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Qing (Dolores) Zhou April 9, 2025

Symptom Profiles Related to Psychotropic Medications in Youth at Clinical High-Risk for Psychosis

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Abstract

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Background:
For individuals at clinical high risk for psychosis (CHR-P), research suggests that baseline antipsychotic use is linked with higher psychosis conversion, but this may be due to confounding symptom severity with medication. This study examines associations between post-baseline psychotropic medication by CHR-P youth and changes in symptoms at 4-month follow-up.

Methods:
Utilizing data from the North American Prodrome Longitudinal Study 3 (NAPLS-3), we examined symptom severity reduction between baseline and 4-month follow-up among CHR-P youth not on baseline psychotropics. Positive, Negative, Disorganization, and General domains were evaluated using the Scale of Prodromal Symptoms (SOPS). We hypothesized that the initiation of antipsychotics post-baseline would be associated with reduced symptom severity at the follow-up compared to no psychotropic medication. Data analyses included nonparametric and propensity score matching methods to explore symptom trajectories across 3 medication types (antipsychotics, antidepressants, and antipsychotics with other psychotropics).

Results:
The sample included 138 participants in four groups: those receiving antipsychotic medication only (AP, n = 9), antipsychotic with other psychotropic medications (n = 8), antidepressant medication only (n = 17), and a group with no psychotropic medications (n = 104). In the non-parametric test, significant medication group differences were found in positive ($\chi^2(3, 138) = 9.67$, p = .022) and general ($\chi^2(3, 138) = 9.3$, p = .022) symptoms. Post-hoc tests showed that antidepressants group had less positive symptom reduction compared to the antipsychotic group ($Z = 2.48$, $p = 0.039$) and the antipsychotic with another psychotropic medication group ($Z = 2.40$, $p = 0.041$. The antipsychotics ($Z = -2.23$, $p = 0.076$) and antidepressants group ($Z = -2.21$, $p = 0.068$) exhibited a greater decrease in general symptoms compared to no-medication control group.

Conclusions:
New antipsychotic medication prescription was associated with reductions in symptom severity over time, with variations observed across different symptom domains, underscoring the potential benefits of tailored symptom-specific management strategies in psychiatric care.

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Symptom Profiles Related to Psychotropic Medications in Youth at Clinical High-Risk for Psychosis

Schizophrenia and other psychotic disorders, are complex and often persistent disorders that impact millions of people worldwide, and pose a huge public health concern because of their profound impact and elevated mortality level (McGrath et al., 2008). With an incidence of 4.1 to 13.2 per 100,000 people per year, schizophrenia and other psychotic disorders contribute significantly to the global health burden (Crespo-Facorro et al., 2021; McGrath et al., 2004). The Diagnostic and Statistical Manual of Mental Disorders-5 TR (American Psychiatric Association & American Psychiatric Association, 2013) defines psychotic disorders on the basis of the presence of two of the following three symptoms: delusions, hallucinations and/or disorganized speech.

Because psychotic disorders are often debilitating and chronic, clinical researchers have expanded their focus to include the prodromal phase of psychosis. The prodrome is the period of functional decline and the gradual emergence of symptoms that typically precedes the clinical onset of psychotic symptoms (Powers et al., 2020; Yung & McGorry, 1996). This period prior to the first episode of psychosis (FEP) can range from months to years and is now considered the most likely stage for the provision of preventive interventions. Further, evidence that longer periods of untreated psychosis can worsen the long-term prognosis (Yu et al., 2023), has contributed to efforts to study the potential predictors of the transition from the prodromal stage to the onset of symptoms that cross the severity threshold to a psychotic disorder.

Based on retrospective and prospective research findings, investigators have developed standardized measures of the subclinical symptoms that often precede psychosis onset (Miller et al., 2003; Modinos & McGuire, 2015; Powers et al., 2020). These are typically structured

diagnostic interviews that measure the severity of attenuated (i e., subclinical) psychotic symptoms. Individuals who meet empirically-based criteria for being at risk for psychosis are often referred to as being at clinical high-risk for psychosis (CHR-P). Because the modal age at onset of psychotic disorders is usually in the early to mid 20s, individuals who meet CHR-P criteria usually are adolescents or young adults (De Pablo et al., 2021).

The present naturalistic study addresses an important question in the field of CHR-P research; specifically, whether psychotropic medications that are commonly used to treat patients with psychosis have the potential to reduce the severity of CHR-P symptoms and thereby potentially prevent or delay the FEP. Because antipsychotics (AP), antidepressants (AD) and stimulant medications are the most commonly prescribed medications for CHR-P youth, they are the focus of this investigation.

The symptoms of Psychosis

The symptoms of schizophrenia and other psychosis are typically grouped into two general classes, positive and negative, with some proposing that cognitive deficits constitute a separate class (Ginovart & Kapur, 2012; Habtewold et al., 2020). Positive symptoms, which include hallucinations, delusions, and disordered thinking, represent an impairment of normal processes and are considered the defining indicators of psychosis. Positive symptoms are characterized by features not present in individuals without psychosis, making them distinct and reliable diagnostic criteria for the disorder (McGrath et al., 2008). Negative symptoms are another domain that frequently occur in conjunction with the positive symptoms of psychosis. Included in this domain are affective blunting, social withdrawal, speech reduction, anhedonia, and avolition. By definition, negative symptoms entail a reduction or lack of normative experiences or behaviors. While the presence of one or more negative symptoms is not required

for a diagnosis of a psychotic disorder, negative symptoms are present in a large proportion of individuals who meet diagnostic criteria for a psychotic disorder. There is some evidence that negative symptoms can arise or worsen in response to AP medications or chronic psychotic illness (American Psychiatric Association & American Psychiatric Association, 2013; Lehman et al., 2004), however recent large studies indicate that there is an average beneficial effect of AP medication for reducing the severity of both positive and negative symptoms (McCutcheon et al., 2022; Sabe et al., 2021).

Like negative symptoms, cognitive symptoms are not required for a diagnosis of schizophrenia or any other psychotic disorder, but they are present in a large proportion of cases. Cognitive symptoms include deficits in attentional, working memory, and cognitive control functions (Kapur & Mamo, 2003). If they are severe, cognitive symptoms can substantially impair general functional abilities, including communication (Diagnostic and statistical manual of mental disorders: DSM-5™, 2013). Nonetheless, it is well-documented that some patients with psychosis manifest cognitive abilities that are above average (Lee et al., 2024).

Epidemiology of Schizophrenia and other Psychoses

Recent systematic reviews have documented evidence for a variety of demographic correlates of psychosis (Staines et al., 2022). Typically first manifesting in adolescence and young adulthood, the peak age at clinical onset is about 20.5 years based on global population data (Solmi et al., 2022). Among individuals diagnosed with FEP, 51% progress to schizophrenia, and 33% develop non-affective psychotic disorders (Kirkbride et al., 2017). Early intervention in FEP has been shown to enhance long-term prognosis by minimizing the duration of untreated psychosis (DUP), thereby reducing disability linked to psychotic disorders (Catalan et al., 2024). The adverse correlates of DUP as measured at first presentation, include more

severe negative symptoms and attempts at self-harm, and longitudinal follow-ups reveal poorer prognosis and lower chance of remission in those with longer DUP (Howes et al., 2021).

Sociodemographic factors are also linked with psychosis. Evidence suggests that sex is associated with schizophrenia and other psychotic disorders, such that males show a higher incidence (Giordano et al., 2021), earlier age at onset of symptoms, and poorer long-term prognosis than females (Aleman et al., 2003). Lower socioeconomic status (McGrath et al., 2008), migrate status (Saha et al., 2005), and racial minority status are also associated with an elevated risk for schizophrenia and other psychoses (Bresnahan et al., 2007). It has also been shown that childhood abuse, season of birth, urbanicity, and substance use act in shifting toward a spectrum encompassing severe psychotic symptoms, ranging from mild subclinical psychosis to fully developed FEP (Alemany et al., 2015; Oliver et al., 2019). Understanding these epidemiological trends is vital for advancing our comprehension of the etiological complexities of schizophrenia, paving the way for targeted research into its pathophysiological underpinnings and treatment responses.

Etiological Factors for Psychosis.

Research accumulating over the past 4-5 decades has led to the conclusion that the etiology of psychotic disorders is complex and multifaceted in nature, with genetic, environmental, and neurobiological factors interacting to impact the emergence and trajectory of the disease (Kim, 2016). Genetic and other neurobiological vulnerabilities have been shown to have compelling implications for CHR-P and FEP (Bocchio-Chiavetto et al., 2018).

Genetic contributions to schizophrenia are significant, with an estimate of approximately 80% heritability based on Family and Twin studies (Trifu et al., 2020). These studies show a proportionally increased risk with genetic proximity to the affected individuals. However, to

date, no single gene has been identified to account for a large proportion of the variance in risk. Instead, with advances in genetic research, especially genome-wide association studies, researchers have identified more than 100 loci linked to schizophrenia risk. Among these, key genes such as ZNF804A, DISC1, and NRG1 have been implicated in synaptic functioning and neurodevelopment. In addition, there is evidence that mutations, usually *de novo,* are often the source of vulnerability to psychosis. These involve genetic variations that have a large effect size, such as deletions at 22q11.2 which dramatically increases the risk of psychosis (Legge et al., 2021). Epigenetic mechanisms, including DNA methylation, further modulate gene expression in response to environmental influences. The genetic architecture of schizophrenia remains complex, involving interaction between numerous small-effect variants, rare structural mutations, and environmental factors, hence pointing to the multifactorial nature of the disorder.

One ongoing line of investigation is concerned with prenatal development, and has yielded evidence that risk for schizophrenia can originate during fetal stages, based on data showing elevated obstetric complications (DiPiro et al., 2014) and fetal neurodevelopmental disturbances (Vanes et al., 2022). These findings suggest that these prenatal factors may disrupt neurodevelopment, potentially leading to abnormalities in fetal brain structure and/or function. Further, seasonal exposure to prenatal maternal viral infections increase susceptibility to developing the disorder (Walker et al., 2004) as does elevated maternal prenatal stress levels and infections (Mawson & Morris, 2023).

At the level of neurotransmitters, common theories of the biological substrate of schizophrenia emphasize the fundamental role of neurotransmission imbalances, including abnormalities in neurotransmitters such as dopamine and serotonin, as well as alterations of neurochemicals like glutamate and gamma-aminobutyric acid (GABA) (Oliver D. Howes et al.,

2024; Patel et al., 2014). There is evidence consistent with abnormalities in all of these neurotransmitters in some patients with psychosis, and the variability in the findings likely reflects etiological heterogeneity in psychosis (O. D. Howes et al., 2024). There is broadest consensus concerns the dopamine hypothesis, which posits that schizophrenia patients exhibit elevated dopamine levels in the amygdala and a reduction in GABAergic neurons, particularly in the hippocampus (Reynolds, 2022). Currently, D2 and D3 receptor blockade via AP medication remains the primary treatment focus, though its efficacy in addressing functional and cognitive deficits is limited. The hypothesis suggesting heightened D4 receptor activity in schizophrenia has not produced consistent results across studies (Reynolds, 2022). Findings such as reduced medial temporal lobe size and enlarged ventricles further connect the risk of developing schizophrenia to brain alterations (DiPiro et al., 2014).

The biopsychosocial model is commonly employed to describe the etiology of DSM-defined schizophrenia and other psychotic disorders, highlighting the complex interplay of genetic, biological, and environmental factors (Bolton, 2023). However, clear distinctions between the etiologies of schizophrenia and other psychotic disorders remain elusive (Bhati, 2013). Even within the spectrum, numerous overlaps and shared features have been identified among schizophrenia-related conditions, suggesting the potential absence of distinct etiological boundaries between various psychotic disorders (Loch, 2019).

Clinical High-Risk for Psychosis CHR-P and FEP

As noted above, investigations of prodromal pathways to psychosis can aid in monitoring ongoing risk status and inform prevention efforts. The Structured Clinical Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2010), which is widely used in clinical research, include three categories of CHR-P syndromes. The Attenuated Psychotic Symptoms

(APS) refers to attenuated positive psychotic symptoms that are milder, subclinical manifestations of psychosis, such as odd beliefs or unusual perceptual experiences, that do not reach full psychotic intensity but indicate a risk for future psychosis. Brief Limited Intermittent Psychotic Symptoms (BLIPS) involve short periods with fully developed psychotic symptoms, like hallucinations or delusions, which appear only intermittently without persisting. Genetic Risk and Functioning Deterioration (GRFD) applies to individuals with genetic risk for psychosis, for example, having a close family history of the disorder, along with a marked deterioration in their social or occupational functioning in last year (Poletti et al., 2024). These three CHR-P subtypes are often followed by full-blown psychosis, and even among those who do not convert to psychosis, 75% still exhibit functional deficits despite reduced psychotic symptoms (Allswede et al., 2020). Based on the most recent data, approximately 25% of those who meet CHR-P criteria eventually go on to develop a DSM psychotic disorder (Worthington et al., 2020).

Pursuing the goal of targeted preventive intervention for psychosis necessitates predicting the risk of psychotic transition with optimal accuracy, thus highlighting the potential utility of risk calculators and prognostic markers. Several variables obtained in a standard clinical setting—such as the severity of APS, impairment in social functioning, and reduction in verbal learning and retention—demonstrate a significant correlation with the progression to psychosis and are incorporated into the risk calculator (Cannon et al., 2016).

Inflammatory biomarkers, such as cortisol, albumin, and interleukins (e.g., IL-1β, IL-6), have also been studied as indicators of prodromal symptoms in CHR-P individuals, with biomarkers shown to predict the transition to psychosis (Khoury & Nasrallah, 2018). For example, cell-adhesion molecules, fatty acids, and salivary cortisol have been identified as

potential state indicators (Khoury & Nasrallah, 2018; Perkins et al., 2015; Walker et al., 2013). However, findings on CRP as a biomarker are inconsistent due to its nonspecific nature and confounding factors (Miller et al., 2014; Singh & Chaudhuri, 2014).

