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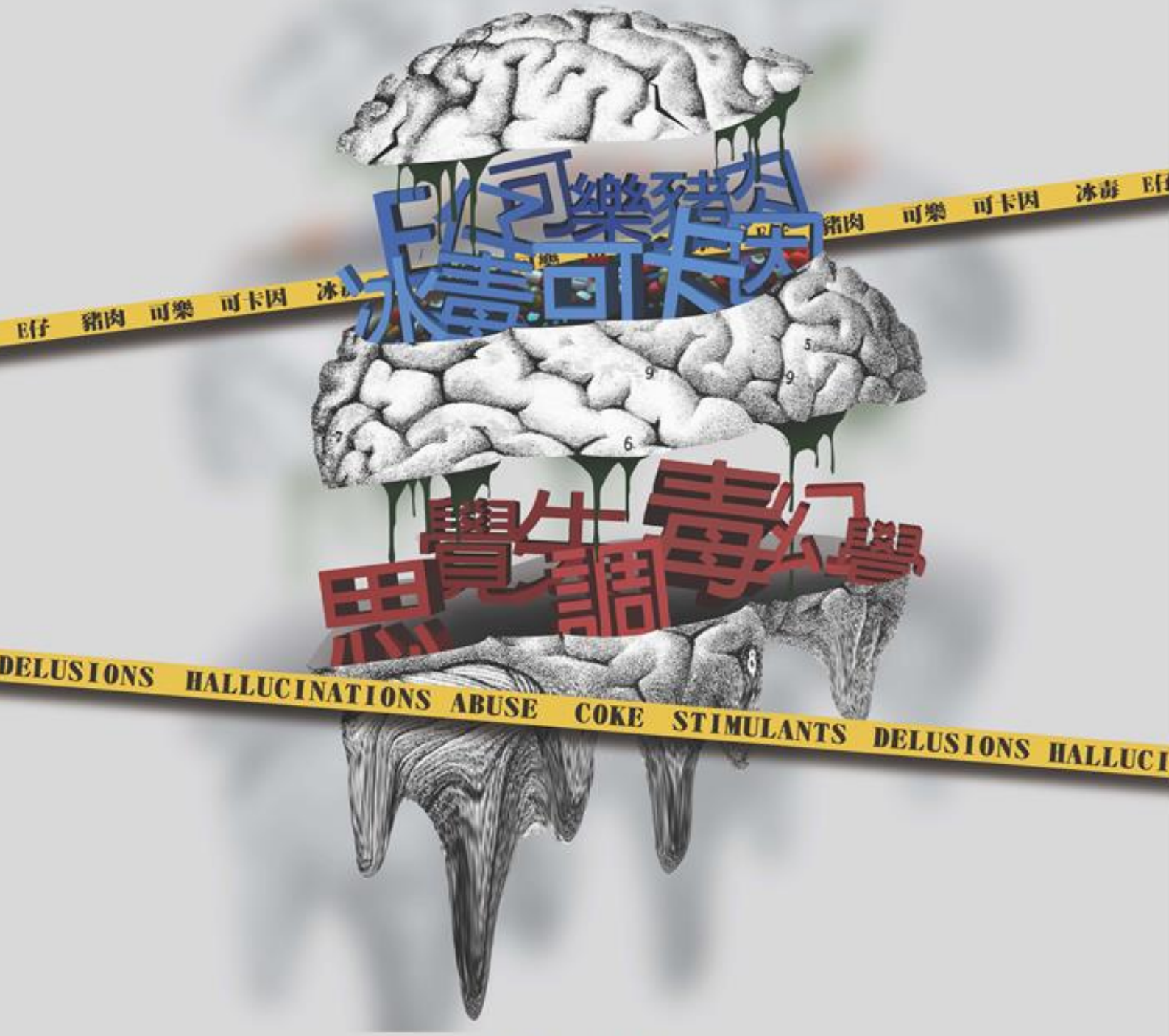
Dr. Chung Kar Kin Albert
Department of Psychiatry, LKS Faculty of Medicine, The University of Hong Kong



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Substance misuse To Psychosis for Stimulants (SToP-S) - An Early Assertive Pharmacotherapy Intervention Study

Final Research Report

HKU Med LKS Faculty of Medicine Department of Psychiatry

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Abstract

Background

Both cocaine and methamphetamine are the top two commonest abused stimulants in Hong Kong. It is well established that stimulant use can induce psychotic disorder, and a substantial proportion of stimulant associated psychosis will convert to schizophrenia. Thus, early assertive pharmacotherapy is in utmost need. Scanty evidence is available on the suitable choices of antipsychotics that can benefit both stimulant abuse and the associated psychosis.

Aims

This study aimed to compare the clinical outcomes from using aripiprazole or paliperidone to treatment-as-usual (TaU) in stimulant abusers with stimulant associated psychosis on their efficacies in treating psychosis, stimulant dependence, and changes in mood, cognitive and functional outcomes. It also looked into the conversion rate from stimulant-induced psychotic disorder to schizophrenia after the use of early assertive pharmacotherapy among stimulant users.

Method

This study was a 24-month, two phases, three-arm, prospective longitudinal interventional study. Consented stimulant abusers with psychotic symptoms were randomized to receive either aripiprazole, paliperidone or TaU in the 1:1:2 ratio for 12 months in the "Active Intervention" phase, followed by another 12 months in the "Observation Maintenance" phase when the interventions could be continued, stopped or changed to other medications. Outcomes including BPRS-24, CGI, GASS, SDS, severity of DSM-5 defined stimulant use disorder (SUD), SOCRATES-D, BAI, BDI-II, FAB, MoCA, and ASI-Lite were assessed by investigators blinded to the randomized interventions.

Results

165 stimulant abusers with psychotic symptoms were randomized. At the end of the "Active Intervention" phase and the "Observation Maintenance" phase, there were no significant intervention group differences in BPRS-24, GASS, CGI-S, SDS and SUD for cocaine, SOCRATES-D, BAI, BDI-II, FAB and ASI-Lite. There could be a potential transient worsening of psychological dependence to methamphetamine when aripiprazole and paliperidone were prescribed in the first six months when compared to TaU group ($p < .05$). Stimulant abusers taking aripiprazole had better CGI-I scores ($p < .001$), and mitigated methamphetamine use disorder severity when compared to the TaU group ($p < .05$). Stimulant abusers taking paliperidone showed the worst MoCA scorings ($p < .05$) among the three intervention groups. The prevalence of schizophrenia converted from stimulant-induced psychotic disorder was 10%.

Conclusions

Clinicians should aware that early antipsychotic pharmacotherapy can help lowering the conversion rate of stimulant induced psychosis to schizophrenia. Aripiprazole and paliperidone were well tolerated in stimulant abusers with associated psychosis. Aripiprazole demonstrated significantly better clinical improvement in stimulant associated psychotic symptoms and was able to improve the severity of methamphetamine use disorder than the other two intervention groups. When paliperidone is prescribed to stimulant abusers with associated psychosis, their cognitive function should be monitored.

Keywords

Stimulant, cocaine, methamphetamine, dependence, psychosis, cognition

Research team members

Psychiatrists:

Dr. Chung Kar Kin Albert (lead principal investigator)

Dr. Chan Fu (principal investigator at North District Hospital)

Dr. Cheung Ngo

Dr. Lee Chi Kei Krystal

Dr. Tam Tsz Ying

Research Nurse:

Ms. Tang Sau Wan

Research Assistants:

Mr. Chiu Chun Yuen

Mr. Law Kai Chun Johnson

Mr. Leung Welton

Mr. Tse Cheuk Yin

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Glossary of acronyms

ASI-Lite: Addiction Severity Index-Lite

ASI-Lite_A: Addiction Severity Index-Lite Alcohol

ASI-Lite_D: Addiction Severity Index-Lite Drug

ASI-Lite_E: Addiction Severity Index-Lite Employment/Support

ASI-Lite_F: Addiction Severity Index-Lite Family/Social relationships

ASI-Lite_Freq: Addiction Severity Index-Lite Frequency of stimulant use

ASI-Lite_L: Addiction Severity Index-Lite Legal status

ASI-Lite_M: Addiction Severity Index-Lite Medical status

ASI-Lite_P: Addiction Severity Index-Lite Psychiatric status

BAI: Beck Anxiety Inventory

BDI-II: Beck Depression Inventory-II

BPRS-24: 24-item Brief Psychiatric Rating Scale

CGI: Clinical Global Impression

CGI-I: Clinical Global Impression-Global Improvement

CGI-S: Clinical Global Impression-Severity of illness

COC: cocaine

CocUD: cocaine use disorder

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

ECG: electrocardiogram

FAB: Frontal Assessment Battery

GASS: Glasgow Antipsychotic Side-effect Scale

GLM: generalized linear model

GLMM: generalized linear mixed model

HA: Hospital Authority

ICD-10: International Classification of Diseases, 10th Revision

ITT: intention-to-treat

LAI: long-acting injectable

LOCF: last observation carried forward

M: mean

MAR: missing-at-random

MD: mean difference

MET: methamphetamine

MetUD: methamphetamine use disorder

MH: marginal homogeneity

MoCA: Montreal Cognitive Assessment

N: number of participants

NCD: neurocognitive disorder

SDS: Severity of Dependence Scale

SE: standard error

SOCRATES-D: Stages of Change Readiness and Treatment Eagerness Scale-Drug

SOCRATES_amb: Stages of Change Readiness and Treatment Eagerness Scale-Drug Ambivalence subscale

SOCRATES_rec: Stages of Change Readiness and Treatment Eagerness Scale-Drug Recognition subscale

SOCRATES_ts: Stages of Change Readiness and Treatment Eagerness Scale-Drug Taking Steps subscale

SToP-S: Substance misuse To Psychosis for Stimulants

SUD: substance use disorder

TaU: treatment-as-usual

Introduction

In Hong Kong, while the total number of reported drug abusers for psychotropic substances progressively decreased by 34% since 2014, the proportion of methamphetamine (MET) and cocaine (COC) abusers were, however, increased by 6.0% points within the same decade (Narcotics Division, 2024). Both MET and COC are now the top two commonest abused substances in Hong Kong, accounting for 52.6% and 56.0% of all reported and of newly reported psychotropic substance abusers, respectively in 2023 (Narcotics Division, 2024).

It is well-established that stimulant use is associated with perceptual disturbances and might induce transient psychotic disorder, characterized by the presence of hallucinations, paranoia, and/or persecutory delusion that could last between one and six months (American Psychiatric Association, 2013; World Health Organization, 1993). Despite stimulant associated psychotic symptoms would usually ablate within 24 hours (Lappin, Sara, & Farrell, 2017), prolonged symptoms for more than a month following discontinuation of MET use might happen in 26% of abusers (Chen et al., 2003; Sato, Numachi, & Hamamura, 1992). The prevalence for MET- and COC- induced psychosis had been reported as high as 40% and 60%, respectively (Boden, Foulds, Newton-Howes, & McKetin, 2023; Sabe, Zhao, & Kaiser, 2021). Weekly use, recent use, and clinical dependence on MET and COC are known risk factors for their associated psychotic disorders (Arunogiri, Foulds, McKetin, & Lubman, 2018; Boden et al., 2023; Tang, Tang, & Chan, 2017). Consequently, the prevalence of stimulant-induced psychotic disorders could be on the rise if the continual increase in stimulant abuse is left unattended.

Previous studies suggested that MET abusers with induced psychosis had a higher prevalence of numerous psychiatric comorbidities, including major depression, alcohol dependence, and antisocial personality disorder (Chen et al., 2003); whereas in COC abusers with attention

deficit-hyperactivity disorder, cannabis dependence, and antisocial personality disorder (Roncero et al., 2014). They were also less adherent to psychiatric services (Crebbin, Mitford, Paxton, & Turkington, 2009). The risk of developing schizophrenia is substantially increased with MET and COC abuse (Callaghan et al., 2012), and 25-30% of abusers initially diagnosed with amphetamine-induced psychosis went on to develop schizophrenia spectrum disorders later in life (Murrie, Lappin, Large, & Sara, 2020; Niemi-Pynttari et al., 2013). Thus, early assertive intervention should be prioritized in the integrated care across substance misuse and mental health services for young psychotropic substance abusers with substance use disorders or substance-induced psychosis to counteract the future development into more debilitating conditions arising from schizophrenia and its related disorders (Lappin et al., 2017; National Collaborating Centre for Mental Health (UK), 2011).

Dopaminergic agents, including both dopamine D_2/D_3 antagonists and dopamine partial D_2 agonists, have been effective for treating psychosis. However, their efficacies in treating substance dependence, or co-morbid substance abuse with psychosis, had not yet been well studied. Traditional antipsychotics with high and potent D_2 affinity, such as haloperidol, had not been consistently shown being effective in treating substance dependence due to their strong D_2 blockade at the limbic striatum interfering the rewarding circuits that might potentially cause an increase in craving instead. In contrast, newer second-generation antipsychotics with D_2/D_3 and serotonin $5HT_{2A}$ antagonisms as core receptor profiles appeared to be promising (Lalanne et al., 2016), with the findings in an animal study also showing inhibition of dopamine D_3 receptor attenuated the rewarding effect of MET (Yu, Zhu, Shen, Bai, & Di, 2015). Several preliminary laboratory studies using oral aripiprazole, a potent D_2/D_3 antagonist and a low-efficacy partial D_2/D_3 agonist (Strange, 2008), ranged in 15-20mg had shown marked effects in attenuating the discriminative stimulus of d-amphetamine in healthy

volunteers (Stoops, 2006), the reinforcing and subject-rated effects of oral MET in recreational stimulant users (Stoops, Bennett, Lile, Sevak, & Rush, 2013), and in reducing the self-reported effects of COC in cocaine-dependent subjects (Lile, Stoops, Glaser, Hays, & Rush, 2011). Nonetheless, two fixed-dose placebo-controlled clinical trials administering 15mg of oral aripiprazole failed to demonstrate its effectiveness in treating neither intravenous amphetamine (Tiihonen et al., 2007) nor intravenous MET (Newton et al., 2008) dependence. Such discrepancies of findings were attributed to the differences from the routes of administration of the stimulants, their acute effects in human laboratory studies, and their chronic effects in clinical subjects with stimulants dependence. On the other hand, open labelled-trials using oral and long-acting injectable (LAI) risperidone, a potent D_2 and $5HT_{2A}$ antagonist, showed decreased MET use in dependent subjects even at low doses (Karila et al., 2010; Meredith et al., 2009). Unfortunately, the evidence on paliperidone, a metabolite of risperidone using the OROS® controlled release system with the advantages on once-daily oral dosing frequency and minimal hepatic metabolism, remains scarce up to date.

In Hong Kong, less than 5% of stimulants abusers were reported to misuse these substances via injection (Narcotics Division, 2024). Patients with co-morbid substance abuse/dependence and psychosis or schizophrenia spectrum disorders are also prone to earlier treatment discontinuation and higher oral medication non-adherence, resulting in poorer overall outcomes (Colizzi et al., 2016; Engh & Bramness, 2017; Kane, Kishimoto, & Correll, 2013; Perkins et al., 2008). With the territory-wide availabilities of the 4-weekly LAI aripiprazole, and the 4-weekly and the 3-monthly LAI paliperidone palmitate, together with the surging prevalence of stimulant abuses in Hong Kong, it is therefore a timely opportunity to conduct an early pharmacotherapy intervention study to offer an evidence-based strategy that aims at

stopping individuals with stimulant use disorders with psychosis from developing into a more chronic debilitating dependence or co-morbid state.

The present study aimed to compare the clinical outcomes from early assertive pharmacotherapy intervention using aripiprazole or paliperidone to Treatment-as-Usual (TaU) in patients with stimulant use disorder (SUD) and co-morbid psychosis on the efficacy in preventing psychosis relapse, changes in the severity of SUD and stimulant dependence, and cognitive and functional outcomes. The study was also designed to compare the effects of the maintenance of pharmacotherapy against discontinuation and TaU on the severity of SUD and stimulant dependence, the rate of conversion to schizophrenia spectrum disorders, and cognitive and functional outcomes. Lastly, the present study would estimate the prevalence of stimulant-induced psychosis converting to schizophrenia spectrum disorders.

We hypothesized that the use of aripiprazole or paliperidone as compared to TaU would: (1) be more efficacious in preventing psychosis relapse, (2) be better in reducing the severity of SUD and/or stimulant dependence, and (3) have better mood, cognitive and functional outcomes at 12^{th} month and at 24^{th} month.

Methods

Study design

The present study was a 24-month multicentre, three-arm, prospective longitudinal interventional study. The study comprised two 12-month phases: during the first single-blind "Active Intervention" phase, participants were randomized to receive either aripiprazole (S1 group), paliperidone (S2 group), or TaU (S3 group) as active interventions for 12 months. Only assessors on outcome measures were blinded to the intervention group which the participants

were allocated throughout. During the second naturalistic, open-labelled "Observation Maintenance" phase, participants in all three groups could maintain or discontinue the randomized medications and/or interventions. The original blinding on interventions would no longer be preserved to the outcome assessors.

Each consented participant would receive the randomly assigned intervention and continued his/her follow-up assessments for 24 months at the participating sites in the Hong Kong West Cluster and at the North District Hospital.

The present study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB Reference: UW 18-094) and the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CREC Reference: 2018.156-T). Certificates of Clinical Trail from the Department of Health, HKSAR (No. 101536, No. 101128, and No. 200061) were granted to conduct the study. This study was also registered at the free public research website *clinicaltrials.gov* (NCT03485417).

Subject recruitment

Participants were recruited territory-wide from the psychiatric services and medical health services under Hospital Authority (HA), from the community, and from non-governmental organizations. All participants provided written informed consent prior to any study procedure. Participants would receive HKD$200 upon completing all the assessments with provision of a urine sample at each assessment time-point.

Inclusion criteria

Participants were aged between 16 and 50 years at the time of enrolment. They were able to give informed consent, and read and communicate in Chinese or English. For patients attending HA Psychiatric Services, they were diagnosed with SUD with co-morbid stimulant-induced psychotic disorders under the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American Psychiatric Association, 2013), or with stimulant harmful use or dependence syndrome, with co-morbid psychotic disorders or late-onset psychotic disorders due to use of cocaine or other stimulants under the International Classification of Diseases, 10th Revision (ICD-10) (World Health Organization, 1993). Subjects from other medical services and community referrals were eligible if they had at least two positive urine test results for stimulants within one month and had psychotic symptoms at the time of recruitment.

Exclusion criteria

Subjects who were younger than 16 or older than 50 years of age, were unable to give consent, and unable to communicate in Chinese or English were deemed ineligible for the present study. If the subjects had been diagnosed with any of the following psychiatric diagnosis according to DSM-5 or ICD-10 prior to their stimulant use, they would also be excluded:

- Intellectual Disabilities or Mental Retardation;
- Schizophrenia, Schizotypal (Personality) Disorders, or Schizoaffective Disorders;
- Other substance-induced psychotic or mood disorders, including alcohol;
- Bipolar Disorders, manic episode, or Bipolar Affective Disorders;
- Major Depressive Disorders with psychotic features, or severe depressive episode with psychotic symptoms, or Recurrent Depressive Disorders, current episode severe with psychotic symptoms.

Furthermore, if the subjects had been taking any maintenance dose of oral or receiving any maintenance dose of LAI/depot antipsychotics with psychotic symptoms in remission, had known hypersensitivity to risperidone, paliperidone, or aripiprazole, had suffered from tardive dyskinesia or neuroleptic malignant syndrome before, was pregnant or breast-feeding, had a past history of prolonged QTc ≥500ms and/or known unstable or untreated cardiac disorders, or had mild to severe renal impairment as indicated by the glomerular filtration rate lower than 80 mL/min, they would also be excluded from the current study as well.

Sample size

With reference to the meta-analysis on the efficacy among antipsychotics on overall changes in symptoms in schizophrenia (Huhn et al., 2019), the present study aimed to enrol 168 participants to ensure sufficient statistical power to detect medium effect sizes (α=0.05, β=0.20) with a statistical power of 80%.

Intervention allocation and Randomization

In light of the previous report that aripiprazole might worsen amphetamine dependence in stimulant users (Tiihonen et al., 2007), the limited safety data on using paliperidone in stimulant dependence (Cuomo et al., 2018), and to maximize subject recruitment, participants were randomly allocated in the 1:1:2 ratio for aripiprazole, paliperidone and TaU, respectively (Office of New Drugs, 2013). Hence, it was expected that 42 participants would be randomized to receive aripiprazole, 42 randomized to receive paliperidone, and 84 to the TaU group.

Randomization was performed using the sealed envelope system once the subjects fulfilled the inclusion/exclusion criteria and consented to participate in the current study. Each opaque envelope contained a sheet of paper reading SToP-S1, SToP-S2, or SToP-S3 that corresponded to the interventions with aripiprazole (S1 group), paliperidone (S2 group), or TaU (S3 group).

All envelopes were sealed and held in an opaque paper box. After the subject consented, staff member independent to the study would randomly draw an envelope from the opaque box and handed to the attending psychiatrist. The attending psychiatrist would then provide the respective allocated treatment to the participant.

Interventions

Following group allocation, all participants entered the first 12-month "Active Intervention" phase. For participants in S1 group and S2 group, 2mg of aripiprazole and 3mg of paliperidone were initiated orally with the 1st week tolerability lead-in, respectively. The dosages of both medications were adjusted depending on the clinical requirements in the first 4 weeks. Thereafter, the dosages were preferentially fixed as maintenance treatment. Nevertheless, if deemed clinically indicated, dosages of the medications were adjusted within the recommended dosing range for the treatment of schizophrenia according to the prescribing information (Janssen Pharmaceuticals, 2021, 2022a, 2022b; Otsuka Pharmaceutical, 2020, 2022). There were no restrictions on other concomitant non-antipsychotic medications use in both groups.

