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Research paper

Does drug use affect the efficacy of amisulpride, aripiprazole and olanzapine in patients with schizophrenia spectrum disorders? Results from a pragmatic, randomised study

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ABSTRACT

Objectives: Drug use is prevalent in patients with schizophrenia spectrum disorders (SSD) but there is limited knowledge about the influence of drug use on the effectiveness of antipsychotic medication. This secondary explorative study compared the effectiveness of three antipsychotics in patients with SSD, with and without drug use.

Methods: The BeSt InTro multi-centre, head to head, rater-blinded randomised study compared amisulpride, aripiprazole and olanzapine over a 1-year follow-up period. All patients ($n = 144$) were aged ≥18 years and met the ICD-10 criteria for SSD (F20–29). Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). The primary outcome was reduction of a PANSS positive subscale score.

Results: At baseline, 38% of all patients reported drug use in the last 6 months before inclusion, with cannabis as the main drug (85%), followed by amphetamine-type stimulants (45%), sedatives (26%), hallucinogens (19%), cocaine (13%), opiates (4%), GHB (4%), solvents (4%), analgesics (4%) and anabolic steroids (2%). The predominant pattern was the use of several drugs. There were no significant overall differences in the PANSS positive subscale score reduction for the three studied antipsychotics among patients either with or without drug use. In the drug use group, older patients treated with amisulpride showed a greater PANSS positive subscale score reduction during the treatment period compared to younger patients.

Conclusion: The current study showed that drug use does not appear to affect the overall effectiveness of amisulpride, aripiprazole and olanzapine in patients with SSD. However, amisulpride may be a particularly suitable choice for older patients with drug use.

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1. Introduction

Substance use, including the use of illicit drugs and prescription medication, is common in patients with schizophrenia spectrum disorders (SSD). Drug use in psychosis may negatively affect medication adherence and clinical outcomes, and may lead to relapse and re-hospitalisation, increased treatment needs due to greater symptom severity and heightened suicide risk, thus worsening the prognosis compared to psychosis without drug use [1–4]. Disrupted neurotransmitter signalling through multifactorial pathological mechanisms is widely documented in SSD [5] and may be affected by drug use [6]. Signalling disturbances are complex, but dopamine dysregulation with hyperdopaminergic states seems to contribute to positive symptoms [7]. Antipsychotic medication is the mainstay of the treatment of psychoses, with the strongest effect on positive symptoms [8,9]. Inter-individual variations in effectiveness exist for any particular medication that may be influenced by drug use. Drug use could potentially affect these dopaminergic mechanisms differently [6] and the specific exploration of effectiveness in patients with psychosis, with and without drug use, may contribute to a more targeted treatment approach. The elimination time for most drugs in the body is within approximately 5 days [10] but drug metabolites can persist for longer than 2 weeks and produce long-lasting alterations, both behavioral and in the brain, including neurotoxicity [11]. Drugs may also lead to alterations in receptor activity and bioavailability [12,13]. Drug use could thus interact with the effects of antipsychotic medication on the brain receptor level, contribute to a reduction in responsivity [14] and negatively affect the efficacy of antipsychotics.

The prevalence of substance use in patients with schizophrenia was reported to be 60% in the CATIE trial [15] and up to 50% in first-episode psychosis [16]. Polysubstance use is the most typical pattern seen in daily clinical practice [17]. Cannabis is the most frequently used drug [17,18] in this patient group, followed by stimulants such as amphetamines or cocaine [19,20]. The strongest evidence is for cannabis and amphetamine-type stimulants in relation to their effect on the development of psychosis [6,21,22], but psychotic symptoms are also commonly associated with cocaine and hallucinogen use [6,23]. These drugs may induce acute psychosis [22] or exacerbate psychotic episodes in patients with SSD [24].

Previous research on the effect of drug use on antipsychotic effectiveness is scarce and shows inconsistent results, including in relation to different types of antipsychotics. In a previous study from our research group, patients with psychosis and drug use showed similar responses to antipsychotic medications compared to non-users with psychosis [25], which is in line with another study reporting comparable responses in relation to symptom reduction and global improvement [26]. In contrast, there are studies reporting that concomitant drug use is linked to increased treatment, with poorer treatment response to antipsychotics [27,28]. There are some methodological issues to consider when interpreting these studies, however. Patients with multiple drug use are often excluded from efficacy trials, or the focus is on a single drug type [29]. Disease course and duration has been shown to influence the effectiveness of antipsychotic treatment [30], i.e. patients with a first episode of schizophrenia or with a shorter illness duration appear to be more responsive to antipsychotics as compared to chronic patients [30]. Possibly, drug use status may have an impact on antipsychotic responsiveness, which can also be differently influenced by age and disease status. There is thus an incomplete clinical picture of the effectiveness of antipsychotics for SSD with drug use, which reduces the generalisability to clinical practice. It is challenging to make strong clinical recommendations for this patient group based on the available evidence. From the meta-analytical findings of Smith and colleagues [31], based on the different efficacies of the first-choice antipsychotics in patients with schizophrenia, amisulpride, aripiprazole and olanzapine were chosen for their different pharmacological profiles and potentially different interaction effects with drug use, with the intention of contributing to more individualized clinical recommendations for patients with drug use.

