



Original article

Levels of and changes in psychosis symptoms and clinical insight: Exploring the impact of differential antipsychotic mechanisms

Lena Antonsen Stabell^{a,b,*}, Erik Johnsen^{a,b,c}, Rune Kroken^{a,b}, Else-Marie Løberg^{a,d}, Eirik Kjelby^a, Inge Joa^{e,f}, Solveig Klæbo Reitan^{g,h}, Maria Rettenbacherⁱ, Kenneth Hugdahl^{a,j,l}, Rolf Gjestad^{a,k}

^a Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

^b Department of Clinical Medicine, University of Bergen, Bergen, Norway

^c Mohn Research Centre for Psychotic Disorders, Bergen, Norway

^d Faculty of Psychology, Department of Clinical Psychology, University of Bergen, Bergen, Norway

^e TIPS, Centre for Clinical Research in Psychosis, Stavanger University Hospital, Stavanger, Norway

^f Institute of Public Health, Faculty of Health Sciences, University of Stavanger, Stavanger, Norway

^g Department of Mental Health, Nidely DPS, St. Olav University Hospital, Trondheim, Norway

^h Department of Mental Health, Faculty of Medicine and Health Sciences, NTNU, Trondheim, Norway

ⁱ Department of Psychiatry, Psychotherapy and Psychosomatics, Medical University of Innsbruck, Innrain 52, Innsbruck, Austria

^j Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway

^k Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital, Bergen, Norway

^l Department of Complex Systems, Institute of Computer Science, Czech Academy of Sciences, Prague, Czech Republic

ARTICLE INFO

ABSTRACT

Keywords:

Dopamine antagonist
Partial dopamine agonist
Schizophrenia
Latent growth curve models
Illness awareness

Background: Impaired clinical insight is common in schizophrenia spectrum disorders (SSDs) and predicts poor treatment adherence and outcomes. It is linked to disorganized, positive, negative, and hostility symptoms. However, few studies repeatedly assess insight after antipsychotic initiation while comparing pharmacologically distinct agents. This study examined how symptom levels and changes predict the development and endpoint of clinical insight over 6 weeks, contrasting the partial dopamine agonist aripiprazole (PDA) with two dopamine antagonists (DAs).

Methods: Data from 144 SSD patients in the Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTro) trial, a pragmatic, semi-randomised study of amisulpride, aripiprazole, and olanzapine, were analysed using latent growth curve models. Insight was measured by PANSS Item G12; symptom factors (positive, negative, hostility, cognitive/disorganized) were derived from PANSS.

Results: Lower baseline symptoms and greater improvement between weeks 3 and 6 predicted better insight at 6 weeks across all factors. For positive symptoms, improvement between weeks 1 and 3 ($b = 0.57$, $p = 0.009$) also predicted better insight. Patients on aripiprazole showed less improvement in insight, though some findings lost significance after correction.

Conclusion: Symptom reduction is associated with improved insight, with early changes in positive symptoms exerting the fastest effect. Despite symptom improvement, aripiprazole PDA treatment was linked to less insight gain than DA treatment. These preliminary findings warrant further study.

1. Introduction

Impaired insight, a core feature of schizophrenia spectrum disorders

(SSDs), is observed in up to 80 % of patients with SSDs (Amador and Gorman, 1998) and is reported in both first- and multiple-episode schizophrenia (Lysaker et al., 2018). Clinical insight is characterised

* Corresponding author at: Research Department, Sandviken Sykehus, Haukeland University Hospital, P. Box 1400, 5021 Bergen, Norway.

E-mail addresses: lena.antonsen.stabell@helse-bergen.no (L.A. Stabell), erik.johnsen@helse-bergen.no (E. Johnsen), rune.andreas.kroken@helse-bergen.no (R. Kroken), else.-marie.loberg@helse-bergen.no (E.-M. Løberg), eirik.kjelby@helse-bergen.no (E. Kjelby), inge.joa@sus.no (I. Joa), solveig.reitan@ntnu.no (S.K. Reitan), Maria.Rettenbacher@i-med.ac.at (M. Rettenbacher), Hugdahl@uib.no (K. Hugdahl), rolf.gjestad@helse-bergen.no (R. Gjestad).

by awareness of the illness, the ability to recognise symptoms as abnormal, and the capacity to acknowledge the need for treatment (David, 1990). Poor clinical insight hampers shared decision-making and the ability to consent to treatment (Owen et al., 2009; Spencer et al., 2018), poses a challenge to treatment adherence, and worsens treatment outcomes (Kim et al., 2020). Both antipsychotic treatment and non-pharmacological interventions can help mitigate issues related to poor insight (Phelan and Sigala, 2022).

The relationships between insight and various other psychosis symptoms have been well documented in the literature. Impaired insight has been associated with disorganisation (Subotnik et al., 2020), positive symptoms (Mintz et al., 2003), negative symptoms (Raucher-Chéné et al., 2022), and hostility (Reinhardt et al., 2014; Volavka et al., 2016). Psychosis-related comorbid conditions may also influence insight. Findings regarding depression are mixed. One meta-analysis found a weak association between poor insight and depressed mood (Subotnik et al., 2020), whereas other studies have reported a small positive relationship between good clinical insight and depression in patients with schizophrenia (Belvederi Murri et al., 2015; Mintz et al., 2003). A network analysis further suggested that depressive symptoms were associated with good insight (Amore et al., 2020). Substance use is another comorbidity that both directly and indirectly affects insight, influencing the rate of change in other psychosis symptoms (Alisauskienė et al., 2019), the severity of psychosis symptoms (Talamo et al., 2006), and cognitive capacity.

While evidence suggests that insight improves with antipsychotic treatment due to a reduction in symptom load (Mattila et al., 2017; Mervis et al., 2022; Pijnenborg et al., 2015; Stabell et al., 2023), few studies have conducted repeated assessments of insight during the initial treatment phase, when symptoms improve rapidly (Agid et al., 2003). Consequently, it remains difficult to determine which specific changes in psychosis symptoms are associated with improvements in insight. Our study aims to address this gap by examining how changes in insight relate to changes in other symptom domains over time. This longitudinal approach may offer a more nuanced understanding of the interplay between insight and symptomatology, especially in the early phase of treatment. Additionally, prior exposure to antipsychotic treatment may influence the efficacy of antipsychotics (Zhu et al., 2017) and, in turn, may also affect their impact on insight.

The neurobiological substrates of clinical insight remain only partially understood, but several studies have shown that reduced grey matter volume in prefrontal cortex (PFC) areas is associated with lower insight (Pijnenborg et al., 2020). These areas are involved in cognitive functions such as attention, executive function, and self-reflection, which may be important for clinical insight (Shad et al., 2006; Song et al., 2025; van der Meer et al., 2013). Similarly, functional magnetic resonance imaging studies have demonstrated positive associations between impaired clinical and cognitive insight and reduced activation in several brain regions, including prefrontal and hippocampal areas (Buchy et al., 2016; van der Meer et al., 2013). However, these findings are less consistent than structural findings, possibly because clinical insight is not linked to discrete brain regions but rather involves a network of interconnected areas in a complex relationship (Pijnenborg et al., 2020). Additionally, reduced PFC dopaminergic function has been implicated in schizophrenia and is associated with both negative and cognitive symptoms (Howes et al., 2024). Treatments that enhance PFC activity may therefore be theoretically relevant for improving cognitive functions. Given that clinical insight is a construct that intersects with multiple cognitive domains, including metacognition (Vohs et al., 2018) and executive functioning (Aleman et al., 2006), it is plausible that enhancing PFC activity could also improve clinical insight.

The newer class of antipsychotic drugs, partial dopamine agonists (PDAs), has been found to increase activity in PFC areas compared with traditional dopamine antagonists (DAs) (Tuplin and Holahan, 2017). This effect may be at least partly due to the partial agonist activation of dopamine receptors in these brain regions. Regarding clinical insight,

this mechanism may be particularly relevant, as reviewed by Pijnenborg et al. (Pijnenborg et al., 2020) and supported by a study reporting a positive effect on insight following treatment with the PDA aripiprazole during the high-risk state of psychosis (Kobayashi et al., 2009). Aripiprazole has also been shown to have beneficial cognitive effects (Taminga, 2002), although its superiority over other antipsychotic drugs in terms of efficacy has not been established (Anda et al., 2021; Feber et al., 2025).

The current study presents data from the Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTro) trial, a novel head-to-head comparison of amisulpride, aripiprazole, and olanzapine. Previously published BeSt InTro studies reported differential effects of the three drugs on total psychosis symptoms after just 3 weeks of treatment (Johnsen et al., 2020). However, regarding clinical insight, no differential effects were observed during the first 6 weeks of treatment on total psychosis symptoms (Stabell et al., 2023). The present study complements our earlier work by shifting the focus from total psychosis symptoms to symptoms dimensions, and from the effectiveness of individual compounds to broader pharmacological mechanisms—specifically, dopaminergic action. The study drugs include two dopamine antagonists (DAs), amisulpride and olanzapine, and one partial dopamine agonist (PDA), aripiprazole, selected in part for their distinct dopaminergic profiles. This provides a unique opportunity to investigate whether dopamine antagonism and partial dopamine agonism influence clinical insight differently. To our knowledge, this represents a novel comparison within a single, well-characterised sample.