Trait biomarkers, such as elevated levels of IL-12, TNF-α, and IFN-γ, are consistently observed throughout all stages of schizophrenia, while state biomarkers like IL-1 and IL-6 increase during acute episodes (Miller et al., 2011). Serum albumin reductions have also been proposed as a trait indicator for psychosis, with significant baseline reductions observed in CHR-P individuals who later developed psychosis, independent of AP use or diet (Khoury & Nasrallah, 2018). Elevated serum complement expression has been linked to higher symptom scores in FEP but not in CHR-P (Cropley et al., 2023).

Overall, when compared to ratings of the severity of APS, the research on biomarkers in CHR-P indicate that they are more accurate and have stronger predictability in predicting conversion to psychosis (Ciarleglio et al., 2019).

Treatment

Given the profound adverse effect of symptoms on daily life for both patients and those around them, pharmacological intervention serves as a primary treatment modality for psychosis, particularly during the early critical phase of the disorder (Lehman et al., 2004). In addition, because mood disorders are often comorbid with psychosis or precede psychosis (Buckley et al., 2009), many psychosis patients are also prescribed an antidepressant or mood stabilizing medication (Correll et al., 2015). Another class of drugs that are also administered to patients with psychosis are the stimulants, such as methylphenidate. As with AD, the reason for this is that attentional deficits are often observed prior to or following the onset of psychotic symptoms. Not surprisingly, individuals who meet criteria for CHR-P are also more likely than healthy

controls to be prescribed the above medications by community psychiatric practitioners (Fusar-Poli et al., 2019). The reason for this is that practitioners sometimes view subclinical psychotic symptoms as warranting an AP treatment (Larson et al., 2010). In the sections below, the characteristics and effect of these medications are described.

Antipsychotics

AP medications, normally prescribed for the treatment of psychotic disorders (e g., schizophrenia, schizophreniform disorder, schizoaffective disorder, and brief psychotic disorder), are classified into first-generation AP (FGAs) and second-generation AP (SGAs) (Emsley et al., 2013). Both have been shown to be highly effective in reducing the severity of symptoms, the likelihood of relapse after the first episode of psychosis, and the impairment in role function that is often associated with psychosis (Tibbo et al., 2014). Thus, AP medications are considered the standard, first line of care in treating FEP patients (Gómez-Revuelta et al., 2020).

The extrapyramidal side effects (EPSEs) associated with FGAs served as the impetus for the development of SGAs, which are labeled 'atypical' due to their distinct binding affinity and significantly lower likelihood of inducing such side effects (Ginovart & Kapur, 2012). AP medications primarily reduce the severity of positive symptoms of psychosis, and it is presumed that this is a result of the inhibition of dopamine activity in D_2 receptors in subcortical brain regions (Galletly et al., 2016). There is also evidence of treatment efficacy for negative and cognitive symptoms with the prescription of SGAs, likely attributable to their modulation of dopamine activity in the prefrontal cortex by 5-HT2A antagonism with D2 blockade (DiPiro et al., 2014).

AP have also been shown in various studies to be associated with improved sleep quality, likely due to their sedative properties (Lambert et al., 2004). However, other research has

indicated that these medications may also prolong REM sleep latency and reduce slow-wave sleep (Doghramji & Jangro, 2016; Krystal et al., 2008). This discrepancy underscores the potential for individual variability in the effect of AP on neurotransmitter systems (Lin et al., 2023). Given that the principal symptoms, particularly the positive symptoms of schizophrenia, can contribute to significant interpersonal and occupational impairments (*Diagnostic and statistical manual of mental disorders : DSM-5™*, 2013), the use of AP in mitigating positive symptoms may also exert broader effects on overall symptomatology.

Antidepressants

Because of the high rate of comorbidity of mood disorders, especially depression, and psychoses, many patients diagnosed with a psychotic disorder are also prescribed an antidepressant. The impact of AD on psychosis remains contentious, as some studies identify them as potential triggers for mania and psychosis (Adrian Preda et al., 2001). However, Helfer et al. found that complementary AD yields modest benefits for depressive and negative symptoms, with minimal risk of psychosis exacerbation or side effects (Helfer et al., 2016). Numerous studies also demonstrated that combining AP with AD is better at alleviating negative symptoms of schizophrenia (Singh et al., 2010), though this efficacy appears confined to FGAs (Galling et al., 2018). A systematic review of research with CHR-P individuals identified an association between the use of AD at baseline in a longitudinal setting and a reduced conversion rate of psychosis in individuals, although the underlying mechanisms have not yet been investigated (Raballo et al., 2023a). Sleep disturbances, including insomnia, are a key symptom in major depressive disorder, functioning both as a predictor and a secondary manifestation of the condition (Fang et al., 2019). Consequently, the sedative properties of AD may play a

beneficial role in addressing sleep-related issues in patients with psychoses or at CHR-P, functioning similarly to those of melatonin receptor stimulants (Kamath et al., 2015).

Mood Stabilizers

Mood stabilizers, such as lithium and carbamazepine, referring to medication that functions in prevention or treatment of bipolar symptoms (Bauer & Mitchner, 2004), are commonly used alongside AP in improving emotional regulation and behavioral patterns (Leucht et al., 2003); however, there is a notable absence of reliable randomized controlled trials evaluating their effectiveness for CHR-P individuals (Leucht et al., 2014).

Psychotropic medication and CHR-P

AP have been demonstrated to effectively reduce the severity of psychotic symptoms in individuals diagnosed with psychosis (Correll et al., 2018). A recent meta-analysis of real-world cases has shown the significant efficacy under randomized clinical trials (RCTs) settings (Efthimiou et al., 2024). However, counterintuitively, some recent naturalistic study findings on CHR-P samples have found that AP prescription at baseline (Zhang et al., 2022) or following baseline assessment (Preti et al., 2022) was associated with more severe symptoms and baseline impairment and served as a predictor of subsequent symptom severity and higher likelihood of conversion to psychosis at 1-year follow-up (TianHong Zhang et al., 2022). In another naturalistic study, CHR-P individuals who were AP-naïve were compared to those on an AP at baseline; those exposed to AP manifested greater baseline positive symptom severity, lower Global Assessment of Functioning scores, and higher rates of prior hospitalization, but also greater improvement in negative and disorganized symptoms, although there were no differences in follow-up psychosis transition or symptomatic improvement as a function of baseline AP(Pelizza et al., 2024). In terms of cognitive functioning, the absence of AP has been shown to

be associated with better cognitive recovery in CHR youth (Zhang et al., 2024). Some other naturalistic studies demonstrated that CHR-P individuals who were prescribed AP had a higher transition rate to psychosis compared to those who did not receive such prescriptions (Pelizza & Di Lisi, 2023), particularly among those with mild symptoms (e.g., SIPS total positive score <10) (Raballo et al., 2023a). The transition rate appeared dose-dependent, with higher doses of AP linked to an increased likelihood of progression to psychosis (Raballo et al., 2020, 2023b, 2024). Consistent with previous reports on patients diagnosed with FEP, a study at the Shanghai Mental Health Center found higher functional remission rates in individuals treated with AP during FEP compared to those treated during the CHR phase (Zhang et al., 2021).

Most of the above naturalistic studies focused on baseline medication status in CHR-P participants, as opposed to the introduction of AP after baseline. Further, they did not control for other psychotropic medications, such as AD, which often prescribed in conjunction with AP. There are only a few placebo-controlled clinical trials of AP treatment in CHR-P samples. One investigation of 60 CHR-P patents revealed no significant difference between the groups (olanzapine versus placebo) in the rate of conversion to psychosis over a one-year period (McGlashan et al., 2006). But olanzapine did reduce the severity of positive symptoms. In a more recent placebo-controlled clinical trial of cognitive behavior therapy (CBT) and AP for CHR-P youth, the results showed no significant difference in the progression of symptoms (including transition to psychosis) among the treatment groups, with all showing a decline in positive symptoms as well as other symptoms domains (Bechdolf et al., 2023). However, the study had a high level of attrition, with most participants expressing a preference to be in the CBT treatment groups, and those in the AP or placebo group showed greater and earlier attrition. Of those who discontinued the medication/placebo trial, most did so because they did not want to

take any medication or had experienced adverse medication side effects. These findings led to the conclusion that CBT is more acceptable and tolerable than AP in people meeting criteria for CHR-P.

For CHR-P individuals, a positive correlation between higher symptom scores as well as increased conversion rates and AP drugs was discovered in many studies, independent of preliminary risk enrichment (Raballo et al., 2021a, 2021b, 2024). This result likely reflects the tendency of treatment providers to prescribe medication to individuals with more severe CHR-P symptoms. Additionally, after adjusting for age, sex, and level of education, the results indicate that positive and disorganization symptoms were the primary factor that clinicians took into account when choosing AP for CHR-P people (Zeng et al., 2022). Ethical concerns and methodological challenges have limited the number of RCTs on AP use in CHR-P populations (Di Lisi et al., 2024). While evidence for preventing transition to psychosis remains weak, AP are supported in reducing symptom severity even though in a mild way (Zhang et al., 2020).

More studies have been able to demonstrate the difference between CHR-P subgroups. Zeng and colleagues found that CHR-P participants prescribed AP had a lower mean age, a higher percentage of female participants, more severe psychotic symptoms, and more degraded general function compared to those not on AP medication, based on data drawn from the Shanghai Mental Health Center in China (Zeng et al., 2022).

The side effects of AP medication have resulted in hesitation among clinicians and clinical researchers to recommend AP medication for CHR-P individuals. Common side effects of AP medications include weight gain, sedation, and anticholinergic effects. The prevalence of these side effects varies among different AP agents and individual patient variations (Leucht et al., 2013). Thus, the prescription of AP, including both first and second generations, is not

advised as the initial course of treatment for CHR-P due to the side effects (Galletly et al., 2016). Typically, SGAs are more likely to be suggested given attenuated extrapyramidal side effects and greater tolerance' compared to FGAs, whereas the efficacy of SGAs requires further examination assessing the potential confounders that may affect compliance rate (Kahn et al., 2008).

ADs are commonly prescribed for patients with psychosis, particularly those exhibiting prominent negative symptoms (reference). A naturalistic study identified an association between antidepressant use and reduced rates of delayed psychosis-related hospitalization (Puranen et al., 2023). This result aligns with the prevailing prognostic role of depression in psychosis (Upthegrove et al., 2017). While the present evidence for AD in preventing psychotic transition in CHR-P subjects is still under debate, a few studies have suggested that they can contribute towards minimizing accompanying symptoms such as depression and anxiety (Raballo et al., 2023a). Unlike AP, whose administration is intended to minimize psychotic symptoms, AD have a function in regulating affective disturbances, contributing towards minimizing functional impairments (Anand et al., 2007). However, direct efficacy in minimizing psychotic symptoms and altering the course of psychosis is less established and some studies have raised a concern of potential negative AD-related functional deficits (A. Preda et al., 2001). Further studies will have to establish whether AD have a function in regulating symptoms in CHR-P subjects and in altering long-term prognosis in terms of psychotic risk.

Purpose of the Present Study

As noted, there have been relatively few clinical trials of AP medication in CHR-P samples, and those conducted have limitations, such as small numbers of subjects and high rates of attrition often due to side effects. Moreover, most clinical guidelines have reached a consensus

that AP should not be prioritized in preventive strategies and should be administered with considerable caution (Poletti et al., 2024) due to the potential adverse side effects, particularly in younger individuals with less severe symptoms (Raballo et al., 2021a). As a result, few clinical trials with AP are currently being conducted with CHR-P samples.

In sum, although the efficacy of AP for treating psychosis has been well established through many large-scale clinical trials, the findings on AP in CHR-P samples suggest less efficacy and have raised questions (Di Lisi et al., 2024). The seemingly inconsistent results are likely attributable to a variety of factors. First, in naturalistic studies there is typically a relation of positive symptom severity with the likelihood of medication prescription to CHR-P individuals, with community clinicians appropriately prescribing AP based on symptom severity. While the confound of baseline positive symptom severity with medication status presents challenges, it can be reduced in naturalistic studies by excluding CHR-P participants who are on psychotropic medication at baseline. A second challenge is the fact that many CHR-P individuals are on multiple psychotropic medications, and previous naturalistic studies have generally not taken this into consideration. Thus, separate examination of medication classes is needed to understand the potential effects of a specific medication. To date, this has not been done in naturalistic studies of medication in CHR-P. Finally, in the case of placebo-controlled clinical trials, there is another set of challenges, with the most important being the reluctance of CHR-P patients to agree to take any psychotropic or placebo and the higher rate of attrition due to medication side effects.

The significant limitations of previous naturalistic studies of psychotropic medications in CHR-P will be addressed in the present study with some methodological improvements. Specifically, the present study will 1) include only CHR-P participants who are not on

psychotropic medication at baseline, but begin taking one before the follow-up, 2) examine medication subtypes (AD and AP) separately, and 3) use a baseline to follow-up interval that optimizes the detection of beneficial medication effects but minimizes attrition due to adverse side effects, and 4) examine changes in symptom severity relative to baseline, rather than absolute levels across medication groups. Identification of such temporal changes in symptom profiles in response to specific treatments over time could give invaluable insight into what works best for preventing worsening of symptoms or onset of psychosis. Addressing this gap could lead to more accurate and timely therapeutic approaches, potentially improving prognosis and patient outcomes in CHR-P population. Hence, we hypothesize the following: (1) There will be significant differences in the changes in symptom profiles from baseline to the 4-month follow-up between the medication groups and the CHR-P control group. Specifically, individuals receiving AP will demonstrate a more pronounced decline in symptom severity ratings compared to those without medication. Likewise, those prescribed AD will experience a more substantial reduction in symptoms, highlighting the pharmacological impact of these treatments. (3) We further expect that these differences will be evident in both the severity and type of symptoms, with both AP group and showing greater improvement in the positive and general symptom scales compared to CHR-P control group, and (4) antidepressant group exhibiting more pronounced improvements in the negative symptom and general symptom domain compared to CHR-P control group, consistent with the specific targets of these treatments.

