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Impact of childhood trauma on antipsychotic effectiveness in schizophrenia spectrum disorders: A prospective, pragmatic, semi-randomized trial

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ABSTRACT

Antipsychotic medications are generally effective in ameliorating psychotic symptoms in schizophrenia spectrum disorders (SSDs). Identifying predictors associated with poor treatment response is important for a personalized treatment approach. Childhood trauma (CT) may have a general and differential effect on the effectiveness of different types of antipsychotics in SSDs. The Bergen-Stavanger-Trondheim-Innsbruck (BeSt InTro) study is a pragmatic, researcher-initiated, semi-randomized trial. The present study aimed to investigate symptom change (the Positive and Negative Syndrome Scale) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment (amisulpride, aripiprazole and olanzapine) by group (CT/no CT). Participants (n = 98) with diagnoses within the schizophrenia spectrum (F20–29 in the International Classification of Diseases — 10th Revision) were randomized to receive amisulpride, aripiprazole or olanzapine, and for this study categorized into groups of none and low CT, and moderate to severe CT according to thresholds defined by the Childhood Trauma Questionnaire Short-Form manual. CT in SSDs predicted an overall slower treatment response and less antipsychotic effectiveness after 26 weeks of treatment, which was statistically nonsignificant at 52 weeks. Secondary analyses showed a differential effect of CT related to type of antipsychotic medication: patients with SSDs and CT who received olanzapine showed less antipsychotic effectiveness throughout 52 weeks of treatment. The intention-to-treat and per-protocol analyses were convergent. Our findings indicate that in patients with SSD and CT, delayed response to antipsychotics could be expected, and a longer evaluation period before considering change of medication may be recommended.

1. Introduction

Antipsychotic medication is generally effective in ameliorating psychotic symptoms, and is to date the most researched, recommended, and widely used treatment for schizophrenia spectrum disorders (SSDs) (McGregor et al., 2018). However, antipsychotic treatment response shows heterogeneity: about one third of patients treated with first-line (non-clozapine) antipsychotics, did not show a satisfactory response (Demjaha et al., 2017). Identifying predictors associated with poor treatment response in SSDs is important for a more targeted, personalized treatment approach. Previously identified clinical predictors of poor response to antipsychotics has been male sex, younger age at illness debut, longer duration of illness and untreated psychosis, worse premorbid functioning, as well as psychiatric comorbidity, and lack of response to treatment in the early phase of illness (Carbon and Correll, 2014; Cavalcante et al., 2020; Zhu et al., 2017). It has been reported that

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Table 1
Mean (SD) clinical and demographic characteristics by CT and no CT groups and antipsychotic medication subgroups.

	No CT group (n = 43)	CT group (n = 55)	Statistics (t, f or chi)	p-Value	Amisulpride (n = 32)	Aripiprazole (n = 31)	Olanzapine (n = 35)	Statistics (f or chi)	p-Value	Total (n = 98)
Age, years	31.2 (13.2)	30.8 (12.4)	0.170	0.864	30.5 (11.5)	30.8 (12.8)	31.5 (13.9	0.05	0.964	30.95 (12.68)
Men	32/43 (74%)	31/55 (56%)	3.426	0.064	21/32 (66%)	19/31(61%)	23/35 (66%)	0.177	0.915	63/98 (64%)
Caucasian	35/43 (81%)	45/55 (82%)	0.003	0.957	29/32 (91%)	23/31 (74%)	28/35 (80%)	2.932	0.231	80/98 (81%)
Years of education	12.7 (3)	11.9 (2.7)	1.313	0.192	13.0 (3.1)	11.6 (2.6)	12.1 (2.8)	2.20	0.116	12.2 (2.8)
Living alone (yes) (n = 92)	15/43 (35%)	24/55 (44%)	0.693	0.405	15/31 (48%)	9/29 (31%)	15/32 (47%)	2.251	0.324	39/98 (42%)
Employed (yes) (n = 93)	14/43 (33%)	12/55 (22%)	1.728	0.189	12/32 (37%)	6/31 (19%)	8/35 (23%)	3.036	0.219	26/98 (28%)
DDD (n = 94)	1.10 (0.52)	1.08 (0.44)	0.204	0.838	1.01 (0.47)	1.04 (0.54)	1.21 (0.38)	1.80	0.170	1.09 (0.47)
DUP, weeks (n = 53)	40.6 (79.0)	80.9 (121.5)	1.456	0.152	66.1 (118.1)	46.2 (82.4)	74.8 (115.5)	0.32	0.727	63.4 (106.2)
Psychosis onset age, years (n = 69)	23.8 (7.1)	23.3 (9.7)	0.244	0.807	24.9 (10)	20.9 (5.6)	24.1 (8.9)	1.26	0.289	23.5 (8.6)
Diagnosis										
Schizophrenia	19/43 (44%)	35/55 (64%)	3.690	0.055	18/32 (56%)	16/31 (52%)	20/35 (57%)	0.228	0.892	54/98 (55%)
Schizotypal	0/43 (0%)	2/55 (4%)	1.596	0.206	1/32 (3%)	0/31 (0%)	1/35 (3%)	0.950	0.622	2/98 (2%)
Delusional disorder	7/43 (16%)	6/55 (11%)	0.604	0.437	3/32 (9%)	5/31 (16%)	5/30 (14%)	0.673	0.714	13/98 (13%)
Brief psychotic disorder	8/43 (19%)	6/55 (11%)	1.167	0.280	8/32 (25%)	2/31 (6%)	4/35 (11%)	4.787	0.091	14/98 (14%)
Schizo-affective disorder	5/43 (12%)	2/55 (4%)	2.323	0.127	2/32 (6%)	4/31 (13%)	1/35 (3%)	2.558	0.278	7/98 (7%)
Other psychotic disorder	1/43 (2%)	0/55 (0%)	1.293	0.256	0/32 (0%)	1/31 (3%)	0/35 (0%)	2.184	0.336	1/98 (1%)
Unspecified psychotic disorder	3/43 (7%)	4/55 (7%)	0.003	0.955	0/32 (0%)	3/31 (10%)	4/35 (11%)	3.731	0.155	7/98 (7%)
Smoking (yes) (n = 90)	21/40 (52%)	36/50 (72%)	3.638	0.056	20/30 (67%)	19/29 (65%)	18/31 (58%)	0.574	0.751	57/90 (63%)
CAUS (abuse or dependence) (n = 93)	2/40 (5%)	7/53 (13%)	1.175	0.185	3/32 (9%)	5/29 (17%)	1/32 (3%)	3.473	0.176	9/93 (10%)
CDUS (abuse or dependence) (n = 93)	10/40 (25%)	10/53 (19%)	0.507	0.476	9/32 (28%)	5/29 (17%)	6/32 (19%)	1.287	0.525	20/93 (21%)
Antipychotics naive	18/43 (42%)	16/55 (29%)	1.736	0.188	10/32 (31%)	13/31 (42%)	11/35 (31%)	1.049	0.592	34/98 (34%)
PANSS total	76.2 (18.4)	79.9 (13.5)	−1.142	0.255	78.1 (17.7)	76.5 (12.4)	79.8 (17.1)	0.35	0.707	78.2 (15.9)
PANSS positive	20.7 (4.8)	21.9 (4.9)	−1.242	0.216	21.5 (4.7)	21.4 (5.3)	21.2 (4.8)	0.03	0.975	21.4 (4.9)
PANSS negative	16.6 (6.6)	18 (5.4)	−1.159	0.249	16.5 (5.5)	17.0 (6.0)	18.4 (6.3)	0.86	0.426	17.3 (5.9)
PANSS general	38.9 (10.1)	40 (7.2)	−0.599	0.550	40.1 (10.2)	38.1 (6.4)	40.2 (8.8)	0.59	0.555	39.5 (8.6)
CGI	5 (0.8)	5.2 (0.7)	−0.992	0.323	5.03 (0.93)	5.13 (0.62)	5.17 (0.78)	0.27	0.086	5.1 (0.1)
GAF (n = 97)	35.6 (6.4)	35.7 (9.4)	−0.037	0.970	38 (9.2)	34 (6.4)	35 (8.4)	2.15	0.122	35.6 (8.2)
CDSS (n = 91)	5.7 (5.1)	9 (5.2)	−3.071	0.002*	8.2 (5.8)	6.1 (4.4)	7.9 (5.6)	1.38	0.257	7.5 (5.4)
BMI (n = 86)	24.4 (4.6)	25.7 (5.7)	−1.192	0.236	24.7 (5.3)	26.3 (5.0)	24.5 (5.3)	1.00	0.372	25.1 (5.2)
CTQ-SF sum	31.1 (4.2)	54.3 (13.6)	−10.812	0.000*	41.7 (16.1)	45.5 (16.7)	45.0 (14.4)	0.57	0.566	44.1 (15.6)
Emotional abuse	6.4 (1.7)	13.3 (4.7)	−9.107	0.000*	9.7 (5.5)	10.5 (4.9)	10.7 (4.8)	0.38	0.682	10.3 (5.1)
Physical abuse	5.3 (0.6)	8.5 (4.1)	−5.071	0.000*	6.3 (2.3)	7.9 (4.6)	6.9 (3.1)	1.87	0.160	7.1 (3.5)
Sexual abuse	5.0 (0)	7.4 (4)	−3.948	0.000*	6.3 (2.2)	6.9 (4.6)	5.9 (2.3)	0.95	0.389	6.3 (3.2)
Emotional neglect	8.1 (2.7)	15.1 (4.6)	−8.988	0.000*	11.3 (5.5)	12.1 (4.6)	12.6 (5.5)	0.53	0.589	12.0 (5.2)
Physical neglect	6.3 (1.5)	9.9 (3.7)	−6.041	0.000*	8.1 (3.5)	8.0 (2.9)	8.9 (3.9)	0.63	0.537	8.4 (3.5)
Other psychotropics (n = 33)			8.589	0.572				16.416	0.69	
Zopiclone	5 (15.2%)	4 (12.1%)			3 (27%)	4 (36%)	2 (18%)			9 (27.3%)
Diazepam	3 (9.1%)	3 (9%)			2 (18%)	2 (18%)	2 (18%)			6 (18.2%)
Oxazepam	5 (15.2%)	3 (9%)			3 (27%)	1 (9%)	4 (36%)			8 (24.2%)
Setraline	0 (0%)	1 (3%)			0 (0%)	1 (9%)	0 (%)			1 (3%)
Biperiden	0 (0%)	1 (3%)			0 (0%)	0 (0%)	1 (9%)			1 (3%)
Venlafaxin	1 (3%)	1 (3%)			1 (9%)	0 (0%)	1 (9%)			2 (6.1%)
Pregabaline	0 (0%)	1 (3%)			1 (9%)	0 (0%)	0 (%)			1 (3%)
Paroxetine	1 (3%)	0 (0%)			0 (0%)	1 (9%)	0 (%)			1 (3%)
Fluoxetine	0 (0%)	1 (3%)			0 (0%)	1 (9%)	0 (%)			1 (3%)
Lorazepam	0 (0%)	2 (6.1%)			1 (9%)	1 (9%)	0 (%)			2 (6.1%)