1.1. Study aim

This secondary explorative study aimed to compare the effectiveness of the three antipsychotics amisulpride, aripiprazole and olanzapine in a pragmatic RCT in patients with SSD with and without drug use controlling for age. We expected the antipsychotic treatment effects to be different for the drug using subjects than those without such use.

2. Materials and methods

2.1. Study design and participants

Patients from the BeSt InTro (Bergen-Stavanger-Innsbruck-Trondheim) trial were included in this study; see our previous publication for further details [8]. The study is a randomised, rater-blinded, head-to-head comparison of amisulpride, aripiprazole and olanzapine over a 1-year follow-up period. Patients were computer-generated randomly assigned to receive oral medication. Randomisation lists for each study centre were prepared by statisticians at the University of Bergen (Bergen, Norway), who were independent of the study. Patients were recruited from Bergen, Stavanger and Trondheim in Norway and from Innsbruck in Austria. The study was approved, in Norway, by the Regional Committees for Medical and Health Research Ethics and the Norwegian Medicines Agency and, in Austria, by the Etikkommission der Medizinische Universität Innsbruck and the Austrian Federal Office for Safety in Health Care (BASG). Clinical monitoring according to the ICH-GCP was conducted by the Department of Research and Development at Haukeland University Hospital in Norway and by the Clinical Trial Centre at the Medical University Innsbruck in Austria. The BeSt InTro did not receive any financial or other support from the pharmaceutical industry. *Trial Registration*: ClinicalTrials.gov ID: NCT01446328. The present study is a secondary and explorative study.

Included patients (n = 144) were 18 years of age or older, with a score of ≥4 on at least one of the Positive and Negative Syndrome Scale (PANSS) items [32]: P1 (Delusions), P3 (Hallucinatory behaviour), P5 (Grandiosity), P7 (Suspiciousness/Persecution) or G9 (Unusual thought content). All included patients were considered candidates for oral antipsychotic medication therapy and diagnosed with SSD according to the 10th Revision of the International Classification of Diseases (ICD-10) diagnostic criteria for F20–F29. Diagnostic interviews were performed either by trained psychiatrists or clinical psychologists. Written informed consent was obtained from the patients prior to inclusion. The exclusion criteria were: inability to understand the spoken native language; pregnancy or breastfeeding; hypersensitivity to the active medication or to any of the excipients of the study medications; prolactin-dependent tumors; phaeochromocytoma; concomitant use of medications that could induce torsade de pointes; use of levodopa; and known risk of narrow-angle glaucoma.

2.2. Study medications

Patients were consecutively randomised to amisulpride, aripiprazole or olanzapine [8], and all doses were within the recommended dosing ranges: amisulpride, 50–1200 mg/day; aripiprazole, 5–30 mg/day; and olanzapine, 2.5–20 mg/day. The mean doses for the three antipsychotics were: amisulpride, 396.9 mg (SD = 206.9); aripiprazole, 14.6 mg (SD = 7.0); and olanzapine, 12.3 mg (SD = 3.8). Doses were converted to defined daily dose (DDDs): the assumed average maintenance dose per day for a medication used for its main indication in adults, developed by the World Health Organization's Collaborating Centre for Drug Statistics Methodology [33].

2.3. Assessment

Baseline demographics included age, education, marital status, employment status, age at onset of psychosis and age at onset of drug use. Psychosis-related symptomatology was assessed on eight measurement occasions using the Structured Clinical Interview for the PANSS (SCI-PANSS) [34] by raters certified by the PANSS Institute: at baseline and at Weeks 1, 3, 6, 12, 26, 39 and 52. The positive subscale score on the PANSS was used as the main outcome variable in the analyses. The Clinical Global Impression-Severity of Illness (CGI-S) [35] scale was used to assess overall symptom severity. The CAUS (Clinical Alcohol Use Scale) was used to determine alcohol use levels [36].

Information about drug use was collected by the Drug Use Disorders Identification Test (DUDIT) [37,38] and by the Clinical Drug Use Scale (CDUS) [39]. The psychometric properties of the DUDIT are evaluated in an 11-item questionnaire developed to screen individuals for drug use during the last 12 months [38]. The DUDIT includes lists of different illegal drugs and prescription medications, has good predictive validity, as suggested by high sensitivity and specificity [34,40,41], and collects data in the following areas: frequency of administration of specific drugs [e.g. cannabis, cocaine, amphetamines, opiate (heroin, opium), GHB, etc.] and prescribed medications used illegally [e.g. benzodiazepines, analgesics (opioid-analgesics, ketamine), steroids]; drug-related problems; and drug dependence symptoms.

Further validation of current drug use was by means of the CDUS [39], which has demonstrated high sensitivity and specificity. The CDUS rates clinically significant drug use over the last 6 months and the last 2 weeks on a scale from 1 to 5 (1 = abstinence, 2 = use without impairment, 3 = abuse, 4 = dependence, 5 = severe dependence).