Method

Participants

This sample comprises 138 CHR-P participants who completed a baseline assessment as well as a 4-month follow-up in a longitudinal study conducted as part of the North American

Prodrome Longitudinal Study 3 (NAPLS-3), a multi-site, collaborative consortium comprising nine distinct study sites. Participants in the NAPLS-3 study consist of self-referrals as well as recruitment and referrals from healthcare professionals and providers. Most CHR-P minors face significant barriers to independently accessing mental health resources; thus, parents are usually seeking help through clinical studies on behalf of minors. The baseline recruitment period spanned from February 2015 to November 2018. Data were obtained through standardized clinical assessments conducted bi-monthly during the initial 8-month period for medical and biological evaluations, followed by clinical assessments at 12, 18, and 24 months for longitudinal follow-up. The exclusion criteria are a present or past diagnosis of a psychotic disorder, any diagnosed central nervous system disorder, or an IQ score below 70 (Addington et al., 2022). In addition, for the present study, only those who were medication free at baseline were included. Thus, all CHR-P participants who were not on any psychotropic medication at baseline assessment but who either initiated treatment with an AP, AD, or psychostimulants, or remained medication-free between the baseline and 4-month follow-up were included. The sample of this study is restricted to CHR-P individuals who meet the Criteria of Psychosis-Risk Syndromes (COPS), as determined by the Structured Interview for Psychosis-Risk Syndromes (SIPS). Given the expected natural decline in sample size over time due to subject attrition or missed appointments, this study focused on baseline and four-month follow-up assessments as those assessment time points were available for largest number.

All participants included in the present study reported not being on psychotropic medication at baseline assessment but initiated treatment with any of 3 types psychotropics (AP, AD, psychostimulants), or remained medication-free prior to the four-month assessment. All medication information was updated at each visit through parent-reported or self-reported

medication logs (Addington et al., 2022). Detailed description of NAPLS-2 study procedures can be found elsewhere (Addington et al., 2007; Cannon et al., 2008).

In this study, a 4-month follow-up was selected to balance the need for sufficient time to observe meaningful symptom changes and minimize confounding factors. A shorter follow-up, such as two months, would likely suffer from limited sample size and insufficient time for medications to show measurable effects, as most require at least a week. Conversely, extending the follow-up beyond four months could introduce uncontrollable variables, such as hospitalization or medication changes, potentially confounding the results. The 4-month interval provides an optimal timeframe to capture clinically relevant changes while maintaining control over intervening variables.

Measures

SIPS and SOPS

Using the standardized, structured SIPS clinical interview, symptoms were classified into five categories (positive, negative, general, disorganization, and total) based on the Scale of Psychosis-Risk Symptoms (SOPS), with all scores assessed through the SIPS, administered by trained interviewers (McGlashan et al., 2010). In this study, symptom severity was evaluated using a comprehensive scale that encompasses four general categories: positive symptoms (5 items), negative symptoms (6 items), disorganized symptoms (4 items), and general symptoms (4 items), with each item rated on a scale from 0 to 6. The total symptom severity score was derived by summing the ratings across all items within each symptom domain, yielding an overall measure of symptom severity for each domain.

Statistical Analysis

Tests of the dependent variables were conducted to determine if parametric procedures

were appropriate for the data. The results showed that the following assumptions were violated. The Shapiro-Wilk test for residuals of the symptom scores revealed a significant deviation from normality ($W = 0.91$, $p < .001$). Additionally, Levene's test for homogeneity of variance indicated violations for total symptoms ($F = 2.96$, $p = .04$), positive symptoms ($F = 2.79$, $p = .04$), and disorganization symptoms ($F = 3.56$, $p = .02$) at baseline.

Because the dependent variable distributions did not meet requirements for parametric tests, all data analyses were conducted with nonparametric procedures. First, Friedman and Kruskal Wallis tests were conducted, then Kruskal Wallis tests were performed again after propensity score matching analyses. Nonparametric tests were conducted using R and SPSS due to violations of the assumptions underlying a series of univariate and multivariate analyses of variance (ANOVA). Tests focused on assessing the overall effect of the four medication groups (AD, AP, stimulants or no medication) and time on the difference in symptom scores across the four symptom domains including positive, negative, general, and disorganization. Non-parametric tests were the Friedman test and Kruskal-Wallis test. The Friedman test is a repeated measures test designed to account for within-subject variability as an extension of the Wilcoxon signed-ran test and was applied to assess differences between baseline and four-month time points. The rank-based Kruskal-Wallis test is used to compare three or more independent groups to detect distinctions between differences of distributions (Hazra & Gogtay, 2016) and was employed for comparisons across independent medication groups. For these analyses, symptom scores were calculated by subtracting baseline symptom scores from four-month follow-up values for each symptom domain in Kruskal-Wallis test, with these changes in symptom scores serving as the dependent variables. The change scores were used due to inability of Kruskal-Wallis test in directly capturing the magnitude of symptom improvement or deterioration over time, allowing for a more precise comparison of treatment

effects across medication groups while accounting for baseline variability. Pairwise post-hoc comparisons were conducted using the Wilcoxon rank-sum test. This approach facilitated the analysis of both the main effects of treatment and time, as well as the interaction effects between treatment group and time on symptom changes.

To further examine medication effects, a propensity score matching (PSM) was employed to identify medication-control subjects for participants receiving AP only (AP, n=9), AP with other psychotropic medications (AP+, n=8), and AD (n=17). PSM is a causal inference method used to reduce confounds or selection bias in an observational study by matching participants from different groups based on their probability of receiving a treatment (Austin, 2011). The matching was selected from medication-control group and was solely based on baseline positive symptoms, given the findings described above that more severe baseline symptoms tend to be associated with medication in CHR-P samples. For each medication group, nearest-neighbor matching without replacement was performed using logistic regression to estimate propensity score. The number of paired matches chose from medication-control group was exactly the same as medication groups. Balance between matched groups was assessed through t-test comparisons of baseline characteristics (sex, age, years of education, positive symptoms scores, negative symptom scores, general symptom scores, and disorganization symptom scores) (see **Table 6**). The same set of non-parametric tests were then performed again with the matching data. This approach helped control selection bias and allowed for more reliable comparisons in this naturalistic design.

Data completeness was assessed within each symptom domain, as a majority of participants were evaluated solely for positive symptoms, given that positive symptoms are the primary criteria for determining CHR-P status. Cases with entirely missing data for one assessment point (either baseline or four-month follow-up) were excluded from the analysis (n = 3). This left a total of

XXX cases with data for positive symptoms only and XXX with data for all of the symptom domains.

Results

Participant Demographic and Clinical Characteristics

The study included 138 participants (M = 17.7 years, SD = 3.58), of which 78 (56.1%) were male. Baseline demographic and symptom comparisons of included versus excluded are shown in **Table 1**. Individuals excluded from the analyses due to missing data at follow-up were characterized by more severe ratings on the following symptoms at baseline: P1. Unusual Thought Content/Delusional Ideas ($t(804) = -2.74$, $p = .002$), P3. Grandiose Ideas ($t(804) = 4.18$, $p < .001$) and P4. Perceptual Abnormalities/Hallucinations ($t(804) = -4.6$, $p < .001$) demonstrated a statistically significant difference. It has previously been shown that the severity of symptoms is associated with attrition in longitudinal studies (McCabe, et al.,2022). Thus, as reported for other CHR-P samples, those lost to follow-up tended to have more severe positive symptoms at baseline.

Table 1

Demographic and Symptom Comparison of Included v. Excluded CHR-P Participants

	Included	Excluded	P value
Sample Size (N)	138	668	
Male (%)	77 (55.8%)	356 (53.3%)	.66
Age (mean (SD))	17.7 (3.6)	18.4 (4.1)	.08
Education (mean (SD))	11.2 (2.9)	11.6 (3.2)	.18
Baseline Positive Symptoms			
P1. Unusual Thought Content/ Delusional Ideas	3.60 (1.24)	3.27 (1.59)**	.02
P2. Suspiciousness/Persecutory Ideas	2.99 (1.45)	2.71 (1.67)	.07

P3. Grandiose Ideas	0.49 (0.98)	0.90 (1.33) **	<.001
P4. Perceptual Abnormalities/ Hallucinations	3.30 (1.40)	2.68 (1.65) **	<.001
P5. Disorganized Communication	1.83 (1.54)	1.83 (1.52)	.97
Negative Symptoms			
N1. Social Anhedonia	2.21 (1.75)	3.66 (12.46)	.17
N2. Avolition	2.11 (1.58)	3.93 (12.43)	.09
N3. Decreased Expression of Emotion	0.99 (1.18)	2.91 (12.53)	.07
N4. Decreased Experience of Emotions and Self	1.85 (1.47)	3.37 (12.49)	.15
N5. Decreased Ideational Richness	1.01 (1.23)	2.87 (13.07)	.10
N6. Occupational Functioning	1.91 (1.79)	3.98 (12.47)	.05
General Symptoms			
G1. Sleep Disturbance	2.11 (1.41)	3.86 (12.97)	.11
G2. Dysphoric Mood	2.78 (1.58)	4.53 (12.37)	.10
G3. Motor Disturbances	0.93 (1.04)	2.68 (13.62)	.13
G4. Impaired Tolerance to Normal Stress	2.51 (1.89)	4.50 (13.47)	.08
Disorganization Symptoms			
D1. Odd Behavior or Appearance	0.55 (1.06)	2.37 (12.57)	.09
D2. Bizarre Thinking	0.88 (1.20)	2.48 (12.56)	.13
D3. Trouble with Focus and Attention	2.37 (1.32)	3.92 (12.40)	.14
D4. Impairment in Personal Hygiene	0.64 (1.16)	2.51 (13.11)	.09

* $p < .05$

** $p < .001$

Demographic characteristics and baseline clinical ratings of the sample by medication status (4 groups) are presented in **Table 2**, showing no significant differences in age, sex, education, and symptom domains across groups. The average age is similar across all groups (ranging from 16.1 to 18.9 years) although some nonsignificant variation was found in sex-at-

birth distribution, with the AP group having the highest percentage of males (66.7%) and the AP+ group having the lowest (33.3%). The sample consists of 4 First Nations participants (2.9%), 10 East Asians (7.25%), 3 Southeast Asians (2.17%), 5 South Asians (3.62%), 20 Black participants (14.49%), 7 Central/South Americans (5.07%), 69 White participants (50%), 1 Native Hawaiian or Pacific Islander (0.72%), and 19 Interracial participants (13.77%). Only one participant was identified in the psychostimulant group and was removed from the study due to insufficient comparative data.

As illustrated in Table 2, the trend for symptom scores is similar across domains, with medicated groups showing higher baseline scores than the medication-control group, though the differences do not reach significance.

Table 2

Demographic Characteristics and Baseline Symptom Ratings of Participants by Medication Group

Variable	AP (n= 9)	AP with other (n= 8)	AD (n= 17)	Medication-control (n= 104)	Estimate	*p*
Age (mean (SD))	16.1 (3.0)	18.9 (4.4)	16.7 (3.1)	17.9 (3.6)	F=1.10	.36
Male (%)	6 (66.7)	2 (33.3)	8 (47.1)	61 (58.7)	χ^2=5.17	.27
Total: Baseline Score (mean (SD))	43.9 (16.8)	41.1 (10.4)	36.8 (6.8)	33.5 (13.3)	F=2.63	.05
Positive: Baseline Score (mean (SD))	14.4 (2.4)	13.6 (2.1)	11.3 (2.6)	12.1 (3.5)	F=2.34	.08
Negative: Baseline Score (mean (SD))	12.8 (8.2)	12.8 (4.2)	10.9 (5.2)	9.5 (5.8)	F=1.63	.19
General: Baseline Score (mean (SD))	9.7 (4.1)	9.5 (4.1)	10.4 (2.6)	7.8 (4.6)	F=2.32	.08
Disorganization: Baseline Score (mean (SD))	7.0 (5.3)	5.2 (2.1)	4.2 (2.4)	4.2 (2.9)	F=2.67	.05

Note. AP with other =AP+.

