds of having deterioration in functioning over time when compared to the individuals in the early response and stable trajectory (Abdin 2017).

In the Abdin et al. sample, the Poor symptom trajectories described above were also significantly predicted by younger age, male gender, unemployed and economically inactive status, lower education, longer duration of untreated psychosis and diagnosis of schizophrenia spectrum and delusional disorders (Abdin 2017).

Rammou et al. (2019) conducted a study based on the London Early Intervention for Psychosis services to examine the association of negative symptoms with the clinical features of psychosis at first presentation to mental health services for psychosis with outcomes at 1-year follow-up (Rammou 2019). The subjects were 484 first-episode psychosis patients who had complete Positive and Negative Syndrome Scale data at baseline and 1-year follow-up (Rammou 2019). At 1-year follow-up, Negative Symptoms at presentation were associated with worse Global Assessment of Functioning Scale for symptom ($B = -0.28$, $P < 0.01$) and disability ($B = -0.27$, $P < 0.05$) and with hospital admission ($OR = 1.06$, $P < 0.01$) (Rammou 2019). Thus, Negative symptoms at presentation to Early Intervention Services were associated with worse functioning at entry and poorer outcomes 1 year later (Rammou 2019).

A study by Suen et al. of 330 patients with first-episode schizophrenia spectrum disorders over 12 years (Suen 2023), supports the idea that severity of early Negative Symptoms influences the prognosis of schizophrenia (Suen 2023). Furthermore, the severity and variability of early Negative Symptoms is differentially associated with long-term clinical symptoms, executive function, and functional outcomes via distinct pathways (Suen 2023).

INTERPLAY BETWEEN TRAJECTORIES OF POSITIVE AND NEGATIVE SYMPTOMS

Understanding the relationship between the trajectories of positive and negative symptoms of schizophrenia is of significant interest, and various studies have explored this complex relationship.

Schizophrenia is a highly heterogeneous disorder with positive and negative symptoms being the characteristic manifestations of the disease (Chen 2013). Little is known about the longitudinal pattern of negative symptoms and their linkage with the positive symptoms (Chen 2013). Therefore Chen et al. (2013) assessed the inter-relationship between these two groups of symptoms in 399 patients to find out whether they are related to or independent of each other (Chen 2013). The Positive and Negative Syndrome Scale (PANSS) was used to assess the symptoms. Chen et al. identified four distinct negative symptom trajectories and three positive symptom trajectories (Chen 2013). The trajectory matrix formed 11 combined trajectory patterns (Chen 2013), which showed that negative and positive symptom trajectories moved generally in parallel (Chen 2013). The eleven trajectory patterns combined into three major distinct patterns: (1) dramatic and sustained early improvement in both negative and positive symptoms ($n = 70$, 18%), (2) mild and sustained improvement in negative and positive symptoms ($n = 237$, 59%), and (3) no improvement in either negative or positive symptoms ($n = 82$, 21%) (Chen 2013). Chen et al's one year study of symptom trajectories showed that the changes in negative and positive symptoms were neither inversely nor independently related with each other (Chen 2013). However, the relationship between the positive and negative symptom domains in schizophrenia appeared to depend on each other and this was deemed to suggest a unified pathological disease process in spite of there being different symptom groups (Chen 2013).

RELATIONSHIP OF TRAJECTORIES OF POSITIVE AND NEGATIVE SYMPTOMS TO ANTIPSYCHOTIC USE

One important application of trajectory studies in schizophrenia is to observe whether the use of antipsychotic drugs leads to changes in the trajectory of the illness, including potential improvements in symptom severity and overall patient functioning. By analysing these trajectories, researchers can assess the long-term efficacy and impact of antipsychotic treatments on the progression of schizophrenia.

Using trajectory studies to compare patient response to different types of antipsychotic drugs was one of the first applications of trajectory studies.

Levine et al. published two papers in 2010 (Levine 2010a,b) which demonstrated the heterogenicity of trajectories of response of first episode psychosis to antipsychotic treatment. Both papers used the Positive and Negative syndrome scale PANSS in order to measure symptoms and thence trajectories. Heterogenicity could be seen because symptom improvement ranged from very good response to poor response.