Note. N = 98 unless otherwise specified. DDD = defined daily dose of antipsychotic medication. CT = childhood trauma. CTQ-SF = childhood trauma questionnaire short-form. PANSS = positive and negative syndrome scale. CGI = clinical global impression scale. GAF = global assessment of functioning. CDSS = Calgary depression scale for schizophrenia. BMI = body mass index. Other psychopharmaca registered at baseline.

* p level significant at 0.05.

childhood trauma (CT) can affect the outcome of pharmacotherapy for other mental disorders (Nikkheslat et al., 2020; Williams et al., 2016). Possibly, CT could influence the general and differential response by type of antipsychotic medication in SSDs, although the literature is scarce.

CT, including sexual, physical, and emotional abuse, and physical and emotional neglect, has been found to be associated with factors implicated in treatment-resistant schizophrenia, such as variability in treatment response, and poor adherence to treatment, especially to antipsychotics (Hassan and De Luca, 2015). CT is commonly reported in SSDs: Almost 70% of patients with SSDs reported moderate to severe CT, as compared to 34% in patients with other mental health disorders (Mørkved et al., 2017). A dose-response relationship between CT and psychosis symptoms (Sahin et al., 2013) has been shown, and a meta-analysis found CT to be associated with a three-fold risk of developing SSDs (Varese et al., 2012). Moreover, CT may be associated with worse outcome from psychosis (Trauelsen et al., 2016).

There is however a paucity of research on CT in relation to antipsychotic treatment effectiveness in SSDs. CT was more frequently reported in first episode psychosis (FEP) non-responders to antipsychotic treatment after 12 weeks, as compared to FEP responders (Misiak and Frydecka, 2016). CT exposure in SSDs was associated with a slower treatment response, higher dosages of antipsychotic treatment, and less likelihood of remission compared to those with low CT exposure (Kilian et al., 2020). Misiak et al. (2017) has suggested that the preliminary findings regarding CT and antipsychotics could imply that SSDs patients exposed to CT have a more severe biological dysregulation underlying a less favorable treatment outcome.

Moreover, CT has been suggested to be related to SSDs through sensitization of the dopamine system (Dahoun et al., 2019), elevating central dopaminergic neurotransmission (Valenti et al., 2011). A stress-induced activation of the HPA-axis could lead to dopamine sensitization in mesolimbic areas, and increased stress-induced striatal dopamine release (Van Winkel et al., 2008). Stimulation of D_2 receptors across brain regions are implicated in the pathophysiology of SSDs and has been supported by the observed antipsychotic effect of dopamine receptor antagonists (Popovic et al., 2019). As for older antipsychotic drugs, the newer atypical antipsychotics (AAPs) are functional striatal dopamine D_2 antagonists, however different AAPs are heterogeneous in terms of affinity for other dopaminergic and non-dopaminergic receptor systems (Conley and Kelly, 2005). Theoretically, CT could exert a differentiated effect on antipsychotic treatment response depending on which type of AAP is used: Olanzapine has greater affinity for serotonin 5-HT_{2A} than for dopamine D_2 receptors, and amisulpride binds selectively to D_2 and D_3 receptors. Aripiprazole is a partial D_2 agonist, thus functioning as an antagonist during a hyperdopaminergic state and agonistically during hypodopaminergica, often referred to as a dopamine system stabilizer (Conley and Kelly, 2005).

More knowledge on CT in relation to antipsychotic effectiveness is needed to facilitate a more targeted, personalized treatment approach. This is the first study to investigate CT in relation to SSDs and antipsychotic treatment effectiveness over 52 weeks in three AAPs (amisulpride, aripiprazole, and olanzapine). We aimed to compare symptom change from baseline as a measure of the treatment effectiveness in SSDs with CT and without CT. We further aimed to examine whether CT predicted a differentiated pattern of symptom change depending on type of AAP: amisulpride, aripiprazole and olanzapine.

2. Methods and material

2.1. Study design

This study is a part of the Bergen, Stavanger, Innsbruck, and Trondheim (BeSt InTro) study, Haukeland University Hospital, Bergen, Norway. The BeSt InTro study is a researcher-initiated, head-to-head, semi-randomized multi-site prospective study comparing amisulpride, olanzapine and aripiprazole in SSDs. The BeSt InTro was approved in Norway by the Regional Committee for Medical Research Ethics (2010-3387) and the Norwegian Medicines Agency, and in Austria by the ethics committee at the Medical University of Innsbruck, and the Federal Office for Safety in Health Care (BASG) and registered as a clinical trial 10/03/2011 (NCT01446328). Clinical monitoring according to ICH-GCP was done by the Department of Research and Development, at the Haukeland University Hospital in Norway, as well as by the Austrian equivalent: Clinical Trial Centre at the Medical University Innsbruck. Participants for the current sub-study were recruited at the Medical University in Innsbruck, Innsbruck, Austria (n = 12); Stavanger University Hospital, Stavanger, Norway (n = 8); and Haukeland University Hospital, Bergen, Norway (n = 78). All gave informed consent to participate.

2.2. Sample

The current sample consisted of 98 patients with SSDs, 63 (64%) males, mean age 30.9 years (SD = 12.7 years). Thirty-four (35%) were naïve to antipsychotics, meaning no lifetime exposure to antipsychotics before inclusion in the study (demographic and clinical information in Table 1).

Table 1.

Participants were required to meet diagnostic criteria for SSDs in the range F20–29 of the ICD-10 (World Health Organization, 1992): F20 Schizophrenia (n = 54), F21 Schizotypal disorder (n = 2), F22 Persistent delusional disorder (n = 13), F23 Acute and transient psychotic disorders (n = 14), F25 Schizoaffective disorder (n = 7), F 28 Other psychotic disorder (n = 1) or F29 Unspecified nonorganic psychosis (n = 7), as determined by the Structural Clinical Interview for Axis I Disorders (SCID; Spitzer et al., 1992), be ≥18 years of age, be able to understand the native language, and score ≥ 4 on at least one of the following items in the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987): delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6) or unusual thought content (G9). Exclusion criteria were organic psychosis or psychosis due to psychoactive substance use; however psychoactive substance use was not an exclusion criterion. Hypersensitivity to the active substance or to any of the excipients of the study drugs qualified for exclusion, as did prolactin-dependent tumors, phaeochromocytoma, and concomitant use of medications which could induce torsade de pointes, use of levodopa, and known risk of narrow-angle glaucoma. Suicidal ideation was not defined as reason for exclusion.