For participants in the TaU (S3) group, the need for medication treatment would be decided by the attending psychiatrists. If antipsychotic medication was considered appropriate, participants in the S3 group could receive any kind of antipsychotic medication, except aripiprazole and paliperidone. Again, there were no restriction on other concomitant non-antipsychotic medications use in the S3 group.

From the 13th month to the 24th month, all participants would enter the "Observation Maintenance" phase. In this phase of the study, participants from all the 3 groups could choose

to either discontinue (observation) or continue (maintenance) their originally assigned interventions.

There was no restriction for all the participants to receive psychological intervention or psychotherapy if the attending psychiatrists regarded that it was clinically indicated. However, other physical treatment modalities for treating stimulant use disorder or psychosis were not permitted.

Outcome measures and assessment

Outcome measures in this study were assessed by research assistants, research nurse and psychiatrists at baseline, 4 weeks from baseline, at the 3rd, 6th, 12th and 24th month. Research assistants and nurse were trained by board-certified psychiatrists for conducting the semi-structured interview and outcome measure assessments. In addition, all the DSM-5 and/or ICD-10 diagnoses of the participants were made and/or verified by board-certified psychiatrists.

The outcome measures employed in the current study included the following:

- Antipsychotics-related assessment scales:
    - **Brief Psychiatric Rating Scale-24** (BPRS-24) for assessing the severity of psychotic symptoms and a ≥ 50% of reduction of the total scores from baseline would indicate a clinically meaningful improvement (Leucht et al., 2005);
    - **Clinical Global Impression** (CGI) for assessing efficacy with CGI-severity of illness (CGI-S) and/or CGI-global improvement (CGI-I) scorings of ≤ 3 meant responders to the intervention (Busner & Targum, 2007); and

- **Glasgow Antipsychotic Side-effect Scale** (GASS) for assessing the severity of side-effects, defined by a total score of ≤ 21 (absent/mild side-effects), 22-42 (moderate side-effects), and ≥ 43 (severe side-effects) (Waddell & Taylor, 2008).

- Stimulant use assessments:
  - **Self-reported use** over the past 30 days;
  - **Urine Quick Test** kits/**HA Laboratory Urine Toxicology Screening Test** for detecting the presence of methamphetamine, cocaine, and their metabolites;
  - **Severity of Dependence Scale** (SDS) for assessing the psychological dependence on stimulants with the cut-offs of ≥ 3 and ≥ 5 signifying dependence on cocaine and methamphetamine/amphetamines, respectively (National Centre for Education and Training on Addiction, 2021);
  - **DSM-5** for assessing the severity of SUD that classifies cocaine use disorder (CocUD) and methamphetamine use disorder (MetUD) as mild, moderate, or severe; and
  - **Stages of Change Readiness and Treatment Eagerness Scale-Drug** (SOCRATES-D) for assessing the readiness for change in stimulant use.
- Mood symptoms assessment scales:
  - **Beck Anxiety Inventory** (BAI) for assessing anxiety with the severity of anxiety defined by the overall total scorings of ≤ 7 (minimal anxiety), 8-15 (mild anxiety), 16-25 (moderate anxiety) and ≥ 26 (severe anxiety); and
  - **Beck Depression Inventory-II** (BDI-II) for assessing depression with the severity of depression defined by the overall total scorings of ≤ 13 (normal), 14-19 (mild depression), 20-28 (moderate depression) and ≥ 29 (severe depression).
- Cognitive assessment scales:

- **Frontal Assessment Battery** (FAB) for assessing the frontal executive function with a cut-off score of <12 to indicate the presence of frontal dysexecutive syndrome (T. L. Wang, Hung, & Yang, 2016); and
- **Montreal Cognitive Assessment** (MoCA) for assessing the global cognitive function with a score of < 26 as cut-off to identify mild neurocognitive disorder (NCD) as defined in DSM-5 (Nasreddine et al., 2005).

- Functional outcome assessment scale:
  - **Addiction Severity Index-Lite** (ASI-Lite) for assessing stimulant abuse related impairments. A higher component score indicates a more severe impairment, except for employment/support status.

As both aripiprazole and paliperidone had very good tolerability and acceptability as treatments for schizophrenia and psychosis (Huhn et al., 2019), physical monitoring and investigations would be performed by the attending psychiatrists when considered clinically indicated. These monitoring would include measurements of body weight, waist circumference, body mass index, blood pressure, and pulse rate; other investigations might also involve electrocardiogram (ECG), blood tests with complete blood count, liver and renal function tests, thyroid function tests and plasma prolactin levels.

Blinding

During the first 12-month "Active Intervention" phase, single-blinding approach was applied. Assessors who administered the semi-structured interview and/or rating scales were blinded to the group allocation. The attending psychiatrists who prescribed the randomized interventions to the participants would not assess the same participants they treated. Participants were instructed not to disclose their received intervention to the assessors.

During the last 12-month "Observation Maintenance" phase, all assessors were unblinded to the group allocation. The attending psychiatrists who prescribed the randomized interventions to the participants during the "Active Intervention" phase would be allowed to assess the same participants they treated. This unblinding phase served as the pragmatic trial approach closest to the routine clinical practice to provide the "real-world" experience (Monaghan et al., 2021).

Statistical Analysis

All the statistical analyses were performed using IBM SPSS version 29.0 and R version 4.3.3. The primary endpoint of the current study was at the 12th month (i.e., the end of the "Active Intervention" phase), whereas the secondary endpoint was at the 24th month (i.e., the end of the "Observation Maintenance" phase).

Since stimulant abusers and individuals with psychotic disorders are usually having socioeconomic disadvantages, are prone to early treatment discontinuation and non-adherence to medication with poorer outcomes (Colizzi et al., 2016; Engh & Bramness, 2017; Kane et al., 2013; Perkins et al., 2008) irrespective of their insights (Lecomte et al., 2008), the present study presumed any outcome data missing to be missing-at-random (MAR) (Pugh, Brown, & Enserro, 2022). Therefore, intention-to-treat (ITT) analysis and the Last Observation Carried Forward (LOCF) method were chosen *a priori* in the research protocol. ITT analysis helped to maintain the comparability of the three intervention groups after randomization and to minimize the risk of bias resulting from drop-outs. And with the assumptions that the data missing rate would be small and the effects from aripiprazole (S1 group) and paliperidone (S2 group) as compared to TaU (S3 group) might be small at the primary and secondary endpoints, LOCF was used for its ease of execution to handle the MAR data (Zhu, 2014).

Demographic data of all the participants and their history of stimulant use were presented with descriptive statistics. Continuous variables were compared by the Kruskal-Wallis test. Categorical variables were compared by the Chi-squared test.

For the primary analyses, to evaluate the effects of the three intervention groups: aripiprazole (S1 group), paliperidone (S2 group), and TaU (S3 group) on all continuous outcome measures over multiple timepoints, including baseline, at the 4^{th} week, 3^{rd} month, 6^{th} month, 12^{th} month, and 24^{th} month, generalized linear mixed models (GLMM) regression analyses were employed. GLMM holds the advantage that no data imputation is necessary for missing data if the missing data rate is eventually high over these five timepoints. The fixed effects in the model included the intervention groups, and the interaction between group and time. The models were adjusted for a set of covariates: gender, age, education, marital status, forensic history, smoking status, drinking status, drinking years, number of psychiatric in-patient admissions, total number of hospital admissions, psychiatric out-patient usage, as well as the number of admissions to detox institute. In the current study, the primary analyses involved LOCF analyses in accordance with the protocol, followed by the sensitivity analyses without LOCF for all parametric treatment outcomes. The models were adjusted using the Satterthwaite method for degrees of freedom estimation and employed Bonferroni adjustments for multiple comparisons.

For the analyses on the non-parametric outcomes from CGI, SDS, CocUD and MetUD, and BPRS-24 as listed below, Chi-square tests and the generalized linear model (GLM) regression analyses or Stuart-Maxwell test with Bonferroni corrections were conducted. No LOCF imputation was employed. The GLM was adjusted for gender, age, education, marital status, forensic history, smoking status, drinking status, drinking years, number of psychiatric in-

patient admissions, total number of hospital admissions, psychiatric out-patient usage, and the number of detox institute admissions as covariates.

	Clinical Responders	**Clinical Non-responders**
BPRS-24	≥ 50% reduction in total score from baseline	< 50% reduction in total score from baseline
CGI-S	≤ 3	> 3
CGI-I	≤ 3	> 3
	Dependence	**Non-dependence**
SDS-COC	Total score ≥ 3	Total score < 3
SDS-MET	Total score ≥ 5	Total score < 5
	DSM-5 defined Severity	
CocUD	None/ Mild/ Moderate/ Severe	
MetUD	None/ Mild/ Moderate/ Severe	

All analyses had the significance of alpha = .05. Significant results rejected the null hypotheses that:

1. Efficacy-H_0: participants taking either aripiprazole or paliperidone has the same efficacy in managing psychosis in stimulant abusers as compared to the treatment-as-usual group separately
2. Severity-H_0: participants taking either aripiprazole or paliperidone has similar severity of stimulant use disorder as compared to the treatment-as-usual group separately

Results

This study started in June 2019 and the COVID-19 pandemics started shortly after. Eventually, 165 participants (98.2%) consented and participated in the study instead of the original planned sample size of 168 subjects before the completion of the study in May 2024. Forty-two

participants (100%) were randomized to receive aripiprazole (S1 group), 40 participants (95.2%) to paliperidone (S2 group) and 83 participants (98.8%) to TaU (S3 group) (Figure 1).

Figure 1. CONSORT flow diagram. (n = number of subject)

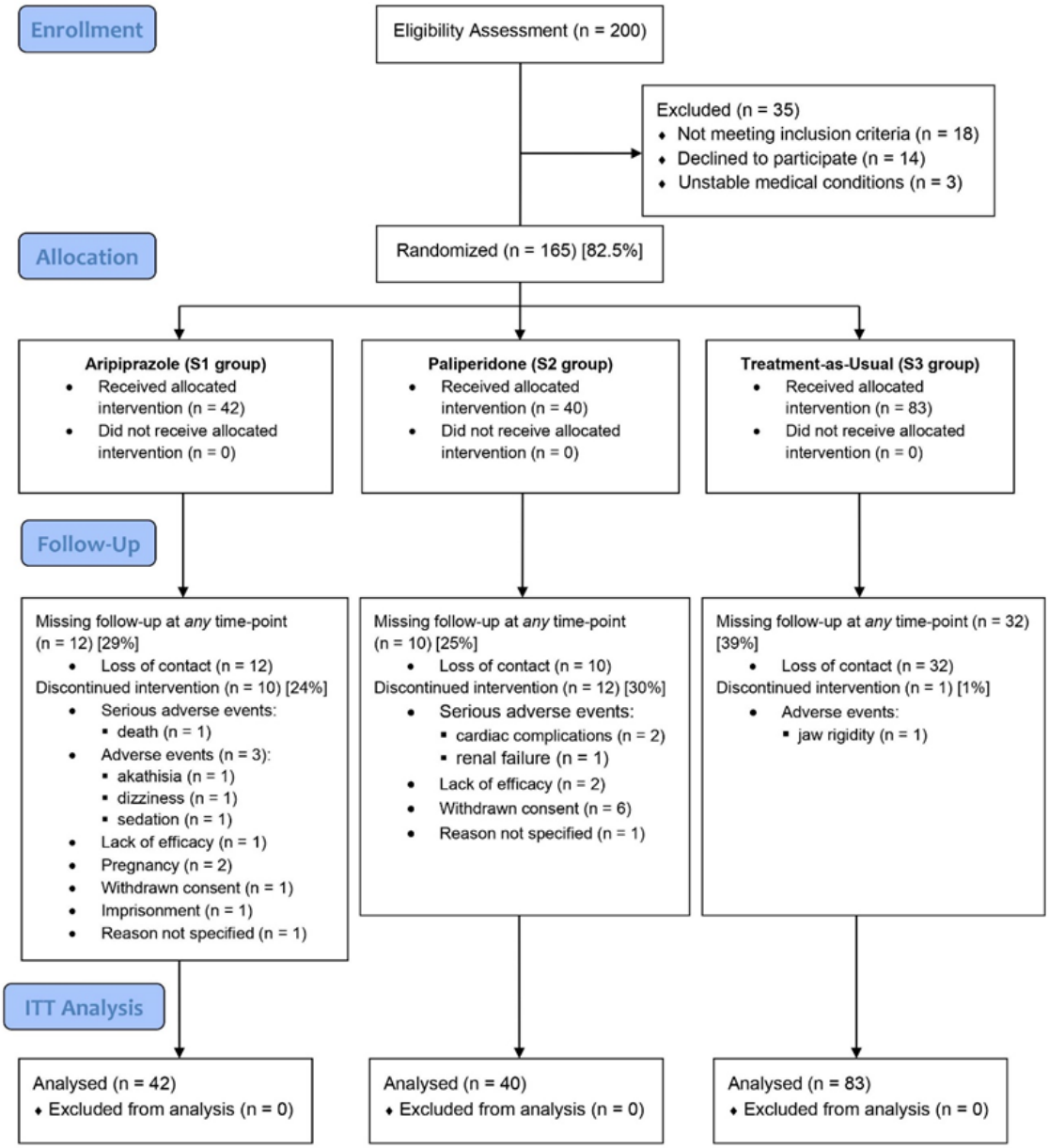

Figure 1. CONSORT Flow Diagram of the SToP-S Study.

Four participants (2.4%) had serious adverse events reported during the study. One participant in S1 group was recorded death due to suicide after 6 months. Three participants in S2 group discontinued paliperidone: two were due to cardiac events with symptomatic atrial fibrillation and prolongation of Bazett-corrected QTc (472ms) after 3 months and 6 months, respectively; and one due to acute renal failure after 6 months related to pneumonia. Three participants in S1 group discontinued aripiprazole due to side-effects after three to six months of treatment. One participant in S3 group discontinued brexpiprazole after 6 months due to extrapyramidal side-effect with jaw rigidity.

The baseline demographics of the participants were presented in Table 1. Overall, there were significantly more male stimulant users participated in the current study. The mean age of the participants was 38.7 years, with those randomized to the S1 group being significantly younger than the other two groups. There were significantly larger percentage of participants in the S2 group having forensic records. Among all the participants, 66 participants (40.2%) and 16 participants (9.8%) reported using MET and COC as the sole stimulant, respectively. 82 participants (50%) reported using both MET and COC in their lifetime. One participant misused phentermine only throughout the whole study period.

Table 1. Demographic characteristics and stimulant use status of all participants at baseline.

	Total (n = 165)	**Aripiprazole (S1)** (n = 42)	**Paliperidone (S2)** (n = 40)	**TaU (S3)** (n = 83)	***p*-value**
Gender (%)					**< .001**
Male	115 (69.7)	19 (45.2)	33 (82.5)	63 (75.9)	
Female	50 (30.3)	23 (54.8)	7 (17.5)	20 (24.1)	
Age, Mean (SD)	38.7 (10.1)	34.4 (10.0)	40.0 (8.3)	40.3 (10.4)	**.008**

Educational level (%)					.599
Primary or below	49 (29.7)	12 (28.6)	13 (32.5)	24 (28.9)	
Secondary	94 (57.0)	25 (59.5)	19 (47.5)	50 (60.2)	
Tertiary or above	22 (13.3)	5 (11.9)	8 (20.0)	9 (10.8)	
Marital status (%)					.217
Single	88 (53.3)	29 (69.0)	19 (47.5)	40 (48.2)	
Married	32 (19.4)	6 (14.3)	9 (22.5)	17 (20.5)	
Divorced	45 (27.3)	7 (16.7)	12 (30.0)	26 (31.3)	
Forensic History (%)	105 (63.6)	20 (47.6)	29 (72.5)	56 (67.5)	**.038**
Smoker (%)	147 (89.1)	36 (85.7)	38 (95.0)	73 (88.0)	.353^
Drinker (%)	116 (70.3)	27 (64.3)	26 (65.0)	63 (75.9)	.284
Drinking years, Mean (SD)	20.7 (10.6)	17.0 (10.3)	23.3 (8.1)	21.2 (11.3)	.101
Psychiatric Services (%)					
In-patient	117 (70.9)	31 (73.8)	33 (82.5)	53 (63.9)	.092
Out-patient	143 (86.7)	36 (85.7)	35 (87.5)	72 (86.7)	.972
All-cause hospitalizations, Mean (SD)	3.4 (5.6)	4.1 (5.5)	2.2 (1.7)	3.6 (6.7)	.240
Detox centre admission (%)	91 (55.2)	22 (52.4)	21 (52.5)	48 (57.8)	.785
Other substance use (%)					
Cannabis	123 (74.5)	34 (81.0)	26 (65.0)	63 (75.9)	.233
Ketamine	99 (60.0)	29 (69.0)	20 (50.0)	50 (60.2)	.212
MDMA	76 (46.1)	22 (52.4)	16 (40.0)	38 (45.8)	.530
Imovane	66 (40.0)	15 (35.7)	19 (47.5)	32 (38.6)	.514
Heroin	46 (27.9)	11 (26.2)	11 (27.5)	24 (28.9)	.948
Cough syrup	42 (25.5)	9 (21.4)	12 (30.0)	21 (25.3)	.672
Nimetazepam	35 (21.2)	11 (26.2)	8 (20.0)	16 (19.3)	.656
Dormicum	28 (17.0)	6 (14.3)	3 (7.5)	19 (22.9)	.090
Methadone	24 (14.5)	4 (9.5)	3 (7.5)	17 (20.5)	.091
Methamphetamine Use					
Lifetime use (%)	148 (89.7)	39 (92.9)	36 (90.0)	73 (88.0)	.752^
Active use# (%)	131 (79.4)	31 (73.8)	34 (85.0)	66 (79.5)	.456
Duration of use in months, Mean (SD)	116.3 (101.5)	96.9 (86.8)	99.2 (84.9)	135.3 (113.6)	.241
Cocaine Use					
Lifetime use (%)	98 (59.4)	29 (69.0)	19 (47.5)	50 (60.2)	.136
Active use# (%)	40 (24.2)	12 (28.6)	7 (17.5)	21 (25.3)	.480

Duration of use in months, Mean (SD)	59.3 (79.8)	54.2 (71.0)	53.8 (78.2)	64.4 (86.3)	.763

n: number of participants; SD: standard deviation; TaU: Treatment-as-Usual
[#] Active use referred to the use of stimulants in the past 3 months.
[^] Compared using Fisher's exact test.

The completion rates at the various assessments timepoints were presented in Table 2. During the "Active Intervention" phase, 70.3% of all participants completed the assessments, where the completion rates were 57.1%, 70.0%, and 77.1% for S1, S2, and S3, respectively. However, during the naturalistic "Observation Maintenance" phase, the overall completion rate dropped to 53.3%. There were no significant differences noted on the completion rates for all the three groups over the subsequent follow-up timepoints.

Table 2. Completion rates of the three intervention groups at different assessment timepoints.

	Total (n = 165)	**Aripiprazole (S1)** (n = 42)	**Paliperidone (S2)** (n = 40)	**TaU (S3)** (n = 83)	***p*-value**
Timepoint					.175
4th week	111 (67.3%)	30 (71.4%)	29 (72.5%)	52 (62.7%)	.442
3rd month	119 (72.1%)	32 (76.2%)	31 (77.5%)	56 (67.5%)	.404
6th month	113 (68.5%)	29 (69.0%)	28 (70.0%)	56 (67.5%)	.957
12th month	116 (70.3%)	24 (57.1%)	28 (70.0%)	64 (77.1%)	.070
24th month	88 (53.3%)	20 (47.6%)	18 (45.0%)	50 (60.2%)	.196

n: number of participants.

Mean dosages and types of medications for the three intervention groups at the primary and secondary study endpoints were presented in Tables 3 and 4, respectively. During the "Active

Intervention" phase, 8 (19.0%), 11 (27.5%), and 2 (2.4%) participants in S1, S2, and S3 were on depot. Two participants from S1 discontinued aripiprazole and remained medication-free. Two participants from S2 discontinued paliperidone, and were prescribed with quetiapine and olanzapine. One participant from S3 was prescribed oral aripiprazole during the "Observation Maintenance" phase. Throughout the 24-month study period, 24 participants in TaU (S3) group had never received any medication. No participant had received any therapeutic course of psychotherapy from clinical psychologist.

Table 3. Mean dosages and types of medications of participants at the primary endpoint.

Mean (range) at 12th month	**Aripiprazole (S1)** (n = 24)	**Paliperidone (S2)** (n = 28)	**TaU (S3)** (n = 64)
Antipsychotics (mg/day)			
Aripiprazole			
oral	15.0 (2 - 30)	NA	NA
every 4-week LAI* (oral-equivalent)	15.0 (15 - 15)	NA	NA
Paliperidone			
oral	NA	7.42 (3 - 12)	NA
every 4-week LAI* (oral-equivalent)	NA	9.75 (6 - 12)	NA
every 12-week LAI* (oral-equivalent)	NA	10.0 (6 - 12)	NA
Amisulpride	--	--	900.0 (900 - 900)
Brexpiprazole	--	--	1.00 (1 - 1)
Haloperidol LAI* (oral-equivalent)	--	--	3.33 (3.33 - 3.33)
Lurasidone	--	--	160.0 (160 - 160)
Olanzapine	--	13.3 (5 - 20)	9.69 (5 - 20)
Quetiapine	39.1 (12.5 - 100)	104.5 (25 - 200)	191.1 (25 - 750)
Risperidone	--	2.00	1.33 (1 - 2)
Sulpiride	--	--	400.0 (400 - 400)
Ziprasidone	--	--	80.0 (40 - 120)
Trifluoperazine	--	--	3.00 (3 - 3)
Clopixol LAI* (oral-equivalent)	--	20.0	55.0 (40 - 70)
Antidepressants			
Desvenlafaxine	62.5 (25 - 100)	66.7 (50 - 100)	66.7 (50 - 100)
Escitalopram	--	--	20.0 (20 - 20)
Mirtazapine	37.5 (37.5 - 37.5)	--	15.0 (15 - 15)
Sertraline	100.0 (100 - 100)	58.3 (50 - 75)	70.8 (25 - 150)
Trazodone	112.5 (50 - 200)	87.5 (75 - 100)	165.0 (25 - 300)
Venlafaxine	37.5 (37.5 - 37.5)	--	--
Mood-stabilizing agents			
Lithium	--	400.0 (400 - 400)	--
Lamotrigine	25.0 (25 - 25)	--	--
Sodium valproate	1000.0 (1000 - 1000)	500.0 (300 - 700)	600.0 (500 - 700)
Adjunctive medications			
Trihexyphenidyl	4.22 (2 - 12)	5.14 (2 - 12)	4.40 (2 - 6)
Propranolol	30.0 (30 - 30)	20.0 (20 - 20)	14.0 (10 - 20)
Diazepam	9.00 (9 - 9)	5.67 (5 - 7)	6.00 (2 - 10)

LAI: long injectable; n: number of participants; SD: standard deviation; TaU: Treatment-as-Usual
**LAI dosages were converted to oral equivalent doses according to the prescription information and literature.*

Table 4. Mean dosages and types of medications of participants at the secondary endpoint.