It is generally accepted that antipsychotics are more effective than placebo (Marques 2011) in treating schizophrenia. Marques et al. studied data on 420 patients with schizophrenia treated for 6 weeks in two studies comparing Olanzapine and Haloperidol (Marques 2011), to determine whether drug-treated and placebo-treated subjects show similar or distinct patterns of response or trajectories (Marques 2011). The technique used was "growth mixture modelling" (Marques 2011). It was reported that positive symptoms were found to respond along four distinct trajectories, of which the two most common trajectories were (1) 'Partial responder' and (2) 'Responder' and accounted for 70% of the patients and were seen proportionally in both drug- and placebo-treated patients (Marques 2011). The most striking drug-placebo difference was in the (3) 'Dramatic responders', which were only found among the drug-treated patients (Marques 2011). The fourth trajectory were (4) 'poor responders'. The response of

negative symptoms in this group of patients was more modest and did not show such distinct trajectories (Marques 2011). Marques et al. concluded that trajectory models of response, rather than simply dividing patients into responders and non-responders provides a better statistical account of how antipsychotics work (Marques 2011).

Stauffer et al. (2011) studied data from 1990 patients with chronic schizophrenia treated for 24 weeks. They aimed to use trajectory analysis to identify homogeneous subpopulations within the larger heterogeneous population (Stauffer 2011).

In this large, pooled, heterogeneous population of patients treated for schizophrenia 5 distinct trajectories were identified (Stauffer 2011), listed as trajectories 1 to 5 (Stauffer 2011):

- *Trajectory 1*. Dramatic Responders (n=47/1990, 2.4%), severely-ill patients (PANSS=124) with rapid and sustained improvement (51%) by Week 3 (Stauffer 2011).
- *Trajectory 2*. Partial Responders (n=1802/1990, 90.6%), moderately-ill (PANSS=90) with minimal improvement (21%) by Week 4, and little further improvement (Stauffer 2011).
- *Trajectory 3*. Partial Responders-Unsustained (Late) (n=32/1990, 1.6%), markedly-ill (PANSS=95) with minimal initial improvement followed by worsening after Week 12 (Stauffer 2011).
- *Trajectory 4*. Partial Responders-Unsustained (Early) (n=28/1990, 1.4%), markedly-ill (PANSS=102) with minimal initial improvement followed by worsening after Week 8 (Stauffer 2011).
- *Trajectory 5*. Delayed Responders (n=81/1990, 4.1%), markedly-to-severely-ill (PANSS=113) with minimal (11%) improvement at Week 8, but noticeable improvement thereafter (49%) (Stauffer 2011).

The Dramatic Responders were found to be younger and were more likely to be female and Hispanic with higher baseline illness severity (Stauffer 2011).

Stauffer et al. reported that most patients had modest and sustained improvements during treatment with atypical antipsychotics, regardless of the patient's baseline illness severity (Stauffer 2011). This demonstrated that most patients had a partial response to currently available antipsychotic treatments (Stauffer 2011).

The heterogenicity of Schizophrenia in terms of patient response to antipsychotic treatment was demonstrated by Case et al. (2011). They studied the trajectory of response over 12 weeks of study of 628 patients with schizophrenia or schizo-affective disorder treated with risperidone or olanzapine (Case 2011). They found four distinct response trajectories (referred to as Classes) based on Positive and Negative Syndrome Scale (PANSS) total score over 12 weeks: (1) Class 1 (420 patients, 80.6%) with moderate average baseline PANSS total score showing gradual symptom improvement; (2) Class 2 (65 patients, 12.5%) showing rapid symptom improvement; (3) Class 3 (24 patients, 4.6%) with high average baseline PANSS total score showing gradual symptom improvement; and Class 4 (12 patients, 2.3%) showing unsustained symptom improvement (Case 2011). This study identified four distinct treatment response patterns with predominant representation of responders or non-responders to treatment in these classes (Case 2011). It was suggested that this heterogeneity of response may represent discrete endophenotypes of response to treatment which could have different etiologies (Case 2011).

Levine et al. (2012) studied trajectories of 1124 patients with chronic schizophrenia based on the database of the CATIE trial (Levine 2012). The response trajectories for the following antipsychotic medications were evaluated; olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone (Levine 2012). Trajectory analysis of the whole sample showed that 18.9% of participants were in the group of responders(Levine 2012). Olanzapine treated patients were significantly more likely than other treatment groups to belong to the trajectory of responders (n=69, 32.55%; Chi=20.13, df=2, $p<0.01$) (Levine 2012). Each medication group showed that all medication groups had two trajectories except in the case of olanzapine which had three trajectories and olanzapine had the only trajectory which showed a 20% PANSS reduction by the endpoint (Levine 2012). It was commented that these trajectory studies highlighted the heterogeneity in treatment response to different antipsychotics (Levine 2012).