2.3. Study drug and randomization

The study participants were randomly assigned to receive orally administered amisulpride (n = 37; 37.7%), aripiprazole (n = 34; 34.7%) or olanzapine (n = 27; 27.5%) (see Table 1 for demographic and clinical information by medication group). Dosages were decided upon by the patient and his or hers attending physician and was within the following ranges: Amisulpride 50–1200 mg/d, aripiprazole 5–30 mg/d, and olanzapine 2.5–20 mg/d.

Study-independent statisticians from the University of Bergen prepared the randomization by means of computer-generated sequences of the three study drugs in random order (Johnsen et al., 2020). Each randomized sequence of study drugs was put in a sealed envelope, and the attending physician offered the first drug in the sequence whenever a new participant was included. If the first study drug was not chosen (tolerability issues or previous inefficacy), the reason was registered and

Table 2
Number of patients in the ITT and PP-groups by visit number.

	Medication group	Baseline	Week 1	Week 3	Week 6	Week 12	Week 26	Week 39	Week 52
ITT group	Amisulpride	32	30	30	31	25	19	20	19
	Aripiprazole	31	29	28	24	20	17	11	9
	Olanzapine	35	33	33	33	28	19	20	21
	Total	98	92	91	88	73	55	51	49
PP group	Amisulpride	37	36	35	35	30	24	25	23
	Aripiprazole	34	30	31	28	21	16	11	9
	Olanzapine	27	26	25	25	22	15	15	17
	Total	98	92	91	88	73	55	51	49

Note. ITT = intention to treat group, PP = per protocol group. ITT constitutes the randomization drug, whereas the PP group shows the medication actually used.

the next study drug in the sequence was offered, and repeated if the second drug was not eligible (Johnsen et al., 2020). Previous experience with the drug was not reason for rejection, due to the pragmatic design. The research team assessing the participants was blind to the randomization, whereas the treatment allocation was open to the patient and the clinical team. The participants were instructed not to reveal the study drug to the research team. The first study drug in the randomized sequence constituted the intention to treat (ITT) group, whereas the drug chosen for treatment was the basis for the per-protocol (PP) analyses.

2.4. Measurement

2.4.1. Childhood trauma

The Childhood Trauma Questionnaire Short-Form (CTQ-SF) is a 28-item self-report questionnaire screening for five subtypes of childhood trauma: childhood sexual, physical, and emotional abuse, and physical and emotional neglect (Bernstein et al., 2003). Each subscale consists of five items scored on a five-point Likert scale ranging from 1 (*never true*) to 5 (*very often true*), summarized into an overall CTQ-SF sum score ranging from 25 to 125. Three items make up the Minimization-denial subscale, a validation scale, which was not used in the present study. The CTQ-SF has shown good internal consistency, test-retest reliability, and excellent internal reliability for the total scale, good to excellent internal reliability for the subscales as well as good sensitivity and specificity (Bernstein et al., 2003; Dovran et al., 2013). For the present study, the overall reliability estimate for the CTQ-SF was high: Cronbach's $\alpha = 0.92$.

2.4.2. Other measures

The Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) is a clinician administered clinical interview measuring symptom severity in SSDs (Kay et al., 1987). The PANSS is categorized into the positive, negative, and general psychopathology subscales. The items are scored on a 7-point Likert scale, ranging from 1 (*absent*) to 7 (*extreme*), and the range of PANSS scores is 30–210 points. Strong psychometric properties related to reliability, validity and sensitivity have been reported (Leucht et al., 2005). All raters were trained and certified by the PANSS Institute (panss.org).

The Calgary Depression Scale for Schizophrenia (CDSS) was used for rating depression symptoms in our sample of SSDs (Addington et al., 1993). Alcohol and drug use was assessed by means of the Clinician Alcohol Use Scale (CAUS) and Clinician Drug Use Scale (CDUS) (Drake et al., 1990; Mueser et al., 1995). Severity of illness was assessed by means of the Clinical Global Impression — Severity of Illness scale (CGI-S), a brief, clinician-rated instrument where the severity of the illness is rated on a Likert scale ranging from 1 to 7 (Guy, 1976).

3. Procedure

The PANSS was administered at baseline and at all follow-up points: weeks 1, 3, 6, 12, 26, 39 and 52 corresponding to visits 1, 2, 3, 4, 5, 6, 7 and 8. The CTQ-SF was administered at the 6-weeks follow-up when participants were more likely to be in a clinically stable phase, thus increasing assessment validity. The SCID diagnostic interview was administered as early as possible to confirm the diagnoses, whereas the other measurements (i.e., CAUS, CDUS) were collected within the first three months of study inclusion.

4. Statistical analyses

Categorical and continuous variables were analyzed by means of chi-square tests and *t*-tests in STATA. Measures are presented as means (*M*) and standard deviations (*SD*), or as number (*n*) and percentages (%). A *p*-level of < 0.05 was considered statistically significant for all analyses.

The CTQ-SF scores were categorized into none, low, moderate and severe abuse or neglect, according to the threshold scores from the CTQ-SF manual (Bernstein and Fink, 1998). A dichotomous variable was created, grouping none and low levels of CT (no CT group; $n = 43$), for comparison to a group of moderate to severe levels of CT (CT group; $n = 55$) (Bernstein and Fink, 1998), for the purpose of examining SSDs CT and no CT group differences in psychosis symptom change.

Statistical models were fitted using R (version 4.0.2: https://www.r-project.org), and by using the statistical packages mice version 3.1-152 (multiple imputation) and nlme version 3.13.0 (LME-models). The primary analyses were based on the ITT groups, as determined in the pre-study protocol. LME models were chosen for its ability to account for dependency in the data due to repeated measures, and for handling missing data (assumed missing at random). The models were fitted to the PANSS total and subscale scores to examine symptom change from baseline to 52 weeks in the CT and no CT groups. Secondarily, analyses were performed to examine symptom change for the CT and no CT groups within each medication subgroup (olanzapine, amisulpride and aripiprazole). We included years of education, gender, age of illness onset, duration of untreated psychosis (DUP), previous exposure to antipsychotics, dosage of antipsychotic medication, and baseline psychosis symptoms as fixed effects in all models. A random intercept for each individual was included as a random effect to account for dependencies in the data. Dosages of medication were converted to Defined Daily Doses (DDD), meaning the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/atc_ddd_index/). Multiple imputation was used on demographic and clinical variables included as covariates in the LME models in data to keep all participants in the analyses. Missing PANSS values were not imputed. Models were also fitted using no imputed values, i.e., removing patients with incomplete data, this did not alter the results. Data on sample size by visit number and medication group is provided in Table 2.

5. Results

5.1. Clinical and demographic data

Mean age at baseline was 31.0 years ($SD = 12.7$), and mean age of illness onset was 23.5 years ($SD = 8.6$). The mean DUP was about two years ($M = 105$ weeks, $SD = 244.2$). When examining the CTQ-SF scores,

Table 3
LME-ITT models examining symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by SSDs group (CT and no CT).