Mean (range) **at 24th month**	**Aripiprazole (S1)** (n = 20)	**Paliperidone (S2)** (n = 18)	**TaU (S3)** (n = 50)
Antipsychotics (mg/day)			
Aripiprazole			
oral	15.6 (5 - 30)	--	5.00 (5 - 5)
every 4-week LAI* (oral-equivalent)	15.0 (15 - 15)	--	--
Paliperidone			
oral	--	7.25 (3 - 12)	--
every 4-week LAI* (oral-equivalent)	--	12.0 (12 - 12)	--
every 12-week LAI* (oral-equivalent)	--	12.0 (12 - 12)	--
Brexpiprazole	--	--	3.00 (1 - 4)
Lurasidone	--	--	120.0 (120 - 120)
Olanzapine	--	10.0 (5 - 15)	12.1 (5 - 20)
Quetiapine	51.8 (12.5 - 100)	106.8 (25 - 250)	238.9 (25 - 750)
Risperidone	3.00	1.00	--
Sulpiride	--	--	400.0 (400 - 400)
Ziprasidone	--	--	75.0 (40 - 120)
Trifluoperazine	--	--	2.00 (2 - 2)
Clopixol LAI* (oral-equivalent)	--	--	55.0 (30 - 80)
Antidepressant			
Citalopram	--	--	20.0 (20 - 20)
Desvenlafaxine	75.0 (50 - 100)	75.0 (75 - 75)	75.0 (50 - 100)
Escitalopram	--	--	20.0 (20 - 20)
Mirtazapine	37.5 (37.5 - 37.5)	--	30.0 (15 - 45)
Sertraline	100.0 (100 - 100)	75.0 (75 - 75)	75.0 (25 - 150)
Trazodone	112.5 (75 - 200)	--	162.5 (100 - 250)
Mood-stabilizing agents			
Lamotrigine	150.0 (150 - 150)	--	--
Sodium valproate	1000.0 (1000 - 1000)	--	750.0 (500 - 1000)
Adjunctive medications			
Trihexyphenidyl	4.67 (2 - 12)	3.50 (2 - 4)	3.89 (2 - 8)
Propranolol	26.7 (20 - 30)	15.0 (10 - 20)	13.3 (10 - 20)
Diazepam	9.00 (9 - 9)	--	3.00 (2 - 5)

LAI: long injectable; n: number of participants; SD: standard deviation; TaU: Treatment-as-Usual
**LAI dosages were converted to oral equivalent doses according to the prescription information and literature.*

The test results from urine test kits throughout the whole study period were presented in Table 5. There were no significant differences observed between the three groups with the positive test results on methamphetamines, cocaine, as well as their metabolites.

Table 5. Participants with urine tested positive for stimulants and their metabolites at different timepoints.

Urine Positive (%)	**Total** (n = 165)	**Aripiprazole (S1)** (n = 42)	**Paliperidone (S2)** (n = 40)	**TaU (S3)** (n = 83)	***p*-value**
METmet					**.866**
Baseline	63 (38.2%)	12 (28.6%)	14 (35.0%)	37 (44.6%)	
4th week	35 (21.2%)	8 (19.0%)	11 (27.5%)	16 (19.3%)	
3rd month	39 (23.6%)	9 (21.4%)	10 (25.0%)	20 (24.1%)	
6th month	39 (23.6%)	7 (16.7%)	7 (17.5%)	25 (30.1%)	
12th month	32 (19.4%)	4 (9.5%)	7 (17.5%)	21 (25.3%)	
24th month	27 (16.4%)	7 (16.7%)	4 (10.0%)	16 (19.3%)	
COC					**.917**
Baseline	22 (13.3%)	9 (21.4%)	3 (7.5%)	10 (12.0%)	
4th week	11 (6.7%)	4 (9.5%)	2 (5.0%)	5 (6.0%)	
3rd month	10 (6.1%)	4 (9.5%)	2 (5.0%)	4 (4.8%)	
6th month	8 (4.8%)	4 (9.5%)	2 (5.0%)	2 (2.4%)	
12th month	13 (7.9%)	2 (4.8%)	3 (7.5%)	8 (9.6%)	
24th month	7 (4.2%)	2 (4.8%)	2 (5.0%)	3 (3.6%)	
MET					**.179**
Baseline	91 (55.2%)	18 (42.9%)	20 (50.0%)	53 (63.9%)	
4th week	56 (33.9%)	9 (21.4%)	18 (45.0%)	29 (34.9%)	
3rd month	59 (35.8%)	12 (28.6%)	16 (40.0%)	31 (37.3%)	
6th month	58 (35.2%)	12 (28.6%)	15 (37.5%)	31 (37.3%)	
12th month	56 (33.9%)	11 (26.2%)	14 (35.0%)	31 (37.3%)	
24th month	39 (23.6%)	10 (23.8%)	12 (30.0%)	17 (20.5%)	
At least 1 stimulant(s)					**.378**
Baseline	105 (63.6%)	24 (57.1%)	22 (55.0%)	59 (71.1%)	.302
4th week	66 (40.0%)	13 (31.0%)	19 (47.5%)	34 (41.0%)	.076
3rd month	65 (39.4%)	15 (35.7%)	16 (40.0%)	34 (41.0%)	.362
6th month	61 (37.0%)	14 (33.3%)	16 (40.0%)	31 (37.3%)	.850
12th month	66 (40.0%)	12 (28.6%)	18 (45.0%)	36 (43.4%)	.558
24th month	45 (27.3%)	10 (23.8%)	13 (32.5%)	22 (26.5%)	.108

METmet: methamphetamine metabolites; COC: cocaine; MET: methamphetamine; n: number of participants

Throughout the study, the overall prevalence of stimulant-induced psychotic disorders among all participants was 72.1% (N = 119), and the prevalence was 85.7% (N = 36), 77.5% (N = 31), and 62.7% (N = 52) for S1, S2, and S3, respectively. The conversion rate to schizophrenia was 10.1% (N = 12) overall, and 0.0% (N = 0), 19.4% (N = 6), and 11.5% (N = 6) for S1, S2, and S3, respectively. S1 was significantly better with less conversion to schizophrenia as compared to S2 ($p < .001$), and to S3 albeit close to significance ($p = .017$).

I) Efficacy in Psychosis

BPRS-24

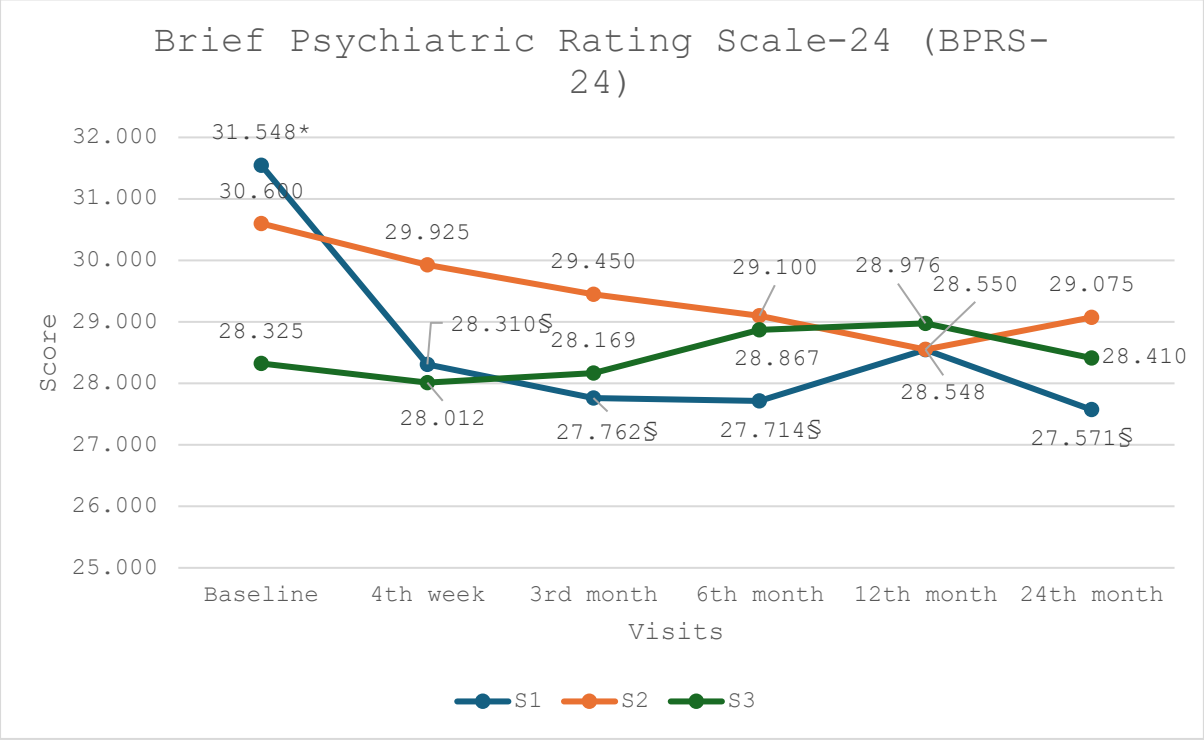

Figure 2. BPRS-24 scores over the entire study period.
*: $p < .05$ as compared to S3 TaU group; §: $p < .05$ as compared to baseline.

At baseline, only participants in S1 group had significantly worse psychosis symptoms than S3 group ($p = .013$), whereas S2 participants had comparable psychosis symptoms to S3. Despite participants in both S1 and S2 groups showed lessening of their psychosis symptoms over time,

only S1 group showed significant within-group improvement (F (5, 302.32) = 2.87, p = .0156) (Figure 2). Nevertheless, there was no significant between-group differences between the three groups over the whole study period. Sensitivity analysis confirmed comparable results that within-group improvement occurred only in the S1 group (F (5, 257.24) = 3.20, p = .008) with no between-group differences demonstrated (Table 6).

Table 6. Between-group comparisons for the BPRS-24 scores.

	M (SE)	S1 [MD (SE)]	S2 [MD (SE)]	S3 [MD (SE)]
	Primary Analysis Group: F (2, 958.903) = 2.82, p = .060 Group × Visit: F (15, 315.12) = 1.32, p = .191			
Aripiprazole (S1)	28.58 (0.34)	-	-0.86 (0.49)	0.12 (0.42)
Paliperidone (S2)	29.45 (0.35)	-	-	0.99 (0.43)
TaU (S3)	28.46 (0.24)	(reference group)		
	Sensitivity Analysis Group: F (2, 605.65) = 0.80, p = .45 Group × Visit: F (15, 197.54) = 1.70, p = .054			
Aripiprazole (S1)	28.43 (0.41)	-	-0.55 (0.58)	0.07 (0.49)
Paliperidone (S2)	28.97 (0.41)	-	-	0.61 (0.50)
TaU (S3)	28.36 (0.28)	(reference group)		

*: p < .05; M: mean; MD: mean difference; SE: standard error

Table 7. Number of clinical responders and non-responders as measured by BPRS-24 at the end of the "Active Intervention" phase.

	Aripiprazole (S1)	Paliperidone (S2)	TaU (S3)
Clinical Responders	6	11	19
Clinical Non-responders	18	17	45
Total	24	28	64

The number of clinical responders as defined by a reduction in BPRS-24 ≥ 50% at the primary endpoint for the three intervention groups were presented in Table 7. Overall, 25.0%, 39.3%, and 29.7% of participants had clinically meaningful improvements in S1, S2, and S3 groups, respectively. There were no between-group differences detected in the proportion of clinical responders in each group (Wald χ^2 (2) = 1.435, p = .488). The group assignment did not predict clinical response either, after adjusting for the covariates (χ^2 (14) = 17.77, R^2 = 0.23, p = .218). Nevertheless, participants with history of receiving detoxification treatment were significantly less likely to yield meaningful clinical responses (B = -1.21, SE = 0.60, Wald χ^2 (1) = 4.01, p = .045, Exp(B) = 0.30).

Table 8. Number of clinical responders and clinical non-responders as measured by BPRS-24 at the end of the "Observation Maintenance" phase.

	Aripiprazole (S1)	Paliperidone (S2)	TaU (S3)
Clinical Responders	5	6	2
Clinical Non-responders	15	12	48
Total	20	18	50

The number of clinical responders as defined by a reduction in BPRS-24 ≥ 50% at the secondary endpoint for the three intervention groups were presented in Table 8. Overall, 25.0%, 33.3%, and 4.0% of participants had clinically meaningful improvements in S1, S2, and S3 groups, respectively. An overall between-group difference was detected (Wald χ^2 (2) = 6.625, p = .036), but was nullified following pairwise comparisons *post-hoc*. The use of paliperidone predicted a meaningful clinical response after adjusting for the covariates (B = 2.26, SE = 0.91, Wald χ^2 (1) = 6.125, p = .013, Exp(B) = 9.58). Previous admissions to detoxification no longer predicts the clinical response.

CGI-S

Table 9. Number of clinical responders and non-responders as measured by CGI-S at different assessment timepoints.

	Aripiprazole (S1)		Paliperidone (S2)		TaU (S3)	
CGI-S	Clinical Responders	Clinical Non-responders	Clinical Responders	Clinical Non-responders	Clinical Responders	Clinical Non-responders
Baseline	23	19	20	20	49	34
4th week	26	4	19	10	37	15
3rd month	24	8	20	11	41	15
6th month	22	7	19	9	32	24
12th month	16	8	20	8	42	22
24th month	15	5	13	5	34	16

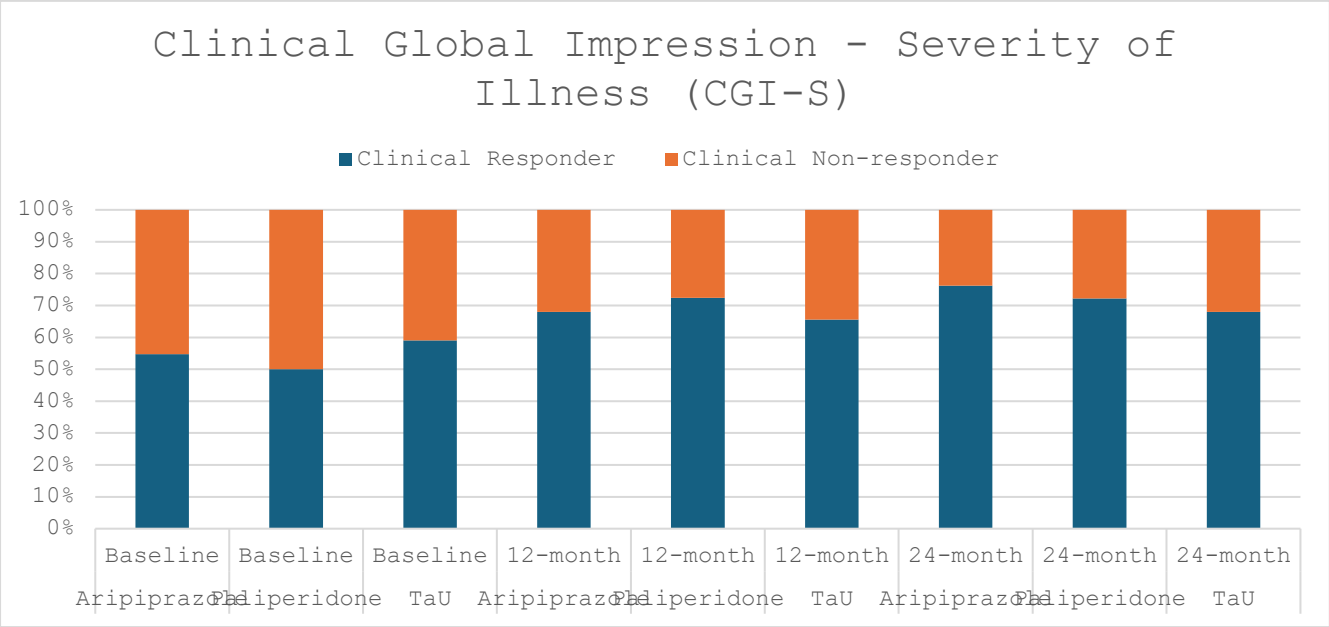

Figure 3. Proportion of clinical responders and non-responders as measured by CGI-S at baseline, at the primary (12th month) and secondary (24th month) endpoints.

No significant differences were detected regarding psychosis severity from S1 or S2 groups as compared to S3 group at any study timepoints when participants with CGI-S of "mildly ill" or better were classified as "clinical responders" (Wald χ^2 (17) = 27.127, p = .056) (Table 9).

CGI-I

Table 10. Number of clinical responders and non-responders as measured by CGI-I at different assessment timepoints.

	Aripiprazole (S1)		Paliperidone (S2)		TaU (S3)	
CGI-I	Clinical Responders	Clinical Non-responders	Clinical Responders	Clinical Non-responders	Clinical Responders	Clinical Non-responders
4th week	**23***	7	17	12	16	36
3rd month	20	12	21	10	27	29
6th month	19	10	**23***	5	25	31
12th month	19	5	20	8	28	36
24th month	15	5	7	11	26	24

*as compared to S3 group at that specific timepoint ($p < .001$).

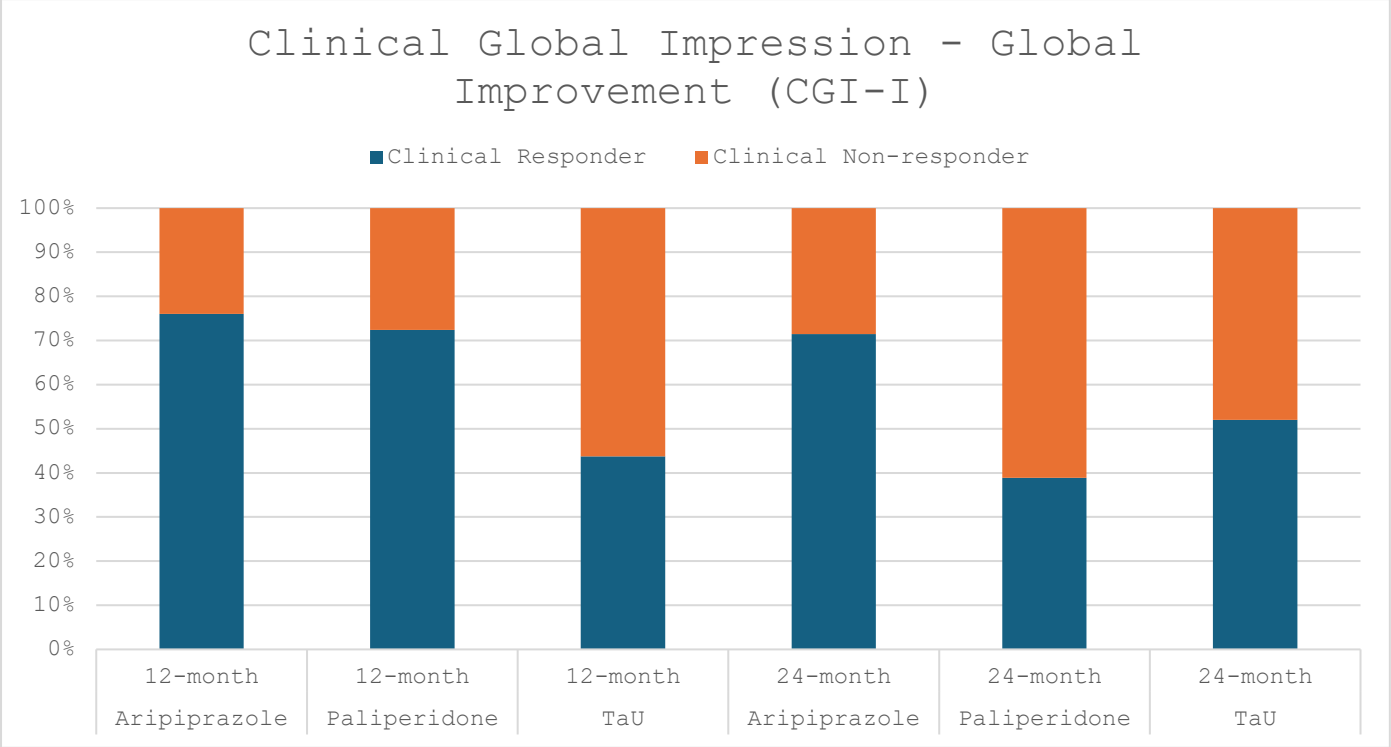

Figure 4. Proportion of clinical responders and non-responders as measured by CGI-I at the primary (12th month) and secondary (24th month) endpoints.