This study aimed to investigate how baseline levels and changes in psychosis symptoms predict both clinical insight over a six-week period, in the context of treatment with either dopamine antagonists (DA) or partial dopamine agonists (PDA).

Hypothesis:

We hypothesised that higher baseline psychosis symptoms and greater symptom reduction over time would be associated with greater improvement in clinical insight, and that these relationships would differ between individuals treated with DA versus PDA antipsychotics.

More specifically:

- 1) Positive symptoms will have a stronger predictive value for changes in clinical insight than other dimensions of symptoms.
- 2) Individuals treated with PDA antipsychotics will show a steeper improvement in clinical insight compared to those treated with DA antipsychotics.

2. Methods

2.1. Design

This is a sub-study¹ of the BeSt InTro trial, a multicentre, longitudinal, pragmatic, semi-randomised trial. Participants with a schizophrenia spectrum disorder were treated with amisulpride, aripiprazole, or olanzapine. The three drugs were randomly assigned to a sequence for each participant. Upon entering the study, participants began antipsychotic treatment based on the first drug in their assigned sequence. However, if they had previously experienced unsatisfactory effects or intolerable side effects with that drug, they could switch to the next drug in the sequence, hence the classification as a semi-randomised trial. This paper reports on the drug actually chosen at baseline, in collaboration with the treating physician, and present a per-protocol analysis of the first 6 weeks of the trial, with assessments conducted at baseline and at weeks 1, 3, and 6. For a more detailed description of the BeSt InTro

¹ The change in insight was a planned secondary outcome of the BeSt InTro study, as documented in the approved pretrial protocol. However, this sub-study was not registered at clinicaltrials.gov (NCT01446328). The study protocol is available upon request.

study, please refer to the primary outcome paper (Johnsen et al., 2020).

2.2. Sample

Participants were recruited as inpatients and outpatients from hospitals at the four study sites: Bergen, Stavanger, and Trondheim in Norway and Innsbruck in Austria. Inclusion took place from 20 October 2011 to 30 December 2016. The inclusion criteria were an age of ≥ 18 years, the ability to take oral antipsychotic medication, a diagnosis within chapter F20–F29 of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) based on the SCID-I interview, and active-phase psychosis, defined as a score of ≥ 4 on at least one of the following PANSS items: P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual thought content). The exclusion criteria were pregnancy or lactation, organic psychosis, an inability to understand the native language, hypersensitivity to the active substances in the study drugs, or somatic contraindications related to the study drugs, such as a known risk of narrow-angle glaucoma or prolactin-dependent tumours.

2.3. Measurements

2.3.1. Positive and negative syndrome scale (PANSS)

The PANSS was used to assess psychosis symptoms. This scale comprises 30 items, each rated from 1 (symptoms not present) to 7 (symptoms present at the highest possible level). All assessors were trained and calibrated by the PANSS Institute until inter-rater reliability was deemed satisfactory. Assessments were conducted at baseline and at weeks 1, 3, and 6. Based on a recent meta-analysis evaluating the PANSS structure (Lim et al., 2021), we used the following factors in our analysis. The **positive factor** included P1 (delusions), G9 (unusual thought content), P6 (suspiciousness/persecution), P3 (hallucinatory behaviour), and P5 (grandiosity). The **negative factor** comprised N2 (emotional withdrawal), N4 (passive/apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), N3 (poor rapport), N1 (blunted affect), G16 (active social avoidance), and G7 (motor retardation). The **cognitive/disorganisation factor** consisted of P2 (conceptual disorganisation), G11 (poor attention), N7 (stereotyped thinking), N5 (difficulty in abstract thinking), G13 (disturbance of volition), G5 (mannerism and posturing), and G10 (disorientation). Finally, the **hostility factor** included P7 (hostility), P4 (excitement), G14 (poor impulse control), G8 (uncooperativeness), and G4 (tension).

Item G12 of the PANSS assesses insight, specifically the individual's ability to recognise symptoms, the need for treatment, and the capacity to make judgements. Higher scores indicate more impaired insight. The score for this item is highly correlated with other measures of insight in schizophrenia (Parellada et al., 2011; Sanz et al., 1998) and separating this item from the rest of the PANSS is common in studies investigating clinical insight when a dedicated insight assessment has not been used, including large-scale studies such as EULAST and CATIE (Ozzoude et al., 2019; Pijnenborg et al., 2015). According to the meta-analysis by Lim et al. (Lim et al., 2021), G12 is classified under the positive factor. However, we excluded this item from the positive factor analysis in our study because it served as our outcome variable. This decision was made to avoid analytical circularity and is consistent with previous research practices when clinical insight is the focus of investigation. It enabled a more precise examination of how changes in symptom domains relate to changes in insight over time.

2.3.2. Covariates

Based on their different dopaminergic antipsychotic mechanisms, treatment with amisulpride and olanzapine was classified as DA treatment, while aripiprazole was classified as PDA treatment. Baseline depression levels were assessed using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990), a scale recognised for its reliability and strong predictive, divergent, and concurrent validity

(Lako et al., 2012). Participants were classified as antipsychotic-naïve if they had no prior exposure to antipsychotic medication before enrolment. Treatment information was self-reported and verified against medical records. Illicit drug use classification was based on combined baseline scores from the Drug Use Disorders Identification Test (DUDIT) (Hildebrand, 2015) and the Clinician Drug Use Scale (CDUS) (Drake RE, 1996), both of which have demonstrated high sensitivity and specificity (Hildebrand, 2015; Møller and Linaker, 2010). Patients who used only alcohol and/or tobacco were not included in the illicit drug use group (Alisauskiene et al., 2023). Symptom severity and functioning were assessed with the Clinical Global Impression-Severity (CGI-S) (Guy, 1976) and the split version of the Global Assessment of Functioning (GAF) (Karterud et al., 1998).

2.4. Statistics

Descriptive analyses were conducted using SPSS statistical software package, version 29 (IBM, 2022). The Benjamini-Hochberg (BH) corrections were computed using R version 4.5.0 (R, 2025). All other operations and analyses were performed in Mplus version 8.9 (Muthén and Muthén, 2023). To account for missing data in the CDSS, DUDIT, or CDUS results for some patients, multiple imputation was applied, generating 100 datasets.

To ensure consistency across variables, the total score for each PANSS factor was divided by the number of items included in that factor. We examined levels and changes in clinical insight, the four PANSS factors, and the mPANSS score. Model fit was evaluated using the chi-square significance test (acceptable fit: $p > 0.05$), the comparative fit index ($CFI > 0.95$), the Tucker-Lewis index ($TLI > 0.95$), and the root mean square error of approximation (RMSEA), with thresholds indicating a mediocre fit (< 0.10), a fair fit (< 0.08), and a close fit (< 0.05), using a standard 90 % confidence interval (Wang and Wang, 2012).

Five separate latent growth curve (LGC) models, incorporating intercept and slope factors, were estimated to describe both the mean and individual variations in trajectories for G12 insight and four predictor domains: the mPANSS total score, and the Positive, Negative, Cognition/Disorganisation, and Hostility factors (Bollen KA, 2006; Wang and Wang, 2012). Where linear change did not adequately fit the data, piecewise growth models were applied to allow for multiple slope factors representing different time intervals. To ensure model identification, constraints were placed on residuals over time, as well as on slope variances and covariances. Time was specified in weeks.

Multivariate LGC models were then used to examine how both the level and change in these time-varying predictors, alongside static predictors, influenced changes and final levels in G12 insight. This was done by reversing the time scores in the outcome. PANSS levels and changes predicted outcome changes within the same intervals as well as in later intervals, including the final insight level. Interaction terms between the PDA predictor and other predictor processes explored potential moderation effects.

Aripiprazole, classified as a PDA, was assigned a value of 1, while amisulpride and olanzapine, classified as DAs, were assigned a value of 0. The per-protocol use of a PDA versus a DA, drug use, antipsychotic naïvety, and baseline CDSS scores were included as static predictors, enabling analysis of their relationships with both outcomes and the main predictors. Cross-titration of medication was permitted during the study; however, because only four participants switched from PDA to DA and only one switched from DA to PDA within the six-week treatment period, the treatment group based on antipsychotic mechanism (PDA vs DA) was treated as a time-independent variable.