Antipsychotic medication	Outcome		Baseline[b] (M, SE)	1 week	3 weeks	6 weeks	12 weeks	26 weeks	39 weeks	52 weeks
Overall	PANSS total scores	No CT	78.2 (15.9)	66.7 (4.5)	59.9 (4.5)	56.5 (4.5)	54.1 (4.6)	48.5 (4.7)	47 (4.8)	49 (4.8)
		CT	78.2 (15.9)	69.5 (4.7)	64.1 (4.7)	62.2 (4.7)	60.3 (4.7)	62.3 (4.9)	55.5 (5)	54.9 (5.1)
		Δ[a]	NA	2.8 (3.2) [0.389]	4.2 (3.3) [0.213]	5.7 (3.3) [0.083]	6.2 (3.5) [0.093]	13.8 (3.8) [<0.001]*	8.6 (4) [0.03]*	6 (4) [0.112]
	PANSS positive	No CT	21.3 (4.9)	17.4 (1.4)	14.8 (1.4)	12.9 (1.4)	12.3 (1.5)	10.1 (1.5)	10.1 (1.6)	10.7 (1.5)
		CT	21.3 (4.9)	18.5 (1.5)	16 (1.5)	14.7 (1.5)	13.1 (1.5)	13.5 (1.6)	12.8 (1.6)	12.9 (1.6)
		Δ[a]	NA	1.1 (1) [0.265]	1.3 (1) [0.172]	1.8 (1) [0.077]	0.8 (1.1) [0.484]	3.4 (1.2) [0.005]*	2.7 (1.2) [0.035]*	2.2 (1.2) [0.097]
	PANSS negative	No CT	17.4 (6)	16.2 (1.8)	15.1 (1.8)	15.5 (1.8)	14.8 (1.8)	14.1 (1.9)	13.6 (1.9)	13.8 (1.9)
		CT	17.4 (6)	15.7 (1.9)	15.4 (1.8)	16.3 (1.9)	17.4 (1.9)	17 (1.9)	16 (2)	14 (2)
		Δ[a]	NA	−0.5 (1.1) [0.657]	0.3 (1.1) [0.757]	0.7 (1.1) [0.48]	2.6 (1.2) [0.035]*	3 (1.4) [0.031]*	2.4 (1.4) [0.077]	0.1 (1.4) [0.946]
	PANSS general psychopathology	No CT	39.5 (8.6)	33.1 (2.3)	30 (2.3)	28 (2.3)	27 (2.3)	24.4 (2.4)	23.2 (2.5)	24.5 (2.5)
		CT	39.5 (8.6)	35.2 (2.4)	32.6 (2.4)	31.1 (2.4)	29.7 (2.4)	31.5 (2.5)	26.7 (2.5)	28.1 (2.6)
		Δ[a]	NA	2.1 (1.7) [0.231]	2.7 (1.7) [0.138]	3.1 (1.7) [0.064]	2.8 (1.9) [0.159]	7.2 (2.1) [0.001]*	3.6 (2.1) [0.085]	3.6 (2.1) [0.084]
Amisulpride	PANSS total scores	No CT	78.1 (17.7)	67.7 (7.4)	61.6 (7.4)	55 (7.4)	53.7 (7.5)	48 (7.7)	44.4 (7.6)	48.6 (7.7)
		CT	78.1 (17.7)	67 (6.4)	62.6 (6.5)	55.8 (6.5)	54.1 (6.5)	53 (7.1)	51.7 (7.1)	49.7 (7.1)
		Δ[a]	NA	−0.8 (4.6) [0.866]	1 (4.7) [0.839]	0.7 (4.6) [0.986]	0.5 (4.9) [0.932]	4.9 (5.5) [0.337]	7.2 (5.5) [0.193]	1.1 (5.5) [0.863]
	PANSS positive	No CT	21.5 (4.7)	17.8 (2.2)	14.8 (2.2)	12.5 (2.2)	11.5 (2.2)	9.48 (2.3)	9 (2.3)	9.81 (2.3)
		CT	21.5 (4.7)	16.4 (2)	14 (2)	12.5 (2)	10.8 (2)	11.4 (2.3)	10.9 (2.3)	9.65 (2.3)
		Δ[a]	NA	−1.4 (1.4) [0.327]	−0.8 (1.5) [0.566]	0.1 (1.4) [0.907]	−0.7 (1.6) [0.65]	1.9 (1.8) [0.289]	1.9 (1.8) [0.284]	−0.1 (1.8) [0.945]
	PANSS negative	No CT	16.5 (5.5)	15.8 (4.5)	14.8 (4.5)	14.8 (4.5)	15.4 (4.5)	13.5 (4.5)	13.1 (4.5)	14.4 (4.5)
		CT	16.5 (5.5)	15.6 (3.8)	15.2 (3.8)	13.8 (3.8)	16 (3.8)	13.7 (4)	15.2 (4)	12.8 (4)
		Δ[a]	NA	−0.2 (1.9) [0.903]	0.4 (1.9) [0.892]	−1 (1.9) [0.612]	0.7 (2) [0.792]	0.2 (2.2) [0.919]	2.2 (2.2) [0.34]	−1.6 (2.2) [0.426]
	PANSS general psychopathology	No CT	40.1 (10.2)	33.8 (4.1)	31.8 (4.1)	27.6 (4.1)	26.6 (4.1)	24.5 (4.2)	22.1 (4.2)	24.3 (4.2)
		CT	40.1 (10.2)	34.9 (3.5)	33.6 (3.6)	29.7 (3.6)	27.5 (3.6)	28.3 (4)	25.5 (3.9)	27.4 (3.9)
		Δ[a]	NA	1 (2.5) [0.684]	1.7 (2.6) [0.499]	2.1 (2.5) [0.402]	0.9 (2.7) [0.752]	3.8 (3) [0.235]	3.4 (3) [0.267]	3.1 (3.1) [0.352]
Aripiprazole	PANSS total scores	No CT	76.3 (12.5)	66 (15.4)	64.3 (15.8)	65.4 (15.4)	62.9 (15.5)	52.7 (15.5)	58.9 (15.8)	56.5 (15.5)
		CT	76.3 (12.5)	65.4 (16.4)	66.2 (16.4)	63.8 (16.5)	56.7 (16.4)	57.4 (16.7)	57.7 (16.8)	49.1 (18.1)
		Δ[a]	NA	−0.7 (7.4) [0.93]	1.8 (7.5) [0.804]	−1.7 (7.7) [0.836]	−6.2 (8.1) [0.422]	4.6 (8.4) [0.552]	−1.3 (9.6) [0.912]	−7.4 (11.6) [0.497]
	PANSS positive	No CT	21.2 (5.2)	17 (7.4)	15.7 (7.5)	15.4 (7.4)	14.7 (7.4)	11.5 (7.4)	13.7 (7.5)	12.1 (7.5)
		CT	21.2 (5.2)	19.2 (7.8)	17.9 (7.8)	15.7 (7.8)	12.3 (7.9)	11.7 (7.9)	14.2 (7.9)	11.1 (8.2)
		Δ[a]	NA	2.2 (2.9) [0.465]	2.2 (2.9) [0.427]	0.4 (3) [0.92]	−2.4 (3.2) [0.434]	0.3 (3.3) [0.892]	0.5 (3.5) [0.906]	−1 (4.1) [0.813]
	PANSS negative	No CT	17.1 (6.1)	15.5 (10.1)	15.2 (10.1)	16.7 (10.1)	15 (10.1)	14.2 (10.1)	16.1 (10.1)	15 (10.1)
		CT	17.1 (6.1)	14.1 (10.2)	15.6 (10.2)	17.2 (10.3)	17.3 (10.1)	19.1 (10.2)	19 (10.2)	14.3 (10.7)
		Δ[a]	NA	−1.4 (2.2) [0.537]	0.4 (2.2) [0.857]	0.5 (2.4) [0.865]	2.2 (2.5) [0.372]	4.9 (2.7) [0.067]	2.8 (3.2) [0.382]	−0.8 (4) [0.864]
	PANSS general psychopathology	No CT	38 (6.4)	32.3 (8.3)	32.1 (8.6)	32.1 (8.3)	32 (8.4)	26.2 (8.4)	28.2 (8.6)	28.5 (8.4)
		CT	38 (6.4)	33 (9)	33.5 (9)	32.2 (9.1)	28.3 (9)	27.8 (9.2)	26.3 (9.2)	25 (9.9)
		Δ[a]	NA	0.7 (4.2) [0.877]	1.4 (4.3) [0.766]	0.1 (4.5) [0.979]	−3.7 (4.5) [0.401]	1.6 (4.7) [0.756]	−1.9 (5.3) [0.705]	−3.5 (6.3) [0.548]
Olanzapine	PANSS total scores	No CT	79.8 (17.1)	68.1 (9.4)	55.6 (9.6)	53.5 (9.4)	47.9 (9.4)	49 (10.1)	43 (9.8)	44.4 (9.8)
		CT	79.8 (17.1)	73.8 (8.1)	62.7 (8)	63.8 (8)	64.6 (8)	70 (8.5)	56.1 (8.4)	58.7 (8.3)
		Δ[a]	NA	5.7 (5.5) [0.304]	7.1 (5.6) [0.224]	10.4 (5.7) [0.065]	16.7 (6) [0.005]*	21 (7.4) [0.003]*	13.1 (6.8) [0.046]*	14.4 (6.8) [0.031]*
	PANSS positive	No CT	21.2 (4.9)	17.6 (2.7)	14.2 (2.8)	12.4 (2.7)	11.4 (2.7)	11 (3)	9.67 (2.9)	11.1 (2.9)
		CT	21.2 (4.9)	19 (2.3)	15.7 (2.3)	15 (2.3)	14.5 (2.3)	16 (2.5)	12.9 (2.4)	14.3 (2.4)
		Δ[a]	NA	1.4 (1.7) [0.416]	1.5 (1.7) [0.393]	2.7 (1.8) [0.109]	3.2 (1.9) [0.077]	5 (2.3) [0.027]*	3.3 (2.1) [0.141]	3.2 (2.2) [0.147]
	PANSS negative	No CT	18.4 (6.3)	15.7 (4)	14 (4.1)	14.3 (4)	12.4 (4)	13.4 (4.2)	11.2 (4.1)	10.7 (4.1)
		CT	18.4 (6.3)	17.7 (3.6)	16.1 (3.5)	18 (3.6)	18.9 (3.5)	18.7 (3.7)	16 (3.7)	15.2 (3.6)