More participants in S1 and S2 groups showed significant global improvement than those in S3 groups when participants with CGI-I of "minimally improved" or better were classified as "clinical responders" (Wald χ^2 (2) = 34.776, $p < .001$). In addition, there was also significant difference in time when the improvement developed between the three groups (Wald χ^2 (14) =

62.981, p <.001). Participants taking aripiprazole had improvement the earliest at the 4th week (M = -0.46, SE = 0.10, p < .001), with improvement started later for those in the paliperidone group at the 6th month (M = -0.37, SE = 0.11, p < .001) as compared to those in the TaU group.

GASS

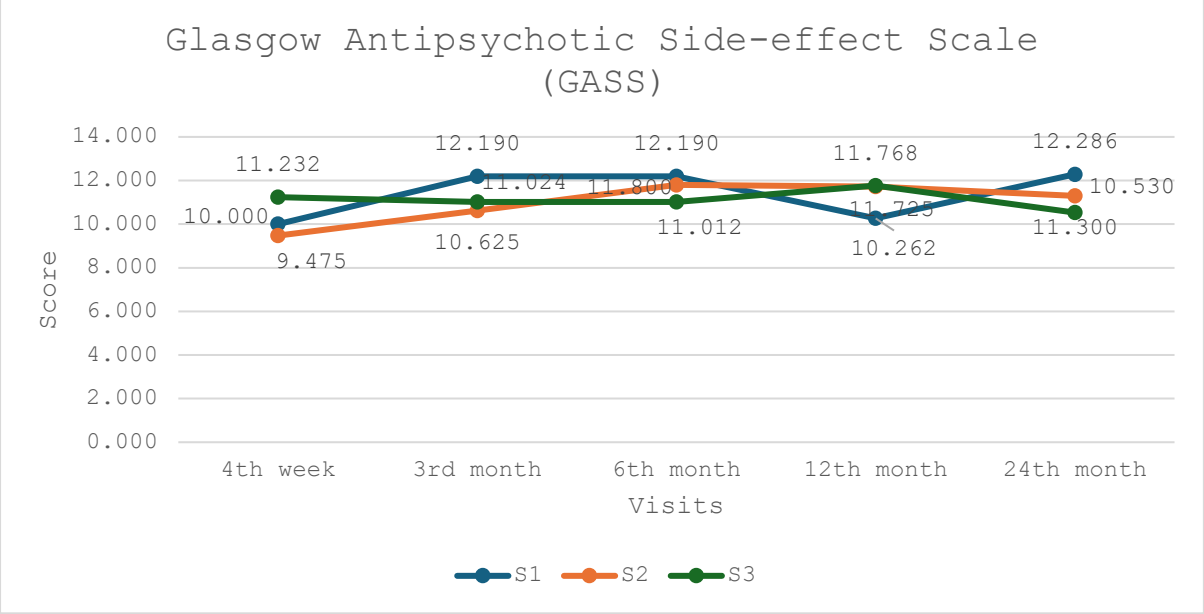

Figure 5. GASS scores over the entire study period.

Participants from all intervention groups reported minimal side-effects experienced (Figure 5). No within-group or between-group differences in GASS were found throughout the whole 24-month study period (all p > .05).

II) Changes in Stimulant Use

SDS for Cocaine

Table 11. Number of cocaine dependent participants as defined by SDS ≥ 3 at different assessment timepoints.

	Aripiprazole (S1)		Paliperidone (S2)		TaU (S3)	
	Non-dependence	Dependence	Non-dependence	Dependence	Non-dependence	Dependence
Baseline	1	9	2	3	3	11
4th week	1	7	2	1	1	6
3rd month	2	6	3	0	1	8
6th month	1	6	1	3	1	5
12th month	0	6	2	1	1	7
24th month	1	2	0	1	4	2

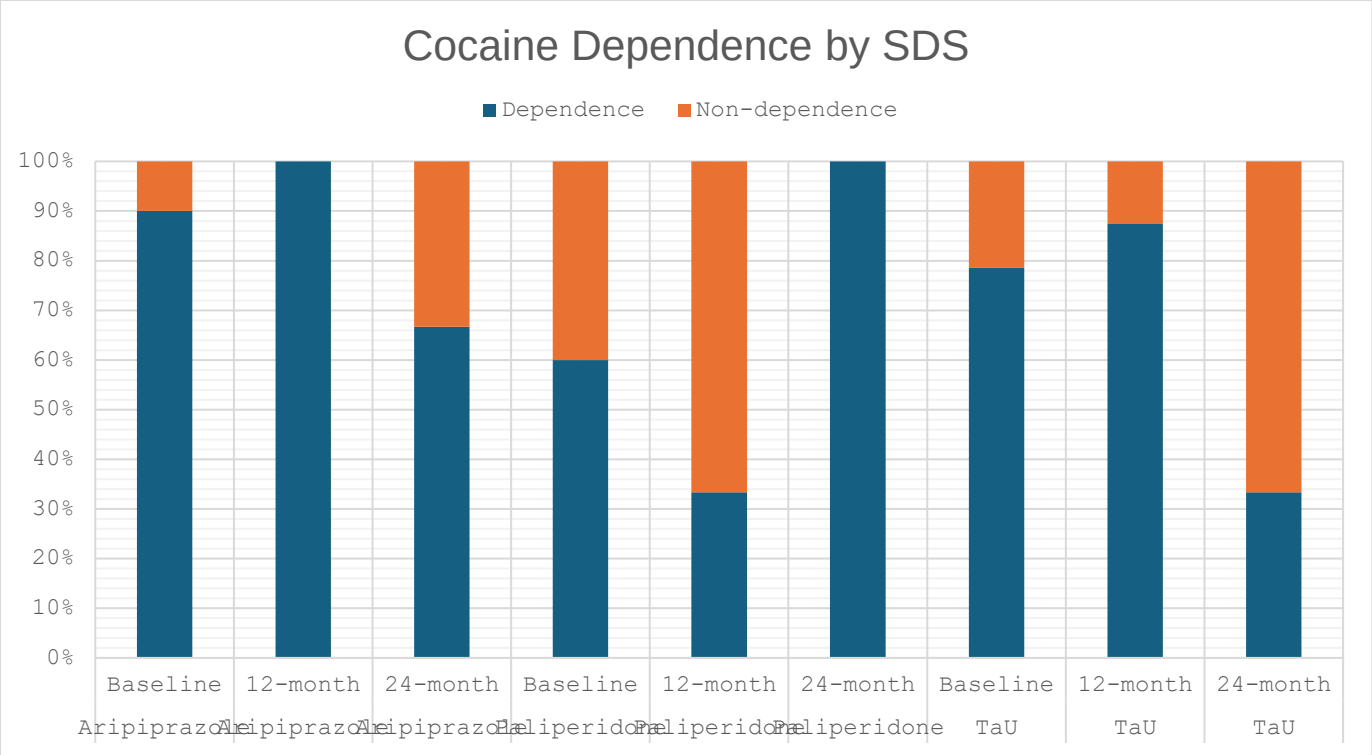

Figure 6. Proportion of SDS-defined cocaine dependent users at baseline, at the primary (12th month) and secondary (24th month) endpoints.

At baseline, 79.3% of all participants solely using cocaine (N = 29) were having SDS-defined dependence, indicated by an SDS score of ≥ 3. At the end of the "Active Intervention" phase (primary endpoint) and the "Observation Maintenance" phase (secondary endpoint), 82.4% and 50.0% of the cocaine-using participants remained having dependence, respectively (Table 11).

There was no significant association between the intervention groups and the dependence status at baseline ($\chi 2$ (2) = 1.837, p = .399). At 12th month, an association between intervention group and dependence status was found ($\chi 2$ (2) = 6.392, p = .041). However, there was no significant changes in dependence status between baseline and 12th month (MH = 0.000; two-tailed p = 1.000). At 24th month, there was no association between intervention group and dependence status ($\chi 2$ (2) = 2.000, p = .368), nor a significant change in dependence status between baseline and 24th month (MH = -3.000; two-tailed p = .180) (Figure 6).

SDS for Methamphetamine

Table 12. Number of methamphetamine dependent participants as defined by SDS ≥ 5 at different assessment timepoints.

	Aripiprazole (S1)		Paliperidone (S2)		TaU (S3)	
	Non-dependence	Dependence	Non-dependence	Dependence	Non-dependence	Dependence
Baseline	7	**21***	14	19	29	28
4th week	8	**13***	9	15	19	19
3rd month	7	14	14	**12***	17	23
6th month	6	**13***	12	**12***	17	25
12th month	8	10	11	14	28	20
24th month	6	10	6	11	22	17

*: p < .05 as compared to S3 group at that specific timepoint.

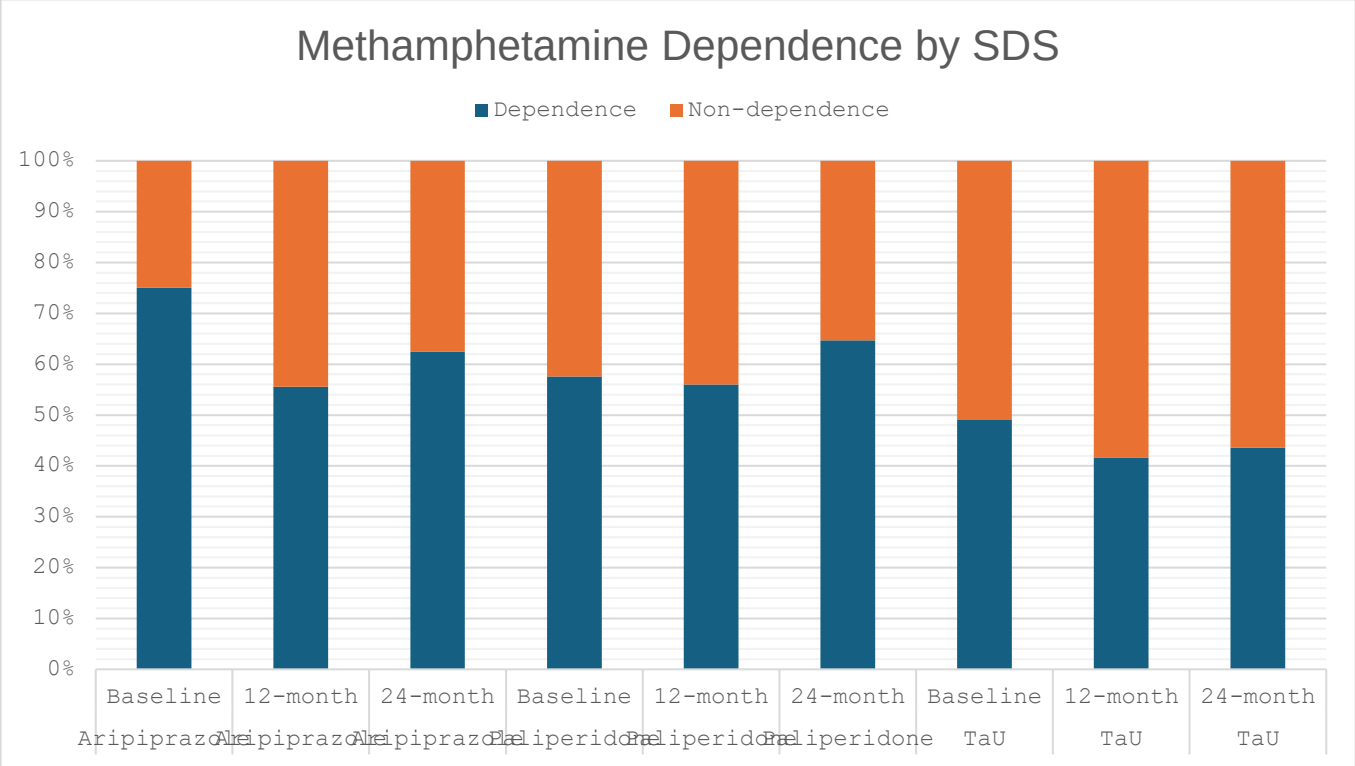

Figure 7. Proportion of SDS-defined methamphetamine dependent users at baseline, at the primary (12th month) and secondary (24th month) endpoints.

At baseline, 57.6% of all participants solely using MET (N = 118) were having SDS-defined dependence, indicated by an SDS score of ≥ 5. At the end of the "Active Intervention" phase (primary endpoint) and the "Observation Maintenance" phase (secondary endpoint), 48.4% and 52.8% of the MET-using participants remained having dependence, respectively (Table 12).

Overall, there were significant between-group differences in SDS-defined MET dependence throughout the 24-month study period (χ^2 (17) = 31.687, p = .016). The changes in dependence between different groups varied across different timepoints (Wald χ^2 (10) = 22.939, p = .011). Participants in both S1 (B = 1.386, SE = 0.559, Wald χ^2 (1) = 6.150, p = .013) and S2 (B =1.068, SE = 0.528, Wald χ^2 (1) = 4.096, p = .043) groups were more likely to have MET dependence as compared to those in the S3 group over the entire study period. However, specifically at the

primary and the secondary endpoints, neither the S1 nor the S2 group were more likely to have more SDS-defined MET dependent participants than the S3 group (all $p > .05$).

Within-group differences over the study period were also noted for the S1 aripiprazole group (χ^2 (5) = 13.751, p = .017) and the S2 paliperidone group (χ^2 (5) = 12.170, p = .033), but not for the S3 TaU group (χ^2 (5) = 5.174, p = .395). Participants in both S1 and S2 groups tended to be methamphetamine dependent in the first 6 months. Such trend, however, was only present for the S1 group (χ^2 (1) = 4.520, p = .033) but not the S2 group (χ^2 (1) = 2.596, p = .107). Such tendency did not persist longer to the primary and secondary endpoints.

Severity of DSM-5 CocUD

Table 13. Severity of CocUD over the entire study period.

Visit	Group	None	Mild	Moderate	Severe
Baseline	Aripiprazole (S1)	1	1	8	3
	Paliperidone (S2)	0	1	4	2
	TaU (S3)	5	5	6	9
4th week	Aripiprazole (S1)	1	3	7	2
	Paliperidone (S2)	0	2	2	3
	TaU (S3)	8	5	5	7
3rd month	Aripiprazole (S1)	4	2	4	3
	Paliperidone (S2)	1	3	0	3
	TaU (S3)	7	5	5	8
6th month	Aripiprazole (S1)	3	3	6	2
	Paliperidone (S2)	1	3	3	1
	TaU (S3)	11	3	4	6
12th month	Aripiprazole (S1)	3	3	6	2
	Paliperidone (S2)	1	2	3	1
	TaU (S3)	8	3	4	8
24th month	Aripiprazole (S1)	4	2	4	3
	Paliperidone (S2)	2	3	1	1
	TaU (S3)	7	5	4	9

Table 14. Relative proportions of severity of CocUD at baseline, at the primary (12th month) and secondary (24th month) endpoints.

		Severity of CocUD			
Group	**Timepoint**	**None**	**Mild**	**Moderate**	**Severe**
Aripiprazole (S1)	**Baseline**	7.7%	7.7%	61.5%	23.1%
Paliperidone (S2)		0.0%	14.3%	57.1%	28.6%
TaU (S3)		20.0%	20.0%	24.0%	36.0%
Aripiprazole (S1)	**12-month**	23.1%	15.4%	46.2%	15.4%
Paliperidone (S2)		28.6%	57.1%	14.3%	0.0%
TaU (S3)		32.0%	20.0%	16.0%	32.0%
Aripiprazole (S1)	**24-month**	30.8%	15.4%	30.8%	23.1%
Paliperidone (S2)		28.6%	42.9%	14.3%	14.3%
TaU (S3)		28.0%	20.0%	16.0%	36.0%

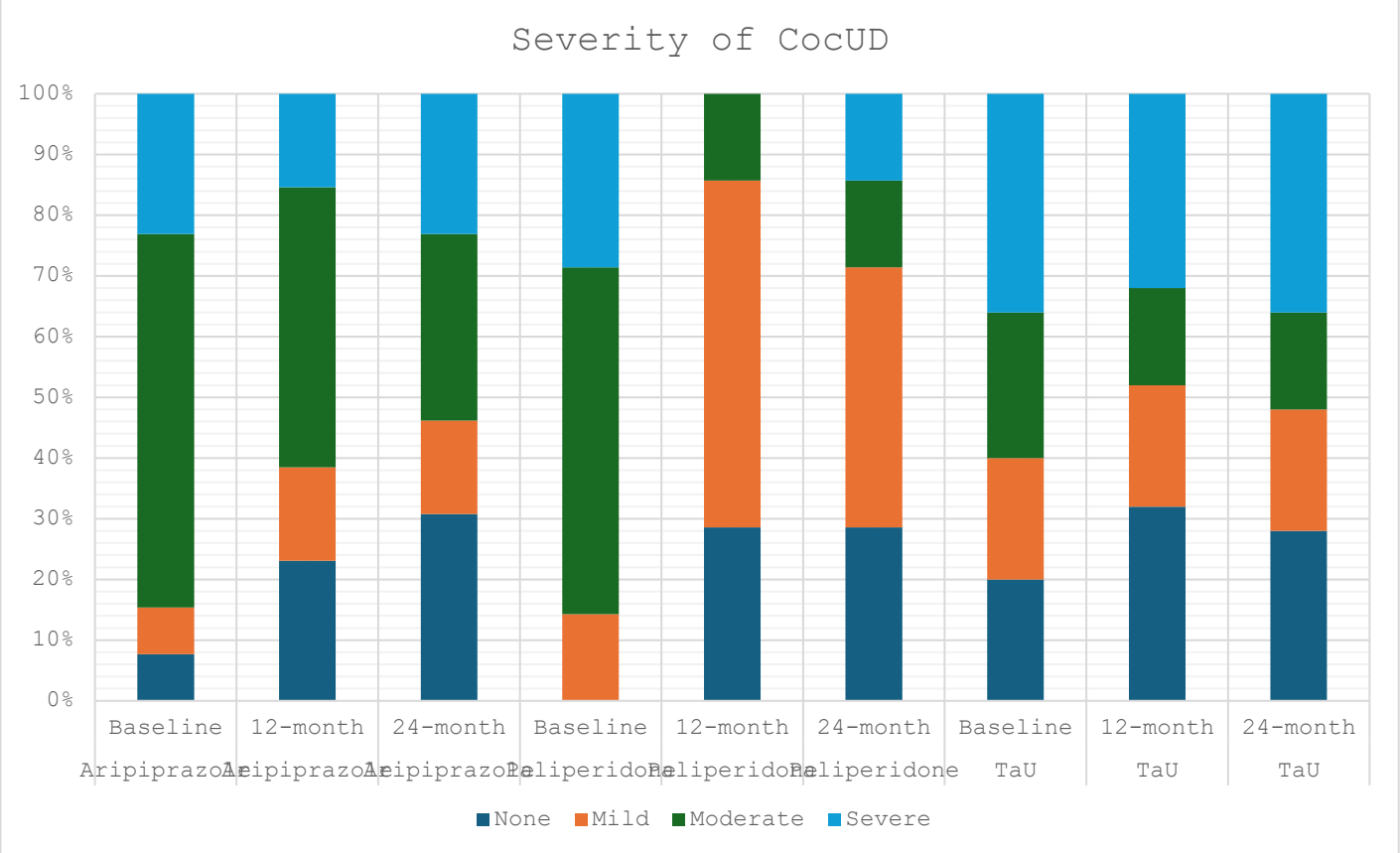

Figure 8. Proportion of different severity of CocUD at baseline, at the primary (12th month) and secondary (24th month) endpoints.

At baseline, more than half of the participants in the S1 and S2 groups were suffering from moderate CocUD, while around one-third of the participants in the S3 group were having severe CocUD (Tables 13 and 14). After adjusting for the covariates, the comparisons between the three intervention groups remained non-significant at either the primary endpoint (Wald χ^2 (3) = 5.238, p = .155) or the secondary endpoint (Wald χ^2 (3) = 3.348, p = .341). There were also no within-group differences noted when comparing the severity of CocUD at the two endpoints to the baseline for each individual group (Figure 8).

Severity of DSM-5 MetUD

Table 15. Severity of MetUD over the entire study period.

Visit	Group	None	Mild	Moderate	Severe
Baseline	Aripiprazole (S1)	0	6	13	12
	Paliperidone (S2)	3	10	10	11
	TaU (S3)	2	25	20	20
4th week	Aripiprazole (S1)	5	9	7	10
	Paliperidone (S2)	6	9	9	11
	TaU (S3)	12	20	17	19
3rd month	Aripiprazole (S1)	10	6	6	9
	Paliperidone (S2)	5	9	12	9
	TaU (S3)	13	21	19	15
6th month	Aripiprazole (S1)	8	9	7	7
	Paliperidone (S2)	7	8	15	5
	TaU (S3)	17	16	15	20
12th month	Aripiprazole (S1)	8	8	6	9
	Paliperidone (S2)	9	9	8	9
	TaU (S3)	21	20	13	14
24th month	Aripiprazole (S1)	9	7	7	8
	Paliperidone (S2)	10	7	9	9
	TaU (S3)	24	14	13	17

Table 16. Relative proportions of severity of MetUD at baseline, at the primary (12th month) and secondary (24th month) endpoints.