Whether PDA moderated the relationships between PANSS factor levels and changes in insight was analysed using latent interaction terms, which were removed if not statistically significant. To reduce the number of estimates, residuals were constrained to be equal across time points, and negative slope residuals in the structural models were constrained to zero if necessary. The maximum likelihood robust estimator

was used to account for minor non-normality in the outcome measure (Wang and Wang, 2012). The level of statistical significance was set at $\alpha = 0.05$ (two-tailed).

To correct for multiple testing, we analysed the omnibus test using the Model Test function in Mplus for defined families of relationships: baseline predictors, within-time predictors, cross-lagged predictors over time, end-level predictors, and PDA predictors. If this overall test was statistically significant, the false discovery rate (FDR) correction based on BH corrections was applied. Exploratory interaction models involving PDA by PANSS intercept and slope factors were not corrected, as interaction terms are typically small in effect size and therefore require larger sample sizes to reach statistical significance.

2.5. Ethics

This study was approved by regional ethics committees and medical agencies in both Norway and Austria. Participants provided informed consent before data collection commenced. All methods were conducted in accordance with the Declaration of Helsinki and the ICH guidelines for good clinical practice. Participants were reimbursed for travel expenses.

3. Results

3.1. Descriptive

This study involved 144 participants, with 93 participants in the DA group receiving olanzapine or amisulpride and 51 in the PDA group receiving aripiprazole. The sample comprised both first- and multiple-episode patients as indicated by prior antipsychotic use. The patients' baseline characteristics are presented in Table 1. There were no significant differences between the DA and PDA groups except for a higher proportion of men and poorer insight in the PDA group ($\chi^2 = 4.88$, df = 1, $p = 0.027$ and $t = 2.81$, df = 123.41, $p = 0.006$, respectively). At baseline, the mean clinical insight score indicated moderate impairment, while the CGI score reflected marked illness. After 6 weeks of antipsychotic treatment, 21 % of participants still exhibited impaired clinical insight as indicated by a score of ≥ 4 on PANSS item G12 (range: 1–6, with 8 patients scoring ≥ 5), while the CGI score indicated moderate illness. See the flow chart (Fig. 1) for details on attrition during the first 6 weeks of the study.

3.2. Levels of and changes in clinical insight, the four PANSS factors, and the mPANSS score

The levels and changes in clinical insight, the four PANSS factors, and the mPANSS score are presented in Table 2. Measures of model fit for each analysis can be found in the supplementary material. Clinical insight improved from baseline to week 1 and again from week 3 to week 6. The mPANSS score, hostility factor score, and positive symptom factor score showed improvements at all time points. By contrast, the negative factor score and the cognitive/disorganized factor score improved from baseline to week 3 but did not show further improvement from week 3 to week 6. All models demonstrated individual variance across all time intervals.

3.3. Symptom predictors of clinical insight development and endpoint

Table 3 presents the relationships between the levels and changes in clinical insight and the levels and changes in the predictor variables, as well as the differences between patients receiving a PDA and those receiving DAs. No significant associations were found between being antipsychotic-naïve or baseline depression levels and clinical insight in any of the symptom models. All models reported were part of our general hypothesis that higher baseline psychosis symptoms and greater symptom reduction over time would be associated with greater

Table 1
Baseline characteristics of patient sample in the BeSt InTro trial.

	Total sample (n = 144)	DA treatment (n = 93)	PDA treatment (n = 51)
Age, years	31.7 (12.7)	31.2 (12.5)	32.4 (13.3)
Men	93 (65 %)	54 (58 %)	39 (77 %)
White ethnicity	118 (82 %)	80 (92 %)	38 (81 %)
Years of education	12.3 (2.8)	12.5 (2.9)	11.9 (2.6)
Schizophrenia F20	84 (58 %)	55 (59 %)	29 (57 %)
Schizotypal F21	2 (1 %)	2 (2 %)	0 (0 %)
Delusional disorder F22	21 (15 %)	13 (14 %)	8 (16 %)
Acute and transient F23	18 (12 %)	13 (14 %)	5 (9 %)
Schizoaffective F25	10 (7 %)	6 (7 %)	4 (8 %)
Other nonorganic F28	1 (1 %)	0 (0 %)	1 (2 %)
Unspecified nonorganic F29	8 (6 %)	4 (4 %)	4 (8 %)
Antipsychotic-naïve	56 (39 %)	33 (36 %)	23 (45 %)
PANSS G12 Insight	3.4 (1.2)	3.2 (1.3)	3.8 (1.0)
mPANSS total	75.0 (15.5)	76 (16.4)	73.3 (13.6)
PANSS positive	21.2 (4.8)	21.1 (4.7)	21.5 (4.9)
PANSS negative	17.8 (6.1)	18.2 (6.5)	17.2 (5.4)
PANSS general - G12	36.0 (8.3)	36.6 (8.4)	34.7 (8.1)
PANSS positive factor total	17.6 (4.1)	17.6 (4.1)	17.7 (4.1)
PANSS negative factor total	14.3 (5.6)	14.9 (5.8)	13.1 (5.3)
PANSS cognitive/ disorganized factor total	16.6 (5.3)	16.5 (5.9)	16.6 (4.3)
PANSS hostility factor total	10.0 (4.1)	10.0 (4.1)	10.0 (4.1)
CDSS	6.7 (5.1)	7.2 (5.3)	5.9 (4.9)
CGI	5.0 (0.8)	5.0 (0.8)	4.9 (0.8)
GAF	35.8 (9.3)	36.2 (9.5)	35.5 (8.8)
Substance use	53 (36.8 %)	29 (32 %)	24 (48 %)

Data are presented as mean (standard deviation) or n (%).

Abbreviations: N: number in total sample; n: number in subsample based on antipsychotic mechanism; DA: dopamine antagonist; PDA: partial dopamine agonist; PANSS: Positive and Negative Syndrome Scale; PANSS G12: General Item 12 assessing insight; CDSS: Calgary Depression Scale for Schizophrenia; CGI: Clinical Global Impression Scale; GAF: Global Assessment of Functioning Scale-split version.

Positive factor: P1 Delusions, G9 Unusual thought content, P6 Suspiciousness/persecution, P3 Hallucinatory behaviour, P5 Grandiosity.

Negative factor: N2 Emotional withdrawal, N4 Passive/apathetic social withdrawal, N6 Lack of spontaneity and flow of conversation, N3 Poor rapport, N1 Blunted affect, G16 Active social avoidance, G7 Motor retardation.

Cognitive/Disorganized factor: P2 Conceptual disorganization, G11 Poor attention, N7 Stereotyped thinking, N5 Difficulty in abstract thinking, G13 Disturbance of volition, G5 Mannerism and posturing, G10 Disorientation.

Hostility factor: P7 Hostility, P4 Excitement, G14 Poor impulse control, G8 Uncooperativeness, G4 Tension.

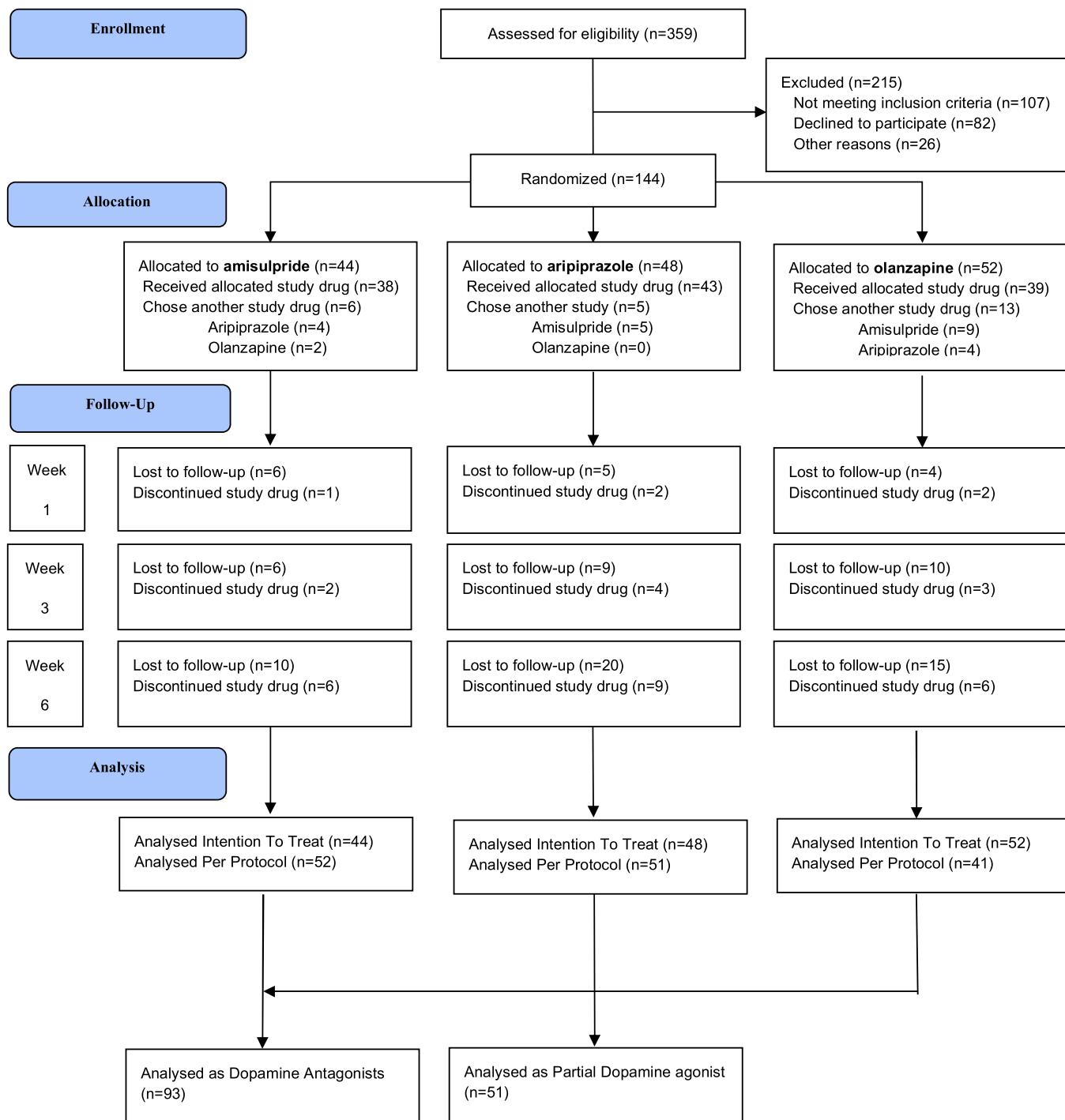
improvement in clinical insight.