(*continued on next page*)

Table 3 (*continued*)

Antipsychotic medication	Outcome		Baseline[b] (M, SE)	1 week	3 weeks	6 weeks	12 weeks	26 weeks	39 weeks	52 weeks
		Δ[a]	NA	2 (2.2) [0.344]	2.1 (2.2) [0.31]	3.6 (2.2) [0.092]	6.5 (2.3) [0.007]*	5.2 (2.8) [0.058]	4.7 (2.6) [0.068]	4.4 (2.6) [0.105]
	PANSS general psychopathology	No CT	40.2 (8.8)	34.1 (5.5)	26.8 (5.5)	26.1 (5.5)	23.6 (5.5)	23.8 (5.8)	21.4 (5.6)	21.8 (5.6)
		CT	40.2 (8.8)	37.2 (5.1)	31.1 (5.1)	31.3 (5.1)	31.4 (5.1)	35.4 (5.3)	27.4 (5.3)	29.3 (5.2)
		Δ[a]	NA	3.1 (2.8) [0.267]	4.3 (2.8) [0.123]	5.2 (2.8) [0.068]	7.8 (3) [0.009]*	11.6 (3.7) [0.002]*	6 (3.5) [0.079]	7.4 (3.4) [0.028]*

Note. $N = 98$. LME = linear mixed effects model. ITT = intention-to-treat. PANSS = positive and negative syndrome scale. SSDs = schizophrenia spectrum disorders. CT = childhood trauma. M = estimated mean scores. SE = standard error. NA = not applicable.

* Significant $p < 0.05$.

[a] Difference of change from baseline between CT and no CT groups, (standard deviation), [p value].

[b] Mean PANSS score as baseline values are controlled for in the models. Linear mixed effects analyses included the following variables as fixed effects: years of education, gender, age of illness onset, duration of untreated psychosis, previous exposure to antipsychotics, and dosage of antipsychotic medication (defined daily doses) and baseline PANSS values.

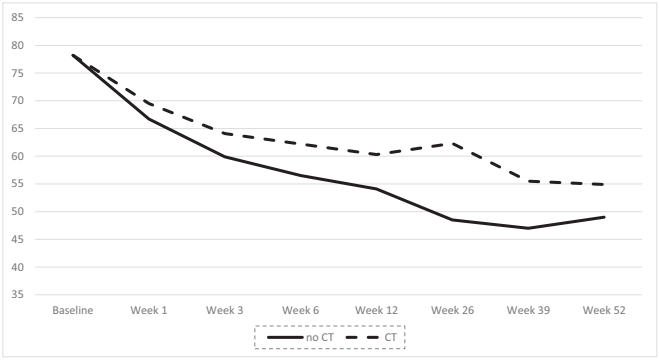

Fig. 1. PANSS total scores by SSDs CT and no CT groups.
Note. SSDs = schizophrenia spectrum disorders. PANSS = positive and negative syndrome scale. CT = childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT. Aggregated data irrespective of medication subgroup.

we found that 55 (56.1%) of the patients reported moderate to severe CT, and 43 (43.9%) reported none or low CT. The CT and no CT groups were not statistically significantly different in alcohol or illegal substance use, nor did the groups differ in terms of psychosis symptoms at baseline, as shown by PANSS total scores, PANSS positive subscale, negative subscale, and general psychopathology subscale scores. There were no significant group differences in other demographic data, except for baseline symptoms of depression. The groups differed in CDSS scores: the CT group reported more depressive symptoms ($M = 9.0$, $SD = 5.2$) as compared to the no CT group ($M = 5.7$, $SD = 5.1$, $t = -3.071$, $p = 0.002$).

The randomization medication was accepted by 81.6% ($n = 80$), while 18.4% ($n = 18$) declined the first medication and was offered next drug in the sequence. Of those that switched medication, 4.1% ($n = 4$) were in the no CT group, and 14.3% ($n = 14$) in the CT group, which was statistically significant (χ^2 (1), 4.119, $p = 0.040$). Mean (SD) [reference range] medication serum level was 610 nmol/L (416) [100–1500] for amisulpride, 762 nmol/L (496) [200−1300] for aripiprazole and 231 nmol/L (288) [30−200] for olanzapine for the Norwegian patients, and the Austrian equivalents were: 203 nmol/L (164) [271–866] for amisulpride, 250 nmol/L (136) [223–781] for aripiprazole and 66.2 (5.30) [62–253] for olanzapine. The mean duration of adherence to antipsychotic treatment during the study was 22.5 weeks ($SD = 20.2$): there were no significant group differences between the no CT group ($M = 25.5$, $SD = 19.0$) and CT group ($M = 20.2$, $SD = 21.4$, $t(84.89) = 1.278$, $p = 0.205$).

5.2. Differences in psychosis symptoms change from baseline to 52 weeks in the CT and no CT groups

The results from the analyses using ITT or PP groups were convergent for all LME models (PP-analyses are provided in the supplementary material). The first LME model examined differences in symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT; see Table 3 and Fig. 1). The following differences in symptom change reached significance: less change in PANSS total scores for the CT group between baseline and 26 ($p < 0.001$) and 39 weeks ($p = 0.030$), PANSS positive subscale scores between baseline and 26 ($p = 0.005$) and 39 weeks ($p = 0.035$), PANSS negative subscale scores between 12 ($p = 0.035$) and 26 weeks ($p = 0.031$) and PANSS general psychopathology subscale scores between baseline and 26 weeks ($p = 0.001$; see Table 4).

5.3. Change in psychosis symptoms by the CT and no CT groups within the three medication groups

Separate LME models examining symptom change (PANSS) for the three antipsychotics from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT (LME-ITT) and PP (LME-PP), respectively, were performed (see Figs. 2 and 3A–C). No significant differences in symptom change between CT and no CT groups emerged for amisulpride or aripiprazole for the LME-ITT or the LME-PP.

For olanzapine, the LME-ITT models showed less change in the CT group for PANSS total scores from baseline to 12, 26, 39 and 52 weeks (p-levels 0.005, 0.003, 0.046 and 0.031, respectively), less change for the CT group in PANSS positive subscale scores from baseline to week 26 ($p = 0.027$), less change for the CT group in PANSS negative subscale scores from baseline to week 12 ($p = 0.007$), and less change for the CT group in PANSS general psychopathology subscale scores from baseline to weeks 12, 26 and 52 (p-levels 0.009, 0.002, and 0.028, respectively). The LME-PP model showed statistically significant comparisons of symptom change: The CT group showed less change in PANSS total scores at weeks 12 ($p = 0.028$) and 26 ($p = 0.050$), PANSS negative subscale scores at weeks 12 ($p = 0.006$) and 39 ($p = 0.026$), and PANSS general psychopathology subscale scores at weeks 6, 12 and 26 (p-level 0.040, 0.022, and 0.026, respectively).

6. Discussion

CT in SSDs predicted a slower treatment response and less antipsychotic effectiveness, which was particularly pronounced after 26 weeks, i.e., midway through the treatment. The differences in symptom change between the CT and no CT groups did however converge and was not statistically significant at 52 weeks, thus showing similarities in

Table 4
LME-PP models examining symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by SSDs group (CT and no CT).