Another study which aimed to explore heterogeneity in the 6-month clinical response to antipsychotic treatment in patients with antipsychotic drug-naive schizophrenia in 467 patients was by Nordon et al. (2014). Five trajectory groups were identified: (1) a rapid response group (n = 45), (2) a gradual response group (n = 204), (3) patients remaining mildly ill (n = 133), (3) (4) patients remaining very ill (n = 23), and (5) a group with unsustained clinical response (n = 62) (Nordon 2014). It was concluded that Clinical response in patients with schizophrenia 6 months after a first-ever antipsychotic drug initiation is heterogeneous (Nordon 2014).

Trajectory studies of different antipsychotic drugs continue to be carried out, in particular to explore response to antipsychotic treatment over longer periods of time, including in chronic patients, whereas earlier studies were often for first episode patients over short periods of time, in order to establish early response.

Takeuchi et al. conducted a study over one year of 2826 patients treated with anti-psychotics. The improvement in positive and negative symptoms was maintained while antipsychotic treatment was maintained, whereas symptoms continuously worsened over time in those switching to placebo treatment (Takeuchi 2017).

In a study of 373 participants in the OPUS trial, (Starzer 2023) trajectories displaying continuous positive and negative symptoms were linked to higher use of antipsychotic medication at 20-year follow-up (continuous positive symptoms: 78%; continuous negative symptoms: 67%).

Drosos et al. (2022) examined the response trajectories and predictors for belonging to different trajectory groups in order to investigate the effectiveness of the three atypical antipsychotic drugs amisulpride, aripiprazole, and olanzapine (Drosos 2022). A three-trajectory model based on the Positive and Negative Syndrome Scale (PANSS) total score reduction was found to adequately describe the findings (Drosos 2022).

The three antipsychotics were tested as predictors for the patients belonging to the different trajectory groups (Drosos 2022). 144 participants were included, of which 41% completed the 12-month study period (Drosos 2022).

- The largest trajectory group, included 74% of participants, showed a PANSS total score reduction of 59% from baseline at 12 months (Drosos 2022). This was the Good response group (Drosos 2022).
- A trajectory group comprising 13% of participants had their PANSS total score reduced by 82.5% at 12 months, called the Strong response group (Drosos 2022).
- The last response trajectory group comprising 13% of the participants had a PANSS total score reduction of 13.6%, called the Slight response group (Drosos 2022).

The greatest part of the total reduction for the Good and Strong response groups occurred within six weeks of treatment, amounting to 45% and 48% reductions from baseline, respectively (Drosos 2022).

In the Drosos study, the use of amisulpride predicted belonging to the Strong response group (Drosos 2022).

In the Drosos study, unemployment, depression, and negative psychotic symptoms at baseline increased the chance of belonging to the Slight response group, indicating a poor response to antipsychotic drug treatment (Drosos 2022).

In the Drosos study most of the participants (87%) had a good outcome after one year (Drosos 2022).

An important *prospective* study of response to antipsychotic treatment is that of Milligate et al. (2022).

Milligate et al. (2022) studied 46 patients with early first episode psychosis to observe prospectively the response to antipsychotic treatment of psychosis (Milligate 2022). They hypothesised that poorer cognitive functioning at the initial assessment would be associated with poorer antipsychotic response following the subsequent 6 weeks (Milligate 2022). The participants had to be within the first 2 years of illness onset, and had received minimal antipsychotic treatment before the trial (Milligate 2022). Antipsychotic response was determined at 6 weeks using the Positive and Negative Syndrome Scale (PANSS), and cognitive performance was assessed at each visit using the Brief Assessment of Cognition in Schizophrenia (BACS) (Milligate 2022). The investigation identified two clear trajectories of treatment response in the first 6 weeks of antipsychotic treatment (Milligate 2022). These were responders and non responders (Milligate 2022). There was no significant relationship between baseline BACS on subscale and total performance (BACS t-score: OR=0.98, p=0.620, Cohen's d=0.218) and antipsychotic response at 6 weeks (Milligate 2022). This suggested that either larger samples may being required or that an association between cognitive performance and antipsychotic response is not observable in the first 2 years of illness onset (Milligate 2022). While the Milligate study is a short term study which measures the trajectory of the initial response of acute psychosis to initial antipsychotic treatment, it is important because it is a prospective study (Milligate 2022).