		Severity of MetUD			
Group	**Timepoint**	**None**	**Mild**	**Moderate**	**Severe**
Aripiprazole (S1)	**Baseline**	0.0%	19.4%	41.9%	38.7%
Paliperidone (S2)		8.8%	29.4%	29.4%	32.4%
TaU (S3)		3.0%	37.3%	29.9%	29.9%
Aripiprazole (S1)	**12-month**	25.8%	25.8%	19.4%	29.0%
Paliperidone (S2)		25.7%	25.7%	22.9%	25.7%
TaU (S3)		30.9%	29.4%	19.1%	20.6%
Aripiprazole (S1)	**24-month**	29.0%	22.6%	22.6%	25.8%
Paliperidone (S2)		28.6%	20.0%	25.7%	25.7%
TaU (S3)		35.3%	20.6%	19.1%	25.0%

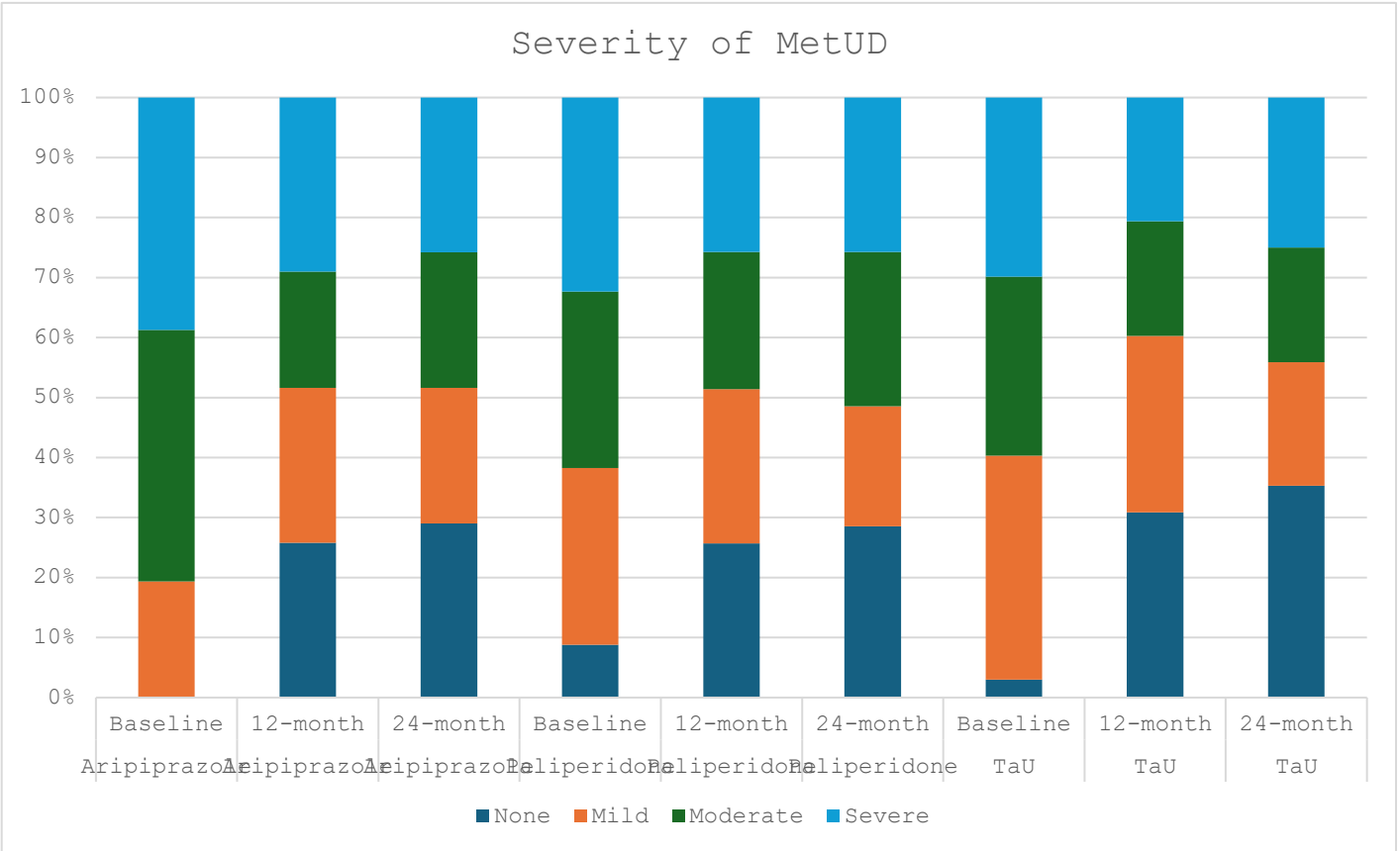

Figure 9. Proportion of different severity of MetUD at baseline, at the primary (12th month) and secondary (24th month) endpoints.

At baseline, the majority of the participants in the S1 group suffered from moderate MetUD, while most of the participants in the S2 and the S3 groups were having severe and mild MetUD,

respectively (Tables 15 and 16). There were significant differences in the severity of MetUD between the intervention groups at the primary endpoint (Wald χ^2 (3) = 16.982, p = .001) and at the secondary endpoint (Wald χ^2 (3) = 15.471, p = .001) after adjusting for the covariates. As compared to baseline, participants taking aripiprazole had significant improvement with the greatest magnitude in their severity of MetUD at both the primary endpoint (B = 1.098, SE = 0.4666, p = .019) and the secondary endpoint (B = 1.161, SE = 0.4663, p = .013). Such improvements were also significant for those in the S3 group at both endpoints but with smaller magnitudes (12th month: B = 0.985, SE = 0.3154, p = .002; 24th month: B = 0.872, SE = 0.3132, p = .005). The changes for those in the S2 group were not significant at both endpoints.

SOCRATES-D

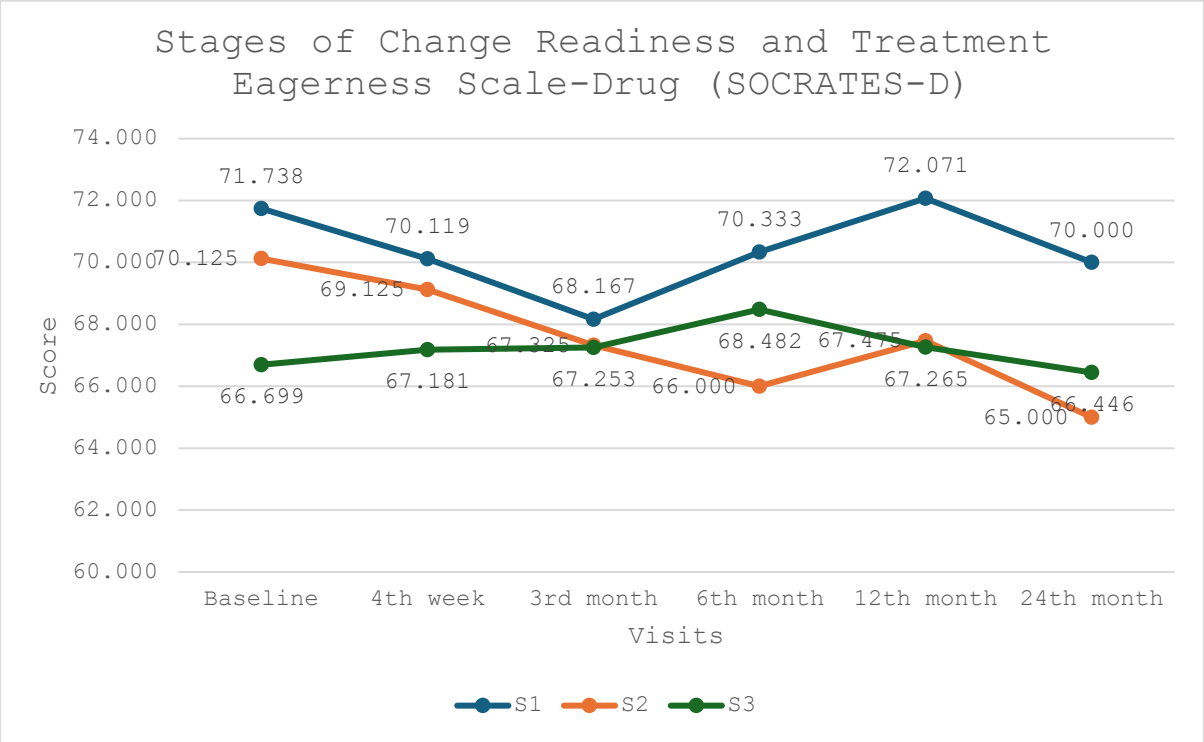

Figure 10. SOCRATES-D composite scores over the entire study period.

At baseline, no significant differences in the SOCRATES-D composite scores were detected among the three intervention groups. Overall, the S3 group had the lowest mean SOCRATES-D composite scores, followed by the S2 group and with the highest scores from the S1 group. Significant between-group differences were detected in both the primary analysis (F (2, 950.51) = 4.79, p = .008) and the sensitivity analysis (F (2, 491.43) = 5.30, p = .005). Participants taking aripiprazole were more ready to change their stimulant use habits than those in the TaU group. Participants taking paliperidone had no significant differences for such readiness as compared to those in the TaU group. Despite the S1 group scoring higher in SOCRATES-D than the S2 group, their readiness to change for stimulant use habits were not significantly different from each other. Nevertheless, there were no significant between-group differences in readiness over the 24-month study period (Table 17).

Table 17. Between-group comparisons for the SOCRATES-D composite scores.

	M (SE)	S1 [MD (SE)]	S2 [MD (SE)]	S3 [MD (SE)]
	Primary Analysis **Group: F (2, 950.51) = 4.79, p = .008** Group × Visit: F (15, 290.16) = 0.47, p = .953			
Aripiprazole (S1)	70.41 (0.87)	-	2.90 (1.24)	**3.18 (1.06)***
Paliperidone (S2)	67.51 (0.89)	-	-	0.29 (1.08)
TaU (S3)	67.22 (0.62)	(reference group)		
	Sensitivity Analysis **Group: F (2, 491.43) = 5.23, p = .005** Group × Visit: F (15, 191.92) = 0.59, p = .879			
Aripiprazole (S1)	70.89 (1.12)	-	3.65 (1.60)	**4.38 (1.36)***
Paliperidone (S2)	67.25 (1.14)	-	-	0.72 (1.38)
TaU (S3)	66.52 (0.76)	(reference group)		

*: $p < .05$; M: mean; MD: mean difference; SE: standard error

Nevertheless, such differences in readiness between groups were not consistently significant across all follow-up timepoints (F (15, 290.16) = 0.47, p = .953). Sensitivity analyses revealed similar results for the between-group comparisons (F (5, 206.18) = 1.54, p = .180) and the comparisons across all timepoints (F (15, 191.92) = 0.59, p = .870). The results suggested that although participants taking aripiprazole appeared most ready to alter their stimulant use habits throughout the study period, such readiness did not reach a statistically meaningful differences as compared to the other 2 intervention groups.

Concerning the scorings for the individual subscale of SOCRATES-D, participants in S1 group had the highest mean scores for all three subscales (Figures 11a-11c). Similar to the composite SOCRATES-D scores, there were no within-group differences for all groups. For between-group differences, only participants in the S1 group had significantly higher mean scores in the recognition subscale and the taking-steps subscale than the S3 group in both the primary and sensitivity analyses. The preliminary significant better scorings in ambivalence subscale for S1 group over S2 group was nullified following sensitivity analysis.

Nevertheless, similar to the SOCRATES-D composite scores, all between-group differences in those three subscales were not consistently significant across all follow-up timepoints in both the primary analysis (SOCRATES_rec: F (15, 307.96) = 0.23, p = .999; SOCRATES_amb: F (15, 290.38) = 0.41, p = .976; SOCRATES_ts: F (15, 301.71) = 0.64, p = .840) as well as the sensitivity analysis (SOCRATES_rec: F (15, 190.51) = 0.43, p = .970; SOCRATES_amb: F (15, 189.63) = 0.38, p = .983; SOCRATES_ts: F (15, 196.16) = 0.85, p = .625).

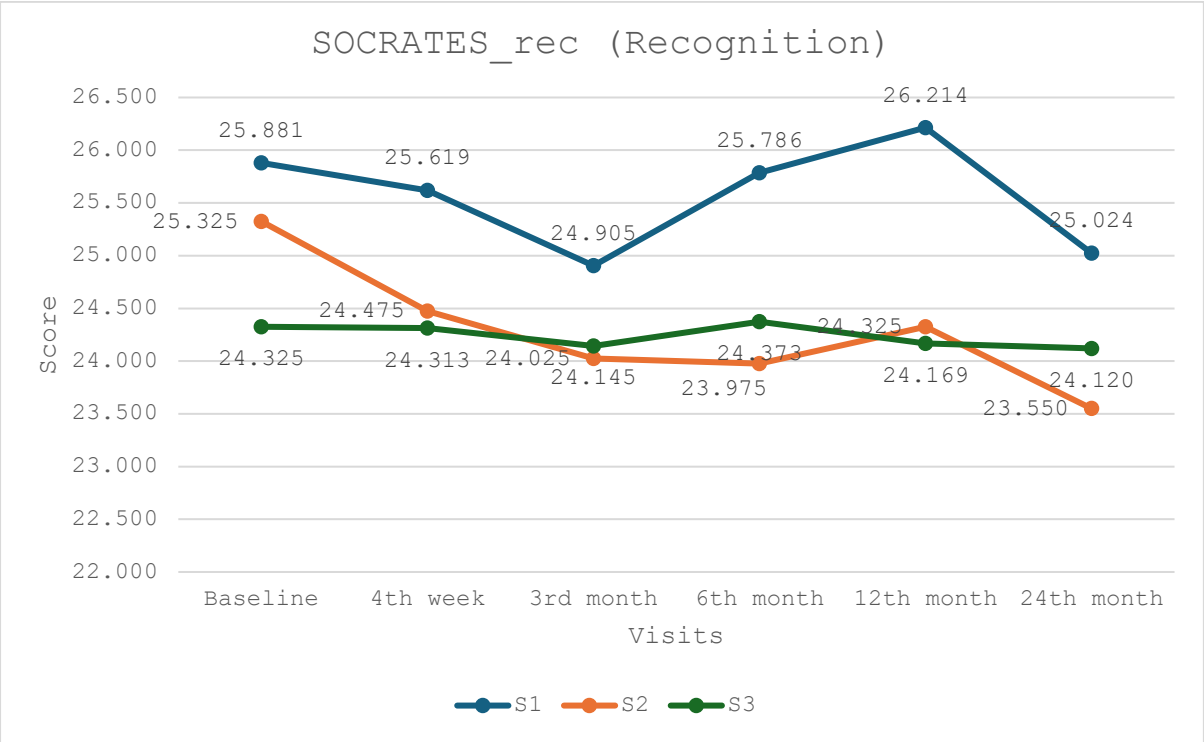

Figure 11a. SOCRATES-D recognition subscale scores over the entire study period.

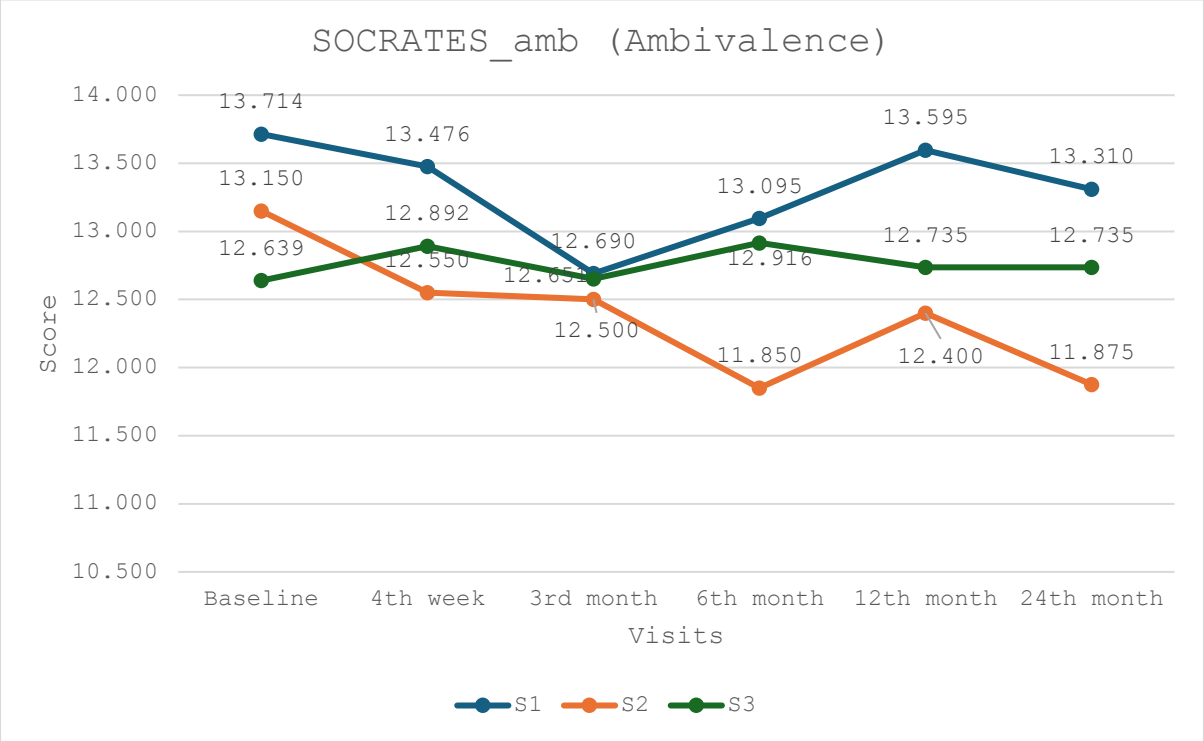

Figure 11b. SOCRATES-D ambivalence subscale scores over the entire study period.

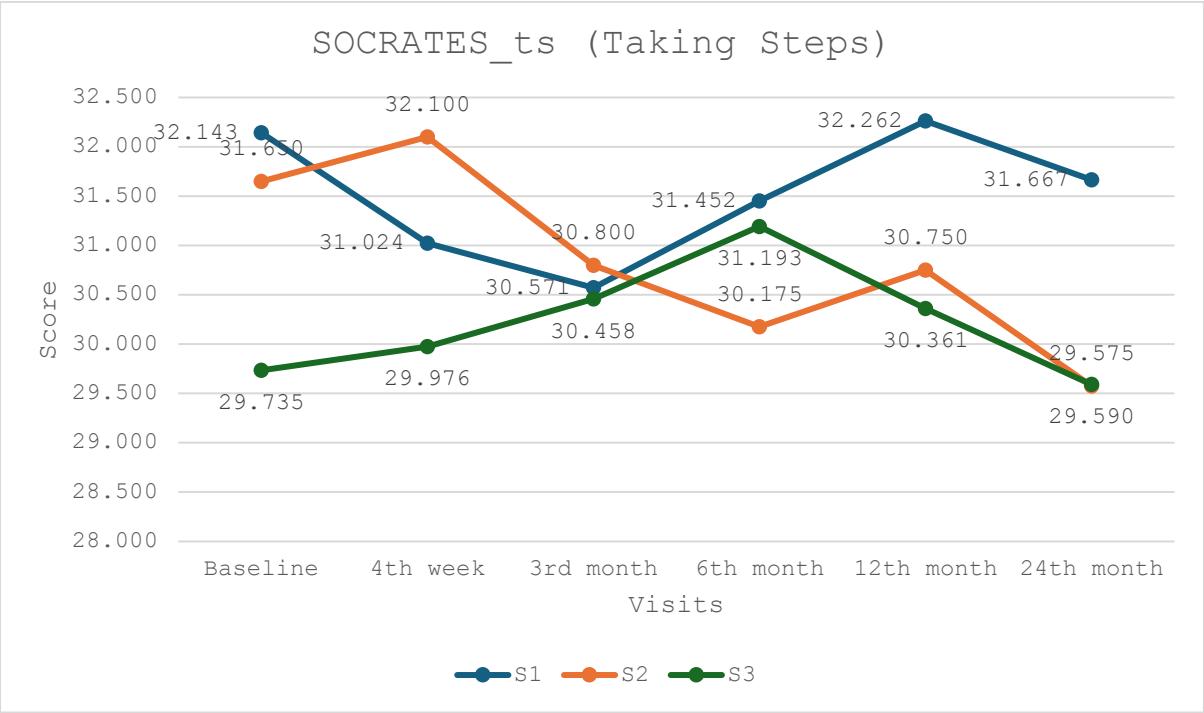

Figure 11c. SOCRATES-D taking-steps subscale scores over the entire study period.

III) <u>Changes in Mood Symptoms</u>

<u>BAI</u>

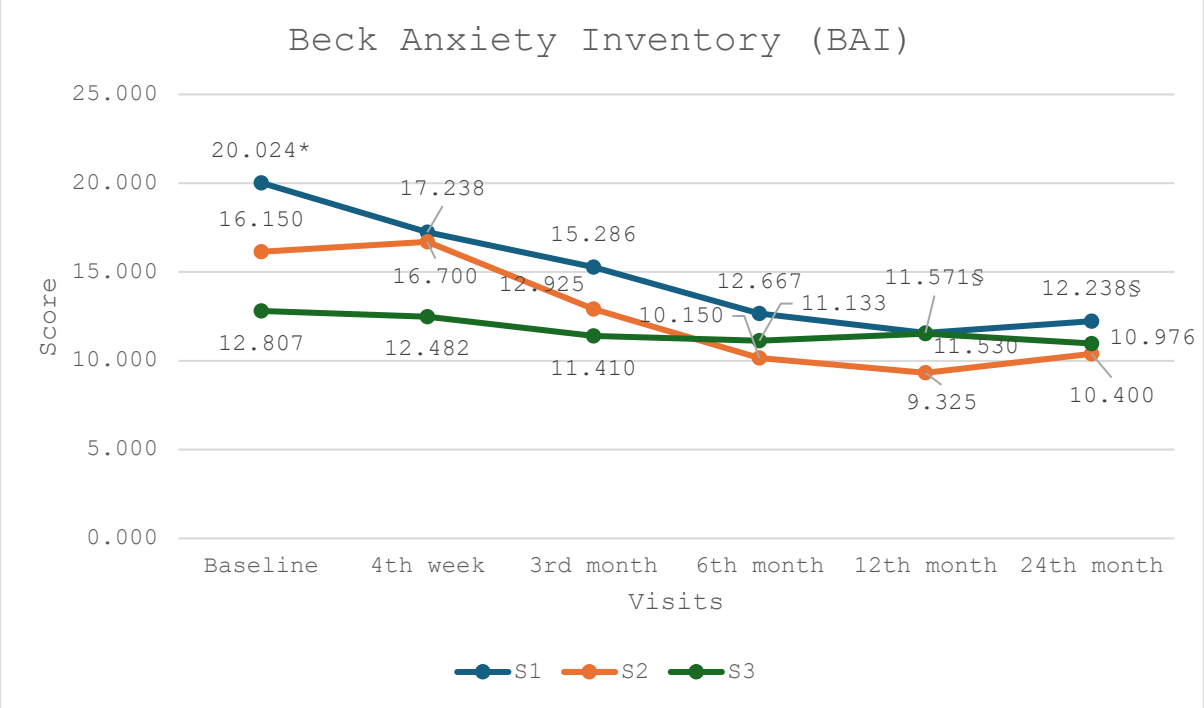

Figure 12. BAI scores over the entire study period.
*: $p < .05$ as compared to S3 TaU group; §: $p < .05$ as compared to baseline.