Patients were classified into two categories at baseline: the Drug Use and No Drug Use groups. The DUDIT and CDUS in combination were used to evaluate frequent/regular drug use in the last 6 months, including drug misuse/dependence and alcohol misuse/dependence. First, patients confirming drug use in the last 12 months (n = 90), in addition to the type of drugs, were detected using the DUDIT. Then, the CDUS was used to select from this group those patients who had used drugs in the last 6 month; finally, only patients confirming frequent/regular drug use were included (n = 53); the period of 6 months was chosen to take into consideration that drug metabolites can persist for longer than 2 weeks and may cause changes lasting for several months [11]. Patients using only alcohol or tobacco were not included in the Drug Use group, in order to better examine the effects of drugs influencing dopamine levels and potentially interacting with antipsychotics. Substance use disorders are underdiagnosed in psychiatric patients in Norway [42]. To avoid false negative drug users, we chose to use a more objective assessment of drug use, and in line with this the Drug Use group also included some patients not diagnosed with substance use disorders. After careful consideration, we chose to use a more objective assessment of drug use and patients diagnosed with and without substance use disorders were considered as the Drug Use group.

2.4. Statistical analysis

IBM SPSS version 26 [43] and Mplus version 8.5 [44] were used for the statistical analyses. Baseline descriptive statistics were calculated using means and standard deviations for continuous variables and frequencies for categorical variables. Group differences of continuous variables were analysed using t-tests and analysis of variance (ANOVA). Bivariate analyses of categorical variables were tested using chi-square tests. Levels and changes in the PANSS positive subscale score were analysed using latent growth curve models (LGC) [45]. These models included estimated time scores between the first and last observation [46]. The first measurement point of time was constrained to zero in order to fix the intercept to the baseline, and the last measurement was set to 1, constituting 100% change. The other time factors were estimated, showing the percentage of total linear change on each measurement occasion. The model is linear but also incorporates non-linear changes. Multi-sample analysis modelling was used to test the differences between the Drug Use and No Drug Use groups. The aripiprazole and olanzapine medication groups were added to the model, for comparison with the reference medication amisulpride (contrast code variables). The age variable and age × medication interaction terms were added in order to test possible medication differences over different levels of age in the Drug Use and No Drug Use groups. The age variable was grand mean centred in order to reduce possible multicollinearity between main- and interaction effects, and ease the interpretation of the intercept level in the interaction model [47,48]. Residual variances and the relations between age and intercept were constrained to be identical over the two groups in order to reduce complexity. The model constraints function was used to test differences in parameter values between and within the two groups. The data coverage for PANSS scores for the 144 patients over the eight occasions were (%): 100, 90, 84, 70, 60, 48, 44 and 44. Full information maximum likelihood (FIML) was used to use all available data in the LGC models, which assumes missingness to be randomly distributed, which is a better strategy than using listwise deletion methods assuming missing completely at random [49].

3. Results

3.1. Drug use

At baseline, 37.9% of patients (n = 53) reported frequent/regular drug use in the last 6 months before inclusion. Cannabis was the main drug used (84.9%, n = 48), either in combination with other drugs or alone. The next most frequently used drugs were amphetamine-type stimulants (45.3%, n = 24): amphetamine (32.1%, n = 17), methamphetamine (13.2%, n = 7) or cocaine (13.2%, n = 7). The further distribution of drugs was 26.4% (n = 14) for sedatives, 18.9% (n = 10) for hallucinogens, 3.8% (n = 2) for opiates, 3.8% (n = 2) for analgesics, 3.8% (n = 2) for solvents, 3.8% (n = 2) for GHB and 1.9% (n = 1) for anabolic steroids. The use of several drugs was predominant. The mean age for drug use debut was 19.9 years (median = 19), with an age range of 10–49 years. The majority of cannabis users (54.0%) had started using cannabis between the ages of 16 and 18 years. The mean debut ages and age ranges for the different drugs were: cannabis, 17.9 (10−31) years; amphetamine-type stimulants, 20.6 (10–35) years; cocaine, 21.3 (15–31) years; hallucinogens, 20.2 (14–29) years; opiates, 25.2 (12–49) years; solvents, 15.7 (6–23) years; gamma-hydroxybutyrate (GHB), 24.3 (18–35) years; anabolic steroids, 20.2 (16–25) years; sedatives, 21.6 (6–46) years; and analgesics, 21.1 (10–35) years.

3.2. Demographic and clinical group differences

The demographic and clinical characteristics by group are presented in Table 1.