3.3.1. mPANSS score

A greater reduction in the mPANSS score was associated with greater improvement in insight across all intervals. A higher baseline mPANSS score predicted a less marked improvement in insight during the week 1–3 interval. After six weeks, less impaired insight was predicted by a lower baseline mPANSS score and a greater reduction in the mPANSS score during the week 3–6 interval. Patients treated with PDA exhibited more impaired insight at the 6-week mark, however, the effect did not survive correction for multiple comparisons ($p = 0.0096$). Additionally, individuals using illicit drugs showed a smaller improvement in insight during the 0–1 week interval ($b = 0.41$, $p = 0.029$).

3.3.2. PANSS positive factor (P1, P3, P5, P6, and G9)

This model addresses our first specified hypothesis. A greater reduction in the PANSS Positive Factor score was associated with greater improvements in insight during the week 0–1 and week 1–3 intervals. After 6 weeks, less severe impairment of insight was predicted by a



Notes: Lost to follow up=explicit withdrawal from further participation in the study or not showing up at subsequent study visits.

Fig. 1. Flow chart of participants in the first 6 weeks of the BeSt InTro trial.

lower baseline Positive Factor score and a greater reduction in positive symptoms during the week 1–3 and week 3–6 intervals.

3.3.3. PANSS negative factor (N1, N2, N3, N4, N6, G7, and G16)

A greater reduction in the PANSS Negative Factor score was associated with greater improvement in insight during the week 1–3 and week 3–6 intervals. Following adjustment for multiple testing, the result no

longer reached statistical significance ($p = 0.054$ for both findings). After 6 weeks, less severe impairment of insight was predicted by a lower baseline Negative Factor score and a reduction in the Negative Factor score during the week 3–6 interval. Additionally, individuals using illicit drugs exhibited a smaller improvement in insight during the week 0–1 interval ($b = 0.48$, $p = 0.013$).

Table 2
Estimated levels of and changes in outcome and predictor processes.

		Mean	p ^a	SD	p ^b
Insight	Baseline	2.23	<0.001	1.12	<0.001
	Change w 0–1	-0.66	0.001	0.65	0.014
	Change w 1–3	-0.65	0.181	0.16	0.416
	Change w 3–6	-0.36	0.021	0.27	0.002
mPANSS score	Baseline	2.59	<0.001	0.50	<0.001
	Change w 0–1	-0.32	<0.001	0.34	<0.001
	Change w 1–3	-0.10	<0.001	0.18	<0.001
	Change w 3–6	-0.03	0.043	0.11	0.001
Positive factor	Baseline	3.52	<0.001	0.68	<0.001
	Change w 0–1	-0.52	<0.001	0.38	0.076
	Change w 1–3	-0.20	<0.001	0.24	0.002
	Change w 3–6	-0.08	0.002	0.18	0.005
Negative factor	Baseline	2.43	<0.001	0.88	<0.001
	Change w 0–1	-0.19	0.002	0.57	<0.001
	Change w 1–3	-0.06	0.049	0.25	<0.001
	Change w 3–6	0.03	0.242	0.16	0.001
Cognitive/Disorganised factor	Baseline	2.37	<0.001	0.73	<0.001
	Change w 0–1	-0.28	<0.001	0.43	<0.001
	Change w 1–3	-0.14	<0.001	0.19	<0.001
	Change w 3–6	-0.01	0.752	0.11	0.007
Hostility factor	Baseline	1.94	<0.001	0.79	<0.001
	Change w 0–1	-0.24	<0.001	0.53	<0.001
	Change w 1–3	-0.05	0.084	0.24	<0.001
	Change w 3–6	-0.03	0.200	0.16	0.005

PANSS: Positive and Negative Syndrome Scale.

Insight: item G12 of the PANSS.

mPANSS score: PANSS total score minus the score for item G12.

Positive factor: P1 (delusions), G9 (unusual thought content), P6 (suspiciousness/persecution), P3 (hallucinatory behaviour), and P5 (grandiosity).

Negative factor: N2 (emotional withdrawal), N4 (passive/apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), N3 (poor rapport), N1 (blunted affect), G16 (active social avoidance), and G7 (motor retardation).

Cognitive/Disorganised factor: P2 (conceptual disorganisation), G11 (poor attention), N7 (stereotyped thinking), N5 (difficulty in abstract thinking), G13 (disturbance of volition), G5 (mannerism and posturing), and G10 (disorientation).

Hostility factor: P7 (hostility), P4 (excitement), G14 (poor impulse control), G8 (uncooperativeness), and G4 (tension).

w: week.

Mean: at the single-item level within the process.

SD: standard deviation.

p ^a: p value for means.

p ^b: p value for standard deviations.

3.3.4. PANSS Cognitive/Disorganised Factor (P2, G11, N7, N5, G13, G5, and G10)

A greater reduction in Cognitive/Disorganised Factor symptoms was associated with greater improvement in insight across all intervals. Greater improvements in insight during the week 1–3 interval was linked to lower baseline scores for the Cognitive/Disorganised Factor. At the 6-week endpoint, a greater level of insight was associated with a lower baseline Cognitive/Disorganised Factor score and a greater

reduction in this score during the week 3–6 interval. Additionally, individuals who used illicit drugs exhibited less marked improvements in insight during the first week of antipsychotic treatment ($b = 0.42$, $p = 0.032$).

3.3.5. PANSS Hostility Factor (P7, P4, G14, G8, and G4)

A greater reduction in the Hostility Factor was associated with greater improvement in insight during the same interval for the week 1–3 and week 3–6 periods. Greater improvement in insight during the week 1–3 interval was linked to a lower baseline level of the Hostility Factor. At the 6-week endpoint, a greater level of insight was associated with a lower baseline Hostility Factor score, yet significance was lost after BH correction ($p = 0.054$) and a greater reduction in hostility symptoms during the week 3–6 interval. Additionally, in the uncorrected model patients treated with PDA exhibited more marked impairment of insight after 6 weeks of treatment. This initially observed statistically significant association did not remain significant after correction for multiple comparisons ($p = 0.072$).

3.4. Differential effects of PDA vs DA antipsychotics on clinical insight

To address our second specified hypothesis, we tested whether the type of antipsychotic treatment (PDA vs DA) moderated the relationship between symptom change and insight. We identified two significant moderated relationships between predictor processes and PDA use on changes in insight. The interaction effect between the baseline level of the Cognitive/Disorganised Factor and PDA use on clinical insight in the 1- to 3-week period was statistically significant (PDA use: $b = -0.75$, $p = 0.025$; cognition: $b = 0.11$, $p = 0.048$; interaction effect: $b = 0.39$, $p = 0.010$). This indicates that the greatest improvement in clinical insight during this period was observed in patients who used a PDA and had less severe cognitive/disorganisation symptoms at baseline. Furthermore, the interaction effect between the change in the mPANSS score in the week 1–3 interval and PDA use was significantly related to changes in clinical insight in the week 3–6 interval (mPANSS score: $b = 0.60$, $p = 0.184$; PDA: $b = 0.73$, $p = 0.063$; interaction effect: $b = -1.37$, $p = 0.007$). This suggests that a stronger improvement in insight was observed in patients who used a PDA and demonstrated a greater reduction in mPANSS scores in the previous interval.