At baseline, participants in both the S1 and S2 groups suffered from moderate anxiety, whereas participants in S3 group only had mild anxiety. The anxiety level of participants in the S1 group was significantly higher than those in the S3 group (MD = 7.22, SE = 2.31, p = .006), but not than those in S2 group (MD = 3.87, SE = 2.69, p = .456). The difference between the S2 group and the S3 group was not significant either (MD = 3.34, SE = 2.35, p = .468).

Overall, the anxiety level for all the participants remained at the mild level at both the primary and sensitivity analyses at both the primary and the secondary endpoints. Participants in the S1 group had significantly higher mean BAI scores than those in S3 group, but not for S2 group as compared to S3 group. However, the overall differences in BAI scores were only significant over the entire study period in the primary analysis but not the sensitivity analysis (Table 18).

Table 18. Between-group comparisons for the BAI scores.

	M (SE)	S1 [MD (SE)]	S2 [MD (SE)]	S3 [MD (SE)]
	Primary Analysis **Group: F (2, 961.64) = 6.30, p = .002** **Group × Visit: F (15, 332.22) = 2.28, p = .004**			
Aripiprazole (S1)	14.84 (0.72)	-	2.23 (1.03)	**3.11 (0.88)***
Paliperidone (S2)	12.61 (0.73)	-	-	0.89 (0.89)
TaU (S3)	11.72 (0.51)	(reference group)		
	Sensitivity Analysis Group: F (2, 609.21) = 2.91, p = .055 Group × Visit: F (15, 332.22) = 2.28, p = .136			
Aripiprazole (S1)	14.57 (0.90)	-	1.62 (1.28)	**2.64 (1.10)***
Paliperidone (S2)	12.95 (0.91)	-	-	1.03 (1.11)
TaU (S3)	11.93 (0.63)	(reference group)		

*: p < .05; M: mean; MD: mean difference; SE: standard error

Within-group differences in anxiety level were detected in S1 and S2 groups but the differences sustained in the S1 group only. The level of anxiety of participants in the S1 group significantly improved from moderate to mild at the end of the "Active Intervention" phase and the effects sustained till the end of the "Observation Maintenance" phase (F (5, 275.07) = 3.44, p = .005) in the primary analysis. Such improvement remained significant in the sensitivity analysis (F (5, 208.06) = 2.27, p = .0049) though only up till the primary endpoint (MD = 8.78, SE = 2.49, p = .036) but not the secondary endpoint (MD = 6.60, SE = 3.16, p = .575). Although there was a similar trend of improvement in anxiety level from moderate to mild for participants in the S2 group, such improvement was only significant in the primary analysis (F (5, 275.07) = 3.07, p = 0.010), but not in the sensitivity analysis (F (5, 203.25) = 1.82, p = 0.111). There was no within-group improvement in anxiety for the S3 group in both primary (F (5, 275.07) = 0.338, p = .889) and sensitivity analyses (F (5, 212.53) = 0.20, p = .964).

BDI-II

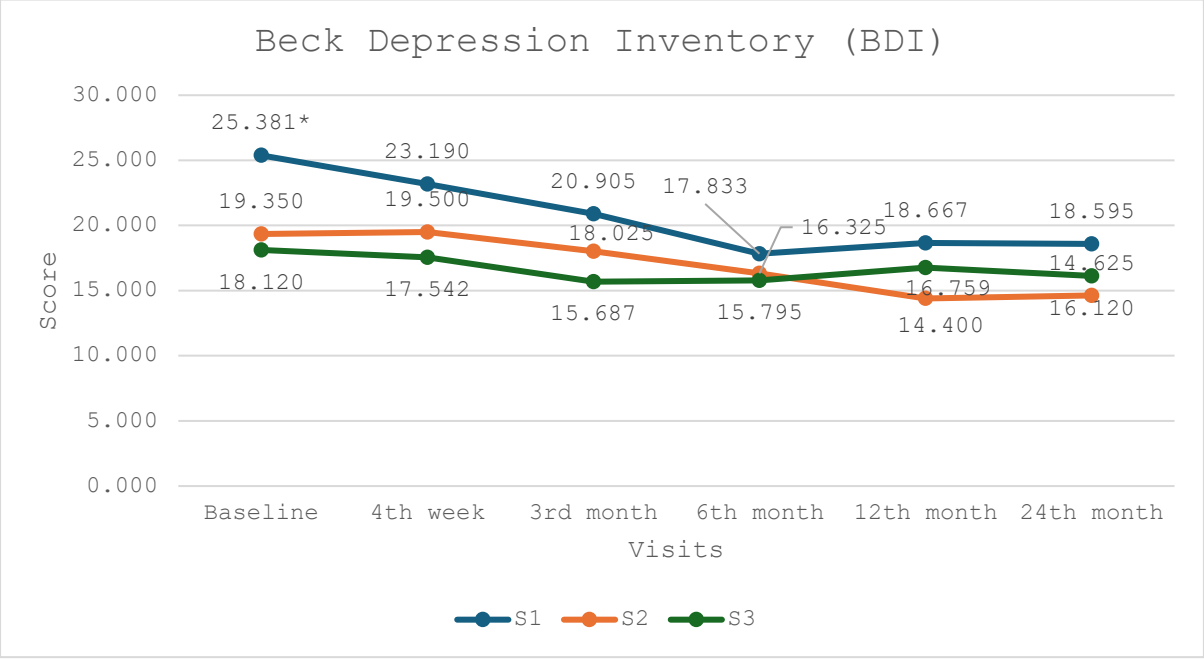

Figure 13. BDI-II scores over the entire study period.
*: p < .05 as compared to S3 TaU group

At baseline, participants in the S1 and S2 groups suffered from moderate depression, whereas participants in the S3 group only had mild depression. The level of depression of participants in the S1 group was significantly higher than those in the S3 group (MD = 7.26, SE = 2.52, p = .0013), but not than those in the S2 group (MD = 6.03, SE = 2.94, p = .125). The difference between the S2 group and the S3 group was not significant (MD = 1.23, SE = 2.56, p = 1.000).

Overall, the level of depression of all participants remained the same in both the primary and sensitivity analyses at both the primary and secondary endpoints. Participants in S1 group had significantly higher mean BDI-II scores than those in the S2 and the S3 groups in the primary analyses, but the differences became non-significant to the S2 groups in the sensitivity analysis. No between-group differences were detected between the S2 and S3 groups in both analyses. Nevertheless, the overall differences in BDI-II scores were not significant over the 24-month study period in both the primary and the sensitivity analyses (Table 19). The level of depression of the three groups remained similar over the entire study period.

Table 19. Between-group comparisons for the BDI-II scores.

	M (SE)	S1 [MD (SE)]	S2 [MD (SE)]	S3 [MD (SE)]
	Primary Analysis **Group: F (2, 969.17) = 8.23, p = .000** Group × Visit: F (15, 297.66) = 1.24, p = .243			
Aripiprazole (S1)	20.76 (0.85)	-	**3.72 (1.22)**[*]	**4.09 (1.04)**[#]
Paliperidone (S2)	17.04 (0.87)	-	-	0.37 (1.06)
TaU (S3)	16.67 (0.60)	(reference group)		

	Sensitivity Analysis **Group: F (2, 567.56) = 4.76, p = .009** Group × Visit: F (15, 195.91) = 0.87, p = .598			
Aripiprazole (S1)	20.70 (1.08)	-	3.13 (1.55)	**4.06 (1.32)***
Paliperidone (S2)	17.57 (1.10)	-	-	0.93 (1.34)
TaU (S3)	16.64 (0.76)	(reference group)		

*: p < .05; #: p < .001; M: mean; MD: mean difference; SE: standard error

No within-group changes in the level of depression were detected in any intervention groups. Participants in the S1 group remained moderately depressed (primary analysis: F (5, 292.97) = 2.10, p = .066; sensitivity analysis: F (5, 206.18) = 1.54, p = .180), while those in the S3 group still suffered from mild depression (primary analysis: F (5, 292.97) = 0.45, p = .816; sensitivity analysis: F (5, 202.93) = 0.35, p = .885). Although participants in the S2 group improved from a moderate depression to a mild depression, such improvement was not significant (primary analysis: F (5, 292.97) = 1.17, p = .326; sensitivity analysis: F (5, 211.11) = 0.73, p = .599).

IV) Changes in Cognitive Functioning

FAB

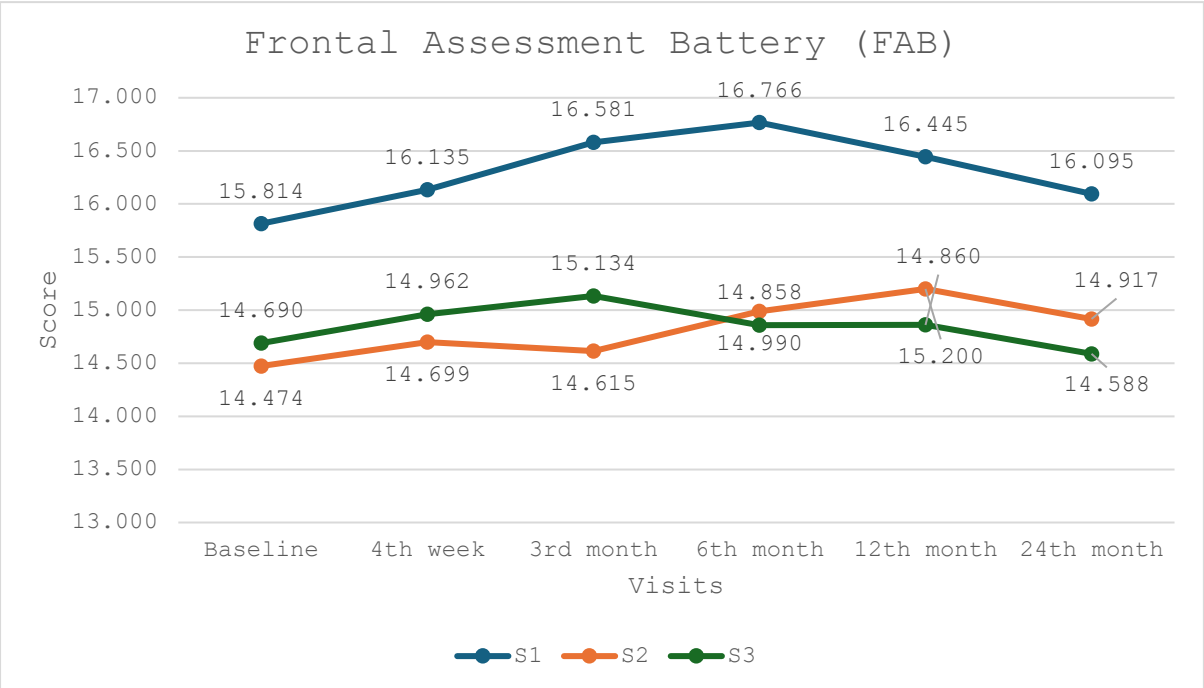

Figure 14. FAB scores over the entire study period.

At baseline, participants in the S1 group had higher FAB scores than the other two groups, albeit statistically not significant. The mean FAB scores of the three intervention groups were above 12 for the diagnostic cut-off of the frontal dysexecutive syndrome. Between-group differences were observed with participants in the S1 group had significant higher mean FAB scores than those in the S2 and S3 groups from both primary and sensitivity analyses. However, these between-group differences in FAB performances did not persist through all assessment timepoints (Table 20). No within-group differences were found for any of the intervention group over the entire study period.

Table 20. Between-group comparisons for the FAB scores.

	M (SE)	S1 [MD (SE)]	S2 [MD (SE)]	S3 [MD (SE)]
	Primary Analysis **Group: F (2, 969.28) = 9.68, p < .001** Group × Visit: F (15, 307.19) = 0.177, p = 1.00			
Aripiprazole (S1)	16.31 (0.29)	-	**1.49 (0.41)***	**1.46 (0.35)#**
Paliperidone (S2)	14.82 (0.30)	-	-	-0.03 (0.36)
TaU (S3)	14.85 (0.21)	(reference group)		
	Sensitivity Analysis **Group: F (2, 595.93) = 6.20, p = .002** Group × Visit: F (15, 92.91) = 0.42, p = .971			
Aripiprazole (S1)	16.02 (0.36)	-	**1.72 (0.51)***	**1.18 (0.43)***
Paliperidone (S2)	14.38 (0.36)	-	-	-0.55 (0.44)#
TaU (S3)	14.93 (0.25)	(reference group)		

*: p < .05; #: p < .001; M: mean; MD: mean difference; SE: standard error

MoCA

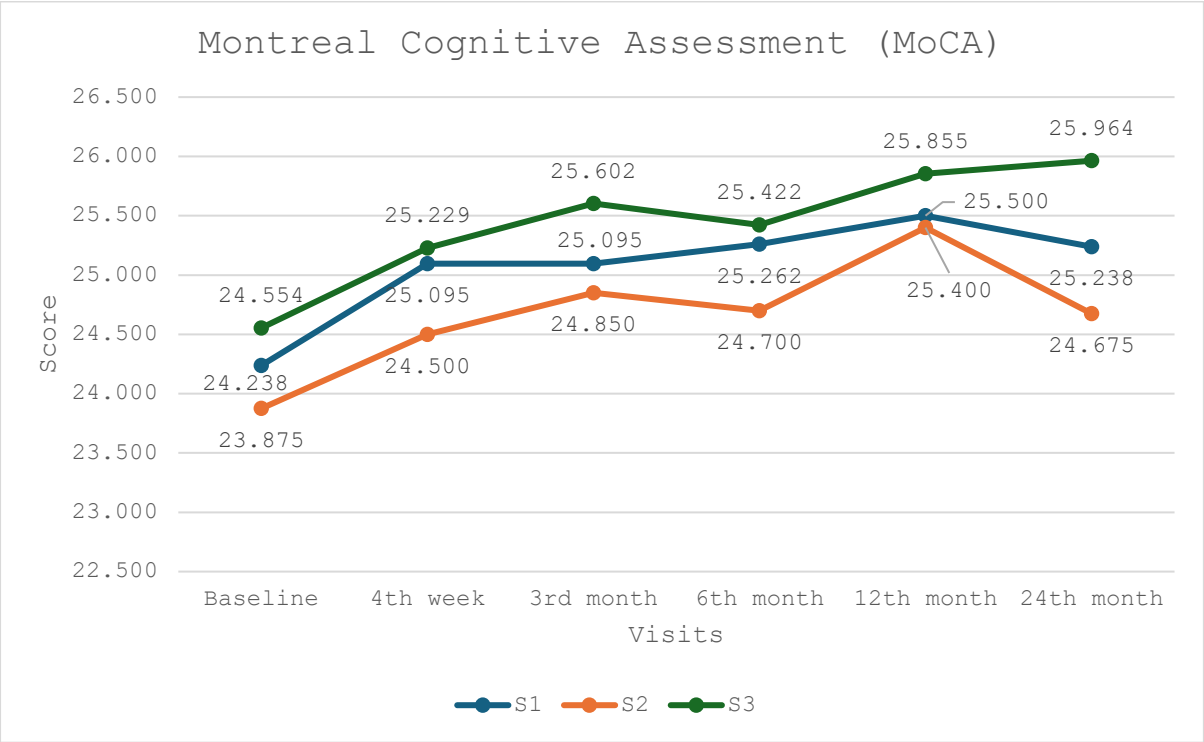

Figure 15. MoCA scores over the entire study period.

At baseline, the mean MoCA scores for all the three groups were < 26, suggesting the presence of cognitive impairments with DSM-5 defined neurocognitive disorder (NCD). There were no significant between-group differences in MoCA scorings at baseline. Overall, the S2 group had the lowest MoCA scores throughout the 24-month study period, followed by the S1 group and the S3 group. There were significant between-group differences in cognitive functions, in which the S2 group had consistently the worst cognitive performances as compared to the S3 group in both the primary and sensitivity analyses, and worse than the S1group in the sensitivity analysis (Table 21). In particular, the S2 group had the worst MoCA score when compared to the S1 group (MD = -2.53, SE = 1.01, p = .042) and the S3 group (MD = -2.81, SE = 0.87, p = 0.005) at the secondary endpoint.

Table 21. Between-group comparisons for the MoCA scores.

	M (SE)	S1 [MD (SE)]	S2 [MD (SE)]	S3 [MD (SE)]
	Primary Analysis **Group: F (2, 969.81) = 4.02, p = .018** Group × Visit: F (15, 278.49) = 1.08, p = .378			
Aripiprazole (S1)	25.07 (0.22)	-	0.41 (0.32)	-0.37 (0.27)
Paliperidone (S2)	24.67 (0.22)	-	-	**-0.77 (0.28)***
TaU (S3)	25.44 (0.16)	(reference group)		
	Sensitivity Analysis **Group: F (2, 604.01) = 9.64, p < .001** **Group × Visit: F (15, 182.98) = 2.13, p = .010**			
Aripiprazole (S1)	25.55 (0.24)	-	**0.94 (0.34)***	-0.35 (0.29)
Paliperidone (S2)	24.61 (0.24)	-	-	**-1.29 (0.29)#**
TaU (S3)	25.90 (0.17)	(reference group)		

*: p < .05; #: p < .001; M: mean; MD: mean difference; SE: standard error

In the primary analysis, no significant within-group differences were detected for all the three intervention groups. However, in the sensitivity analysis, the S3 group had significant within-group improvement in cognitive function (F (5, 247.388) = 3.24, p = .007) that as compared to baseline, their MoCA scores improved significantly at the end of the study (MD = 1.87, SE = 0.59, p = .026). Although the MoCA scores in the S1 group also showed an improving trend, the improvement was not statistically significant (F (5, 222.10) = 1.73, p = 0.13).

V) Changes in Functional Outcomes

ASI-Lite

Within-group differences were only detected in the primary analysis in the S1 group on the Psychiatric Status domain ($F (5, 294.29) = 3.06$, $p = .010$) (Figure 16g) and in S2 group on the Legal Status domain ($F (5, 322.02) = 2.38$, $p = .039$) (Figure 16e). Participants in the S2 group had more impairments from legal problems during the subsequent follow-up timepoints as compared to baseline, whereas participants in the S1 group had an improving trend on their Psychiatric Status during the subsequent follow-up timepoints as compared to baseline. However, such within-group differences became non-significant in the sensitivity analyses for both S1 ($F (5, 225.95) = 1.29$. $p = .268$) and S2 ($F (5, 223.84) = 1.69$. $p = .138$) groups.

There were significant between-group differences in functional impairments among the three intervention groups over various domains of ASI-Lite on the primary and sensitivity analyses, except on the Drug Status where no differences were observed (Figures 16a-h). Nevertheless, there were no consistent between-group differences in any of the ASI-Lite impairments across all timepoints over the 24-month follow-up period (all $p > .05$).

Overall, the findings from ASI-Lite suggested that aripiprazole or paliperidone did not produce better functional outcomes than usual care.

ASI-Lite_M

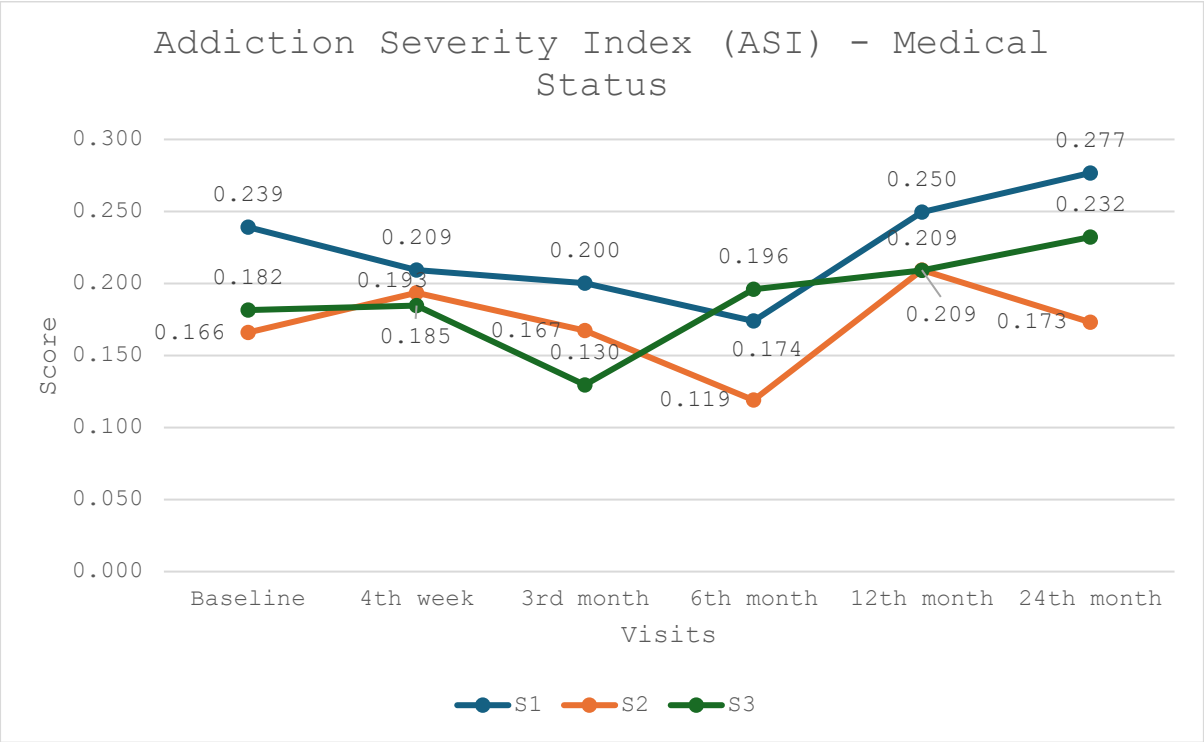

Figure 16a. ASI-Lite Medical status scores over the entire study period.

