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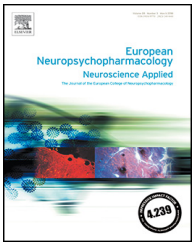

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Efficacy, acceptability and tolerability of antipsychotics in patients with schizophrenia and comorbid substance use. A systematic review and meta-analysis

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Abstract
Patients with schizophrenia and substance related comorbidity or substance induced psychotic disorder are difficult to treat. Although the prevalence of a comorbid substance use is approximately 40% in schizophrenia, such patients are usually excluded from clinical trials. We therefore performed a random-effects meta-analysis of all randomized controlled antipsychotic drug trials in this patient subgroup. We searched multiple databases up to May, 2018. The primary outcome was the reduction of substance user; secondary outcomes were craving, mean reduction of substance use, overall change in schizophrenia symptoms, positive and negative symptoms, response, dropouts, quality of life, social functioning, weight gain, sedation, prolactin, extrapyramidal side effects and use of antiparkinsonian medication. We identified 27 references from 19 RCTs published from 1999 to March 2017 including 1742 participants. The most frequent types of substance abuse were cannabis (8 studies) and cocaine (6 studies) use/dependence. Clozapine was superior to other antipsychotics for reduction of substance use and risperidone to olanzapine for craving. Olanzapine, clozapine and risperidone showed superiority for symptom reduction compared to some other drugs. When reported, results of side-effects followed known patterns. The evidence-base is considerable (19 RCTs), however, firm conclusions cannot be drawn due to small sample sizes of individual studies and insufficient reporting.
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1. Introduction

Schizophrenia is a severe mental disorder affecting more than 21 million people worldwide (Blows, 2016). The World

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Health Organisation (WHO) has ranked the condition as the 8th leading cause of disability among all illnesses worldwide in the age group 15–44 years (World Health Organization, 2002). According to the Global Burden of Disease Study 2015, the number of disability-adjusted life years (DALYs) due to schizophrenia has risen by more than 17% since 2005 (Kassebaum et al., 2016). It has been estimated that approximately 40% of all patients with schizophrenia have an additional comorbid substance use disorder (Hunt et al., 2018), with cannabis (26.2%), alcohol (24.3%), and any illicit substances (27.5%), the latter being the most frequent one, while stimulants are used by the smallest proportion of patients (7.3%) (Hunt et al., 2018).

There are different hypotheses about the reason(s) for the high prevalence of substance abuse in patients with schizophrenia. While the so called "self-medication hypothesis" assumes that patients intend to treat symptoms of the disease or adverse events based on the treatment with antipsychotics (Wilkins, 1997), other theories refer to the role of a better access to substances, genetic factors, or differences in the effect of substances compared to healthy people (D'Souza et al., 2006).

Some types of substance abuse disorder are associated with a causal higher risk of schizophrenia (Andréasson et al., 1987; Miller et al., 2001; Zammit et al., 2002), a poor prognosis of the course of the disease in patients with schizophrenia (van Os et al., 2002) and a higher risk for the development of any other severe disease (Single et al., 1999). Furthermore comorbid substance use disorder can lead to several social problems (Dixon, 1999).

In terms of treatment, the problem of insufficient adherence in patients with schizophrenia is even more severe in patients with a co-occurring substance use disorder (Lacro et al., 2002). Moreover, substance use could negatively interact with the effects of antipsychotic drugs on the brain receptor level. There is extensive evidence about the effects of antipsychotic drugs in general patients with schizophrenia (Leucht et al., 2017,2013). However, the effects of antipsychotic drugs on substance use related outcomes, as well as the efficacy and safety of antipsychotics on schizophrenic symptoms in patients with comorbid substance use disorder, have never been systematically reviewed and summarized. We aimed to fill this gap by a meta-analysis of all randomized controlled trials focusing on this subgroup of patients.