After 6 weeks of treatment, patients who used a PDA and had a lower baseline mPANSS score reported less marked improvement in clinical insight compared with those who took a DA and had a lower baseline mPANSS score (PDA use: $b = 3.24$, $p = 0.007$; mPANSS score: $b = 1.50$, $p < 0.001$; interaction effect: $b = -1.03$, $p = 0.019$), as illustrated in Fig. 2. This group difference was smaller in patients with higher baseline mPANSS scores. The scores for other symptom factors did not show significant relationships with clinical insight at the endpoint.

4. Discussion

This study is the first to investigate the associations between the severity of psychosis symptoms, clinical insight, and changes in these parameters following the initiation of antipsychotic treatment, with a specific focus on differences between patients taking a DA versus a PDA. Improvements in mPANSS and cognitive/disorganised symptoms were consistently associated with improvements in clinical insight across all time intervals. Additionally, early improvements in positive symptoms and later improvements in negative and hostility symptoms were linked to enhanced clinical insight. After 6 weeks of treatment, better clinical insight was predicted by lower baseline scores across all symptom factors and greater symptom improvements in the week 3–6 interval, as well as improvements in positive symptoms during the week 1–3 interval. On average, patients treated with a PDA exhibited poorer clinical insight at baseline, showed more improvement in clinical insight over time, yet still had poorer clinical insight at the 6-week endpoint compared to those treated with DAs.

Table 3

Prediction of clinical insight at the endpoint and changes in clinical insight.

	Changes in insight						Insight at the endpoint	
	Change w 0–1		Change w 1–3		Change w 3–6		Level week 6	
	b	p	b	p	b	p	b	p
mPANSS								
PDA	−0.26	0.177	−0.04	0.685	0.09	0.262	0.60	0.024*
Baseline	−0.40	0.076	0.28	0.007	0.03	0.756	1.08	<0.001
Change w 0–1	1.45	<0.001	−0.10	0.525	−0.27	0.061	0.48	0.249
Change w 1–3			1.36	<0.001	−0.14	0.606	1.57	0.054
Change w 3–6					1.71	0.001	5.99	<0.001
Positive factor								
PDA	−0.44	0.103	−0.03	0.760	0.08	0.376	0.48	0.091
Baseline	−0.10	0.582	0.09	0.184	0.01	0.923	0.57	0.009
Change w 0–1	1.69	0.019	0.05	0.715	−0.19	0.314	0.41	0.502
Change w 1–3			0.64	0.016	0.29	0.220	1.94	0.012
Change w 3–6					0.60	0.078	2.48	0.021
Negative factor								
PDA	−0.24	0.231	0.02	0.854	0.02	0.842	0.47	0.075
Baseline	−0.23	0.112	0.08	0.248	0.06	0.258	0.43	0.014
Change w 0–1	0.47	0.054	−0.03	0.822	−0.11	0.253	−0.07	0.770
Change w 1–3			0.63	0.046*	0.05	0.785	1.26	0.104
Change w 3–6					0.72	0.022*	2.75	0.006
Cog/dis factor								
PDA	−0.19	0.342	0.01	0.891	0.01	0.866	0.05	0.699
Baseline	−0.11	0.422	0.23	0.001	0.03	0.667	0.81	<0.001
Change w 0–1	1.08	0.002	−0.14	0.313	−0.03	0.791	0.50	0.153
Change w 1–3			1.10	0.003	0.08	0.788	1.13	0.253
Change w 3–6					1.84	0.003	5.09	0.022
Hostility factor								
PDA	−0.21	0.315	−0.02	0.819	0.11	0.210	0.64	0.018*
Baseline	−0.12	0.459	0.17	0.013	−0.12	0.100	0.48	0.027*
Change w 0–1	0.54	0.190	0.04	0.806	−0.37	0.013	0.33	0.537
Change w 1–3			0.93	0.001	−0.39	0.113	1.28	0.088
Change w 3–6					1.22	0.011	4.36	0.001

The predictors are levels and changes in the mPANSS score and the scores for the four factors on the PANSS.

PANSS: Positive and Negative Syndrome Scale.

mPANSS: modified Positive and Negative Syndrome Scale.

Insight: item G12 of the PANSS.

mPANSS score: PANSS total score minus the score for item G12.

Positive factor: P1 (delusions), G9 (unusual thought content), P6 (suspiciousness/persecution), P3 (hallucinatory behaviour), and P5 (grandiosity).

Negative factor: N2 (emotional withdrawal), N4 (passive/apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), N3 (poor rapport), N1 (blunted affect), G16 (active social avoidance), and G7 (motor retardation).

Cognitive/Disorganized (Cog/dis) factor: P2 (conceptual disorganization), G11 (poor attention), N7 (stereotyped thinking), N5 (difficulty in abstract thinking), G13 (disturbance of volition), G5 (mannerism and posturing), and G10 (disorientation).

Hostility factor: P7 (hostility), P4 (excitement), G14 (poor impulse control), G8 (uncooperativeness), and G4 (tension).

PDA: partial dopamine agonist.

w: week.

b: regression coefficient.

p: p value.

*: Not significant after Benjamini-Hochberg correction.

In line with our general hypothesis, the finding that improvements in clinical insight are related to reductions in psychosis symptoms aligns with previous research and clinical experience. This association remains consistent across different timeframes, from the short 6-week follow-up in our study to the 2-year period reported by Phahladira et al. (Phahladira et al., 2018). The novelty of our study lies in its more detailed investigation of which changes in specific symptom dimensions predict changes in insight during the early treatment phase, when symptom reduction is typically most pronounced. In line with our first specified hypothesis, our results indicate that improvements in positive symptoms are the first to influence both the change in and the final level of clinical insight. Previous studies have consistently placed the insight item, G12, within the positive factor in PANSS factor analyses, reinforcing the idea that core psychosis symptoms are closely linked to insight impairment (Emsley et al., 2003; Lim et al., 2021; Shafer and Dazzi, 2019). Furthermore, positive symptoms often manifest in behaviour and communication in an overt manner, meaning that their improvement could lead to better cooperation with clinicians, which might be misinterpreted as improved clinical insight. However, it can

also be argued that positive symptoms are often most severe during the acute phase of psychosis, and their rapid alleviation in response to antipsychotic treatment may partly explain our findings (Emsley et al., 2006). By contrast, a recent network analysis of PANSS levels at acute admission suggested that insight belongs to the cognitive domain. However, the authors noted that longitudinal studies are needed to better understand the interplay between symptoms and domains (Redlich Bossy et al., 2024). Our finding that improvements in cognitive/disorganized symptoms were associated with improvements in clinical insight at all time points during the 6-week period provides some support for this perspective, although within a limited timeframe.

Our analysis of static predictors yielded few significant findings. Being antipsychotic-naïve had no significant impact on changes in or the endpoint of clinical insight. Participants classified as using illicit drugs exhibited less marked improvement in insight during the first week of treatment in the mPANSS, negative, and cognitive models; however, illicit drug use had no significant impact on clinical insight after 6 weeks of treatment. The literature remains inconclusive regarding the causal relationship between depression and clinical insight. Given that our

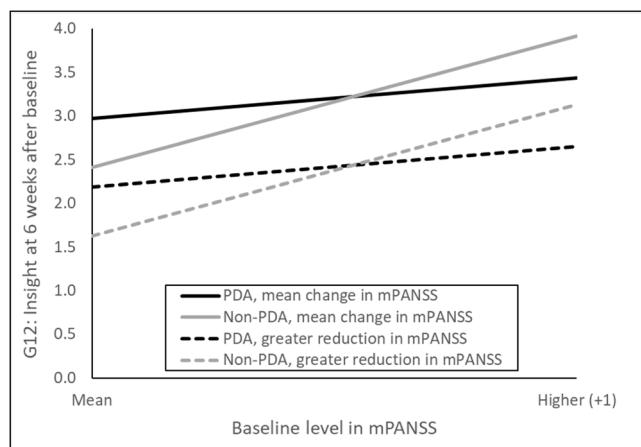


Fig. 2. End level of clinical insight after 6 weeks of antipsychotic treatment, predicted by baseline level and changes in mPANSS score, as well as antipsychotic mechanism

mPANSS score = total Positive and Negative Syndrome Scale (PANSS) score minus item G12.

Estimation of baseline level and change in mPANSS score:

Mean baseline mPANSS score = 2.62, plus 1 unit describing higher levels of mPANSS baseline score (= 3.62).

Mean reduction in mPANSS per week: 0–1 week interval (S1) = −0.04; 1–3 week interval (S2) = −0.33; 3–6 week interval (S3) = −0.36.

Greater reduction: S1 = −0.04; S2 = −0.66; S3 = −0.82.