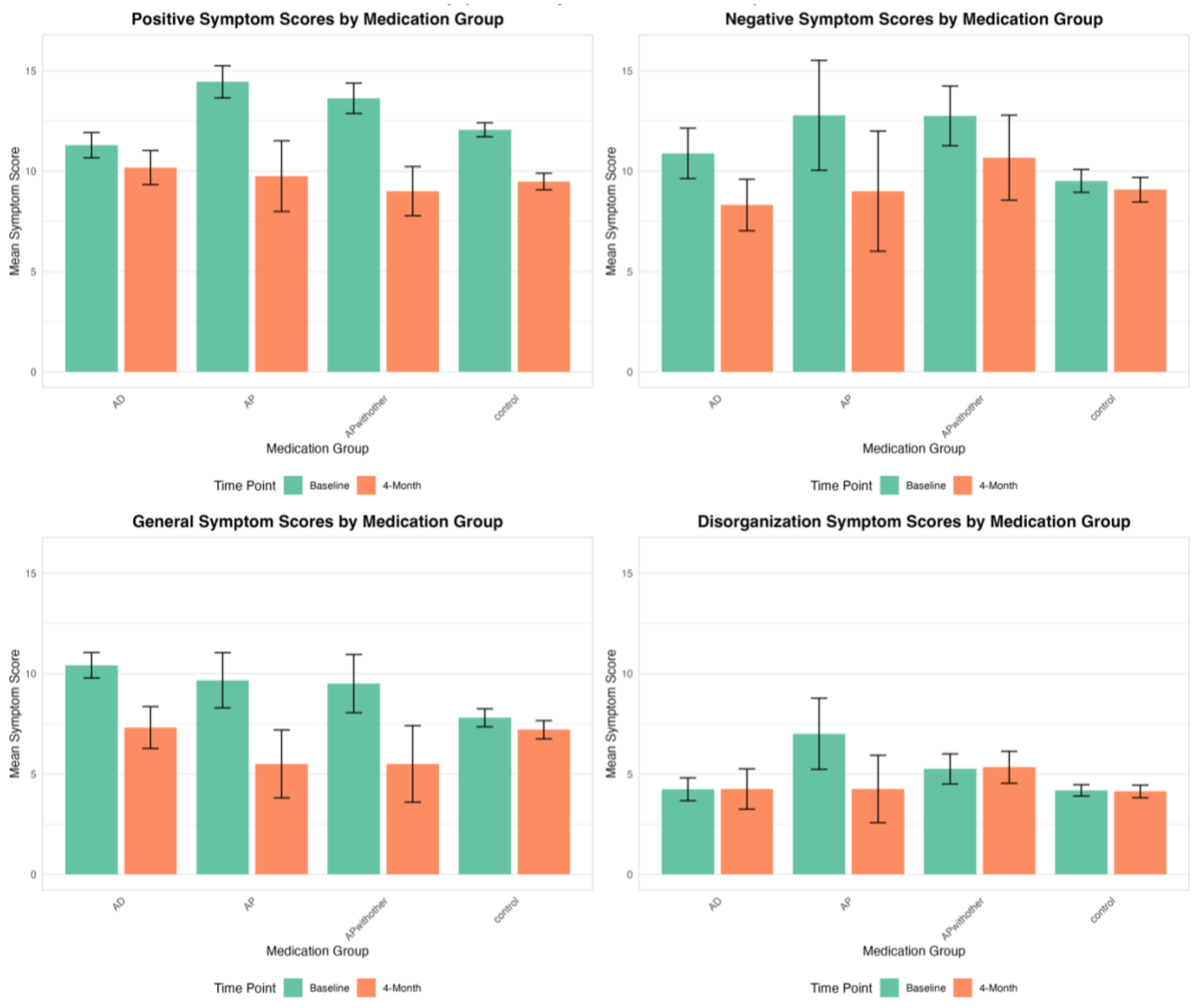
Data Analyses

Non-Parametric Tests Comparing Symptom Changes

The mean symptom scores, with standard error of the mean, by time and group are presented in the bar graph in **Figure 1** below. Consistent with numerous previous reports on post-baseline trends in symptom severity in CHR samples (reference), Figure 1 shows that there is an observable decline across groups and symptom domains.

Figure 1

Symptom Scores (SEM) by Domain, Time, and Medication Group



A Friedman test was conducted to examine differences in symptom domains between baseline and the 4-month follow-up across group. This is a nonparametric repeated measure test used to compare groups by ranks of the values in each matched set (i e., baseline versus follow-

up). All test results are listed in **Table 3**. The results indicated a significant effect of time with significant decreases across all symptom domains including positive ($\chi^2(1) = 47$, $p < .001$), negative ($\chi^2(1) = 9.2$, $p = .002$), general ($\chi^2(1) = 15$, $p < .001$), and disorganization symptoms ($\chi^2(1) = 13$, $p < .001$). The total symptom scores also exhibited significant difference between baseline and follow-up ($\chi^2(1) = 29$, $p < .001$).

Table 3

Friedman Rank-Sum Test Results for Symptom Changes Over Time

Symptom Category	χ^2	df	*p*
Positive	47	1	< .001
Negative	9.2	1	.002
General	15	1	< .001
Disorganization	13	1	< .001
Total	29	1	< .001

Note. df = degrees of freedom.

The Kruskal-Wallis tests were performed to compare symptom score changes by the 4 psychotropic medication groups and the results indicated significant differences between medication groups in positive ($H(3) = 9.67$, $p = .022$) and general ($H(3) = 9.3$, $p = .026$) symptoms. The statistical results are presented in **Table 4**. Post-hoc Dunn's tests with Holm correction showed that the AD group had less positive symptom severity reduction than both the AP group ($Z = 2.48$, $p = .039$) and the AP+ group ($Z = 2.4$, $p = .041$) indicating that AP enhances the post-baseline decline in positive symptoms. (See **Table 5.1** for statistical results.) None of the comparison pairs resulted significantly different in general symptoms compared to the no-medication-control group (see **Table 5.2**).

Table 4

Non-Parametric Kruskal-Wallis Test Results Comparing all Medication Groups by Symptom Domain

Symptom Domain	*H*	df	p
Disorganization	4.43	3	.22
General	**9.30***	3	.03
Negative	1.60	3	.66
Positive	**9.68***	3	.02
Total	4.99	3	.17

Note. df = degrees of freedom.

* $p < .05$

Table 5.1

Non-Parametric Post-hoc Test Results by Medication Group Comparison for Positive Symptom

Comparison	*Z*	Adjusted *p*
AD – AP	**2.48***	.04
AD – AP with other	**2.40***	.04
AP – AP with other	0.14	.44
AD – Control	1.39	.17
AP – Control	-1.91	.11
AP with other – Control	-1.85	.10

Note. AP with other =AP+.

Table 5.2

Non-Parametric Post-hoc Test Results by Medication Group Comparison for General Symptom

Comparison	Z	Adjusted *p*
AD – AP	0.51	0.61
AD – AP with other	-0.2	0.42
AP – AP with other	-0.59	0.83
AD – Control	-2.21	0.07
AP – Control	-2.23	0.08
AP with other – Control	-1.21	0.45

Note. AP with other =AP+.

Propensity Score Matching

As noted, PSM is a data analytic procedure that can be used with observational (naturalistic) data to estimate the effects of a treatment/intervention that is likely influenced by other factors that predict the likelihood of receiving the treatment. The preexisting factors serve as covariates. Thus,

PSM can reduce the bias in estimating treatment effects by controlling for factors that predict the provision of a treatment. Positive symptoms were used as covariates in the matching process, as they are the primary concern for pre-baseline antipsychotic prescriptions.

After PSM, most baseline subject characteristics, including symptom scores, were similar across medication groups and controls at baseline. One exception was social anhedonia where the AP group had significantly higher scores in social anhedonia (N1) compared to their matched controls (p = .020) (see **Table 6.1**). After PSM, no significant differences were observed in any baseline characteristics between the AP+ group and their matched controls (see Table 6.2). However, after PSM, the AD group had significantly higher baseline scores in sleep disturbance (G1; p = .011) and dysphoric mood (G2; p = .001) compared to their matched controls (see **Table 6.3**).

Table 6.1

Baseline Characteristics of AP group and Matched Control group After Propensity Score Matching

Variable	AP	AP_matched	*p*
Sex (Male (%))	1.33 (0.50)	1.22 (0.44)	.62
Age (mean (SD))	16.11 (3.02)	16.78 (2.59)	.62
Education (mean (SD))	9.33 (2.35)	10.78 (3.03)	.27
P1. Unusual Thought Content/ Delusional Ideas (mean (SD))	4.11 (1.05)	4.44 (0.53)	.41
P2. Suspiciousness/Persecutory Ideas (mean (SD))	3.56 (1.33)	3.00 (1.73)	.46
P3. Grandiose Ideas (mean (SD))	0.89 (1.17)	1.00 (1.50)	.86
P4. Perceptual Abnormalities/ Hallucinations (mean (SD))	3.89 (0.93)	3.89 (0.78)	1.00
P5. Disorganized Communication (mean (SD))	2.00 (1.41)	1.89 (1.54)	.88
N1. Social Anhedonia (mean (SD))	**3.22 (1.79)**	**1.22 (1.48)**	**.02**
N2. Avolition (mean (SD))	2.67 (1.58)	1.44 (1.67)	.13
N3. Decreased Expression of Emotion (mean (SD))	1.33 (1.58)	0.78 (0.97)	.39
N4. Decreased Experience of Emotions and Self (mean (SD))	1.78 (1.56)	0.89 (1.05)	.18
N5. Decreased Ideational Richness (mean (SD))	1.67 (1.41)	0.67 (0.87)	.09

N6. Occupational Functioning (mean (SD))	2.11 (1.83)	2.00 (1.94)	.90
D1. Odd Behaviour or Appearance (mean (SD))	2.89 (1.05)	1.89 (1.36)	.1
D2. Bizarre Thinking (mean (SD))	2.78 (1.56)	2.22 (1.92)	.51
D3. Trouble with Focus and Attention (mean (SD))	1.56 (1.01)	0.89 (0.93)	.17
D4. Impairment in Personal Hygiene (mean (SD))	2.44 (2.24)	1.33 (2.06)	.29
G1. Sleep Disturbance (mean (SD))	1.00 (1.41)	1.11 (1.27)	.86
G2. Dysphoric Mood (mean (SD))	1.22 (1.39)	1.33 (1.50)	.87
G3. Motor Disturbances (mean (SD))	3.22 (1.30)	2.33 (1.32)	.17
G4. Impaired Tolerance to Normal Stress (mean (SD))	1.56 (1.81)	0.44 (0.73)	.12

Note. AP_matched = matched CHR-P participants for AP group.

Table 6.2

Baseline Characteristics of AP Compared with Other Psychotropic Medication Users and Matched Control Individuals After Propensity Score Matching

Variable	AP with other	AP with other_matched	*p*
Sex (Male (%))	1.75 (0.46)	1.50 (0.53)	.34
Age (mean (SD))	18.88 (4.42)	19.12 (4.85)	.92
Education (mean (SD))	12.50 (2.39)	11.00 (3.12)	.30
P1. Unusual Thought Content/ Delusional Ideas (mean (SD))	3.50 (1.51)	2.75 (1.04)	.27
P2. Suspiciousness/Persecutory Ideas (mean (SD))	3.38 (1.30)	3.12 (1.25)	.70
P3. Grandiose Ideas (mean (SD))	0.50 (1.41)	0.50 (0.76)	1.00
P4. Perceptual Abnormalities/ Hallucinations (mean (SD))	3.75 (0.89)	4.00 (0.53)	.51
P5. Disorganized Communication (mean (SD))	2.50 (1.60)	2.50 (1.20)	1.00
N1. Social Anhedonia (mean (SD))	2.25 (1.83)	3.00 (2.27)	.48
N2. Avolition (mean (SD))	2.62 (0.74)	3.12 (1.55)	.43
N3. Decreased Expression of Emotion (mean (SD))	1.50 (1.20)	0.88 (1.36)	.35
N4. Decreased Experience of Emotions and Self (mean (SD))	2.50 (1.07)	2.12 (1.13)	.51
N5. Decreased Ideational Richness (mean (SD))	1.25 (1.28)	1.38 (1.60)	.87
N6. Occupational Functioning (mean (SD))	2.62 (1.92)	2.62 (2.50)	1.00
D1. Odd Behaviour or Appearance (mean (SD))	1.50 (1.41)	2.50 (1.60)	.21
D2. Bizarre Thinking (mean (SD))	3.12 (1.81)	3.25 (1.67)	.89
D3. Trouble with Focus and Attention (mean (SD))	1.25 (1.16)	1.50 (1.31)	.69

D4. Impairment in Personal Hygiene (mean (SD))	3.62 (1.69)	2.38 (2.33)	.24
G1. Sleep Disturbance (mean (SD))	0.75 (1.16)	0.12 (0.35)	.18
G2. Dysphoric Mood (mean (SD))	1.38 (1.19)	0.38 (0.74)	.07
G3. Motor Disturbances (mean (SD))	2.88 (0.99)	2.25 (1.75)	.40
G4. Impaired Tolerance to Normal Stress (mean (SD))	0.25 (0.46)	0.50 (0.93)	.51

Note. AP with other =AP+; AP with other_matched = matched CHR-P participants for AP+ group.

Table 6.3

Baseline Characteristics of Antidepressant Users and Matched Control Individuals After Propensity Score Matching

Variable	AD	AD_matched	*p*
Sex (Male (%))	1.53 (0.51)	1.47 (0.51)	.74
Age (mean (SD))	16.71 (3.06)	17.47 (4.27)	.55
Education (mean (SD))	10.76 (3.05)	11.24 (3.09)	.66
P1. Unusual Thought Content/ Delusional Ideas (mean (SD))	3.65 (1.37)	3.53 (1.55)	.82
P2. Suspiciousness/Persecutory Ideas (mean (SD))	2.94 (1.34)	2.71 (1.65)	.65
P3. Grandiose Ideas (mean (SD))	0.06 (0.24)	0.00 (0.00)	.33
P4. Perceptual Abnormalities/ Hallucinations (mean (SD))	3.18 (1.85)	2.94 (1.39)	.68
P5. Disorganized Communication (mean (SD))	1.47 (1.46)	1.65 (1.58)	.74
N1. Social Anhedonia (mean (SD))	2.24 (1.71)	2.12 (1.87)	.85
N2. Avolition (mean (SD))	2.53 (1.37)	2.00 (1.70)	.33
N3. Decreased Expression of Emotion (mean (SD))	1.06 (1.20)	1.18 (1.42)	.80
N4. Decreased Experience of Emotions and Self (mean (SD))	2.18 (1.55)	1.41 (1.54)	.16
N5. Decreased Ideational Richness (mean (SD))	0.88 (1.05)	1.18 (1.42)	.50
N6. Occupational Functioning (mean (SD))	2.00 (1.50)	1.65 (1.73)	.53
D1. Odd Behaviour or Appearance (mean (SD))	**2.76 (1.15)**	**1.47 (1.59)**	**.01**
D2. Bizarre Thinking (mean (SD))	**3.71 (1.10)**	**1.88 (1.58)**	**.001**
D3. Trouble with Focus and Attention (mean (SD))	0.88 (0.99)	0.53 (0.87)	.28
D4. Impairment in Personal Hygiene (mean (SD))	**3.06 (1.43)**	**1.65 (1.87)**	**.02**
G1. Sleep Disturbance (mean (SD))	0.47 (0.80)	0.53 (1.28)	.87
G2. Dysphoric Mood (mean (SD))	1.18 (1.67)	0.53 (1.07)	.19

G3. Motor Disturbances (mean (SD))	2.29 (0.92)	1.47 (1.37)	.05
G4. Impaired Tolerance to Normal Stress (mean (SD))	0.29 (0.59)	0.88 (1.76)	.21

Note. AD = AD; AD_matched = matched CHR-P participants for AD group.