In general, Trajectories of treatment response to the psychopharmacological medication of the negative symptoms of schizophrenia demonstrate substantial heterogeneity (Levine 2014).

CONCLUSIONS

The study from the Opus Study (Starzer 2023) shows that the majority of patients with first-episode schizophrenia spectrum disorder have a trajectory with early stable remission of positive symptoms. Furthermore it is confirmed that long duration of untreated psychosis and comorbid substance abuse are modifiable predictors of poor trajectories for positive symptoms in these patients (Starzer 2023).

In the OPUS study of auditory hallucinations, it was shown that the majority of patients with schizophrenia-spectrum disorder improved on auditory hallucinations during the first ten years, but almost one out of four had a fluctuating course with 13% experiencing an increase to severe and daily auditory hallucinations after ten years (Köhler-Forsberg 2022).

In the Goghari 20 year study, it was shown that the early presence of hallucinations predicted the lack of future periods of recovery in all patients (Goghari 2013). Furthermore, increased hallucinatory activity was associated with reduced likelyhood of returning to work in all patients (Goghari 2013).

Another important point of the Goghari 20 year study of 2013, is that the longitudinal course of hallucinations clearly differentiated between schizophrenia and bipolar disorder with psychosis, and suggested that there were some diagnostic similarities between schizophrenia and schizoaffective disorder, as well as between bipolar disorder and schizoaffective disorder and depression (Goghari 2013).

The Goghari 20 year study of 2016 suggested that the observing of the longitudinal course is more important for differentiating schizophrenia and schizoaffective disorder, whereas the symptoms in the initial years may be more useful to differentiate schizoaffective disorder from bipolar disorder (Goghari 2016). Furthermore, it was found that the early presence of auditory hallucinations was associated with a reduced likelihood for a future period of recovery (Goghari 2016). Regarding olfactory hallucinations none were present at the index hospitalization in any patients, while over the course of 20 years, only a minority of schizophrenia patients presented with olfactory hallucinations, while very few schizoaffective and bipolar patients presented with olfactory hallucinations (Goghari 2016).

Regarding negative symptoms, the OPUS study shows that in about half of patients, negative symptoms do not improve over time (Starzer 2023). Negative symptoms, in addition to being associated with poor social and neurocognitive functioning, may prevent patients from seeking help (Starzer 2023).

The studies emphasize the importance of studying the longitudinal course, or trajectories of symptoms in order to understand the relationship between schizophrenia and related disorders and recovery (Goghari 2016).

The results of the Abdin study confirm that the symptoms trajectories among patients with first episode psychosis are heterogeneous and suggest that a small group of first psychotic episode patients may be at higher risk of deterioration in symptom severity and functioning over the 2-year follow-up period (Abdin 2017). Chan et.al also commented that their results, also on patients who were recruited in their first episode of schizophrenia, demonstrated the heterogeneity of longitudinal outcomes of negative symptoms and therefore the importance of personalized interventions for each patient (Chan 2020). Austin et al. also commented that trajectories of illness for positive and negative symptoms were heterogeneous among people with first episode psychosis (Austin 2015). Nordon too commented that 'It is clear that clinical response in patients with schizophrenia 6 months after a first-ever antipsychotic drug initiation is heterogeneous' (Nordon 2014). Therefore It is advised (Nordon 2014) that therapeutic strategies in first episode psychosis should take into account symptom severity and early clinical response, in order to maximize the chances of recovery.

In light of these findings, a tailored, early intervention approach remains paramount in transforming the heterogeneous trajectories of schizophrenia towards pathways of recovery.

It may be commented that the unanimous view of all the papers reviewed, including the most recent, published in the 2020s that duration of untreated psychosis, drug abuse, poverty, poor education, all can be identified as risk factors for a more pathological outcome in the treatment of Schizophrenia provides further justification for the Early intervention Guidelines first produced in the United Kingdom in the 1990s (IRIS 2012, Birchwood 2013).

Further it can be recommended that the trajectory of all patients with Schizophrenia should be routinely assessed using the PANSS scale repeatedly during the treatment of patients with Schizophrenia and other psychotic illness in order to demonstrate the trajectory of illness in an ongoing fashion and thus guide the treatment process.

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