The data show that 77.4% were males in the Drug Use group, which is significantly more than in the No Drug Use group (56.3%, $\chi^2 = 6.35$, p = .012). Mean and median ages in the total population at baseline were 31.7 and 26.8 years, respectively. The patients were younger in the Drug Use group than in the No Drug Use group. The mean age at psychosis onset was also statistically significantly different between the groups. At baseline, patients in the Drug Use and No Drug Use groups had almost identical PANSS positive subscale scores. There were no statistically significant differences regarding patients diagnosed with substance use disorders (n = 17) at baseline for the PANSS outcome variables compared to other patients in the Drug Use group. Only three patients were diagnosed with alcohol use disorder alone without other drug use. At inclusion, 38.9% of the patients (n = 56) were antipsychotic medication naïve. In the Drug Use group, 35.8% of patients were antipsychotic naïve compared to 42.5% in the No Drug Use group, however these differences were not statistically significant. In the Drug Use

Table 1
Descriptive clinical and demographic data (percent or mean and SD at baseline).

	Total N = 144			Drug Use at baseline N = 53			No Drug Use at baseline N = 87			
	%	*Mean*	*SD*	*%*	*Mean*	*SD*	*%*	*Mean*	*SD*	*P*
Female	35.4			22.6			43.7			*
Age		31.7	12.7		27.2	8.4		34.3	13.9	**
Age at psychosis onset		24.5	8.9		22.1	6.4		26.0	9.9	*
Education (years)		12.3	2.8		11.8	2.1		12.5	3.2	
Living alone	42.0			37.3			50.0			
Employed	26.5			19.2			31.0			
Drug use	37.9			100.0			0.0			**
Subst. abuse/dependence [a]	19.0			100.0			0.0			**
Cannabis use	32.1			84.9			0.0			**
Cannabis only	15.7			41.5			0.0			**
Tobacco smoking	59.0			80.9			32.5			**
Alcohol abuse/dependence [a]	9.0			11.8			6.0			
Diagnosis										
Schizophrenia F20	58.3			54.7			60.9			
Schizotypal F21	1.4			0.0			2.3			
Delusional disorder F22	14.6			13.2			16.1			
Acute and transient F23	12.5			17.0			10.3			
Schizo-affective F25	6.9			9.4			3.4			
Other nonorganic F28	0.7			0.0			1.1			
Unspecified nonorganic F29	5.6			5.7			5.7			
Antipsychotic naïve	38.9			35.8			42.5			
Antipsychotic DDD		1.06	0.5		1.09	0.5		1.03	0.5	
Amisulpride (*N* = 52)	36.1			24.5			43.7			
Mean dose (mg/d)		396.9	206.9		407.6	201.5		392.9	211.5	
Serum level (nm/l)		485.9	392.0		531.4	364.4		463.1	410.8	
Aripiprazole (*N* = 51)	35.4			45.3			29.9			
Mean dose (mg/d)		14.6	7.0		14.6	6.3		14.0	7.1	
Serum level (nm/l)		564.8	470.1		417.8	309.1		671.7	540.1	
Olanzapine (*N* = 41)	28.5			30.2			26.4			
Mean dose (mg/d)		12.3	73.8		11.6	4.3		12.1	4.1	
Serum level (nm/l)		196.2	251.7		189.1	295.7		200.7	233.8	
PANSS Positive		21.2	4.8		21.1	4.6		21.1	4.8	
PANSS Negative		17.8	6.1		17.4	5.4		18.1	6.3	
PANSS Gen.psychopath.		39.4	8.5		39.9	8.7		38.7	8.2	
PANSS Total		78.4	15.8		78.5	14.8		77.8	16.1	
CGI Score		5.0	0.8		5.1	0.8		4.9	0.8	

N = number in the total sample; SSD = schizophrenia spectrum Disorders F20 – F29; Antipsychotic naïve = no previous exposure to antipsychotic medication; Medical DDD = Defined Daily Dosage; Drug Use = based on the Clinician Drug Use Scale; PANSS = Positive, Negative, General psychopathology and Total Syndrome Scale; CGI = Clinical Global Impression severity of illness scale. [a] Abuse/dependence defined by a score ≥ 3 on the CDUS (Clinical Drug Use Scale) and CAUS (Clinical Alcohol Use Scale); *Significant at the 0.05 level; **Significant at the 0.001 level.

group, 24.5% of patients were treated with amisulpride, 45.3% with aripiprazole and 30.2% with olanzapine. These frequencies were not statistically significantly different from the frequencies in the No Drug Use group. Mean DDDs over all visits and medication types were not statistically significantly different in the Drug Use group and in the No Drug Use group. Antipsychotic medication serum levels were generally compatible with the prescribed doses, with no differences between the groups. Among the patients, 38.2% (n = 55) received additional antipsychotic medication. 32.6% (n = 47) benzodiazepines/anxiolytics, 9.3% (n = 13) antidepressants and 4.2%, (n = 6) mood stabilisers, with no group differences at baseline or any follow-up point. Two patients in the drug use group received additional opioid substitution treatment. The time point for when participants dropped out of the study was not statistically different in the Drug Use group (mean visit: M = 5.7; SD = 2.1) compared to the No Drug Use group (mean visit: M = 6.0; SD = 2.3; p = .454). We also examined the follow-up data but differential analysis by medication type was not possible due to drop-outs. However, an expected general effect emerged, suggesting further reduction in the Drug Use group during the follow-up period.