After PSM, Kruskal-Wallis tests comparing medication groups and their matched peers revealed significant differences in symptom reduction between the AP group and their matched controls in negative symptoms ($H(1) = 4.69$, $p = .03$) and general symptoms ($H(1) = 8.42$, $p = .004$), with the AP group demonstrating a greater decrease in symptom severity compared to their matched controls (negative symptoms: AP $M = -3.00$, $SD = 4.34$; matched $M = 2.88$, $SD = 3.87$; general symptoms: AP $M = -3.88$, $SD = 3.56$; matched $M = 1.38$, $SD = 2.56$). All results are presented in **Table 7**. Additionally, the AD group showed significant differences from their matched controls in general symptom reduction ($H(1) = 5.06$, $p = .024$), with a greater decrease in symptom severity (AD $M = -2.94$, $SD = 3.11$; matched $M = -0.17$, $SD = 3.27$). No significant differences were found between the AP+ group and their matched controls across any symptom domains.

Table 7

Kruskal-Wallis Test of Symptom Changes Between Medication Groups and Their Matched Controls

Group	Symptom Domain	*H*	Medication: Matched Symptom Score (Mean (SD))	df	*p*
AP	Positive	0.46	-5.00 (4.87) : -4.11 (3.33)	1	.50
AP	Negative	**4.69**	**-3.00 (4.34) : 2.88 (3.87)**	**1**	**.03**
AP	General	**8.42**	**-3.88 (3.56) : 1.38 (2.56)**	**1**	**<.001**
AP	Disorganization	3.39	-2.50 (2.67) : -0.38 (2.39)	1	.07
AP with other	Positive	2.63	-5.00 (2.97) : -1.88 (3.48)	1	.11
AP with other	Negative	0.19	-2.67 (3.61) : -3.75 (3.87)	1	.67
AP with other	General	1.15	-2.67 (4.41) : -3.75 (3.87)	1	.28

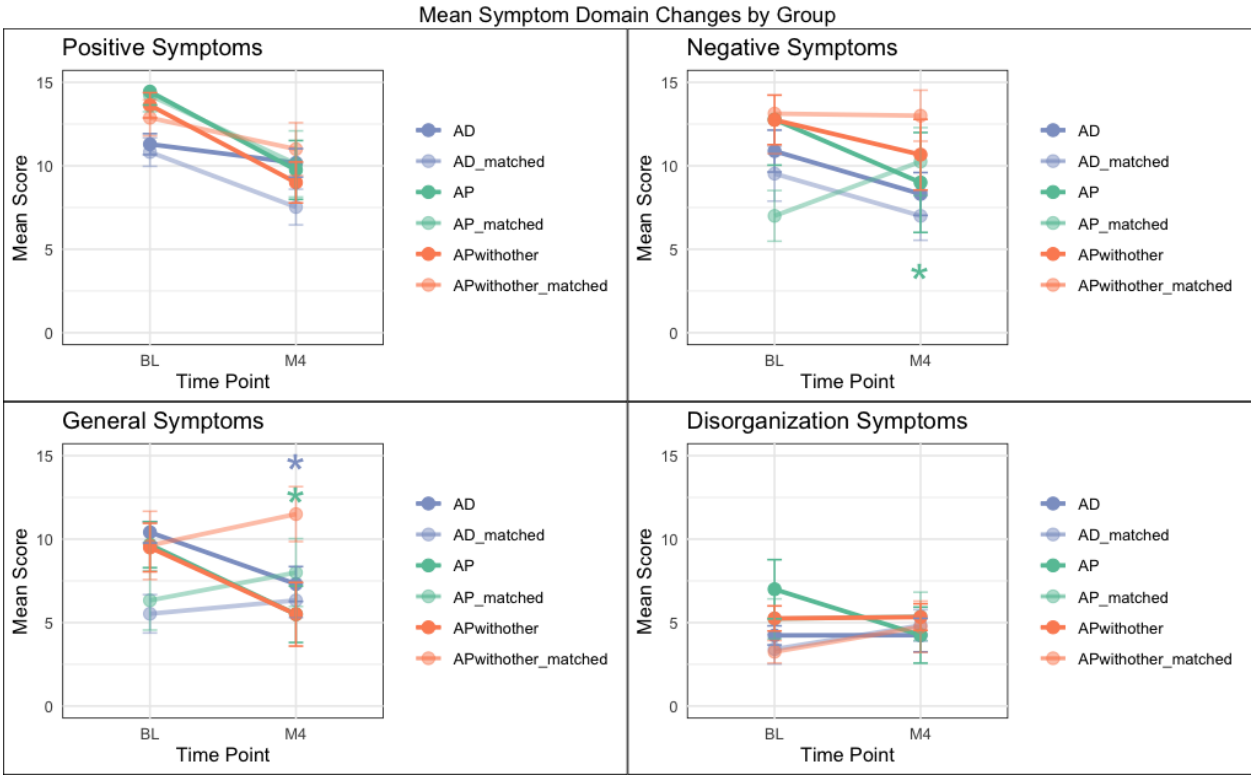
AP with other	Disorganization	1.17	-0.33 (2.25) : -3.75 (3.87)	1	.28
AD	Positive	2.54	-1.12 (4.00) : -3.29 (3.02)	1	.11
AD	Negative	0.56	-1.94 (3.77) : -3.33 (4.10)	1	.46
AD	General	5.06	**-2.94 (3.11) : -0.17 (3.27)**	**1**	**.02**
AD	Disorganization	0.29	0.14 (3.14) : 0.58 (3.00)	1	.59

Note. AP with other =AP+; df = degrees of freedom.

Shown below in Figure 2 are the scores after PSM for symptoms at baseline and follow-up. As with the raw scores, there is a general tendency toward a decline in symptom severity over time, with a few exceptions. As would be expected after PSM, there were no significant differences in symptom severity at baseline. However, at follow-up, there was a trend toward an increase in negative and general symptom severity for the unmedicated group that was matched to the AP group.

Figure 2

Mean Symptom Domain Changes Post-PSM from Baseline to 4-Month by Medication Group



Discussion

This study aimed to examine changes in symptom trajectories in CHR-P youth as a function of type of medication provision post-baseline assessment. Groups included those who were prescribed AP-only, AP combined with other psychotropic medications, AD, or no psychotropic medication. The findings align closely with existing experimental and longitudinal research findings on the relationship between AP and CHR-P symptoms. As hypothesized, there was a greater reduction in symptom severity in response to AP medication.

Initial analyses using nonparametric tests without matching indicated significant group differences in baseline positive and general symptom domains. Post-hoc tests within the positive symptom domain further revealed a significantly greater symptom reduction in AP and AP+ groups compared with AD group. Additionally, before adjusting for multiple comparisons, the AP and AP+ versus medication-control comparisons were also significant, suggesting that AP-treated participants exhibit stronger reductions in positive symptoms in the four-month period.

For general symptoms, even though the Kruskal-Wallis test yielded significant overall effects, no pairwise comparisons remained significant after adjusting for multiple comparisons. Before p-value adjustment, significant differences were observed between the AD versus medication-control and AP versus medication-control comparisons, with medication groups demonstrating greater symptom reductions than their unmedicated peers. These findings suggest a different symptom trajectory in general symptoms between medication groups, but the lack of significance after correction highlights the need for cautious interpretation.

Then using PSM, which controlled for baseline positive symptoms, significant differences were observed for changes in the negative and general symptom domains for the AP

group and in the general symptom domain for the AD group when compared with their matched CHR-P participants. In both cases, medication-treated groups exhibited greater symptom reduction compared to their matched controls, consistent with the trends seen in the raw data.

Previous research has shown that the severity rating for the symptom domains rated with the SIPS are positively intercorrelated especially with general, positive, and mood symptoms (Cowan et al., 2024). Thus, like most psychiatric symptom dimensions, increases in the severity of positive symptoms are associated with increases in negative and general symptoms. This is assumed to be due to increased positive symptom severity contributing to increases in negative and general symptoms. In other words, positive symptoms like suspiciousness can lead to greater social withdrawal as well as depressed mood. Even when controlling for baseline positive symptoms with PSM, AP could have a measurable beneficial effect on negative and general symptoms.

The results suggest that AP and AD are associated with reductions in symptom severity over time, particularly in negative and general symptom domains even after accounting for potential confounders. However, causal interpretations cannot be drawn given the naturalistic design of this study, and findings should be considered within the context of potential unmeasured pre-baseline confounders. Future studies with randomized controlled designs are needed to further clarify the efficacy of these medications in CHR-P populations.

Independent of psychotropic medication use, the present findings indicate that all symptom scores demonstrate a general decline from baseline to the 4-month mark, consistent with findings from the entire sample from the NAPLS-2 study (Addington et al., 2012; Addington et al., 2022; Addington et al., 2015; Walker et al., 2009). Both studies found the declining nature of baseline symptom severity post-baseline (McGlashan et al., 2006; McGorry

et al., 2002). Similar trends toward psychiatric symptom reductions are also found in studies of individuals waitlisted after enrollment in clinical research (Schütz et al., 2024).

The present results are consistent with previous reports that AP prescription for CHR-P youth is associated with more severe positive symptoms at baseline, indicating that positive symptoms are a determinant of AP prescription by community mental health care providers. But even after controlling for baseline positive symptoms with PSM, AP-treated participants manifested a greater reduction in the severity of both negative and general symptoms when compared to AD prescription or no medication. On the other side, the mild decline in positive symptoms observed in the antidepressant group may reflect the beneficial effects of that reducing depression can have on positive symptoms. comorbid presence of mood or anxiety symptoms rather than exclusively psychotic symptoms, which could weaken the association with positive symptom reduction.

Summary of Findings for Positive Symptom Domain

Current results of AP and positive symptom severity reduction is very consistent with previous findings (Zeng et al., 2022). The efficacy of AP in treating positive symptoms is well-established in the treatment of psychosis, where dopamine D2 blockade mainly in the mesolimbic pathway mitigates excessive dopaminergic transmission (Harvey et al., 2016; Kapur & Mamo, 2003). However, the naturalistic design of the study imposes certain limitations in that medication prescription is determined by clinical judgment that can be influenced by multiple factors such as positive symptom severity, comorbidities, and access to treatment, naturally introducing pre-baseline differences as compared with non-medicated peers. The association between receiving APs and symptom decline might not hold after accounting for confounding variables. The absence of significant results after conducting PSM solely based on positive

symptoms supports the interpretation of weak association, indicating that the observed associations could be driven by baseline severity or other unmeasured factors. Given the discrepancy between initial findings and the lack of post-PSM results confirmation, the evidence suggests an association between AP-containing treatments and greater reduction in positive symptoms without an establishment of any causality. Future large-scale longitudinal studies and RCT or more robust matching techniques are necessary to discern the effects.

Summary of Findings for Negative Symptom Domain

For negative symptoms, the lack of differences in initial analysis using raw data is consistent with the broader literature, which suggests that negative symptoms in CHR-P are less responsive to medication treatments compared to positive symptoms (Ricci et al., 2024). The non-significant results implies that psychotropic medication type did not clearly differentiate negative symptom trajectories over the 4-month period.

However, post-PSM analysis yielded a significant finding. AP-only treatment is associated with improved negative symptoms compared to no treatment when baseline positive symptoms are accounted for. The treatment of negative symptoms is more tied to glutamatergic dysfunction or frontal lobe hypoactivity (Correll & Schooler, 2020), which are not the primary mechanisms of APs. A possible explanation is the indirect effects of APs on improving overall functioning or reducing positive symptoms mitigate negative symptoms (Sabe et al., 2021). Treatment of positive symptoms can lead to reduced social withdrawal, motivation, or emotional expression, benefiting negative symptoms in turn (Correll & Schooler, 2020). In some cases, APs may reduce both positive and negative symptoms, though to varying degrees (de Beer et al., 2024). Given the mixed evidence on APs' efficacy for negative symptom intervention, this result is unexpected, and it still remains inconclusive of whether or not AP-prescription CHR-Ps are

distinguishable by negative symptom changes. Even with PSM, unmeasured confounders such as duration of untreated prodromal or psychosocial support could still influence outcomes. The finding suggests a potential differentiation or benefit of AP-only treatment for negative symptoms, but it also requires a RCT setting for causality.

General Symptom Domain

The difference between AP-only and non-medicated peers were consistent across tests even though the pairwise comparisons of raw data remained non-significant after adjustment, likely due to limited statistical power.

The PSM analysis provided further insight as both the AP-only and AD group showing significant reductions in general symptoms compared to their matched medication-controls. This finding reinforces the initial trend observed in the raw data, suggesting that both AP and AD treatments are associated with improved general symptoms when baseline positive symptom differences are controlled. These findings align with the known sedative, mood stabilization, and stress reduction effects of some APs and ADs (Edinoff et al., 2021; Miller, 2004). The consistency across analyses suggests a strong link between clinical decision to prescribe these medications for general symptom management, potentially influenced by factors like psychotherapy, mood or lifestyle changes, which were not controlled for in this study.