Antipsychotic medication	Outcome		Baseline[b] (M, SE)	1 week	3 weeks	6 weeks	12 weeks	26 weeks	39 weeks	52 weeks
Overall	PANSS total scores	No CT	78.2 (15.9)	66.8 (4.5)	60 (4.5)	56.6 (4.5)	54.1 (4.6)	48.8 (4.7)	47.1 (4.8)	49.1 (4.8)
		CT	78.2 (15.9)	69.2 (4.7)	63.9 (4.7)	61.9 (4.7)	59.7 (4.7)	61.9 (4.9)	55.1 (5)	54.9 (5.1)
		Δ[a]	NA	2.4 (3.3) [0.468]	3.9 (3.2) [0.26]	5.3 (3.3) [0.11]	5.7 (3.5) [0.096]	13.1 (3.8) [0.001]*	8 (4) [0.036]*	5.9 (4.1) [0.129]
	PANSS positive	No CT	21.3 (4.9)	17.5 (1.4)	14.8 (1.4)	13 (1.4)	12.3 (1.5)	10.2 (1.5)	10.2 (1.6)	10.7 (1.5)
		CT	21.3 (4.9)	18.5 (1.5)	15.9 (1.5)	14.7 (1.5)	13 (1.5)	13.5 (1.6)	12.7 (1.6)	12.7 (1.6)
		Δ[a]	NA	1 (1) [0.31]	1.1 (1) [0.244]	1.6 (1) [0.117]	0.6 (1.1) [0.517]	3.2 (1.2) [0.005]*	2.4 (1.3) [0.055]	2 (1.3) [0.106]
	PANSS negative	No CT	17.4 (6)	16.2 (1.8)	15.1 (1.8)	15.6 (1.8)	14.8 (1.8)	14.1 (1.9)	13.7 (1.9)	13.9 (1.9)
		CT	17.4 (6)	15.6 (1.9)	15.5 (1.8)	16.3 (1.9)	17.3 (1.9)	17.1 (1.9)	16 (2)	14 (2)
		Δ[a]	NA	−0.6 (1.1) [0.599]	0.3 (1.1) [0.81]	0.7 (1.1) [0.533]	2.4 (1.2) [0.04]*	3 (1.3) [0.019]*	2.3 (1.4) [0.096]	0.1 (1.4) [0.981]
	PANSS general psychopathology	No CT	39.5 (8.6)	33.2 (2.3)	30 (2.3)	28 (2.3)	27 (2.3)	24.4 (2.4)	23.2 (2.5)	24.5 (2.5)
		CT	39.5 (8.6)	35.2 (2.4)	32.5 (2.4)	31.1 (2.4)	29.4 (2.4)	31.4 (2.5)	26.7 (2.5)	28.2 (2.6)
		Δ[a]	NA	2 (1.7) [0.24]	2.5 (1.7) [0.182]	3.1 (1.7) [0.077]	2.4 (1.8) [0.149]	7 (2) [0.001]*	3.6 (2.1) [0.1]	3.7 (2.2) [0.107]
Amisulpride	PANSS total scores	No CT	81 (17.5)	70.1 (7.1)	63.3 (7.1)	58.5 (7.1)	56.2 (7.4)	48.5 (7.6)	46.7 (7.5)	50.5 (7.6)
		CT	81 (17.5)	67.8 (6.3)	60.4 (6.4)	58.2 (6.5)	56.9 (6.5)	60.5 (6.8)	54.1 (6.8)	57.9 (7)
		Δ[a]	NA	−2.2 (5.3) [0.675]	−2.9 (5.4) [0.621]	−0.3 (5.5) [0.941]	0.7 (5.6) [0.922]	12 (6) [0.056]	7.4 (6.1) [0.282]	7.4 (6.2) [0.277]
	PANSS positive	No CT	21.9 (4.8)	18.4 (2.1)	15.3 (2.1)	13.6 (2.1)	12.4 (2.1)	10.1 (2.2)	10.1 (2.2)	10.7 (2.2)
		CT	21.9 (4.8)	15.9 (1.8)	13.4 (1.9)	12.7 (1.9)	11.6 (1.9)	12.7 (2)	11.8 (2)	12.3 (2)
		Δ[a]	NA	−2.5 (1.6) [0.117]	−1.8 (1.6) [0.248]	−0.8 (1.6) [0.624]	−0.8 (1.7) [0.635]	2.7 (1.8) [0.184]	1.7 (1.8) [0.351]	1.6 (1.9) [0.408]
	PANSS negative	No CT	17.6 (5.9)	16.7 (2.9)	16.1 (2.9)	16.2 (2.9)	16.8 (3)	13.8 (3)	13.6 (3)	14.5 (3)
		CT	17.6 (5.9)	16 (2.5)	15.6 (2.6)	15.4 (2.6)	16.3 (2.6)	16.6 (2.7)	15.6 (2.7)	15 (2.8)
		Δ[a]	NA	−0.7 (1.8) [0.705]	−0.5 (1.8) [0.812]	−0.8 (1.8) [0.64]	−0.5 (2) [0.761]	2.8 (2.1) [0.184]	2 (2.1) [0.355]	0.5 (2.1) [0.788]
	PANSS general psychopathology	No CT	41.5 (8.8)	34.4 (3.9)	31.6 (3.9)	28.7 (3.9)	27.2 (4.1)	24.7 (4.2)	23.1 (4.1)	25 (4.2)
		CT	41.5 (8.8)	35.9 (3.5)	31.4 (3.5)	29.9 (3.6)	29.1 (3.6)	31.2 (3.8)	26.3 (3.8)	30.7 (3.9)
		Δ[a]	NA	1.5 (2.9) [0.611]	−0.2 (2.9) [0.9]	1.2 (2.9) [0.617]	1.9 (3.1) [0.555]	6.6 (3.3) [0.048]*	3.2 (3.3) [0.352]	5.7 (3.4) [0.099]
Aripiprazole	PANSS total scores	No CT	76.5 (13.4)	66.4 (13.7)	63 (13.9)	61.1 (13.7)	59.1 (13.7)	52 (13.8)	55.4 (14.3)	54.7 (14.1)
		CT	76.5 (13.4)	66.9 (20.4)	67 (20.3)	62.2 (20.3)	57 (20.4)	57.4 (20.6)	55.5 (20.6)	43.5 (21.4)
		Δ[a]	NA	0.6 (6.8) [0.934]	4 (6.7) [0.544]	1.1 (6.9) [0.871]	−2.1 (7.4) [0.775]	5.4 (7.8) [0.485]	0.1 (8.8) [0.998]	−11.2 (10.6) [0.295]
	PANSS positive	No CT	21.2 (5.2)	16.6 (5.4)	15.2 (5.5)	13.9 (5.4)	13.9 (5.4)	10.9 (5.5)	12.4 (5.6)	11.2 (5.6)
		CT	21.2 (5.2)	19.9 (7.9)	18.2 (7.9)	15.6 (7.9)	11.9 (7.9)	11.7 (8)	13.3 (8)	8.08 (8.3)
		Δ[a]	NA	3.3 (2.2) [0.146]	3 (2.2) [0.174]	1.7 (2.2) [0.445]	−2 (2.4) [0.392]	0.8 (2.6) [0.779]	0.9 (2.8) [0.752]	−3 (3.5) [0.399]
	PANSS negative	No CT	17 (5.7)	15.7 (5.3)	14.4 (5.4)	15.3 (5.3)	12.7 (5.4)	14.2 (5.4)	15.6 (5.6)	15.3 (5.5)
		CT	17 (5.7)	13.3 (7.5)	14.9 (7.5)	15.8 (7.5)	17.4 (7.5)	17.6 (7.6)	16.5 (7.6)	11.4 (7.9)
		Δ[a]	NA	−2.4 (1.9) [0.222]	0.5 (1.9) [0.813]	0.4 (2) [0.81]	4.7 (2.2) [0.034]*	3.4 (2.4) [0.155]	0.9 (2.8) [0.737]	−3.9 (3.6) [0.276]
	PANSS general psychopathology	No CT	38.3 (8.1)	32.8 (7.5)	32.1 (7.7)	30.5 (7.5)	31.4 (7.6)	26 (7.7)	26.6 (7.9)	27.4 (7.8)
		CT	38.3 (8.1)	34 (11.5)	34.1 (11.5)	31.2 (11.5)	28.2 (11.5)	28.6 (11.6)	26.4 (11.6)	24.8 (12.1)
		Δ[a]	NA	1.2 (3.7) [0.746]	1.9 (3.7) [0.616]	0.8 (3.7) [0.828]	−3.2 (4) [0.394]	2.6 (4.3) [0.519]	−0.3 (4.8) [0.978]	−2.7 (5.9) [0.651]
Olanzapine	PANSS total scores	No CT	76.3 (16.6)	64.7 (13.8)	54.7 (13.9)	51 (13.8)	46.8 (13.8)	49.6 (14.4)	42 (14.1)	43.3 (14.1)
		CT	76.3 (16.6)	73.6 (10)	63.2 (9.8)	64.8 (10)	64.7 (9.8)	66.4 (10.2)	55.2 (10.2)	53.4 (10.1)
		Δ[a]	NA	8.9 (7.3) [0.225]	8.5 (7.8) [0.275]	13.8 (7.6) [0.063]	17.9 (8.3) [0.028]*	16.7 (8.6) [0.05]*	13.2 (8.1) [0.105]	10 (7.9) [0.208]
	PANSS positive	No CT	20.6 (4.7)	17 (5)	14.1 (5)	11.5 (5)	10.8 (5)	11.2 (5.4)	9.24 (5.2)	11.1 (5.2)
		CT	20.6 (4.7)	19.5 (2.7)	15.7 (2.8)	15 (2.8)	14.6 (2.8)	14.9 (3)	12.1 (3.1)	13 (3)
		Δ[a]	NA	2.5 (2.5) [0.323]	1.5 (2.6) [0.597]	3.5 (2.6) [0.239]	3.7 (2.7) [0.199]	3.7 (3.2) [0.267]	2.8 (2.9) [0.39]	1.9 (3) [0.578]
	PANSS negative	No CT	17.6 (6.6)	14.4 (5.3)	13.2 (5.4)	13.1 (5.3)	12.1 (5.3)	13.5 (5.7)	10.8 (5.5)	9.97 (5.5)