3.3. Drug use versus no drug use group differences in symptom change

There were some observed group differences for the PANSS positive symptom change at certain time points (see Fig. 1 for estimated values) but the mean differences between the groups for baseline level and change over time were not found to be statistically significant (see Table 2). A subgroup analysis for the Drug Use group and patients who used cannabis only (n = 22) on the PANSS positive symptom outcome measure had similar results (data not presented).PANSS = Positive and Negative Syndrome Scale.

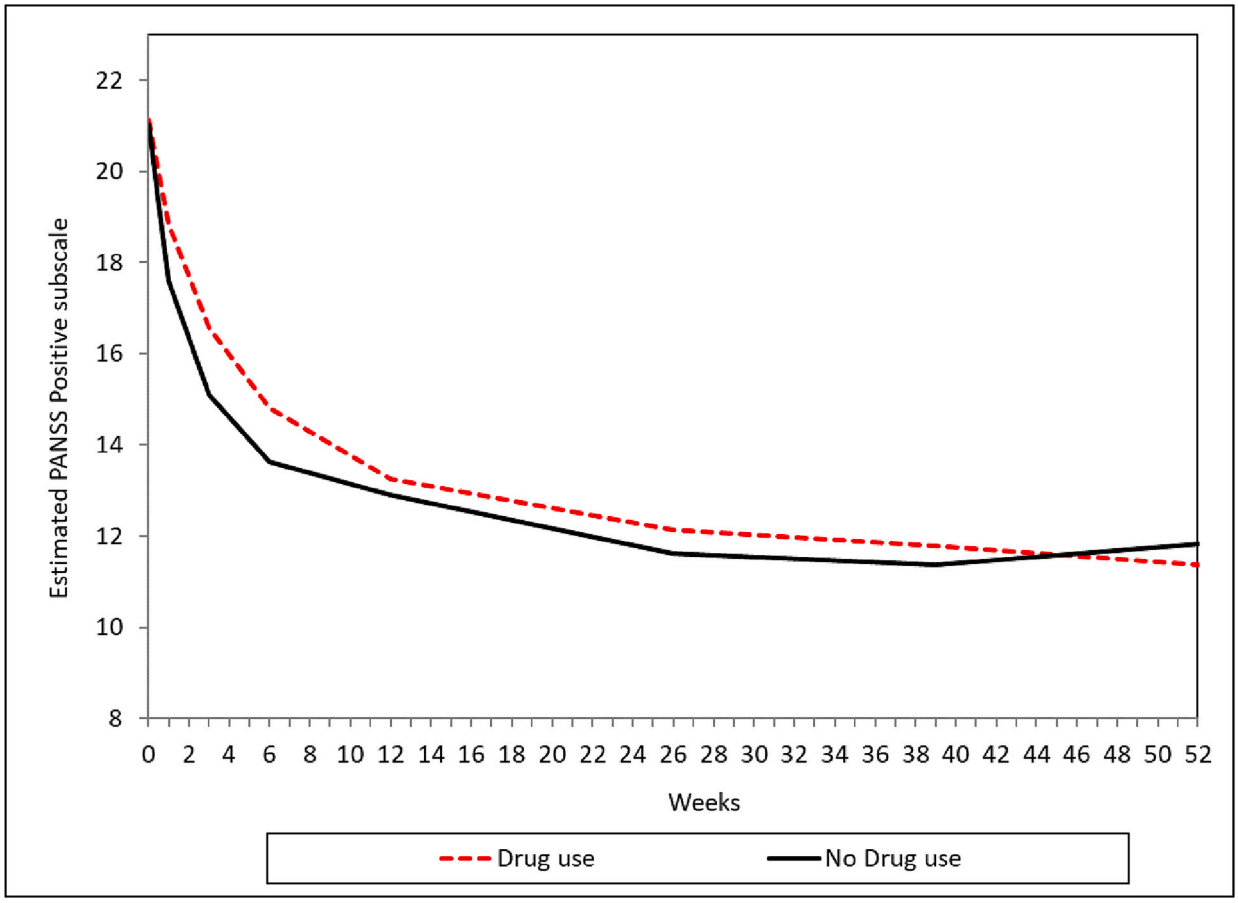

Fig. 1. Estimated Positive and Negative Syndrome Scale (PANSS) positive subscale score by time for the Drug Use and No Drug Use groups.

Table 2
Estimated PANSS Positive subscale score (baseline, overall change and percent change per week) for the total sample and the Drug use and No Drug Use group.