Limitations

The study's limitations should be considered when interpreting the results. First, this is an observational study not a randomized clinical trial, only correlational associations could be established between the symptom condition and medication consumption. Second, consideration of covariates such as medication type, dosage, and other therapeutic approaches was not included due to the small sample size. The PSM was conducted using baseline positive symptoms as the

matching variable, which may not fully account for confounding in other domains. The absence of matching on other domains can lead to residual bias, particularly in results like negative and disorganized symptoms where baselines can strongly differ between groups. Third, the use of nonparametric procedures typically reduces statistical power. Lastly, the 4-month follow-up period may not fully capture long-term trajectories of symptom change, particularly for negative and disorganization symptoms, which are acknowledged to be more chronic and less responsive to short-term interventions. This timeframe might miss delayed effects and potentially underestimating the true impact of medications.

Summary

In summary, this study explored associations between different medication prescription strategies (AP-only, AP combined with other psychotropics, AD, and no medication) and symptom trajectories in CHR-P youth over four months follow-up period. Given recent findings linking baseline AP exposure to a higher conversion probability (Raballo et al., 2023b), we excluded participants with baseline psychotropic use to reduce the effects of preexisting clinical factors on symptom severity post-baseline. Research suggests AP-only treatment may be linked to decreased positive symptom compared to the no-medication group. AP-only treatment may also be associated with attenuation of negative symptom more than paired no-medication peers, but causality is unclear due to the naturalistic design and limited PSM matching. It seems likely that both AP-only and AD treatments are linked to reduced general symptoms compared to no treatment, with PSM supporting this association, aligning with their known calming effects.

The findings highlight the complexity of treating CHR-P, with association between AP-only, AD and symptom domains appears ambiguous. However, the study's limitations, including the inability to establish causality, short follow-up, and reliance on positive symptom matching,

underscore the need for cautious interpretation and future randomized controlled trials to confirm these associations. Previous findings underscore the importance of evaluating and closely monitoring the side effects of psychotropic medications during prodromal progression. This research contributes to understanding symptom-specific treatment responses in CHR-P, but further studies with longer follow-ups and broader matching criteria are essential to assess the predictive, preventive, and therapeutic capabilities of AP, as well as their potential association with non-clinical outcomes such as social and role functioning trajectories for at-risk youth.

Because of concern about adverse side effects, current international practice guidelines discourage AP use with CHR-P youth, so there are unlikely to be any large-scale controlled trials in the near future. However, larger-scale (i e., $n > 2000$), international studies of CHR-P samples are currently underway, and the use of remote follow-up assessments in these studies has reduced attrition due to symptom worsening and/or medication side effects. These study cohorts will, therefore, provide the opportunity for replications of the present naturalistic approach (i e., a focus on individuals for whom medication is prescribed between baseline and follow-up) with a much larger sample. Because DUP can have negative long-term implications, and there is evidence from the present and other studies that AP can be beneficial for at least some CHR-P individuals, it is worth testing AP effects in naturalistic studies of larger CHR-P samples.

References

Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M., Walker, E. F., Woods, S. W., & Heinssen, R. (2007). North American Prodrome Longitudinal Study: a collaborative multisite approach to prodromal schizophrenia research. *Schizophr Bull*, *33*(3), 665-672. https://doi.org/10.1093/schbul/sbl075

Addington, J., Cadenhead, K. S., Cornblatt, B. A., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., Addington, J. A., & Cannon, T. D. (2012). North American Prodrome Longitudinal Study (NAPLS 2): Overview and recruitment. *Schizophrenia Research*, *142*(1), 77-82. https://doi.org/https://doi.org/10.1016/j.schres.2012.09.012

Addington, J., Liu, L., Brummitt, K., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., Keshavan, M., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Stone, W., Tsuang, M. T., Walker, E. F., Woods, S. W., & Cannon, T. D. (2022). North American Prodrome Longitudinal Study (NAPLS 3): Methods and baseline description. *Schizophr Res*, *243*, 262-267. https://doi.org/10.1016/j.schres.2020.04.010

Addington, J., Liu, L., Buchy, L., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., Bearden, C. E., Mathalon, D. H., & McGlashan, T. H. (2015). North American Prodrome Longitudinal Study (NAPLS 2): The Prodromal Symptoms. *J Nerv Ment Dis*, *203*(5), 328-335. https://doi.org/10.1097/nmd.0000000000000290

Aleman, A., Kahn, R. S., & Selten, J. P. (2003). Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Arch Gen Psychiatry*, *60*(6), 565-571. https://doi.org/10.1001/archpsyc.60.6.565

Alemany, S., Ayesa-Arriola, R., Arias, B., Fatjó-Vilas, M., Ibáñez, M. I., Ortet, G., Crespo-Facorro, B., & Fañanás, L. (2015). Childhood abuse in the etiological continuum underlying psychosis from first-episode psychosis to psychotic experiences. *European psychiatry*, *30*(1), 38-42.

American Psychiatric Association, D., & American Psychiatric Association, D. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5). American psychiatric association Washington, DC.

Anand, A., Li, Y., Wang, Y., Gardner, K., & Lowe, M. J. (2007). Reciprocal effects of antidepressant treatment on activity and connectivity of the mood regulating circuit: an FMRI study. *J Neuropsychiatry Clin Neurosci*, *19*(3), 274-282. https://doi.org/10.1176/jnp.2007.19.3.274

Austin, P. C. (2011). An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*, *46*(3), 399-424. https://doi.org/10.1080/00273171.2011.568786

Bauer, M. S., & Mitchner, L. (2004). What is a "mood stabilizer"? An evidence-based response. *American Journal of Psychiatry*, *161*(1), 3-18.

Bechdolf, A., Müller, H., Hellmich, M., de Millas, W., Falkai, P., Gaebel, W., Gallinat, J., Hasan, A., Heinz, A., Janssen, B., Juckel, G., Karow, A., Krüger-Özgürdal, S., Lambert, M., Maier, W., Meyer-Lindenberg, A., Pützfeld, V., Rausch, F., Schneider, F.,…Klosterkötter, J. (2023). Prevention of First-Episode Psychosis in People at Clinical High Risk: A Randomized Controlled, Multicentre Trial Comparing Cognitive-

Behavioral Therapy and Clinical Management Plus Low-Dose Aripiprazole or Placebo (PREVENT). *Schizophr Bull*, *49*(4), 1055-1066. https://doi.org/10.1093/schbul/sbad029

Bhati, M. T. (2013). Defining psychosis: the evolution of DSM-5 schizophrenia spectrum disorders. *Curr Psychiatry Rep*, *15*(11), 409. https://doi.org/10.1007/s11920-013-0409-9

Bocchio-Chiavetto, L., Zanardini, R., Tosato, S., Ventriglia, M., Ferrari, C., Bonetto, C., Lasalvia, A., Giubilini, F., Fioritti, A., Pileggi, F., Pratelli, M., Pavanati, M., Favaro, A., De Girolamo, G., Frisoni, G. B., Ruggeri, M., & Gennarelli, M. (2018). Immune and metabolic alterations in first episode psychosis (FEP) patients. *Brain, Behavior, and Immunity*, *70*, 315-324. https://doi.org/https://doi.org/10.1016/j.bbi.2018.03.013

Bolton, D. (2023). A revitalized biopsychosocial model: core theory, research paradigms, and clinical implications. *Psychol Med*, *53*(16), 7504-7511. https://doi.org/10.1017/s0033291723002660

Bresnahan, M., Begg, M. D., Brown, A., Schaefer, C., Sohler, N., Insel, B., Vella, L., & Susser, E. (2007). Race and risk of schizophrenia in a US birth cohort: another example of health disparity? *Int J Epidemiol*, *36*(4), 751-758. https://doi.org/10.1093/ije/dym041

Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. *Schizophr Bull*, *35*(2), 383-402. https://doi.org/10.1093/schbul/sbn135

Cannon, T. D., Cadenhead, K., Cornblatt, B., Woods, S. W., Addington, J., Walker, E., Seidman, L. J., Perkins, D., Tsuang, M., McGlashan, T., & Heinssen, R. (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry*, *65*(1), 28-37. https://doi.org/10.1001/archgenpsychiatry.2007.3

Catalan, A., Salazar de Pablo, G., Aymerich, C., Guinart, D., Goena, J., Madaria, L., Pacho, M., Alameda, L., Garrido-Torres, N., Pedruzo, B., Rubio, J. M., Gonzalez-Torres, M. A., Fusar-Poli, P., & Correll, C. U. (2024). "Short" Versus "Long" Duration of Untreated Psychosis in People with First-Episode Psychosis: A Systematic Review and Meta-Analysis of Baseline Status and Follow-Up Outcomes. *Schizophr Bull*. https://doi.org/10.1093/schbul/sbae201

Ciarleglio, A. J., Brucato, G., Masucci, M. D., Altschuler, R., Colibazzi, T., Corcoran, C. M., Crump, F. M., Horga, G., Lehembre-Shiah, E., Leong, W., Schobel, S. A., Wall, M. M., Yang, L. H., Lieberman, J. A., & Girgis, R. R. (2019). A predictive model for conversion to psychosis in clinical high-risk patients. *Psychol Med*, *49*(7), 1128-1137. https://doi.org/10.1017/s003329171800171x

Correll, C. U., Detraux, J., De Lepeleire, J., & De Hert, M. (2015). Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry*, *14*(2), 119-136. https://doi.org/10.1002/wps.20204

Correll, C. U., Rubio, J. M., & Kane, J. M. (2018). What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? *World Psychiatry*, *17*(2), 149-160.

Correll, C. U., & Schooler, N. R. (2020). Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. *Neuropsychiatr Dis Treat*, *16*, 519-534. https://doi.org/10.2147/ndt.S225643

Cowan, H. R., Williams, T. F., Mittal, V. A., Addington, J., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Keshevan, M., Perkins, D. O., Mathalon, D. H., Stone, W., Woods, S. W., & Walker, E. F. (2024). The Complex Latent Structure of Attenuated Psychotic Symptoms: Hierarchical and Bifactor Models of SIPS Symptoms Replicated in

Two Large Samples at Clinical High Risk for Psychosis. *Schizophrenia Bulletin*, *50*(6), 1295-1309. https://doi.org/10.1093/schbul/sbae042

Crespo-Facorro, B., Such, P., Nylander, A. G., Madera, J., Resemann, H. K., Worthington, E., O'Connor, M., Drane, E., Steeves, S., & Newton, R. (2021). The burden of disease in early schizophrenia - a systematic literature review. *Curr Med Res Opin*, *37*(1), 109-121. https://doi.org/10.1080/03007995.2020.1841618

de Beer, F., Wijnen, B., Wouda, L., Koops, S., Gangadin, S., Veling, W., van Beveren, N., de Haan, L., Begemann, M. J. H., & Sommer, I. E. C. (2024). Antipsychotic dopamine D2 affinity and negative symptoms in remitted first episode psychosis patients. *Schizophrenia Research*, *274*, 299-306. https://doi.org/https://doi.org/10.1016/j.schres.2024.09.030

De Pablo, G. S., Radua, J., Pereira, J., Bonoldi, I., Arienti, V., Besana, F., Soardo, L., Cabras, A., Fortea, L., & Catalan, A. (2021). Probability of transition to psychosis in individuals at clinical high risk: an updated meta-analysis. *JAMA Psychiatry*, *78*(9), 970-978.

Di Lisi, A., Pupo, S., Menchetti, M., & Pelizza, L. (2024). Antipsychotic Treatment in People at Clinical High Risk for Psychosis: A Narrative Review of Suggestions for Clinical Practice. *J Clin Psychopharmacol*, *44*(5), 502-508. https://doi.org/10.1097/jcp.0000000000001891

Diagnostic and statistical manual of mental disorders : DSM-5™. (2013). (5th edition. ed.). American Psychiatric Publishing, a division of American Psychiatric Association.

DiPiro, J. T., Talbert, R. L., Yee, G. C., Matzke, G. R., Wells, B. G., & Posey, L. M. (2014). Pharmacotherapy: a pathophysiologic approach.

Doghramji, K., & Jangro, W. C. (2016). Adverse effects of psychotropic medications on sleep. *Psychiatric Clinics*, *39*(3), 487-502.

Edinoff, A. N., Akuly, H. A., Hanna, T. A., Ochoa, C. O., Patti, S. J., Ghaffar, Y. A., Kaye, A. D., Viswanath, O., Urits, I., Boyer, A. G., Cornett, E. M., & Kaye, A. M. (2021). Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. *Neurol Int*, *13*(3), 387-401. https://doi.org/10.3390/neurolint13030038

Efthimiou, O., Taipale, H., Radua, J., Schneider-Thoma, J., Pinzón-Espinosa, J., Ortuño, M., Vinkers, C. H., Mittendorfer-Rutz, E., Cardoner, N., Tanskanen, A., Fusar-Poli, P., Cipriani, A., Vieta, E., Leucht, S., Tiihonen, J., & Luykx, J. J. (2024). Efficacy and effectiveness of antipsychotics in schizophrenia: network meta-analyses combining evidence from randomised controlled trials and real-world data. *The Lancet Psychiatry*, *11*(2), 102-111. https://doi.org/10.1016/S2215-0366(23)00366-8

Emsley, R., Chiliza, B., Asmal, L., & Harvey, B. H. (2013). The nature of relapse in schizophrenia. *BMC Psychiatry*, *13*, 50. https://doi.org/10.1186/1471-244x-13-50

Fang, H., Tu, S., Sheng, J., & Shao, A. (2019). Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. *J Cell Mol Med*, *23*(4), 2324-2332. https://doi.org/10.1111/jcmm.14170

Fusar-Poli, P., Davies, C., Solmi, M., Brondino, N., De Micheli, A., Kotlicka-Antczak, M., Shin, J. I., & Radua, J. (2019). Preventive Treatments for Psychosis: Umbrella Review (Just the Evidence). *Front Psychiatry*, *10*, 764. https://doi.org/10.3389/fpsyt.2019.00764

Galletly, C., Castle, D., Dark, F., Humberstone, V., Jablensky, A., Killackey, E., Kulkarni, J., McGorry, P., Nielssen, O., & Tran, N. (2016). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia

and related disorders. *Aust N Z J Psychiatry*, *50*(5), 410-472. https://doi.org/10.1177/0004867416641195

Galling, B., Vernon, J., Pagsberg, A. K., Wadhwa, A., Grudnikoff, E., Seidman, A., Tsoy-Podosenin, M., Poyurovsky, M., Kane, J., & Correll, C. (2018). Efficacy and safety of antidepressant augmentation of continued antipsychotic treatment in patients with schizophrenia. *Acta Psychiatrica Scandinavica*, *137*(3), 187-205.