Participants in the S1 group had significantly worse medical status than those in S2 group only in the sensitivity analysis. Participants in both groups had similar medical status as compared to those in the S3 group.

ASI-Lite_E

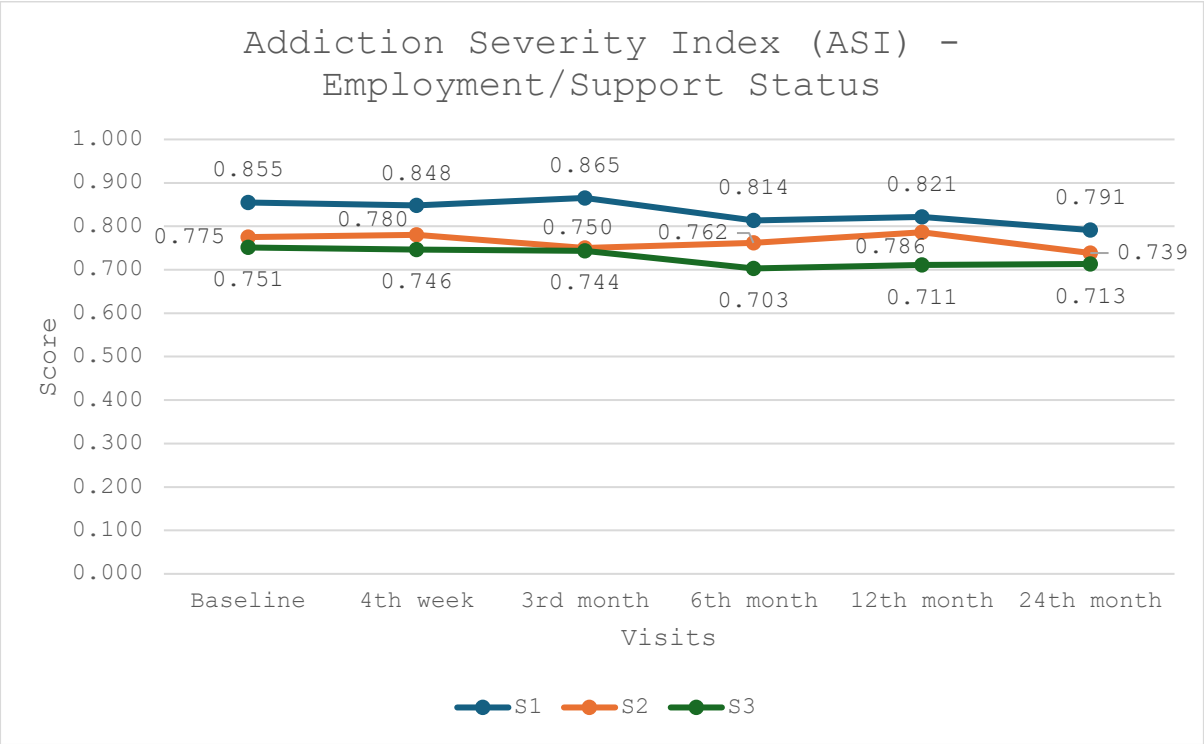

Figure 16b. ASI-Lite Employment/Support status scores over the entire study period.

Participants in the S1 group had significantly better employment or support status as compared to those in S3 group in both primary and sensitivity analyses. The advantages from employment or support from the S1 group over the S2 group, or S2 group over S3 group were equivocal due to the inconsistent findings from the primary and the sensitivity analyses.

ASI-Lite_A

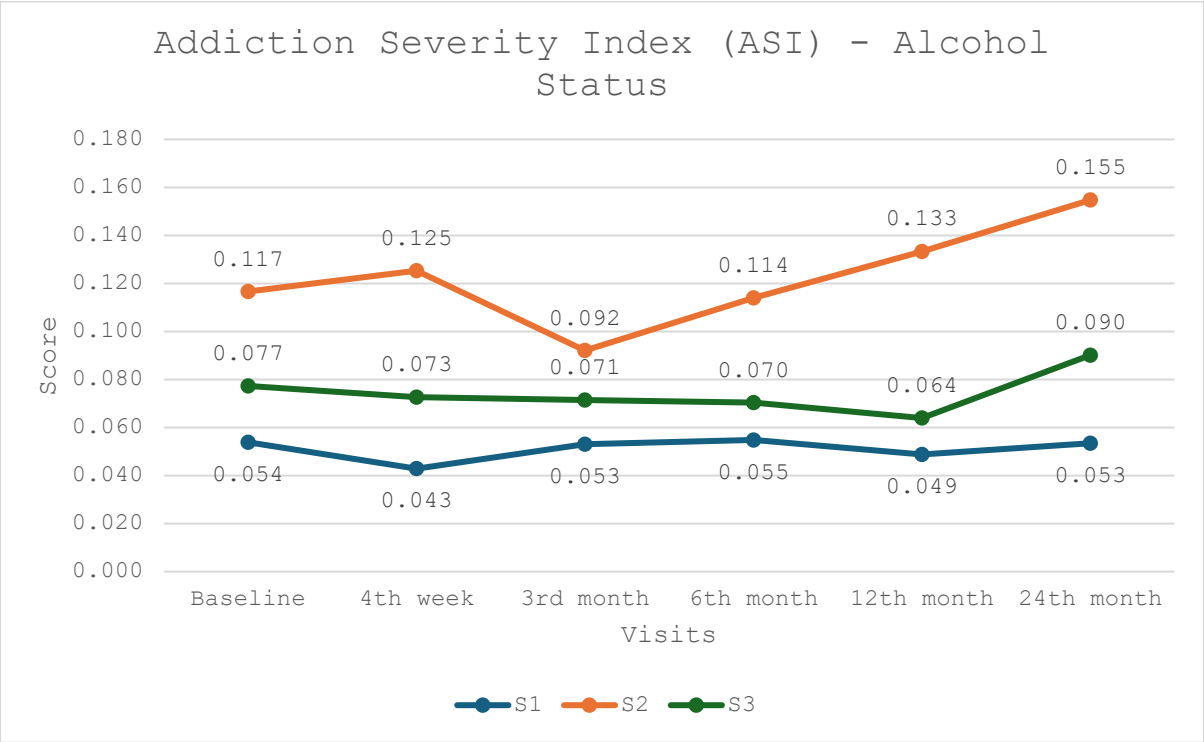

Figure 16c. ASI-Lite Alcohol status scores over the entire study period.

Participants in the S2 group had the worst severity in impairment from alcohol use among the three intervention groups in both the primary and the sensitivity analyses. On the other hand, participants in S1 group had the least alcohol-related impairments among all the groups, albeit not statistically significant when compared to those in S3 group.

ASI-Lite_D

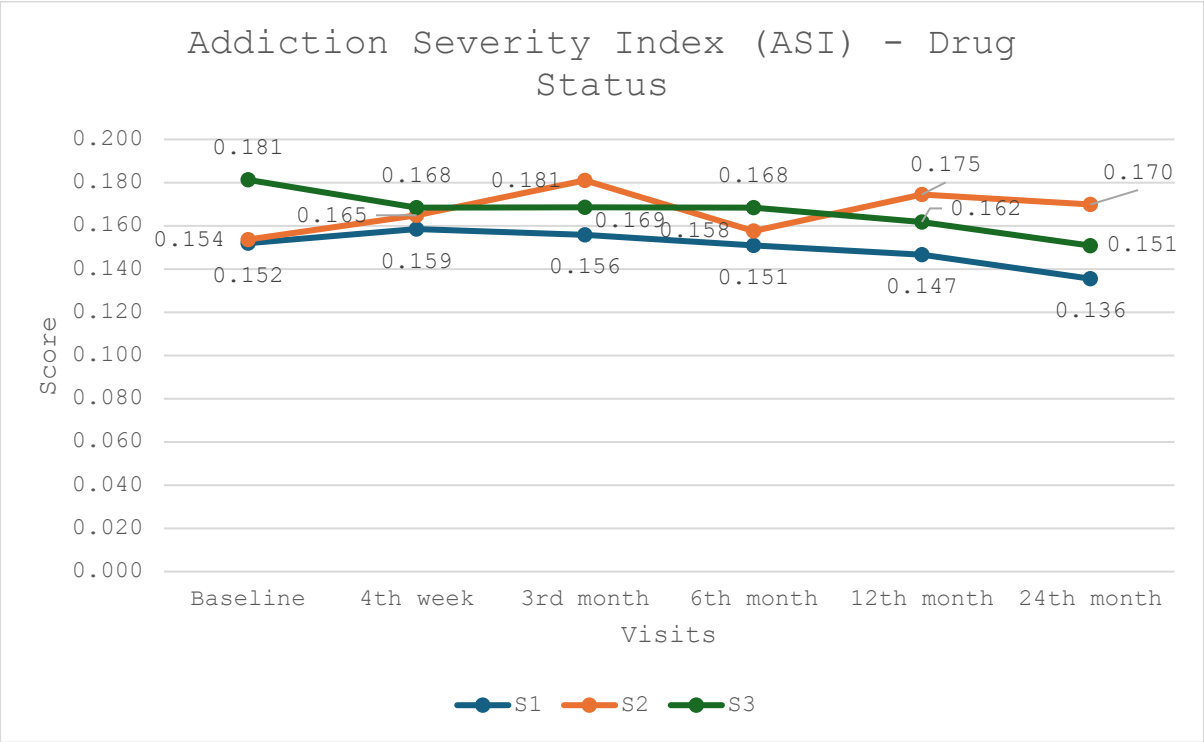

Figure 16d. ASI-Lite Drug status scores over the entire study period.

No between-group differences on impairments related to stimulant use were noted among the three intervention groups.

ASI-Lite_L

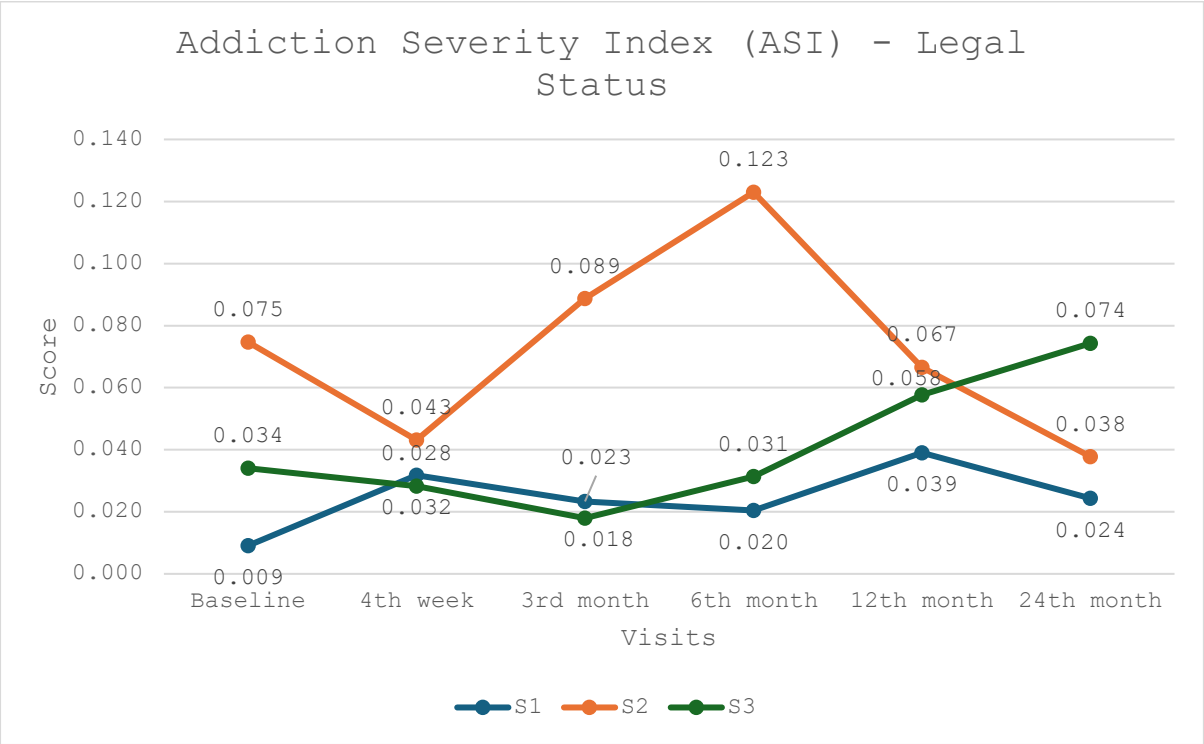

Figure 16e. ASI-Lite Legal status scores over the entire study period.

Participants in the S2 group suffered the most from legal problems among all three intervention groups, though the effects became non-significant in the sensitivity analysis.

ASI-Lite_F

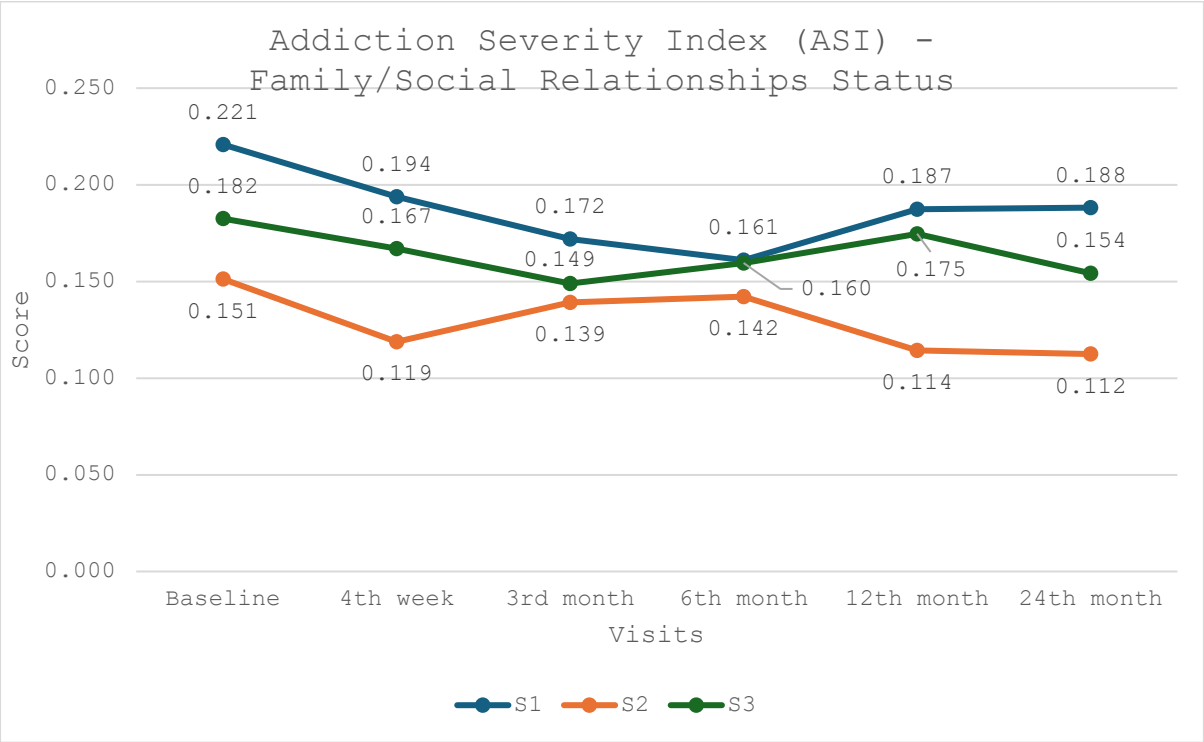

Figure 16f. ASI-Lite Family/Social Relationships status scores over the entire study period.

Participants in the S1 group had significantly more impairments in family or social relationship than those in the S2 group but not in the S3 group as noted in both the primary and sensitivity analyses.

ASI-Lite_P

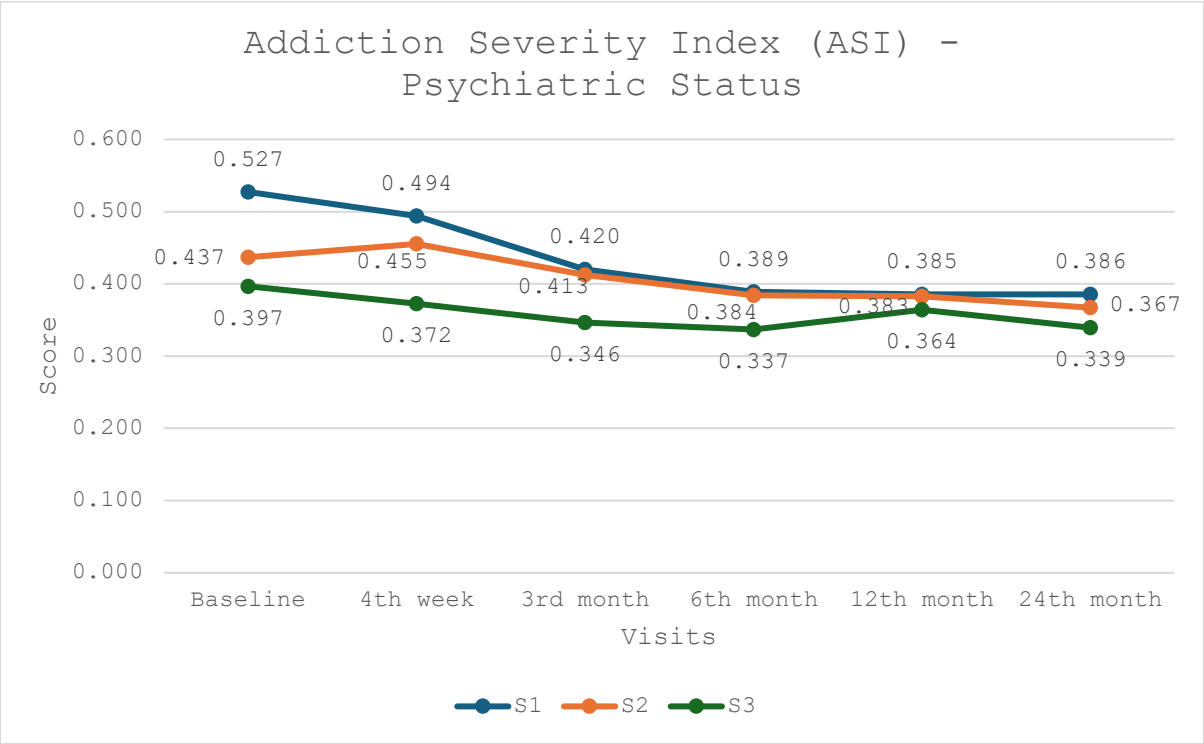

Figure 16g. ASI-Lite Psychiatric status scores over the entire study period.

Participants in the S1 group had significantly worse psychiatric well-being than the S3 group, but similar to the S2 group in both the primary and sensitivity analyses.

ASI-Lite_Freq

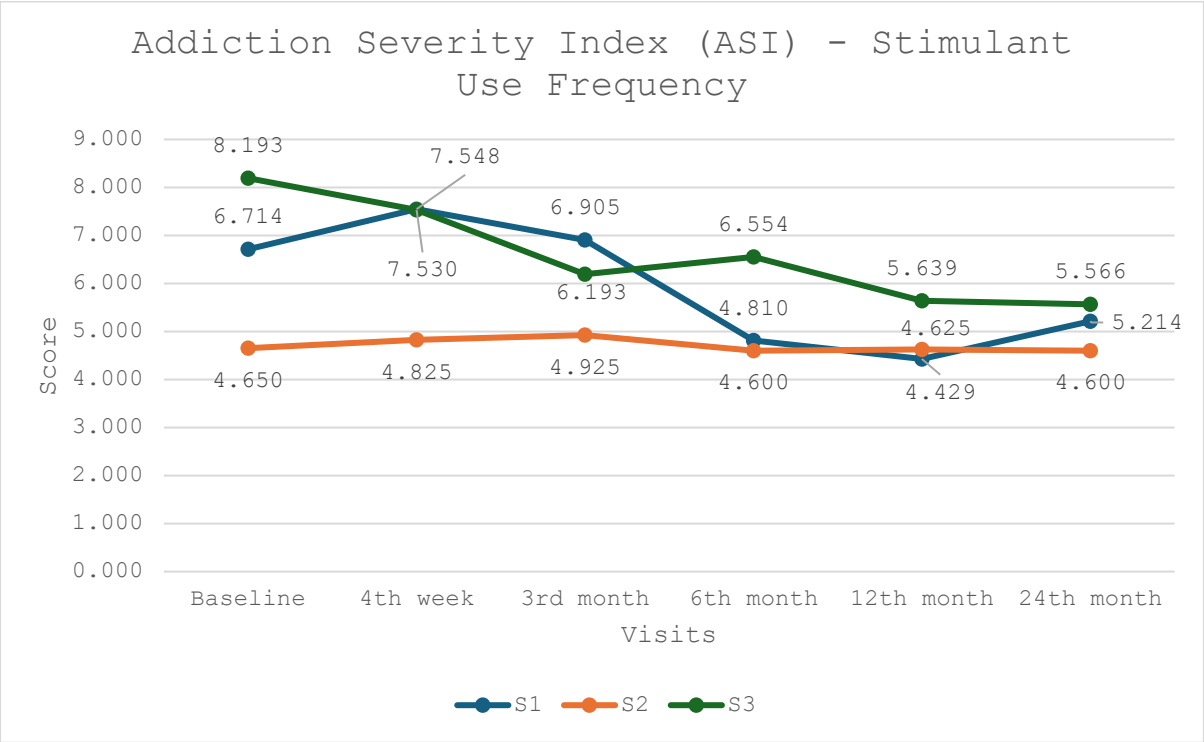

Figure 16h. ASI-Lite Stimulant Use Frequency (per 30 days) over the entire study period.