PANSS: Positive and Negative Syndrome Scale

mPANSS: modified Positive and Negative Syndrome Scale

PDA: partial dopamine agonist

G12: insight item from the PANSS; lower scores indicate better insight

The effect of medication naïvety, CDSS, and illicit drug use on G12 held constant at zero.

sample included participants with both impaired and intact clinical insight, we used baseline depression levels to predict clinical insight after 6 weeks, allowing depression to influence both symptom cluster changes and the insight process. However, we found no significant relationship between baseline depression levels and clinical insight. This negative finding was somewhat unexpected and may be related to the acute or subacute state of our participants. A cross-sectional network analysis examining the relationship between depressive symptoms and insight reported that in clinically stable patients, the global network structure did not differ between individuals with high versus low total PANSS scores (Amore et al., 2020). Our sample size did not allow for an analysis of changes in depressive symptoms or their potential interplay with psychosis symptoms and insight.

This study also contributes to the existing literature by distinguishing between DPA and DA treatment, both as an adjusted main effect and as a moderator of the relationships between predictor dimensions and insight over time. In our sample, the influence of PDA treatment on insight was weaker than that of DA treatment. This was contrary to our second specified hypothesis. However, after correction, the association was no longer statistically significant. At baseline, the PDA group exhibited more impaired insight compared to the DA group, which may have indirectly influenced insight levels after 6 weeks of treatment. Previous research has suggested that clinical symptoms can affect insight differently in men and women (Pousa et al., 2024), and given that there were more men in the PDA group, this demographic difference could have contributed to the observed disparity between the two antipsychotic mechanisms. In both the mPANSS and hostility models, participants treated with a PDA exhibited poorer insight after 6 weeks of treatment. The absence of this relationship in the other models may be attributed to omitted variables, such as antipsychotic drug dosage. Although the correlation between PDA use and clinical insight was not statistically significant in all models, the observed associations were

consistently positive, indicating that those treated with a PDA had poorer insight levels overall. This consistency suggests there may be an underlying signal related to PDA treatment, even though statistical significance was lost following adjustment for multiple comparisons. The interaction analysis further demonstrated that patients treated with a PDA exhibited poorer insight after 6 weeks than those treated with DAs, although improvements in insight were dependent on the degree of symptom reduction. This finding underscores the importance of symptom reduction in improving insight. Nonetheless, our findings suggest that, given an equivalent level of symptom reduction, DAs may be more effective than the PDA aripiprazole in enhancing clinical insight during the initial phase of treatment. These results should be interpreted with caution, but they offer a meaningful contribution to an area that has received limited empirical attention and warrant further investigation in larger, more comprehensive studies. Previous studies have indicated that aripiprazole, the PDA included in this study, may require more time to reach its full therapeutic efficacy. The primary BeSt InTro trial paper reported differential effects among the three study drugs at 3 weeks, but by 26 weeks, aripiprazole was found to be equally effective as olanzapine (Johnsen et al., 2020). Similarly, a systematic review and meta-analysis comparing aripiprazole to DAs in first-episode schizophrenia found that risperidone was more efficacious than aripiprazole in short-term treatment (<6 months), but aripiprazole was superior in long-term treatment (Kim et al., 2021). Additionally, an efficacy and safety study of aripiprazole in first-episode psychosis reported that treatment outcomes at 6 weeks were better predicted by week 3 data rather than week 2 data (Park et al., 2014). Furthermore, a systematic review found that the mean clinical response time for aripiprazole in treating delusional disorders was approximately 5.7 weeks (Miola et al., 2020). Collectively, these findings suggest that our 6-week follow-up period may have been too short for PDA treatment to reach its full effect on insight. Post hoc analyses at both 12- and 26-week endpoints were conducted; however, because of a lack of variance in insight as time progressed, we were unable to estimate these models. Our findings also contrast with previous studies that reported a positive effect of PDA use on insight in a small sample of patients with prodromal psychosis (Kobayashi et al., 2009) and a study that found no differences in the effects of second-generation antipsychotics, including aripiprazole, on insight in patients experiencing psychosis exacerbations (Bianchini et al., 2014). One study revealed differential effects of PDA use in first-episode versus multiple-episode schizophrenia, possibly due to mechanisms such as dopamine supersensitivity (Kim et al., 2021). In our mixed sample of antipsychotic-naïve patients and those previously treated with antipsychotics, we did not replicate this finding, which may have been different with a longer follow-up period. Finally, it is important to acknowledge that the classification of DAs and the PDA aripiprazole in this study was based solely on their different dopaminergic mechanisms, making it a relatively coarse distinction. The three study drugs are pharmacologically heterogeneous and exhibit distinct receptor affinity profiles (Kaar et al., 2020). Consequently, grouping amisulpride and olanzapine together in the DA category may have masked other pharmacological differences that could have influenced the results. However, in a previous head-to-head comparison of the three drugs, no significant differences were found in their effects on clinical insight during the first 6 weeks of treatment (Stabell et al., 2023).

Some of our findings did not remain significant after multiple testing correction. This could be due to multiple reasons like chance, small effect size or sample size or overfitting the data or a combination of these.

Our findings must be interpreted in light of several limitations. Clinical insight was assessed using a single item: G12 of the PANSS. While more comprehensive insight assessments, such as the Scale to Assess Unawareness of Mental Disorders (SUMD), might have yielded different results, prior research has shown that the PANSS insight-related item is highly correlated with scores from more detailed clinical insight measures (Sanz et al., 1998). Furthermore, our study did not assess introspective accuracy or cognitive insight—concepts that could

have provided additional perspectives on our research question (Mervis et al., 2022). We also observed substantial attrition from baseline to the study endpoint, which is a common challenge in antipsychotic drug trials. However, the attrition rate in our study was comparable to that reported in similar trials (Wahlbeck et al., 2001). Missing data were handled using maximum likelihood estimation under the assumption that the data were missing at random. Some of our findings did not remain statistically significant after correction for multiple testing. This may be due to factors such as chance, small effect sizes, limited sample size, overfitting, or a combination of these. We reduced the risk of Type I error by applying omnibus tests and corrections for multiplicity but acknowledge that the complexity of the models warrants cautious interpretation.

In conclusion, this study highlights that symptom reduction leads to improvements in clinical insight, with changes in positive symptoms being the quickest to influence insight. However, although symptom reduction appeared comparable between groups, participants treated with a PDA tended to show poorer clinical insight after six weeks of treatment than those receiving DAs. This may suggest that the PDA used in this study requires more time to reach its full therapeutic effect. Whether this delayed response offsets the potential benefits of fewer side effects remains unclear. The complex interactions between symptom improvements, side effects, changes in insight, treatment adherence, and differential antipsychotic mechanisms warrants further investigation in longitudinal studies. These considerations may be relevant to clinical decision-making, particularly when balancing short-term outcomes with long-term tolerability and adherence.

Data availability

The datasets generated and/or analysed during the current study are not available. According to Norwegian law, data sharing requires approval from the Regional Committees for Medical and Health Research Ethics and the Data Protection Officer at Haukeland University Hospital, based on specific research proposals. Requests can be addressed to Professor Erik Johnsen at erik.johnsen@helse-bergen.no.

CRediT authorship contribution statement

Lena Antonsen Stabell: Writing – original draft, Formal analysis, Data curation. **Erik Johnsen:** Writing – review & editing, Funding acquisition, Conceptualization. **Rune Kroken:** Writing – review & editing, Conceptualization. **Else-Marie Løberg:** Writing – review & editing, Conceptualization. **Eirik Kjelby:** Writing – review & editing, Investigation. **Inge Joa:** Writing – review & editing, Project administration, Data curation. **Solveig Klaubo Reitan:** Writing – review & editing, Project administration, Investigation. **Maria Rettenbacher:** Writing – review & editing, Investigation. **Kenneth Hugdahl:** Writing – review & editing, Conceptualization. **Rolf Gjestad:** Writing – review & editing, Formal analysis, Data curation.

Declaration of competing interest

The authors declare no competing interests.

Acknowledgements

We thank Farivar Fathian, Renata Alisauskienė, Igne Sinkevičiūtė, Liss Gøril Anda, and Berit Walla for their contributions to data collection, and Jill Bjarke for coordinating follow-ups for most of the participants. This study was fully publicly funded by the Research Council of Norway (#213727), the Western Norway Regional Health Trust (#9111679, #9111820, F-12506), and participating hospitals and universities. The funding sources had no role in the study design, data collection, analysis, or interpretation, nor in the writing of the report or the decision to submit the paper for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2026.116948](https://doi.org/10.1016/j.psychres.2026.116948).