Ginovart, N., & Kapur, S. (2012). Role of dopamine D(2) receptors for antipsychotic activity. *Handb Exp Pharmacol*(212), 27-52. https://doi.org/10.1007/978-3-642-25761-2_2

Giordano, G. M., Bucci, P., Mucci, A., Pezzella, P., & Galderisi, S. (2021). Gender Differences in Clinical and Psychosocial Features Among Persons With Schizophrenia: A Mini Review. *Front Psychiatry*, *12*, 789179. https://doi.org/10.3389/fpsyt.2021.789179

Gómez-Revuelta, M., Pelayo-Terán, J. M., Juncal-Ruiz, M., Vázquez-Bourgon, J., Suárez-Pinilla, P., Romero-Jiménez, R., Setién Suero, E., Ayesa-Arriola, R., & Crespo-Facorro, B. (2020). Antipsychotic Treatment Effectiveness in First Episode of Psychosis: PAFIP 3-Year Follow-Up Randomized Clinical Trials Comparing Haloperidol, Olanzapine, Risperidone, Aripiprazole, Quetiapine, and Ziprasidone. *Int J Neuropsychopharmacol*, *23*(4), 217-229. https://doi.org/10.1093/ijnp/pyaa004

Habtewold, T. D., Rodijk, L. H., Liemburg, E. J., Sidorenkov, G., Boezen, H. M., Bruggeman, R., & Alizadeh, B. Z. (2020). A systematic review and narrative synthesis of data-driven studies in schizophrenia symptoms and cognitive deficits. *Translational Psychiatry*, *10*(1), 244. https://doi.org/10.1038/s41398-020-00919-x

Harvey, R. C., James, A. C., & Shields, G. E. (2016). A systematic review and network meta-analysis to assess the relative efficacy of antipsychotics for the treatment of positive and negative symptoms in early-onset schizophrenia. *CNS drugs*, *30*, 27-39.

Hazra, A., & Gogtay, N. (2016). Biostatistics Series Module 3: Comparing Groups: Numerical Variables. *Indian J Dermatol*, *61*(3), 251-260. https://doi.org/10.4103/0019-5154.182416

Helfer, B., Samara, M. T., Huhn, M., Klupp, E., Leucht, C., Zhu, Y., Engel, R. R., & Leucht, S. (2016). Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a systematic review and meta-analysis. *American Journal of Psychiatry*, *173*(9), 876-886.

Howes, O. D., Bukala, B. R., & Beck, K. (2024). Schizophrenia: from neurochemistry to circuits, symptoms and treatments. *Nature Reviews Neurology*, *20*(1), 22-35. https://doi.org/10.1038/s41582-023-00904-0

Howes, O. D., Bukala, B. R., & Beck, K. (2024). Schizophrenia: from neurochemistry to circuits, symptoms and treatments. *Nat Rev Neurol*, *20*(1), 22-35. https://doi.org/10.1038/s41582-023-00904-0

Howes, O. D., Whitehurst, T., Shatalina, E., Townsend, L., Onwordi, E. C., Mak, T. L. A., Arumuham, A., O'Brien, O., Lobo, M., Vano, L., Zahid, U., Butler, E., & Osugo, M. (2021). The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. *World Psychiatry*, *20*(1), 75-95. https://doi.org/10.1002/wps.20822

Kamath, J., Virdi, S., & Winokur, A. (2015). Sleep Disturbances in Schizophrenia. *Psychiatric Clinics of North America*, *38*(4), 777-792. https://doi.org/https://doi.org/10.1016/j.psc.2015.07.007

Kapur, S., & Mamo, D. (2003). Half a century of antipsychotics and still a central role for dopamine D2 receptors. *Prog Neuropsychopharmacol Biol Psychiatry*, *27*(7), 1081-1090. https://doi.org/10.1016/j.pnpbp.2003.09.004

Kim, M. (2016). Understanding the Etiology and Treatment Approaches of Schizophrenia: Theoretical Perspectives and Their Critique. *Open Journal of Psychiatry*, *6*(4), 253-261.
Krystal, A. D., Goforth, H. W., & Roth, T. (2008). Effects of antipsychotic medications on sleep in schizophrenia. *International clinical psychopharmacology*, *23*(3), 150-160.
Lambert, M., Conus, P., Eide, P., Mass, R., Karow, A., Moritz, S., Golks, D., & Naber, D. (2004). Impact of present and past antipsychotic side effects on attitude toward typical antipsychotic treatment and adherence. *European psychiatry*, *19*(7), 415-422.
Larson, M. K., Walker, E. F., & Compton, M. T. (2010). Early signs, diagnosis and therapeutics of the prodromal phase of schizophrenia and related psychotic disorders. *Expert Rev Neurother*, *10*(8), 1347-1359. https://doi.org/10.1586/ern.10.93
Lee, M., Cernvall, M., Borg, J., Plavén-Sigray, P., Larsson, C., Erhardt, S., Sellgren, C. M., Fatouros-Bergman, H., & Cervenka, S. (2024). Cognitive Function and Variability in Antipsychotic Drug–Naive Patients With First-Episode Psychosis: A Systematic Review and Meta-Analysis. *JAMA Psychiatry*, *81*(5), 468-476. https://doi.org/10.1001/jamapsychiatry.2024.0016
Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O., & Kreyenbuhl, J. (2004). Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*, *161*(2 Suppl), 1-56.
Leucht, S., Barnes, T. R., Kissling, W., Engel, R. R., Correll, C., & Kane, J. M. (2003). Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *American Journal of Psychiatry*, *160*(7), 1209-1222.
Leucht, S., Helfer, B., Dold, M., Kissling, W., & McGrath, J. (2014). Carbamazepine for schizophrenia. *Cochrane Database of Systematic Reviews*(5).
Lin, C.-Y., Chiang, C.-H., Tseng, M.-C. M., Tam, K.-W., & Loh, E.-W. (2023). Effects of quetiapine on sleep: A systematic review and meta-analysis of clinical trials. *European Neuropsychopharmacology*, *67*, 22-36.
Loch, A. A. (2019). Schizophrenia, Not a Psychotic Disorder: Bleuler Revisited. *Front Psychiatry*, *10*, 328. https://doi.org/10.3389/fpsyt.2019.00328
Mawson, E. R., & Morris, B. J. (2023). A consideration of the increased risk of schizophrenia due to prenatal maternal stress, and the possible role of microglia. *Prog Neuropsychopharmacol Biol Psychiatry*, *125*, 110773. https://doi.org/10.1016/j.pnpbp.2023.110773
McCutcheon, R. A., Pillinger, T., Efthimiou, O., Maslej, M., Mulsant, B. H., Young, A. H., Cipriani, A., & Howes, O. D. (2022). Reappraising the variability of effects of antipsychotic medication in schizophrenia: a meta-analysis. *World Psychiatry*, *21*(2), 287-294. https://doi.org/10.1002/wps.20977
McGlashan, T., Walsh, B., & Woods, S. (2010). *The psychosis-risk syndrome: handbook for diagnosis and follow-up*. Oxford University Press.
McGlashan, T. H., Zipursky, R. B., Perkins, D., Addington, J., Miller, T., Woods, S. W., Hawkins, K. A., Hoffman, R. E., Preda, A., Epstein, I., Addington, D., Lindborg, S., Trzaskoma, Q., Tohen, M., & Breier, A. (2006). Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry*, *163*(5), 790-799. https://doi.org/10.1176/ajp.2006.163.5.790
McGorry, P. D., Yung, A. R., Phillips, L. J., Yuen, H. P., Francey, S., Cosgrave, E. M., Germano, D., Bravin, J., McDonald, T., Blair, A., Adlard, S., & Jackson, H. (2002).

Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry*, *59*(10), 921-928. https://doi.org/10.1001/archpsyc.59.10.921

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic reviews*, *30*(1), 67-76.

McGrath, J., Saha, S., Welham, J., El Saadi, O., MacCauley, C., & Chant, D. (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med*, *2*, 13. https://doi.org/10.1186/1741-7015-2-13

Miller, D. D. (2004). Atypical antipsychotics: sleep, sedation, and efficacy. *Prim Care Companion J Clin Psychiatry*, *6*(Suppl 2), 3-7.

Miller, T. J., McGlashan, T. H., Rosen, J. L., Cadenhead, K., Ventura, J., McFarlane, W., Perkins, D. O., Pearlson, G. D., & Woods, S. W. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin*, *29*(4), 703-715.

Modinos, G., & McGuire, P. (2015). The prodromal phase of psychosis. *Current Opinion in Neurobiology*, *30*, 100-105. https://doi.org/https://doi.org/10.1016/j.conb.2014.11.003

Oliver, D., Radua, J., Reichenberg, A., Uher, R., & Fusar-Poli, P. (2019). Psychosis polyrisk score (PPS) for the detection of individuals at-risk and the prediction of their outcomes. *Frontiers in psychiatry*, *10*, 174.

Patel, K. R., Cherian, J., Gohil, K., & Atkinson, D. (2014). Schizophrenia: overview and treatment options. *Pharmacy and Therapeutics*, *39*(9), 638.

Poletti, M., Pelizza, L., Preti, A., & Raballo, A. (2024). Clinical High-Risk for Psychosis (CHR-P) circa 2024: Synoptic analysis and synthesis of contemporary treatment guidelines. *Asian J Psychiatr*, *100*, 104142. https://doi.org/10.1016/j.ajp.2024.104142

Powers, A. R., Addington, J., Perkins, D. O., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Mathalon, D. H., Seidman, L. J., Tsuang, M. T., Walker, E. F., McGlashan, T. H., & Woods, S. W. (2020). Duration of the psychosis prodrome. *Schizophrenia Research*, *216*, 443-449. https://doi.org/https://doi.org/10.1016/j.schres.2019.10.051

Preda, A., MacLean, R. W., Mazure, C. M., & Bowers Jr, M. B. (2001). Antidepressant-associated mania and psychosis resulting in psychiatric admissions. *Journal of Clinical Psychiatry*, *62*(1), 30-33.

Preda, A., MacLean, R. W., Mazure, C. M., & Bowers, M. B., Jr. (2001). Antidepressant-associated mania and psychosis resulting in psychiatric admissions. *J Clin Psychiatry*, *62*(1), 30-33. https://doi.org/10.4088/jcp.v62n0107

Puranen, A., Koponen, M., Lähteenvuo, M., Tanskanen, A., Tiihonen, J., & Taipale, H. (2023). Real-world effectiveness of antidepressant use in persons with schizophrenia: within-individual study of 61,889 subjects. *Schizophrenia*, *9*(1), 34. https://doi.org/10.1038/s41537-023-00364-x

Raballo, A., Poletti, M., & Preti, A. (2021a). Antipsychotic treatment in clinical high risk for psychosis: Protective, iatrogenic or further risk flag? *Australian & New Zealand Journal of Psychiatry*, *55*(5), 442-444. https://doi.org/10.1177/0004867420984836

Raballo, A., Poletti, M., & Preti, A. (2021b). Individualized diagnostic and prognostic models for psychosis risk syndromes: Do not underestimate antipsychotic exposure. *Biological Psychiatry*, *90*(6), e33-e35.

Raballo, A., Poletti, M., & Preti, A. (2023a). Do antidepressants prevent transition to psychosis in individuals at clinical high-risk (CHR-P)? Systematic review and meta-analysis. *Psychological medicine*, *53*(10), 4550-4560. https://doi.org/10.1017/S0033291722001428

Raballo, A., Poletti, M., & Preti, A. (2023b). The temporal dynamics of transition to psychosis in individuals at clinical high-risk (CHR-P) shows negative prognostic effects of baseline antipsychotic exposure: a meta-analysis. *Translational Psychiatry*, *13*(1), 112. https://doi.org/10.1038/s41398-023-02405-6

Raballo, A., Poletti, M., & Preti, A. (2024). Baseline Antipsychotic Dose and Transition to Psychosis in Individuals at Clinical High Risk: A Systematic Review and Meta-Analysis. *JAMA Psychiatry*, *81*(7), 727-730. https://doi.org/10.1001/jamapsychiatry.2024.0178

Reynolds, G. P. (2022). The neurochemical pathology of schizophrenia: post-mortem studies from dopamine to parvalbumin. *J Neural Transm (Vienna)*, *129*(5-6), 643-647. https://doi.org/10.1007/s00702-021-02453-6

Ricci, C., Leuci, E., Quattrone, E., Palmisano, D., Pellegrini, P., Menchetti, M., Pupo, S., & Pelizza, L. (2024). Persistent negative symptoms in young people at clinical high risk of psychosis treated with an Italian early intervention program: a longitudinal study. *Eur Arch Psychiatry Clin Neurosci*, *274*(6), 1311-1326. https://doi.org/10.1007/s00406-024-01808-w

Sabe, M., Zhao, N., Crippa, A., & Kaiser, S. (2021). Antipsychotics for negative and positive symptoms of schizophrenia: dose-response meta-analysis of randomized controlled acute phase trials. *npj Schizophrenia*, *7*(1), 43. https://doi.org/10.1038/s41537-021-00171-2

Saha, S., Chant, D., Welham, J., & McGrath, J. (2005). A systematic review of the prevalence of schizophrenia. *PLoS medicine*, *2*(5), e141.