The frequency of stimulant use was reported in ASI-Lite as the number of days of stimulant use over the past 30 days. Participants in the S3 group had the most frequent stimulant use during the study period, followed by those in the S1 group and the least in the S2 group. Participants in the S2 group had only significantly less use-days than those in S3 group but not S1 group in the primary analysis. Such differences became non-significant in the sensitivity analysis. Overall, the frequency of stimulant use showed no significant differences for the three interventions over the 24-month study period.

Subgroup analyses

Subgroup analyses (Table 22) comparing the S1 and S2 groups to those participants taking medications in the S3 group showed consistent findings to the main primary analyses.

Both the S1 and S2 groups remained better in efficacy in managing psychotic symptoms as compared to the S3 TaU-medicated group with more CGI-I defined clinical responders. There were also significantly more BPRS-24 defined clinical responders in the S1 group than the S3 TaU-medicated group at the 12th month primary endpoint, though such between-group differences did not sustain till the 24th month secondary endpoint. The S1 group also had improved severity in methamphetamine use disorder at both primary and secondary endpoints. Similar to the primary analysis, S2 group demonstrated significantly worse MoCA results than the S3 TaU-medicated group (MD = -1.03, SE = 0.295, p = .001).

BAI for all three groups were within the same anxiety level with mild severity. A within-group improvement in CocUD severity for the S3 TaU-medicated group was noted at the primary endpoint (B = 2.558, SE = 1.0024, p = .011) but not at the secondary endpoint. Nevertheless, no between- group differences were noted on CocUD as in the main analysis.

Table 22. Summary of subgroup analyses comparing S1 and S2 groups against S3 participants taking medications.

	Over the 24-month study period
CGI-S	Wald χ^2 (10) = 7.079, p = .718
CGI-I	**Wald χ^2 (8) = 18.242, p = .019**
Cocaine Dependence	Wald χ^2 (10) = 1.429, p = .999
Methamphetamine Dependence	Wald χ^2 (10) = 6.272, p = .792

	Group	Group × Visit
BPRS-24	F(2,802.989) = 2.344, p = .097	F(15,263.009) = 1.222, p = .255
GASS	F(2,673.859) = 0.176, p = .838	F(12,265.072) = 0.488, p = .921
SOCRATES	F(2,798.482) = 7.918, p < .001	F(15,244.104) = 0.539, p = .917
SOCRATES_rec	F(2,805.278) = 10.167, p < .001	F(15,263.026) = 0.281, p = .997
SOCRATES_amb	F(2,812.409) = 6.670, p = .001	F(15,240.644) = 0.473, p = .953
SOCRATES_ts	F(2,784.445) = 2.121, p = .121	F(15,270.722) = 0.729, p = .755
BAI	F(2,802.178) = 3.803, p = .023	**F(15,288.889) = 2.180, p = .007**
BDI	F(2,813.250) = 7.227, p = .001	F(15,243.480) = 1.174, p = .292
FAB	F(2,812.905) = 10.147, p < .001	F(15,251.097) = 0.176, p = 1.000
MoCA	F(2,812.901) = 6.441, p = .002	F(15,247.755) = 0.995, p = .460
ASI_M	F(2,805.886) = 1.690, p = .185	F(15,247.499) = 0.480, p = .949
ASI_E	F(2,811.537) = 6.855, p = .001	F(15,281.862) = 0.580, p = .889
ASI_A	F(2,745.464) = 13.237, p < .001	F(15,245.390) = 0.279, p = .997
ASI_D	F(2,808.639) = 5.250, p = .005	F(15,240.499) = 0.326, p = .992
ASI_L	F(2,746.250) = 9.725, p < .001	F(15,268.462) = 1.655, p = .060
ASI_F	F(2,789.128) = 9.978, p < .001	F(15,247.512) = 0.681, p = .802
ASI_P	F(2,813.163) = 2.011, p = .135	F(15,246.952) = 1.573, p = .082
ASI_freq	F(2,812.351) = 2.802, p = .061	F(15,249.027) = 0.481, p = .949
	12th month Primary Endpoint	24th month Secondary Endpoint
BPRS-24-defined Clinical Responder	**Wald χ^2 (2) = 6.676, p = .036**	Wald χ^2 (2) = 1.323, p = .516
CocUD	**Wald χ^2 (3) = 12.083, p = .007**	Wald χ^2 (3) = 2.963, p = .397
MetUD	**Wald χ^2 (3) = 23.502, p < .001**	**Wald χ^2 (3) = 23.449, p < .001**

Discussion

The present study investigated the efficacy of early assertive pharmacotherapy using aripiprazole and paliperidone compared to Treatment-as-Usual in individuals with stimulant use disorder and co-morbid psychotic symptoms. Our findings concurred with previous reports that stimulant users were predominantly males in 2021 (United Nations Office on Drugs and Crime, 2023) with methamphetamine being the commonest abused stimulant in Hong Kong during 2015 to 2021 (Narcotics Division, 2024). The effects from aripiprazole and paliperidone on the various outcomes as compared to the treatment-as-usual group appeared non-conformational.

Efficacy in Stimulant-related Psychosis

As gauged by BPRS-24, there were drops in mean scores for participants taking aripiprazole or paliperidone as compared to baselines, whereas the mean score hardly changed for those in the TaU groups. Only participants taking aripiprazole had statistically significant improvement but not for those taking paliperidone. However, due to the minor mean differences on BPRS-24 scorings between the three intervention groups, no statistically significant between-group differences could be detected. Such findings on BPRS-24 scorings among the three intervention groups were not surprising because all the antipsychotics prescribed to the participants in the TaU group were having comparable efficacies to aripiprazole and paliperidone in treating schizophrenia. The standardised mean differences were similar when they were compared to placebo or to olanzapine (the antipsychotic most trialled) in various meta-analyses that included both short- and long-term studies (Huhn et al., 2019; Leucht et al., 2017; Leucht et al., 2023; Schneider-Thoma et al., 2022). In addition, similar efficacies among aripiprazole, haloperidol, olanzapine, quetiapine and risperidone (Fluyau, Mitra, & Lorthe, 2019; G. Wang

et al., 2016), and between paliperidone and risperidone, in treating amphetamine- induced/ -associated psychosis had also been reported (G. Wang et al., 2020).

So, in order to translate better for such small changes in BPRS-24 mean scores to day-in-day-out clinical responses (Leucht et al., 2005), we performed analyses on "clinical responder" defined by CGI-S ≤ 3 (mildly ill), CGI-I ≤3 (minimally improved) and with BPRS ≥ 50% ("much improvement"). Except that there were no between-group differences on CGI-S, both the aripiprazole and the paliperidone groups were significantly better than the TaU group to help participants achieving clinical improvements on their psychotic symptoms. Aripiprazole could lead to an improvement the earliest at the 1st month of treatment, whereas paliperidone was showing a later improvement beginning at the 6th month. Most importantly, participants receiving TaU were unable to demonstrate any significant clinically meaningful improvement throughout the study.

The conversion rate of amphetamine-induced psychosis to schizophrenia had been reported to be between 22% and 30% (Murrie et al., 2020; Niemi-Pynttari et al., 2013). As demonstrated in the current study, active interventions might be able to reduce the conversion rate by half (11%). Distinctively, aripiprazole was significantly better in preventing the conversion from stimulant-induced psychosis to schizophrenia than paliperidone.

And as reflected by the findings from GASS, aripiprazole and paliperidone were both well tolerated with minimal side-effects, and there were no tolerability differences to the TaU group.

To sum up, stimulant abusers with stimulant associated psychosis taking aripiprazole showed significant reduction in BPRS-24 scores, which were not found in those taking paliperidone or

within the TaU group. Both aripiprazole and paliperidone were well tolerated in stimulant abusers but better in efficacy than TaU in improving stimulant-related psychotic symptoms clinically. Aripiprazole was also associated with the quickest clinically meaningly improvement. More importantly, only aripiprazole was able to demonstrate the significant prevention in the conversion of stimulant-induced psychosis to schizophrenia.

Stimulant Use and Dependence

Concerning cocaine use, no differences were noted for the three interventions in managing cocaine dependence or CocUD. There was an earlier study showing aripiprazole LAI might reduce CocUD in participants with schizophrenia (Szerman et al., 2020). Our current study did not replicate similar results, though an improving trend on the severity of CocUD was observed among those receiving aripiprazole, albeit statistically non-significance. Nevertheless, these lack of differences were likely related to the small sample sizes as only 25% of the participants were active cocaine users with a total of 16 participants used cocaine as their sole stimulant in the current study.

Regarding the methamphetamine use, participants taking both aripiprazole and paliperidone appeared to be more SDS-defined psychological dependent to methamphetamine than those in the TaU group during the initial six months. However, such significant differences in dependence no longer existed thereafter in the study. Furthermore, participants taking aripiprazole had significant improvement with the greatest amelioration in the severity of MetUD at the 12^{th} and 24^{th} months. A smaller yet significant degree of improvement was also noted for the TaU group. No significant improvement was observed for those taking paliperidone. Our finding on such temporary worsening in psychological dependence for methamphetamine from aripiprazole use concurred with a previous 20-week randomized trial

report that it might be associated with a worsening in methamphetamine use (Tiihonen et al., 2007). Nevertheless, our current study provided evidence that with prolonged treatment > 6 months, the use of aripiprazole would no longer be associated with psychological dependence. On the contrary, it was able to improve the severity of MetUD. Such reversal of effect was not observed from the use of either paliperidone or TaU.

Throughout the whole 24-month study period, there were no significant differences on the positive detection on stimulant use from urine tests among the three intervention groups. There were also no significant differences between the three intervention groups on the frequency of stimulant use as measured buy ASI-Lite.

Participants taking aripiprazole, but not paliperidone, had greater readiness to change for their stimulant use habit as compared to the TaU group, especially in recognising their problematic stimulant use and taking step to make a positive change for their stimulant use. In order words, aripiprazole might have enhanced stimulant abusers' motivation to quit their stimulant use. Despite significantly better than the TaU group, such differences were averaged over time. Stimulant use, particularly in chronic methamphetamine use might result in psychosis, apathy, amotivation and anhedonia due to the disruption of the mesolimbic dopaminergic pathway (Costello, Husain, & Roiser, 2024; Rawson, 2013; Stacy, Frantz, Miller, Merrill, & Gainer, 2024). This shares the common pathophysiological pathway for both positive and negative symptoms in psychosis and schizophrenia. Strikingly, apathy has been associated with poorer self-efficacy for methamphetamine abstinence (Hussain et al., 2021). Therefore, we postulate that such enhancement in motivation for methamphetamine abusers taking aripiprazole might have contributed to the improvements in their severity of MetUD over time as well.

Changes in Mood, Cognitive and Functional Outcomes

There were no significant differences between the three intervention groups in anxiety and depressive symptoms. However, only stimulant abusers receiving aripiprazole demonstrated a significant reduction in anxiety level for at least 12 months.

Although stimulant abusers taking aripiprazole appeared to have better frontal executive functions than the other two groups, the differences did not reach statistical significance over time. In contrast, all stimulant abusers in this study had the mean MoCA scores < 26, suggesting their potential sufferings from DSM-5 defined mild neurocognitive disorder. Remarkably, stimulant abusers who received paliperidone showed significantly worse global cognitive function than the other two groups.

Overall, with respect to the findings from ASI-Lite, our current study suggested that participants taking aripiprazole or paliperidone did not showed significantly better functional outcomes than those in the TaU group.

The distinct psychopharmacological properties between aripiprazole, paliperidone and those antipsychotic medications used in the current study might provide insights for the substantial differences in outcomes concerning stimulant dependence and motivation to quit stimulants, level of anxiety and global cognitive function.

Decreased D_2 receptors availability and strong antagonistic activity on dopamine D_2/D_3 receptors peculiarly at the orbitofrontal cortex and the striatum (caudate nucleus and putamen) might contribute to drug craving, pleasure from drug use, drug seeking behaviours and compulsive drug taking behaviours in both animal (Dalley et al., 2007) and human studies

(Lingford-Hughes & Nutt, 2003; Volkow et al., 2001; Volkow et al., 1999; Volkow et al., 2015). There was also case report suggesting that dopamine super-sensitivity resulted from antipsychotics use might cause worsening of the stimulant use disorder (Amarasekera & Wood, 2023). Antipsychotics with dopamine antagonistic property might also exacerbate motivational deficits and reduce dopaminergic transmission in the prefrontal cortex, which in return causing more severe apathy (Costello et al., 2024). As a potent D_2/D_3 antagonist and a low-efficacy partial D_2/D_3 agonist (Strange, 2008), aripiprazole might have avoided the disadvantages from the strong D_2 antagonistic property from paliperidone and those antipsychotics used in TaU group (Chung, 2024; Minwalla et al., 2021), leading to its better improvement in the severity of MetUD in the current study. The strongest 5-HT_{1A} partial agonism from aripiprazole among paliperidone and almost all other comparator antipsychotics in TaU (Chung, 2024; Patil & Schwartz, 2018) could increase the dopamine release in the prefrontal cortex, thereby taking off apathy and promoting motivation (Costello et al., 2024), and consequently fostering the readiness in stimulant abusers to quit their stimulant use habit. Since 5-HT_{1A} partial agonism has robust effect to relieve anxiety (Albert, Vahid-Ansari, & Luckhart, 2014), it might also explain why only stimulant abusers taking aripiprazole could achieve a downgrade from moderate to mild anxiety level.

In the current study, the lack of significant changes in cognitive functions among stimulant abusers with psychotic symptoms are likely to be multifactorial. Stimulant abuse has long been associated with cognitive deficits (Bourque & Potvin, 2021). Nonetheless, the non-significance differences in positive stimulant urine tests and frequency of stimulant use among the three intervention groups suggested that the lack of cognitive improvements due to the continuous stimulant use was less plausible. Recent systematic review pointed out that methamphetamine and cocaine abusers with associated psychosis had cognitive deficits worse

than non-psychotic users, and with the magnitude of impairments similar to those with schizophrenia (Gicas, Parmar, Fabiano, & Mashhadi, 2022). Hence, theoretically, the use of antipsychotics with 5-HT_{1A} agonism and balanced D_2 antagonism/agonism (like aripiprazole) which shown to promote cognitive functions in patients with schizophrenia should also improve cognitive deficits in stimulant abusers with psychotic symptoms (Allott, Chopra, Rogers, Dauvermann, & Clark, 2024; Kim et al., 2009; Topolov & Getova, 2016). This might account for why stimulant abusers taking aripiprazole had significantly better cognitive functions on MoCA assessment than those taking paliperidone, which the later lacks significant 5-$HT1_A$ agonism but potent D_2 antagonism hence making it worst in restoring the cognitive deficits among stimulant abusers in this study. In fact, paliperidone had shown equivocal efficacy in cognitive functions among schizophrenic patients in previous studies (Allott et al., 2023; Shi et al., 2016). On the other hand, the diversified cognitive effects from the different constituent antipsychotics in the TaU group (Baldez et al., 2021) might have hindered the detection on the true differences on cognitive function between these three groups.

Study Limitations

Despite its merits as the first long-term, randomized, single-blinded study with early pharmacotherapy intervention for stimulant abusers with psychotic symptoms, there are several limitations warrant consideration.

First, the generalizability of our results may be constrained by the specific demographic characteristics of our samples, predominantly from stimulant abusers in Hong Kong and with the majority of them using methamphetamine.

Secondly, due to the COVID-19 pandemics, the number of participants finally fell short of three participants with a reduction from 168 to 165 stimulant abusers. During the 3-year pandemics in Hong Kong, there were severe disruption and suspension to all face-to-face research activities. With no exceptions, our project had faced significant impacts in subject recruitment and their later follow-up assessments. Despite our research team had already tried multiple means to promote the project and to enhance subject recruitments and follow-ups, for examples, through academic website, delivering talks to various organizations, distributing promotional materials to the non-governmental organizations, community partners, and substance abuse clinics, displaying promotional materials whenever possible during the TV interviews by the grantee, carrying out on-street promotion, out-reaching to outlying islands, and public transport advertisements, our project was at last only able to achieve 98.2% (165 participants) of the target sample size. Nonetheless, the effect size estimated by comparing the aripiprazole and paliperidone groups to Treatment-as-Usual on the changes in BPRS-24 scores at the primary endpoint with 168 subjects while maintaining a moderate effect size of 0.46 was with a statistical power of 83.5%. Although eventually only 165 stimulant abusers participated in the study, with the same effect size 0.46 was detected, the post hoc statistical power was only slightly lowered to 82.8%.

Thirdly, 24 stimulant abusers (28.9%) in the Treatment-as-Usual group had never received any medication throughout the study period. In the current study, we decided intentionally not to have a placebo or medication-free control arm due to the high conversion rate of stimulant-induced psychosis to schizophrenia as reported from previous epidemiological studies (Murrie et al., 2020; Niemi-Pynttari et al., 2013). Notwithstanding, these medication-free participants in the Treatment-as-Usual arm may represent either abusers being less psychotic and/or with better prognostic outcomes that required no active intervention. This could lead to potential

attrition bias in this study. Moreover, the diversity of antipsychotic medications used in the Treatment-as-Usual group hindered any direct comparisons between those specific medications to aripiprazole or paliperidone. In addition, the current study did not control the prescriptions of antidepressants and mood stabilizing agents, and therefore, interpretations on differences in efficacies on cognitive and mood domains required cautions. Again, due to COVID-19 pandemic, the metabolic parameters could not be consistently monitored and thus reported in this study, and so the lack of differences in intolerability from the three interventions might need careful interpretation. Furthermore, as only 12.7% of the participants (21 stimulant abusers) received long-acting injectable antipsychotics at any study timepoint, complete oral medication adherence that was assumed equivalent to the prescriptions collected by the stimulant abusers might lead to type II biases in the current study.

Fourthly, the present study focused on the efficacies of two medications, namely aripiprazole and paliperidone, in treating psychotic symptoms. Although ASI-Lite was used, their impact on daily functioning was not thoroughly assessed.

Last but not the least, the current study did not evaluate if there was any psychological intervention or counselling services that the stimulant abusers had received from other agencies, such as the Counselling Centre for the Psychotropic Substance Abusers, beyond the public health care settings. As motivational interviewing, contingency management and cognitive behavioural therapy are all effective management approaches in reducing stimulant dependence and/or use disorder (Clinical Guideline Committee, ASAM, AAAP, & IRETA, 2024) and are commonly delivered by these agencies, their potential influences on the outcomes about stimulant dependence for the current study should be heeded.

Clinical Implications and Future Directions

Our findings extend the knowledge for clinicians in managing stimulant associated psychosis by providing long term scientific data from early antipsychotic pharmacotherapy intervention to stimulant abusers. The limited restrictions on antipsychotics use in the Treatment-as-Usual group and other non-psychotic medication prescription in this randomized trial provide the *quasi*-real-world evidence to match the routine clinical practices. With early pharmacy-therapeutic interventions, our study proves that the conversion rate of stimulant associated psychosis to schizophrenia can be pruned by half to 10% as compared to previous literature. This study also shows that aripiprazole has comparable efficacy to paliperidone and other commonly used antipsychotics in Hong Kong in managing stimulant associated psychotic symptoms. The findings about aripiprazole can significantly mitigate the progression of stimulant induced psychosis to schizophrenia and the severity of methamphetamine use disorder better than the other interventions, and its potential to enhance the readiness for stimulant abusers to quit their stimulant use habit warrant clinicians' attention. Also, the transient effects from both aripiprazole and paliperidone in increasing psychological dependence to methamphetamine during the first 6 months should prime doctors' awareness to consider other evidence-based interventions, such as psychological interventions with cognitive behavioural therapy, to methamphetamine abusers to tackle their psychological dependence while treating their psychosis with these two medications. Finally, with cognitive deficits being the frequent repercussion among stimulant abusers with or without associated psychosis, monitoring of their cognitive functions should be indispensable if paliperidone is prescribed to this group of patients.

Our study underscores the need for continual research to optimize the pharmacological treatments for stimulant associated psychosis, particularly considering the evolving patterns of

cocaine abuse globally, and the availability of newer types of antipsychotics such as brexpiprazole and cariprazine which coned similar pharmacodynamic properties to aripiprazole. Future study targets on this specific population and newer drugs might elucidate if the aripiprazole shares similar benefits for cocaine, or newer drugs encompass better efficacy in treating stimulant associated psychosis.

Conclusion

In conclusion, our study provides robust evidence supporting the efficacy of early assertive pharmacotherapy, in particular the use of aripiprazole, in improving clinical outcomes for stimulant abusers with stimulant associated psychosis. These findings accentuate the importance of integrating targeted pharmacological interventions within comprehensive treatment frameworks to address the complex interplay of stimulant use and its associated psychotic symptoms.

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