		Total sample		Drug Use		No Drug Use		Difference	
PANSS Positive		*est*	*P*	*est*	*P*	*est*	*P*	*est*	*P*
Baseline (I)	Mean	21.11	<0.001	21.11	<0.001	21.02	<0.001	−0.10	0.908
	SD	4.20	<0.001	3.97	<0.001	4.32	<0.001		
Change (S)	Mean	-9.25	<0.001	−9.76	<0.001	−9.19	<0.001	0.57	0.681
	SD	4.81	<0.001	5.32	0.006	5.01	<0.001		
% change per weeks									
	0	0.0	–	0.0	–	0.0	–		
	1	31.4	<0.001	23.2	<0.001	37.1	<0.001	13.9	
	3	57.7	<0.001	46.6	<0.001	64.6	<0.001	18.0	
	6	76.5	<0.001	64.7	<0.001	80.5	<0.001	15.8	
	12	88.3	<0.001	80.7	<0.001	88.4	<0.001	7.7	
	26	100.7	<0.001	92.1	<0.001	102.0	<0.001	9.9	
	39	102.1	<0.001	95.6	<0.001	105.0	<0.001	9.4	
	52	100.0	–	100.0	–	100.0	–		

est = model estimate.
P-values mean change are testing if change is statistical significant.
P-values of *SD* test for statistical significant individual difference in baseline level and change.

3.4. Drug use versus no drug use group differences in symptom change between the antipsychotics

The conditional multi-sample model, including the medication variables together with the mean centred age of 31.7 years and the medication × age interaction terms, is represented in Table 3.

Differences in the PANSS positive subscale score changes between patients in the Drug Use and No Drug Use groups were first estimated for patients treated with amisulpride; however, the difference was found to be only marginally statistically significant (−4.16, $p = .053$), with the Drug Use group displaying the greatest symptom reduction.

In the Drug Use group we found that the levels of change in the PANSS positive subscale score were dependent on age; furthermore, at the mean age we found a smaller statistically significant reduction for the PANSS positive subscale score in patients treated with aripiprazole and olanzapine compared to amisulpride. The results also showed that older patients had greater reductions during the amisulpride treatment period relative to younger patients. There were statistically significant

Table 3
Estimated changes in PANSS positive subscale score dependent on medication, age and age × medication in the Drug Use and No Drug Use groups ($n = 140$).

	Drug Use $N = 53$			No Drug Use N = 87			Difference	
Predictors of change	*b*	*β*	*P*	*b*	*β*	*P*	Δ	*P*
Amisulpride [a]	−13.71	–	<0.001	−9.54	–	<0.001	−4.16	0.053
Aripiprazole	4.82	0.41	0.007	0.91	0.09	0.467	3.92	0.074
Olanzapine	5.38	0.42	0.004	0.45	0.04	0.724	4.94	0.027
Age (centered)	−0.61	−0.86	0.034	−0.04	−0.12	0.511	−0.57	0.053
Age x Aripiprazole	0.67	0.81	0.023	−0.01	−0.02	0.877	0.68	0.026
Age x Olanzapine	0.74	0.35	0.028	0.01	0.01	0.917	0.73	0.038

PANSS = Positive and Negative Syndrome Scale; *b* = unstandardized regression coefficient;
β = standardized regression coefficient (beta); Δ = difference between percent change at each measurement occasion; Age = Centered at mean level (32 years); [a] estimated slope level (α) for the reference medication (amisulpride).

interactions for aripiprazole and olanzapine between medication and age in the Drug Use group, but in the opposite direction and with almost equal magnitudes. This means that differentiation by age was only relevant for patients treated with amisulpride, and not for the other two study medications. The olanzapine-treated group had the smallest decrease in the PANSS positive subscale score in older patients. We found no statistically significant interactions between age and medication in the No Drug Use group. These results are illustrated in Fig. 2 and show that the Drug Use group had a greater reduction in PANSS positive subscale scores, depending on age, than patients in the No Drug Use group. In the Drug Use group treated with amisulpride, older patients did not have different antipsychotic medication serum levels compared to those treated with olanzapine or aripiprazole. No other statistically significant relationships were found between symptom level and change in the Drug Use and No Drug Use groups.PANSS = Positive, Negative, General psychopathology and Total Syndrome Scale.

The mean age: 32 years. The figure shows estimated change for younger patients, defined as 5 years below mean, and older patients, defined as 5 years above mean. Thus, the different age levels are not different age groups, only different age levels used in the expected