2. Methods

2.1. Participants and interventions

An a priori written study protocol was registered at PROSPERO under the registration number CRD42016052060 and can be found in eAppendix 1 in the Supplement. We included all RCTs of patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder and a diagnosis of substance-related comorbidity (e.g. substance use/abuse) or substance-induced psychosis, however defined in the studies. There were no restrictions on the type of substances. We included 34 different antipsychotics which comprised all second-generation antipsychotics available in the US and/or Europe, and a selection of first-generation antipsychotics, licensed in at least one country, which were considered important based on a survey of international schizophrenia experts (Leucht et al., 2016) (amisulpride, aripiprazole, asenapine, benperidol, brexpiprazole, cariprazine, chlorpromazine, clopenthixol, clozapine, flupenthixol, fluphenazine, fluspirilene, haloperidol, iloperidone, levomepromazine, loxapine, lurasidone, methotrimeprazine, molindone, olanzapine, paliperidone, penfluridol, perazine, perphenazine, pimozide, quetiapine, risperidone, sertindole, sulpiride, thioridazine, thiothixene, trifluoperazine, ziprasidone, zotepine, zuclopenthixol). We included these drugs used as monotherapy at any dose and in any form of administration when compared with another antipsychotic or placebo.

2.2. Search strategy and selection criteria

We performed a comprehensive literature search in MEDLINE, EMBASE, PsycINFO, Cochrane Library, PubMed, Biosis, and ClinicalTrials.gov up to Nov 17, 2016 and a final update search until May, 2018. Detailed search terms are presented in the Supplement (eAppendix 2). Moreover, we inspected the reference lists of the included studies and previous narrative reviews about the effects of antipsychotics in patients with schizophrenia and co-morbid substance use disorder (Hjorthoj et al., 2009; Koola et al., 2012; Sabioni et al., 2013; Wobrock et al., 2008). In the case of crossover studies, we only used the first crossover phase to avoid the problem of carry-over effects (Elbourne et al., 2002), and we excluded cluster-randomized trials (Divine et al., 1992). Studies with a high risk of bias for sequence generation were excluded (Higgins, 2011). If a trial was described as double-blind but randomization was not explicitly mentioned, we assumed that study participants were randomized, but excluded such trials in a sensitivity analysis. Study quality was independently assessed by at least 2 reviewers (MK, IB, JS, MH) who used the Cochrane Collaboration's risk-of-bias tool (Higgins, 2011). Disagreements were resolved by discussions with SL. We excluded studies from mainland China to avoid a systematic bias because many of these studies do not use appropriate randomization procedures, do not report their methods, and have been reported to be not reliable (Bian et al., 2006; Wu et al., 2009). We sent emails to the first and corresponding authors of all included studies to ask for missing data, if contact data were available.

2.3. Outcome measures and data extraction

The primary outcome for this subgroup was the reduction of substance use measured as the number of patients using legal or illegal substances (e.g. alcohol, marijuana, cocaine, or medication). Following the approach of several included studies for which patients with any substance use disorder were eligible, we combined all studies irrespective of the exact type of substance disorder, but we examined specific types of substance disorder in subgroup analyses. Further, outcomes that are specific for people with comorbid substance disorder were mean craving (Montada and Learner, 1998; Smelson et al., 1999) and mean reduction of drug use. Secondary outcomes related to the diagnosis of schizophrenia were the mean change from baseline to endpoint in overall symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Brief Psychiatric Rating Scale (OVERALL, 1962), or any other validated scale for the assessment of overall schizophrenia symptoms. Further outcomes were, clinically important response to treatment as defined by the authors, the mean change in positive and negative symptoms of schizophrenia, dropouts owing to any reason as a proxy for compliance, dropouts owing to inefficacy of treatment, the occurrence of important adverse effects (weight gain, at least one extrapyramidal symptom, sedation, akathisia, prolactin increase), the use of antiparkinsonian medication used at least once as a proxy for extrapyramidal symptoms, quality of life, and social

functioning. We preferred change from baseline to endpoint data for continuous outcomes, but if change data were not available, we used the mean score at study end point of these scales. Intention-to-treat datasets were used whenever available.

Study selection (MK, YZ, MH) and data extraction (MK, MH, JS, PR, IB, KG, SB, YZ, TA, NP, HR, CR, SW, CD and SL) were performed independently by at least 2 reviewers. Disagreement was resolved by discussion. If disagreement could not be resolved, we discussed with the team leader (SL) and contacted the authors via e-mail seeking further information. Missing standard deviations (SDs) were estimated from p-values and other test statistics or, if not possible, we calculated them according to a validated imputation method (Furukawa et al., 2006).