(*continued on next page*)

Table 4 (*continued*)

Antipsychotic medication	Outcome		Baseline[b] (M, SE)	1 week	3 weeks	6 weeks	12 weeks	26 weeks	39 weeks	52 weeks
		CT	17.6 (6.6)	19.2 (4.6)	16.5 (4.6)	19 (4.7)	20 (4.6)	18.7 (4.7)	17.5 (4.7)	14.9 (4.7)
		Δ[a]	NA	4.9 (2.8) [0.092]	3.4 (2.7) [0.233]	5.9 (2.8) [0.051]	8 (2.9) [0.006]*	5.2 (3.3) [0.126]	6.7 (3.1) [0.026]*	5 (2.9) [0.091]
	PANSS general psychopathology	No CT	38.2 (8.7)	32.4 (7.5)	26.6 (7.5)	25.4 (7.5)	22.9 (7.5)	24 (7.7)	21.1 (7.6)	21.4 (7.6)
		CT	38.2 (8.7)	36 (5.9)	31.8 (5.7)	32.1 (5.8)	31.3 (5.7)	33.2 (5.9)	26.9 (5.9)	26.5 (5.8)
		Δ[a]	NA	3.5 (3.3) [0.284]	5.2 (3.2) [0.131]	6.7 (3.3) [0.04]*	8.3 (3.4) [0.022]*	9.1 (4.1) [0.026]*	5.8 (3.9) [0.149]	5.1 (3.8) [0.187]

Note. $N = 98$. LME = linear mixed effects. PP = per protocol. PANSS = positive and negative syndrome scale. SSDs = schizophrenia spectrum disorders. CT = childhood trauma. M = estimated mean. SE = standard error. NA = not applicable.

[*] Significant $p < 0.05$.

[a] Difference of change from baseline between CT and no CT groups, (standard deviation), [p value].

[b] Mean PANSS score as baseline values are controlled for in the models. Linear mixed effects analyses included the following variables as fixed effects: years of education, gender, age of illness onset, duration of untreated psychosis, previous exposure to antipsychotics, and dosage of antipsychotic medication (defined daily doses) and baseline PANSS values.

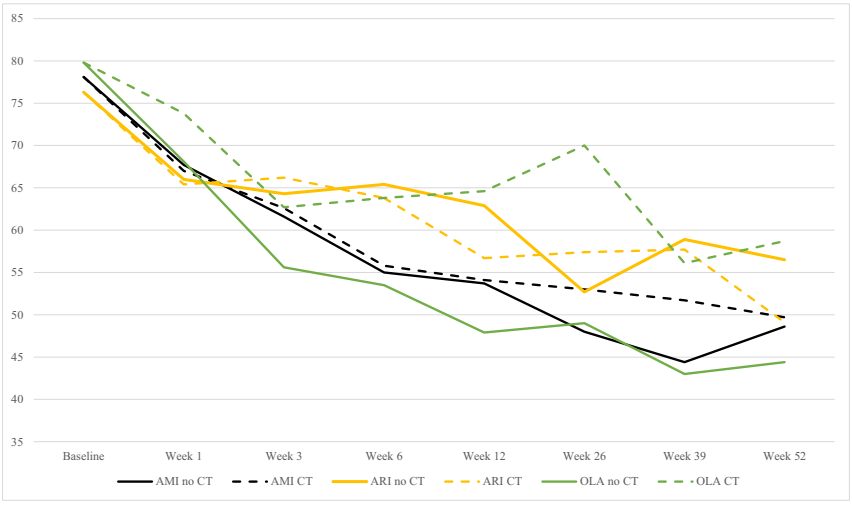

Fig. 2. PANSS total scores by SSDs CT and no CT groups and type of antipsychotic medication.
Note. SSDs = schizophrenia spectrum disorders. PANSS = positive and negative syndrome scale. CT = childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT.

symptom development over time. Secondary analyses showed a differential effect of CT related to type of antipsychotics: SSDs patients that reported CT and received olanzapine showed less antipsychotic effectiveness compared to SSDs patients with no CT receiving olanzapine. This was not observed for amisulpride or aripiprazole. Our results indicate that type of antipsychotic medication, especially the use of olanzapine for SSDs patients reporting CT, could be of relevance in terms of predicting antipsychotic effectiveness the first year after initiation of a new treatment course. We were able to control for several confounding variables that could have influenced the antipsychotic treatment effectiveness: premorbid functioning (education), sex, age of illness onset, DUP, dosage of antipsychotic medication, previous exposure to antipsychotics, and baseline psychosis symptoms.

Our main result that CT was associated with a slower antipsychotic treatment response in SSDs is in line with findings from a recently published study by (Kilian et al., 2020). CT in SSDs predicted a slower response to treatment, but the CT and no CT groups achieved similar symptom levels after 24 months (Kilian et al., 2020). This study did however use the depot formulation of flupentixol (long-acting injectable), an older antipsychotic drug than the AAPs included in the present study. Also, the researchers did not control for DUP or illness duration. Further, CT was found to be related to antipsychotic non-responders in a sample of FEP after 12-months of treatment (Misiak and Frydecka, 2016). Treatment resistance was predicted by CT in a study by (Hassan and De Luca, 2015), where persons with SSDs reporting four or more adverse experiences, were four times more likely to be treatment resistant. Illness onset age and DUP, which our study controlled for, were associated with treatment resistance (Hassan and De Luca, 2015). They did however not report information on type of antipsychotic medication.

Secondary analyses indicated that SSDs patients reporting CT who received olanzapine showed less change in psychosis symptoms after 52 weeks of treatment compared to those with no CT who received olanzapine. The lower treatment effectiveness was particularly visible for overall psychosis symptom load, as well as psychosis-related general psychopathology symptoms related to inner tension/anxiety, manneriisms/postures, motor retardation, unusual thought content, difficulties with attention, insight and impulse control, and social avoidance. Our results on CT and the type of antipsychotic is contrary to Misiak and Frydecka (2016) that reported no differences in terms of type of antipsychotics over 12 weeks in FEP medication-responders compared to FEP non-responders who more frequently reported CT. We have not found any other previous research directly comparable to the present study.