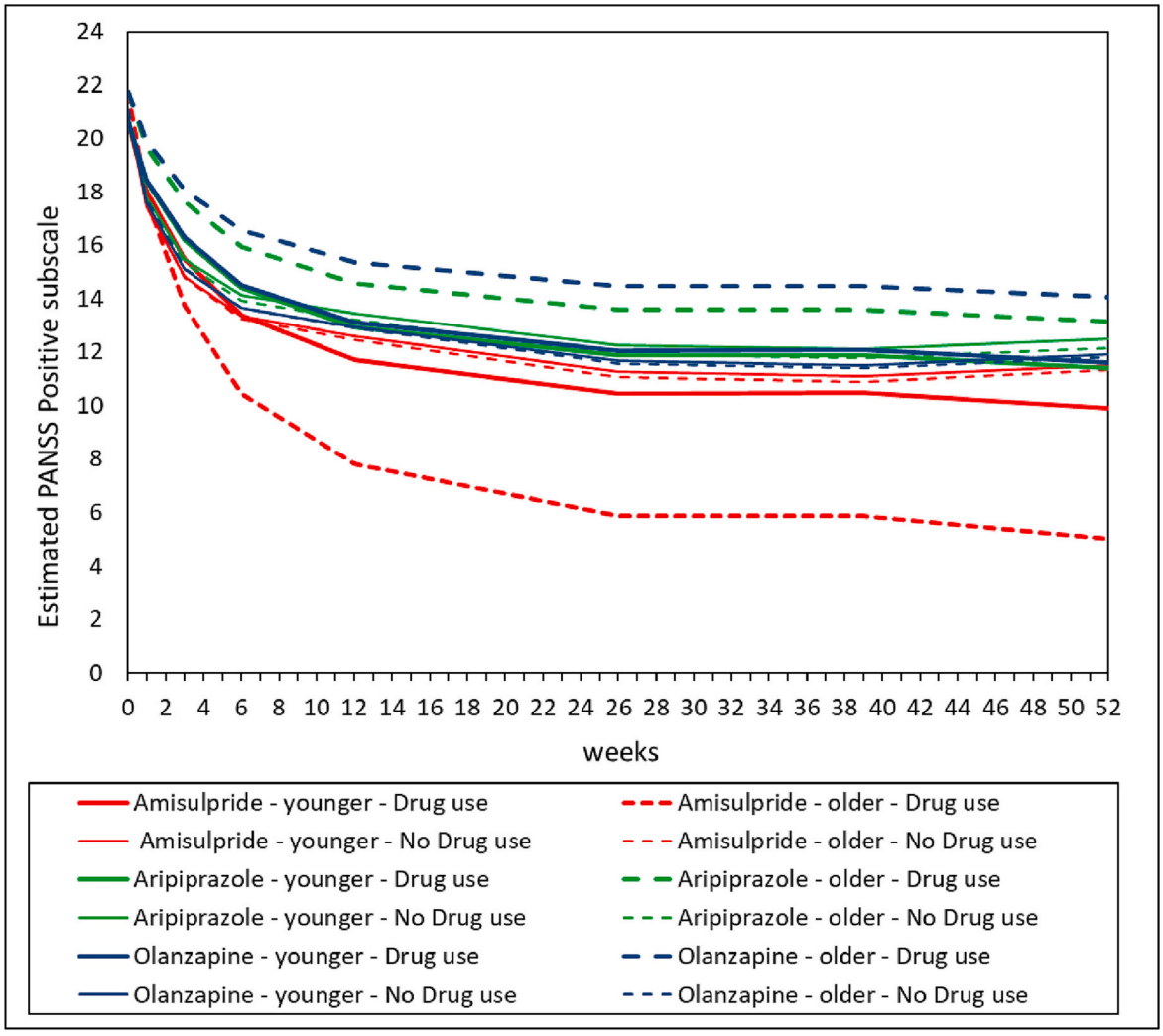

Fig. 2. Estimated PANSS Positive subscale score by time, age, Drug use and No Drug use group for amisulpride, aripiprazole and olanzapine.

trajectory values.

4. Discussion

This secondary explorative study shows that drug use over the last twelve months does not significantly affect the overall effectiveness of amisulpride, aripiprazole and olanzapine in patients with SSD. Patients with drug use showed a similar reduction in PANSS positive symptoms to patients without drug use. A subgroup of older patients with drug use, however, showed more improvement of positive symptoms when treated with amisulpride.

Supporting previous findings [19,50], cannabis, amphetamine-type stimulants and cocaine were among the most commonly used drugs and these were predominantly polyconsumed [51]. Adolescents were the most common consumers and the early versus late age windows for the onset of use varied for different drugs. Underpinning this [52], the majority of patients in our study began their drug use at age 15–18 years. Important neurodevelopmental processes take place throughout adolescence, therefore drug use and its associated lifestyle adjustments may result in biochemical alterations of brain function [53]. Drug use has been suggested as an important risk factor for developing SSD [54]. Our study showed the age of SSD onset to be significantly lower for patients with drug use compared to patients without drug use, supporting previous findings [55,56]. Other studies have suggested a difference in neuronal dynamics, with less stable cognitive deficits in patients with drug use compared to patients without drug use [57,58]. An increased severity of the psychopathology, especially positive symptoms, has been described in patients with comorbid drug use [50,59]. Patients in our study with drug use presented similar PANSS positive and negative symptoms to patients without drug use, in line with some research that found no differences between the groups [60].

Antipsychotic medication effectiveness studies have reported inconsistent findings, with some indicating a decreased response in patients with drug use compared to patients without drug use [27,28], or similar responses to antipsychotic medications [26]. The current study replicated the findings of the latter, in line with previous results from our research group [25], showing a distinct reduction in positive psychotic symptoms irrespective of whether drugs were used or not. The overall findings of antipsychotic effectiveness are also consistent with the CATIE study [26], reporting comparable responses to antipsychotic medications in patients consuming drugs in relation to symptom reduction and global improvement.