Schütz, A., Salahuddin, N. H., Priller, J., Bighelli, I., & Leucht, S. (2024). The role of control groups in non-pharmacological randomised controlled trials of treatment-resistant schizophrenia: A systematic review and meta-analysis. *Psychiatry Res*, *339*, 116069. https://doi.org/10.1016/j.psychres.2024.116069

Singh, S. P., Singh, V., Kar, N., & Chan, K. (2010). Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *The British Journal of Psychiatry*, *197*(3), 174-179.

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J. B., Jones, P., Kim, J. H., Kim, J. Y., Carvalho, A. F., Seeman, M. V., Correll, C. U., & Fusar-Poli, P. (2022). Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. *Molecular psychiatry*, *27*(1), 281-295. https://doi.org/10.1038/s41380-021-01161-7

Staines, L., Healy, C., Coughlan, H., Clarke, M., Kelleher, I., Cotter, D., & Cannon, M. (2022). Psychotic experiences in the general population, a review; definition, risk factors, outcomes and interventions. *Psychol Med*, *52*(15), 1-12. https://doi.org/10.1017/s0033291722002550

Tibbo, P., Malla, A., Manchanda, R., Williams, R., & Joober, R. (2014). Relapse risk assessment in early phase psychosis: the search for a reliable and valid tool. *Can J Psychiatry*, *59*(12), 655-658. https://doi.org/10.1177/070674371405901207

Upthegrove, R., Marwaha, S., & Birchwood, M. (2017). Depression and schizophrenia: cause, consequence, or trans-diagnostic issue? *Schizophrenia Bulletin*, *43*(2), 240-244.

Vanes, L. D., Murray, R. M., & Nosarti, C. (2022). Adult outcome of preterm birth: Implications for neurodevelopmental theories of psychosis. *Schizophrenia Research*, *247*, 41-54. https://doi.org/https://doi.org/10.1016/j.schres.2021.04.007

Walker, E., Kestler, L., Bollini, A., & Hochman, K. M. (2004). Schizophrenia: etiology and course. *Annu. Rev. Psychol.*, *55*(1), 401-430.

Walker, E. F., Cornblatt, B. A., Addington, J., Cadenhead, K. S., Cannon, T. D., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Woods, S. W., & Heinssen, R. (2009). The relation of antipsychotic and antidepressant medication with baseline symptoms and symptom progression: a naturalistic study of the North American Prodrome Longitudinal Sample. *Schizophr Res*, *115*(1), 50-57. https://doi.org/10.1016/j.schres.2009.07.023

Worthington, M. A., Cao, H., & Cannon, T. D. (2020). Discovery and Validation of Prediction Algorithms for Psychosis in Youths at Clinical High Risk. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(8), 738-747. https://doi.org/https://doi.org/10.1016/j.bpsc.2019.10.006

Yu, M., Tan, Q., Wang, Y., Xu, Y., Wang, T., Liu, D., Chen, D., Deng, P., Huang, C., Liang, X., Liu, K., & Xiang, B. (2023). Correlation between duration of untreated psychosis and long-term prognosis in chronic schizophrenia. *Front Psychiatry*, *14*, 1112657. https://doi.org/10.3389/fpsyt.2023.1112657

Yung, A. R., & McGorry, P. D. (1996). The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophrenia Bulletin*, *22*(2), 353-370.

Zeng, J., Raballo, A., Gan, R., Wu, G., Wei, Y., Xu, L., Tang, X., Hu, Y., Tang, Y., & Chen, T. (2022). Antipsychotic exposure in clinical high risk of psychosis: empirical insights from a large cohort study. *The Journal of Clinical Psychiatry*, *83*(3), 40249.

Zhang, T., Xu, L., Tang, X., Wei, Y., Hu, Q., Hu, Y., Cui, H., Tang, Y., Hui, L., Li, C., Cao, L., Lu, Z., & Wang, J. (2020). Real-world effectiveness of antipsychotic treatment in psychosis prevention in a 3-year cohort of 517 individuals at clinical high risk from the SHARP (ShangHai At Risk for Psychosis). *Australian & New Zealand Journal of Psychiatry*, *54*(7), 696-706. https://doi.org/10.1177/0004867420917449

Appendices

sTable1

Baseline Characteristics of Antipsychotic Users and Matched Control Individuals After Propensity Score Matching Using All Symptom Scores

Variable	AP	AP_matched	*p*
Sex (Male (%))	1.33 (0.50)	1.33 (0.50)	1.00
Age (mean (SD))	16.11 (3.02)	17.44 (3.64)	0.41
Education (mean (SD))	9.33 (2.35)	10.44 (2.24)	0.32
P1. Unusual Thought Content/ Delusional Ideas (mean (SD))	4.11 (1.05)	3.67 (1.41)	0.46
P2. Suspiciousness/Persecutory Ideas (mean (SD))	3.56 (1.33)	2.89 (1.62)	0.36
P3. Grandiose Ideas (mean (SD))	0.89 (1.17)	0.22 (0.44)	0.14
P4. Perceptual Abnormalities/ Hallucinations (mean (SD))	3.89 (0.93)	3.78 (0.67)	0.78
P5. Disorganized Communication (mean (SD))	2.00 (1.41)	2.67 (1.50)	0.35
N1. Social Anhedonia (mean (SD))	3.22 (1.79)	3.11 (1.83)	0.90
N2. Avolition (mean (SD))	2.67 (1.58)	2.44 (1.51)	0.76
N3. Decreased Expression of Emotion (mean (SD))	1.33 (1.58)	1.44 (1.59)	0.88
N4. Decreased Experience of Emotions and Self (mean (SD))	1.78 (1.56)	2.00 (1.41)	0.76
N5. Decreased Ideational Richness (mean (SD))	1.67 (1.41)	1.56 (0.88)	0.85
N6. Occupational Functioning (mean (SD))	2.11 (1.83)	1.33 (1.58)	0.35
D1. Odd Behaviour or Appearance (mean (SD))	2.89 (1.05)	2.44 (1.33)	0.45
D2. Bizarre Thinking (mean (SD))	2.78 (1.56)	2.44 (1.33)	0.63
D3. Trouble with Focus and Attention (mean (SD))	1.56 (1.01)	1.22 (1.20)	0.53
D4. Impairment in Personal Hygiene (mean (SD))	2.44 (2.24)	2.56 (1.81)	0.91
G1. Sleep Disturbance (mean (SD))	1.00 (1.41)	0.56 (1.13)	0.47
G2. Dysphoric Mood (mean (SD))	1.22 (1.39)	1.00 (1.22)	0.72
G3. Motor Disturbances (mean (SD))	3.22 (1.30)	2.89 (1.62)	0.64
G4. Impaired Tolerance to Normal Stress (mean (SD))	1.56 (1.81)	0.67 (1.12)	0.23

sTable2

Baseline Characteristics of Antipsychotic with Other Psychotropic Medication Users and Matched Control Individuals After Propensity Score Matching Using All Symptom Scores

Variable	AP with other	AP with other_matched	*p*
Sex (Male (%))	1.75 (0.46)	1.62 (0.52)	0.62
Age (mean (SD))	18.88 (4.42)	18.00 (3.66)	0.67
Education (mean (SD))	12.50 (2.39)	12.00 (3.55)	0.75
P1. Unusual Thought Content/ Delusional Ideas (mean (SD))	3.50 (1.51)	3.38 (1.51)	0.87
P2. Suspiciousness/Persecutory Ideas (mean (SD))	3.38 (1.30)	2.38 (1.92)	0.25
P3. Grandiose Ideas (mean (SD))	0.50 (1.41)	0.50 (0.93)	1.00
P4. Perceptual Abnormalities/ Hallucinations (mean (SD))	3.75 (0.89)	3.62 (1.41)	0.84
P5. Disorganized Communication (mean (SD))	2.50 (1.60)	2.12 (1.55)	0.64
N1. Social Anhedonia (mean (SD))	2.25 (1.83)	2.12 (1.25)	0.88
N2. Avolition (mean (SD))	2.62 (0.74)	2.25 (1.49)	0.54
N3. Decreased Expression of Emotion (mean (SD))	1.50 (1.20)	0.62 (1.41)	0.20
N4. Decreased Experience of Emotions and Self (mean (SD))	2.50 (1.07)	2.25 (1.98)	0.76
N5. Decreased Ideational Richness (mean (SD))	1.25 (1.28)	1.00 (1.60)	0.74
N6. Occupational Functioning (mean (SD))	2.62 (1.92)	1.75 (2.38)	0.43
D1. Odd Behaviour or Appearance (mean (SD))	1.50 (1.41)	1.62 (1.19)	0.85
D2. Bizarre Thinking (mean (SD))	3.12 (1.81)	2.62 (1.51)	0.56
D3. Trouble with Focus and Attention (mean (SD))	1.25 (1.16)	1.00 (1.07)	0.66
D4. Impairment in Personal Hygiene (mean (SD))	3.62 (1.69)	2.50 (2.00)	0.24
G1. Sleep Disturbance (mean (SD))	0.75 (1.16)	0.50 (0.76)	0.62
G2. Dysphoric Mood (mean (SD))	1.38 (1.19)	0.62 (1.19)	0.23
G3. Motor Disturbances (mean (SD))	2.88 (0.99)	2.38 (1.41)	0.43
G4. Impaired Tolerance to Normal Stress (mean (SD))	0.25 (0.46)	0.25 (0.71)	1.00

sTable3

Baseline Characteristics of Antidepressant Users and Matched Control Individuals After Propensity Score Matching Using All Symptom Scores

Variable	AD	AD_matched	*p*
Sex (Male (%))	1.53 (0.51)	1.53 (0.51)	1.00
Age (mean (SD))	16.71 (3.06)	17.12 (3.22)	0.71
Education (mean (SD))	10.76 (3.05)	11.00 (3.18)	0.83

P1. Unusual Thought Content/ Delusional Ideas (mean (SD))	3.65 (1.37)	3.82 (1.24)	0.70
P2. Suspiciousness/Persecutory Ideas (mean (SD))	2.94 (1.34)	2.65 (1.62)	0.57
P3. Grandiose Ideas (mean (SD))	0.06 (0.24)	0.06 (0.24)	1.00
P4. Perceptual Abnormalities/ Hallucinations (mean (SD))	3.18 (1.85)	3.76 (1.44)	0.31
P5. Disorganized Communication (mean (SD))	1.47 (1.46)	1.65 (1.54)	0.73
N1. Social Anhedonia (mean (SD))	2.24 (1.71)	2.29 (1.53)	0.92
N2. Avolition (mean (SD))	2.53 (1.37)	2.71 (1.61)	0.73
N3. Decreased Expression of Emotion (mean (SD))	1.06 (1.20)	1.06 (0.97)	1.00
N4. Decreased Experience of Emotions and Self (mean (SD))	2.18 (1.55)	2.71 (1.21)	0.28
N5. Decreased Ideational Richness (mean (SD))	0.88 (1.05)	1.12 (1.58)	0.61
N6. Occupational Functioning (mean (SD))	2.00 (1.50)	2.12 (1.73)	0.83
D1. Odd Behaviour or Appearance (mean (SD))	2.76 (1.15)	2.82 (1.42)	0.90
D2. Bizarre Thinking (mean (SD))	3.71 (1.10)	3.71 (1.31)	1.00
D3. Trouble with Focus and Attention (mean (SD))	0.88 (0.99)	1.12 (1.17)	0.53
D4. Impairment in Personal Hygiene (mean (SD))	3.06 (1.43)	3.29 (1.61)	0.66
G1. Sleep Disturbance (mean (SD))	0.47 (0.80)	0.35 (1.00)	0.71
G2. Dysphoric Mood (mean (SD))	1.18 (1.67)	0.94 (1.14)	0.64
G3. Motor Disturbances (mean (SD))	2.29 (0.92)	2.71 (1.10)	0.25
G4. Impaired Tolerance to Normal Stress (mean (SD))	0.29 (0.59)	0.24 (0.56)	0.77

sTable4

Kruskal-Wallis Test of Symptom Changes Between Medication Groups and Their Matched Controls

Group	Symptom Domain	*H*	Medication: Matched Symptom Score (Mean (SD))	df	*p*
AP	Positive	1.46	-5.00 (4.87) : -3.44 (3.09)	1	0.23
AP	Negative	0	-3.00 (4.34) : -2.80 (6.98)	1	1.00
AP	General	4.58	-3.88 (3.56) : 0.60 (3.21)	1	0.03
AP	Disorganization	1.58	-2.50 (2.67) : -0.40 (2.61)	1	0.21
AP with other	Positive	2.22	-5.00 (2.97) : -2.25 (3.41)	1	0.14
AP with other	Negative	0.05	-2.67 (3.61) : -4.00 (6.06)	1	0.83

AP with other	General	0.1	-2.67 (4.41) : -3.25 (3.77)	1	0.75
AP with other	Disorganization	0.05	-0.33 (2.25) : -0.25 (1.71)	1	0.83
AD	Positive	0.58	-1.12 (4.00) : -1.94 (2.22)	1	0.45
AD	Negative	0.01	-1.94 (3.77) : -2.08 (4.54)	1	0.92
AD	General	0	-2.94 (3.11) : -2.75 (4.33)	1	0.98
AD	Disorganization	0.72	0.00 (3.14) : -0.75 (1.36)	1	0.40

sFigures1

Mean Symptom Domain Changes Post-PSM from Baseline to 4-Month by Medication Group