References

- Addington, D., Addington, J., Schissel, B., 1990. A depression rating scale for schizophrenics. *Schizophr. Res.* 3 (4), 247–251.
- Agid, O., Kapur, S., Arenovich, T., Zipursky, R.B., 2003. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. *Arch. Gen. Psychiatry* 60 (12), 1228–1235.
- Aleman, A., Agrawal, N., Morgan, K.D., David, A.S., 2006. Insight in psychosis and neuropsychological function: meta-analysis. *Br. J. Psychiatry* 189 (3), 204–212.
- Alisauskienė, R., Johnsen, E., Gjestad, R., Kroken, R.A., Kjelby, E., Sinkevičiūtė, I., Fathian, F., Joa, I., Reitan, S.K., Rettenbacher, M., Løberg, E.-M., 2023. Does drug use affect the efficacy of amisulpiride, aripiprazole and olanzapine in patients with schizophrenia spectrum disorders? Results from a pragmatic, randomised study. *Gen. Hosp. Psychiatry* 83, 185–193.
- Alisauskienė, R., Løberg, E.M., Gjestad, R., Kroken, R.A., Jørgensen, H.A., Johnsen, E., 2019. The influence of substance use on the effectiveness of antipsychotic medication: a prospective, pragmatic study. *Nord. J. Psychiatry* 73 (4–5), 281–287.
- Amador, X.F., Gorman, J.M., 1998. Psychopathologic domains and insight in schizophrenia. *Psychiatr. Clin. N. Am.* 21 (1), 27–42.
- Amore, M., Murri, M.B., Calcagno, P., Rocca, P., Rossi, A., Aguglia, E., Bellomo, A., Blasi, G., Carpinello, B., Cuomo, A., dell'Osso, L., di Giannantonio, M., Giordano, G. M., Marchesi, C., Monteleone, P., Montemagni, C., Oldani, L., Pompili, M., Roncone, R., Rossi, R., Siracusano, A., Vita, A., Zeppogno, P., Corso, A., Arzani, C., Galderisi, S., Maj, M., 2020. The association between insight and depressive symptoms in schizophrenia: undirected and Bayesian network analyses. *Eur. Psychiatry* 1–21.
- Anda, L., Johnsen, E., Kroken, R.A., Joa, I., Rettenbacher, M., Løberg, E.M., 2021. Cognitive change and antipsychotic medications: results from a pragmatic rater-blind RCT. *Schizophr. Res.* 206, 100204.
- Belvederi Murri, M., Respino, M., Innamorati, M., Cervetti, A., Calcagno, P., Pompili, M., Lamis, D.A., Ghio, L., Amore, M., 2015. Is good insight associated with depression among patients with schizophrenia? Systematic review and meta-analysis. *Schizophr. Res.* 162 (1–3), 234–247.
- Bianchini, O., Porcelli, S., Nespeca, C., Cannavò, D., Trappoli, A., Aguglia, E., De Ronchi, D., Serretti, A., 2014. Effects of antipsychotic drugs on insight in schizophrenia. *Psychiatry Res.* 218 (1), 20–24.
- Bollen, K.A., P. C., 2006. Latent Curve models: A structural Equation Perspective. Wiley-Interscience, Hoboken, N.J.
- Buchy, L., Barbato, M., MacMaster, F.P., Bray, S., Clark, D., Deighton, S., Addington, J., 2016. Cognitive insight is associated with cortical thickness in first-episode psychosis. *Schizophr. Res.* 172 (1–3), 16–22.
- David, A.S., 1990. Insight and Psychosis. *Br. J. Psychiatry* 156 (6), 798–808.
- Drake, R.E., K. M., McHugh, G.J., 1996. Clinician rating scales: alcohol Use Scale (AUS), Drug Use Scale (DUS) and Substance Abuse Treatment Scale (SATA). In: B, D., B, S.L. a. (Eds.), Outcome Assessment in Clinical Practice. Williams & Wilkins, Baltimore.
- Emsley, R., Rabinowitz, J., Medori, R., 2006. Time course for antipsychotic treatment response in first-episode schizophrenia. *Am. J. Psychiatry* 163 (4), 743–745.
- Emsley, R., Rabinowitz, J., Torreman, M., 2003. The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis. *Schizophr. Res.* 61 (1), 47–57.
- Feber, L., Peter, N.L., Chiocchia, V., Schneider-Thoma, J., Sifaris, S., Bighelli, I., Hansen, W.P., Lin, X., Prates-Baldez, D., Salanti, G., Keefe, R.S.E., Engel, R.R., Leucht, S., 2025. Antipsychotic drugs and cognitive function: a systematic review and network meta-analysis. *JAMA Psychiatry* 82 (1), 47–56.
- Guy, W., 1976. ECDEU Assessment Manual For Psychopharmacology. US Department of Health, Education, and Welfare, Public Health Service
- Hildebrand, M., 2015. The psychometric properties of the drug use disorders identification test (DUDIT): a review of recent research. *J. Subst. Abuse Treat.* 53, 52–59.
- Howes, O.D., Bukala, B.R., Beck, K., 2024. Schizophrenia: from neurochemistry to circuits, symptoms and treatments. *Nat. Rev. Neurol.* 20 (1), 22–35.
- IBM, 2022. IBM SPSS Statistics for Windows Version 26. IBM, New York.
- Johnsen, E., Kroken, R.A., Løberg, E.-M., Rettenbacher, M., Joa, I., Larsen, T.K., Reitan, S. K., Walla, B., Alisauskienė, R., Anda, L.G., Bartz-Johannessen, C., Berle, J.Ø., Bjarke, J., Fathian, F., Hugdahl, K., Kjelby, E., Sinkevičiūtė, I., Skrede, S., Stabell, L., Steen, V.M., Fleischhacker, W.W., 2020. Amisulpiride, aripiprazole, and olanzapine in patients with schizophrenia-spectrum disorders (BeS InTro): a pragmatic, rater-blind, semi-randomised trial. *Lancet Psychiatry* 7 (11), 945–954.
- Karterud, S., Pedersen, G., Loevdahl, H., Friis, S., 1998. Global Assessment of Functioning-Split Version (S-GAF): Background and Scoring Manual. Ullevaal University Hospital, Department of Psychiatry, Oslo, Norway.
- Kim, D.D., Barr, A.M., Lian, L., Yuen, J.W.Y., Fredriksson, D., Honer, W.G., Thornton, A. E., Procyshyn, R.M., 2021. Efficacy and tolerability of aripiprazole versus D2 antagonists in the early course of schizophrenia: a systematic review and meta-analysis. *npj Schizophr.* 7 (1), 29.
- Kim, J., Ozzuode, M., Nakajima, S., Shah, P., Caravaggio, F., Iwata, Y., De Luca, V., Graff-Guerrero, A., Gerretsen, P., 2020. Insight and medication adherence in schizophrenia: an analysis of the CATIE trial. *Neuropharmacology* 168, 107634.