In our study three antipsychotics were chosen for their different pharmacological profiles. All are functional antagonists at striatal D2 receptors, but olanzapine additionally has a broad affinity for various other neurotransmitter receptors [61,62] whereas amisulpride principally acts on dopaminergic receptors alone [63,64]; aripiprazole also exhibits a broad receptor profile but is a partial D2 agonist [61]. Treatment with amisulpride seems to be effective for treating addictive behaviour and psychotic symptoms in patients with substance use disorders, such as cocaine, heroin and cannabis, [65], with improvement shown in psychological and social functioning for this patient group. Olanzapine has been shown to reduce both positive and negative psychotic symptoms and improve functional outcomes [26], with a subjective well-being effect for patients with cannabis use [66], but efficacy for patients with cocaine use lacks support [67]. Aripiprazole leads to fewer cravings for cocaine [68] and may be useful for treating patients with cannabis-induced psychoses [69]; however, a lack of reduction in subjective methamphetamine craving has also been found [70]. Overall, it appears that patients with drug use fare better if they obtain treatment with antipsychotic medications [26,65,66,71].

Finally, we found some group differences in the pattern of PANSS positive symptom change affected by age. The results suggest that amisulpride-treated older patients in the Drug Use group had a greater reduction of the PANSS positive subscale score over the total study period of 52 weeks. The smallest reduction was found in older patients with drug use treated with olanzapine or aripiprazole. An open question that has not been answered by this study is whether drug use or the disease duration with advanced age may cause different brain responsiveness.

It may be assumed that age-related processes, drug-induced neurotoxicity and neurodegeneration can individually lead to different effectiveness. However, with increasing age, the pharmacodynamic processes, receptor density and activity are altered, resulting in a greater variability of clinical response [72,73]. There have been few studies published on the effectiveness of amisulpride treatment in chronic/subchronic schizophrenia patients or the elderly population [74]. The results of our study support the need for further clinical investigations in a larger heterogeneous population of patients in order to assess treatment effectiveness in young and elderly patients. Moreover, further studies may show the advantages of amisulpride for the treatment of specific subpopulations, particularly elderly patients, given the chronic nature of SSD and the influence of comorbid drug use.

There were no differences in the dose of antipsychotics needed for the two groups, nor in relation to additional medications: benzodiazepines, antidepressants, mood stabilisers or additional antipsychotic medication. A major challenge in all prospective studies is the number of patients lost to follow-up. Our results showed no significant difference between the Drug Use and No Drug Use group in relation to the timing of dropout from the study.

4.1. Strengths and limitations

This study, to our knowledge, is the first to compare the effectiveness of amisulpride, aripiprazole and olanzapine in patients diagnosed with SSD, with and without drug use, over a follow-up period of 52 weeks. The study population was consecutively recruited from a psychiatric department and outpatient clinics and represents the heterogeneity of patients with SSD and drug use through a naturalistic design, which increases the variability and generalisability of this study. A further strength of the randomised design is the minimization of systematic group differences and selection bias in relation to potential confounders and important clinical variables, including the type of substance and severity of use.

The limitations of this study include evaluating drug use without measuring the frequency, quantity or duration of drug use, which may affect outcomes. Unfortunately, urine tests were not systematically used and it cannot be ruled out that symptom reduction was affected by changes in drug use. In agreement with other findings that substance use disorders are underdiagnosed in psychiatric patients [75], only 17 of the patients were diagnosed with a substance use disorder as a secondary diagnosis (ICD-10). With a larger sample size, the potential differential effectiveness in patients with substance use disorders could be examined in more detail. Finally, we did not have repeated information on drug use, which could have changed during the follow-up.

5. Conclusion

The current study showed that drug use does not significantly affect the overall effectiveness of amisulpride, aripiprazole and olanzapine in patients with SSD. These findings are directly relevant for clinical practice and treatment choices; patients with SSD and drug use should be offered the same pharmacological treatments as recommended for patients without drug use. In a subgroup of older patients with drug use, however, amisulpride may be a particularly suitable choice.

Author contribution

RA participated in designing the study, drafted the manuscript, participated in the data collection and participated in the data analyses. EJ participated in designing the study, was a principal investigator, participated in the data collection, contributed to the analyses and

interpretations of the data and helped draft the manuscript. RG provided statistical analyses and made substantial contributions to the analysis and interpretation of the data. RAK, EK, IS, FF and IJ participated in the data collection and helped draft the manuscript. SKR participated in the data collection, was a principal investigator and helped draft the manuscript. MR participated in the data collection, was a principal investigator and helped draft the manuscript. *E*-ML co-designed the study, participated in the data collection, contributed to the analyses and interpretations of the data and helped draft the manuscript.

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ClinicalTrials.gov Identifier: NCT01446328. The supporters had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or the preparation, review or approval of the manuscript.

Ethical standards

The study was approved by the Regional Committees for Medical and Health Research Ethics 2010/3387, the Norwegian Medicines Agency in Norway (11/01070), and by the Etikkommission der Medizinische, Universität Innsbruck, and the Federal Office for Safety in Health Care (BASG) in Austria. The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration of Competing Interest

None.

Data availability

According to Norwegian law, data sharing requires approvals from the Regional Committees for Medical and Health Research Ethics, and from the Data Protection Officer at Haukeland University Hospital, on the basis of specific research proposals.

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