Our results indicate that for SSDs individuals with CT, olanzapine might not be an optimal treatment strategy. The study drugs have distinctly different receptor binding profiles, and it could be speculated that the inferiority of olanzapine might be an effect of CT specifically related to olanzapine and its pharmacological profile. There are

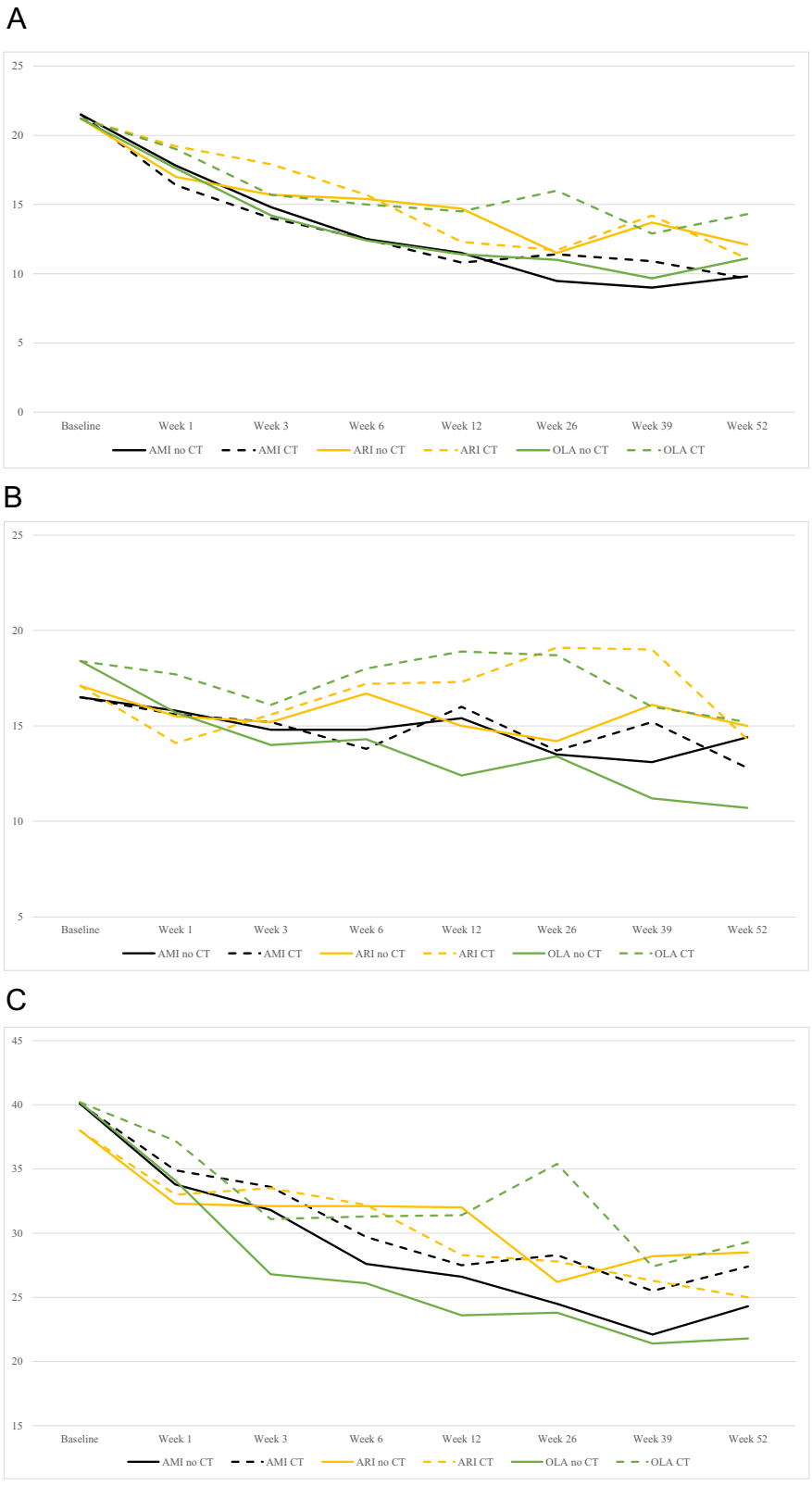

Fig. 3. A. PANSS positive subscale scores by groups (CT and no CT) and antipsychotic medication.
Note. PANSS = positive and negative syndrome scale. CT = childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT.
B. PANSS negative subscale scores by groups (CT and no CT) and antipsychotic medication
Note. PANSS = positive and negative syndrome scale. CT = childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT.
C PANSS general psychopathology subscale scores by groups (CT and no CT) and antipsychotic medication
Note. PANSS = positive and negative syndrome scale. CT = childhood trauma. Estimated symptom change (PANSS) from baseline to 1, 3, 6, 12, 26, 39 and 52 weeks of antipsychotic treatment by group (CT and no CT) based on ITT.

however no overreaching theories explaining the relation between CT and reduced antipsychotic effectiveness in SSDs. Studies indicate that CT could be associated with the development of psychosis through over-activating the HPA-axis which may lead to increased levels of glucocorticoids (Walker et al., 2008). Glucocorticoids have been linked to dysfunctional monoamine and/or dopamine regulation through activation of the mesolimbic dopaminergic circuit. Further, the effect of antipsychotics is described as proportional to the effect on dopamine receptors (Howes and Kapur, 2009). Various AAPs differ in their receptor affinity (e.g., dopamine, serotonin), and one may hypothesize that CT could influence antipsychotic treatment outcomes in SSDs possibly due to a more profound biological dopamine-related

dysregulation in traumatized individuals. A biological dysregulation could potentially be associated with the negative influence of CT on glucocorticoids and dopamine circuits, and possibly also inflammation (Misiak et al., 2017).

There are limitations to consider when interpreting the results. Our sample size is small, which is related to an increased risk for Type II error and of spurious findings. The study might be under-powered to detect differences between the CT and no CT groups: there might be relations between CT and antipsychotic effects that was overlooked. The CTQ-SF scores were dichotomized to create SSDs groups based on level of exposure to CT. As keeping the CT scores continuous could have had advantages in detecting relations between CT and psychosis symptom change, additional analyses were performed (statistics not reported), which did not show statistically significant results when exploring CT continuously, indicating that our approach did not lead to loss of statistical power. The CTQ-SF scores corresponding to low levels of CT were included in the no CT group, as low levels of CT have been found to be quite common in the general population. Using moderate to severe levels of CT as cut-off might therefore provide more sensitivity in measuring CT effects in patient populations (Baker and Maiorino, 2010). Further, data missing not at random cannot be ruled out entirely since we were not allowed to follow participants after dropping out of the study. Concerns have been raised regarding the validity and reliability of retrospective measure of CT in SSDs (Susser and Widom, 2012). However, retrospective reports of CT in SSDs have shown good concurrent and convergent validity, and good stability over a 7-year period (Fisher et al., 2011), and CT reports were not influenced by psychosis symptoms (Simpson et al., 2019). Alcohol or illegal substance abuse was not included in our models, the groups did however not differ in substance or alcohol abuse at baseline.

The BeSt InTro study was designed to mimic clinical practice, increasing generalizability and ecological validity providing treatment of SSDs according to national guidelines (Norwegian Directorate of Health, 2013). The inclusion criteria were broad, and treatment was open label and administered by the psychiatrist in cooperation with the patient. Personnel assessing the patients were uninformed of treatment allocation, ensuring blind rating of effect. Dropout-rates in the BeSt InTro study was comparable to previous research (Johnsen et al., 2020). There is a possibility of treatment discontinuation in SSDs with CT as a consequence of lack of clinically or personally meaningful symptom improvement despite treatment adherence. However, this was not supported by our data, and should be investigated in a larger sample. We investigated the total CTQ-SF scores and not CT subtypes of abuse and neglect, which should be a target for future research (Kilian et al., 2020).

This is, to our best knowledge, the first prospective, pragmatic, and randomized study to investigate the relation between CT and antipsychotic treatment response to three AAPs in SSDs during 52 weeks of treatment. We were able to control for several factors that could have influenced the results. Our results indicated a generally slower antipsychotic treatment response in SSDs exposed to CT compared to those not reporting CT, and SSDs patients with CT showed significantly less treatment effect compared to the no CT SSDs patients when receiving olanzapine. The evidence regarding CT and antipsychotics is to date insufficient to support a specific pharmacological clinical recommendation. We encourage future antipsychotic treatment trials in SSDs to include information on CT exposure and believe that increased knowledge on CT and antipsychotics could be valuable in aiding and facilitating more optimal individualized treatment decision making processes. Our findings indicated that in patients with SSD and trauma experience, delayed response to AAPs could be expected. Given that our results are replicated by other groups, a longer evaluation period before considering change of medication could therefore be in place for patients with CT, compared to those without CT.

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CRediT authorship contribution statement

N. Mørkved: Writing – original draft, Writing – review & editing, Validation, Formal analysis. **E. Johnsen:** Investigation, Writing – original draft, Writing – review & editing, Validation. **R.A. Kroken:** Investigation, Writing – original draft, Writing – review & editing, Validation. **D. Winje:** Writing – original draft, Writing – review & editing, Validation. **T.K. Larsen:** Investigation, Writing – original draft, Writing – review & editing, Validation. **J.C. Thimm:** Writing – original draft, Writing – review & editing, Validation. **M.A. Rettenbacher:** Investigation, Writing – original draft, Writing – review & editing, Validation. **C.A. Bartz Johannesen:** Writing – original draft, Writing – review & editing, Validation, Formal analysis. **E.-M. Løberg:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Validation.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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