- Kobayashi, H., Morita, K., Takeshi, K., Koshikawa, H., Yamazawa, R., Kashima, H., Mizuno, M., 2009. Effects of aripiprazole on insight and subjective experience in individuals with an at-risk mental state. *J. Clin. Psychopharmacol.* 29 (5), 421–425.
- Kaar, S.J., Natesan, S., McCutcheon, R., Howes, O.D., 2020. Antipsychotics: mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. *Neuropharmacology* 172, 107704.
- Lako, I.M., Bruggeman, R., Kneegtering, H., Wiersma, D., Schoevers, R.A., Slooff, C.J., Taxis, K., 2012. A systematic review of instruments to measure depressive symptoms in patients with schizophrenia. *J. Affect. Disord.* 140 (1), 38–47.
- Lim, K., Peh, O.-H., Yang, Z., Rekhi, G., Rapisarda, A., See, Y.-M., Rashid, N.A.A., Ang, M.-S., Lee, S.-A., Sim, K., Huang, H., Lenz, T., Lee, J., Lam, M., 2021. Large-scale evaluation of the Positive and Negative Syndrome Scale (PANSS) symptom architecture in schizophrenia. *Asian J. Psychiatry* 62, 102732.
- Lysaker, P.H., Pattison, M.L., Leonhardt, B.L., Phelps, S., Vohs, J.L., 2018. Insight in schizophrenia spectrum disorders: relationship with behavior, mood and perceived quality of life, underlying causes and emerging treatments. *World Psychiatry* 17 (1), 12–23.
- Mattila, T., Koeter, M., Wohlfarth, T., Storosum, J., van den Brink, W., Derkx, E., Leufkens, H., Denys, D., 2017. The impact of second generation antipsychotics on insight in schizophrenia: results from 14 randomized, placebo controlled trials. *Eur. Neuropsychopharmacol.* 27 (1), 82–86.
- Mervis, J.E., Vohs, J.L., Lysaker, P.H., 2022. An update on clinical insight, cognitive insight, and introspective accuracy in schizophrenia-spectrum disorders: symptoms, cognition, and treatment. *Expert Rev. Neurother.* 22 (3), 245–255.
- Mintz, A.R., Dobson, K.S., Romney, D.M., 2003. Insight in schizophrenia: a meta-analysis. *Schizophr. Res.* 61 (1), 75–88.
- Miola, A., Salvati, B., Sambataro, F., Toffanin, T., 2020. Aripiprazole for the treatment of delusional disorders: a systematic review. *Gen. Hosp. Psychiatry* 66, 34–43.
- Muthén, L.K., Muthén, B.O., 2023. Mplus 8.9 ed. Muthén & Muthén, Los Angeles, CA.
- Möller, T., Linaker, O.M., 2010. Using brief self-reports and clinician scales to screen for substance use disorders in psychotic patients. *Nord. J. Psychiatry* 64 (2), 130–135.
- Owen, G.S., David, A.S., Richardson, G., Szmułek, G., Hayward, P., Hotopf, M., 2009. Mental capacity, diagnosis and insight in psychiatric in-patients: a cross-sectional study. *Psychol. Med.* 39 (8), 1389–1398.
- Ozzoude, M., Nakajima, S., Plitman, E., Chung, J.K., Kim, J., Iwata, Y., Caravaggio, F., Takeuchi, H., Uchida, H., Graff-Guerrero, A., Gerretsen, P., 2019. The effects of illness severity, cognition, and estimated antipsychotic dopamine receptor occupancy on insight into the illness in schizophrenia: an analysis of clinical antipsychotic trials of intervention effectiveness (CATIE) data. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 89, 207–213.
- Parellada, M., Boada, L., Fraguas, D., Reig, S., Castro-Fornieles, J., Moreno, D., Gonzalez-Pinto, A., Otero, S., Rapado-Castro, M., Graell, M., Baeza, I., Arango, C., 2011. Trait and state attributes of insight in first episodes of early-onset schizophrenia and other psychoses: a 2-year longitudinal study. *Schizophr. Bull.* 37 (1), 38–51.
- Park, J.I., Cho, D.H., Hahn, S.W., Jeong, B., Kim, J.H., Kim, S.W., Koo, M.S., Lee, S.H., Lee, S.J., Lee, Y.H., Park, J.I., Rho, S.H., Chung, Y.C., 2014. The advantage of using 3-week data to predict response to aripiprazole at week 6 in first-episode psychosis. *Int. Clin. Psychopharmacol.* 29 (2), 77–85.
- Phahladira, L., Asmal, L., Kilian, S., Chiliza, B., Scheffler, F., Luckhoff, H.K., du Plessis, S., Emsley, R., 2018. Changes in insight over the first 24months of treatment in schizophrenia spectrum disorders. *Schizophr. Res.*
- Phelan, S., Sigala, N., 2022. The effect of treatment on insight in psychotic disorders - a systematic review and meta-analysis. *Schizophr. Res.* 244, 126–133.
- Pijnenborg, G.H.M., Larabi, D.I., Xu, P., Hasson-Ohayon, I., de Vos, A.E., Ćurić-Blake, B., Aleman, A., der Meer, L.V., 2020. Brain areas associated with clinical and cognitive insight in psychotic disorders: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.*
- Pijnenborg, G.H.M., Timmerman, M.E., Derkx, E.M., Fleischhacker, W.W., Kahn, R.S., Aleman, A., 2015. Differential effects of antipsychotic drugs on insight in first episode schizophrenia: data from the European First-Episode Schizophrenia Trial (EUFEST). *Eur. Neuropsychopharmacol.* 25 (6), 808–816.
- Pousa, E., Brébion, G., López-Carrilero, R., Ruiz, A.I., Grasa, E., Barajas, A., Cobo, J., Gutiérrez-Zotes, A., Lorente, E., Barrigón, M.L., Ruiz-Delgado, I., González-
- Higueras, F., Frigola-Capell, E., Ochoa, S., 2024. Predictors of clinical insight in first-episode psychosis: different patterns in men and women. *Psychiatry Res.* 339, 116036.
- R, C.T., 2025. R: A language and Environment For Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria., 4.5.0 ed.
- Raucher-Chéné, D., Bodnar, M., Lavigne, K.M., Malla, A., Joober, R., Lepage, M., 2022. Dynamic interplay between insight and persistent negative symptoms in first episode of psychosis: a longitudinal study. *Schizophr. Bull.* 48 (1), 211–219.
- Redlich Bossy, M., Müller, D.R., Jabat, M., Burrel, A., Spiller, T.R., Vetter, S., Seifritz, E., Egger, S.T., 2024. Relationship between psychopathological symptoms and dimensions in inpatients with schizophrenia: a network analysis. *Schizophr. Res.* 272, 36–38.
- Reinhardt, J., Reynolds, G., Dill, C., Serper, M., 2014. Cognitive predictors of violence in schizophrenia: a meta-analytic review. *Schizophr. Res.: Cogn.* 1 (2), 101–111.
- Sanz, M., Constable, G., Lopez-Ibor, I., Kemp, R., David, A.S., 1998. A comparative study of insight scales and their relationship to psychopathological and clinical variables. *Psychol. Med.* 28 (2), 437–446.
- Shad, M.U., Tamminga, C.A., Cullum, M., Haas, G.L., Keshavan, M.S., 2006. Insight and frontal cortical function in schizophrenia: a review. *Schizophr. Res.* 86 (1–3), 54–70.
- Shafer, A., Dazzi, F., 2019. Meta-analysis of the positive and Negative Syndrome Scale (PANSS) factor structure. *J. Psychiatr. Res.* 115, 113–120.
- Song, J., Carmona-Torres, E., Kambari, Y., Chavez, S., Ueno, F., Koizumi, T., Amaev, A., Abdolizadeh, A., De Luca, V., Blumberger, D.M., Remington, G., Pollock, B., Graff-Guerrero, A., Gerretsen, P., 2025. Impaired insight in schizophrenia is associated with higher frontoparietal cerebral blood flow: an arterial spin labeling study. *Schizophrenia* 11 (1), 2.
- Spencer, B.W.J., Gergel, T., Hotopf, M., Owen, G.S., 2018. Unwell in hospital but not incapable: cross-sectional study on the dissociation of decision-making capacity for treatment and research in in-patients with schizophrenia and related psychoses. *Br. J. Psychiatry* 213 (2), 484–489.
- Stabell, L.A., Johnsen, E., Kroken, R.A., Løberg, E.M., Blindheim, A., Joa, I., Reitan, S.K., Rettenbacher, M., Munk-Jørgensen, P., Gjestad, R., 2023. Clinical insight among persons with schizophrenia spectrum disorders treated with amisulpiride, aripiprazole or olanzapine: a semi-randomized trial. *BMC Psychiatry* 23 (1), 482.
- Subotnik, K.L., Ventura, J., Hellemann, G.S., Zito, M.F., Agee, E.R., Nuechterlein, K.H., 2020. Relationship of poor insight to neurocognition, social cognition, and psychiatric symptoms in schizophrenia: a meta-analysis. *Schizophr. Res.*
- Talamo, A., Centorrino, F., Tondo, L., Dimitri, A., Hennen, J., Baldessarini, R.J., 2006. Comorbid substance-use in schizophrenia: relation to positive and negative symptoms. *Schizophr. Res.* 86 (1–3), 251–255.
- Tamminga, C.A., 2002. Partial dopamine agonists in the treatment of psychosis. *J. Neural. Transm. (Vienna)* 109 (3), 411–420.
- Tuplin, E.W., Holahan, M.R., 2017. Aripiprazole, a drug that displays partial agonism and functional selectivity. *Curr. Neuropsychopharmacol.* 15 (8), 1192–1207.
- van der Meer, L., de Vos, A.E., Stiekema, A.P., Pijnenborg, G.H., van Tol, M.J., Nolen, W.A., David, A.S., Aleman, A., 2013. Insight in schizophrenia: involvement of self-reflection networks? *Schizophr. Bull.* 39 (6), 1288–1295.
- Vohs, J.L., Leonhardt, B.L., James, A.V., Francis, M.M., Breier, A., Mehdiyoun, N., Visco, A.C., Lysaker, P.H., 2018. Metacognitive Reflection and Insight Therapy for Early Psychosis: a preliminary study of a novel integrative psychotherapy. *Schizophr. Res.* 195, 428–433.
- Volavka, J., Van Dorn, R.A., Citrome, L., Kahn, R.S., Fleischhacker, W.W., Czobor, P., 2016. Hostility in schizophrenia: an integrated analysis of the combined Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the European First Episode Schizophrenia Trial (EUFEST) studies. *Eur. Psychiatry* 31, 13–19.
- Wahlbeck, K., Tuunainen, A., Ahokas, A., Leucht, S.J.P., 2001. Dropout rates in randomised antipsychotic drug trials. *lancet* 155 (3), 230–233.
- Wang, J., Wang, X., 2012. Structural Equation Modeling: Applications Using Mplus. Wiley, A John Wiley & Sons, Ltd, West Sussex, UK.
- Zhu, Y., Krause, M., Huhn, M., Rothe, P., Schneider-Thoma, J., Chaimani, A., Li, C., Davis, J.M., Leucht, S., 2017. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses. *Lancet Psychiatry*.