2.4. Statistical analysis

We planned originally to conduct a network meta-analysis. However, there were few studies with usable outcome data for each drug and the definition of the subgroups differed substantially, violating the transitivity assumption which is mandatory for network-meta-analysis (Cipriani et al., 2013; Jansen and Naci, 2013; Salanti, 2012). Therefore, we decided to calculate pairwise, random-effects meta-analyses using Review Manager 5.3. This decision had been foreseen in our protocol (eAppendix 1). For continuous outcomes, the effect sizes were calculated as standardized mean differences (SMDs) using the generic inverse variance method (Higgins, 2011). For binary outcomes, the effect sizes were calculated as odds ratios (ORs) according to Mantel-Haenszel (Higgins, 2011). Both types of effect sizes were presented along with their 95% confidence intervals (CIs). We applied the random-effects model by DerSimonian and Laird (DerSimonian and Laird, 1986) to all outcomes. Heterogeneity was assessed with the I^2 statistic and a chi-square test for homogeneity (Higgins, 2011). In the primary analysis we included all types of substance use disorders, but the type of disorder was examined by subgroup analyses of all outcomes, if possible. Furthermore, we performed a sensitivity analysis excluding studies with substance induced psychotic disorder.

Small trial effects were explored by funnel-plots if at least ten studies were available (Higgins, 2011). As the method is based on symmetry, funnel-plots based on fewer trials are not meaningful (Higgins , 2011).

3. Results

3.1. Description of included studies

We identified 27 references from 19 blinded RCTs published from 1999 to March 2017 including 1742 participants through the literature search. The PRISMA flowchart is shown in Fig. 1, details of all included studies are presented in Table 1 and a list of all included references is shown in eAppendix 3. Of 910 patients with gender indicated, 799 were men (88%). The trial duration ranged from 4 to 72 weeks, but we used mostly the outcome data for short term (3–12 weeks), if available. The assessment for risk of bias is presented in eAppendix 4 in the supplement. The trial reports often did not provide details about randomization procedures (74%) and allocation concealment (74%), because several included reports were subgroup analyses of larger studies (e.g. the CATIE study (Swartz et al., 2008)) which were often reported as conference abstracts. The blinding of patients and personnel was unclear in 26% of the studies and 42% of the studies showed a high risk of bias in terms of blinding. The risk of bias for blinding of outcome assessment was unclear in 37% of the studies and 26% showed high risk. Many studies were poorly reported because they were subgroups of larger trials which were reported only as conference reports. Accordingly, the rates of high risk of bias for incomplete outcome data and selective reporting were rather high, 37% and 32% respectively, and an unclear risk for these variables was found in 26% and 42% respectively. The median sample size was 30 participants (range 4–643). The following eight antipsychotics were included in the meta-analysis: olanzapine (10 studies), risperidone (10 studies), haloperidol (6 studies), clozapine (4 studies), ziprasidone (2 studies), aripiprazole (1 study), perphenazine (1 study) and quetiapine (1 study). Two studies reported intervention groups that included various antipsychotics. The antipsychotic in Smelson et al. (2006b) was mainly perphenazine or haloperidol which were labeled as “conventional antipsychotics,” and Brunette et al. (2011) used a “treatment as usual” group as a comparator.

In most of the included studies the patients had a comorbidity of cannabis (8 studies) or cocaine (6 studies) use disorder or dependence, followed by alcohol (two studies, Green et al., 2015,2004), cannabis induced psychotic disorder (two studies, patients with an illicit drug use or substance use not further specified (two studies: Smelson et al., 2006a; Swartz et al., 2008) and amphetamine induced psychotic disorder (Farnia et al., 2014).

3.2. Outcome results

3.2.1. Number of substance user

Three of 19 included studies reported the number of patients using drugs during the study period (see Fig. 2A). Two studies found no significant difference between olanzapine and haloperidol, nor did another study between olanzapine and risperidone. A fourth study found no significant difference between aripiprazole and perphenazine in terms of the percentage of negative drug screens (Beresford et al., 2017).

3.3. Mean drug use

Three studies reported the mean reduction of drug use (see Fig. 2B). There were no significant differences between clozapine and ziprasidone, nor between olanzapine and risperidone. Nevertheless, in a small single study ($n = 31$) clozapine was better than a control group composed of ‘any other antipsychotic’ ($n = 31$, SMD -1.08, CI -1.84 to -0.32).

3.4. Craving

Three studies presented usable data on craving (see Fig. 2C). Smelson et al. (2006b) found a borderline superiority of olanzapine compared to haloperidol ($p = 0.05$). Sayers et al. (2005) compared the same drugs, but we could not estimate a standard deviation for it so that we were not able to calculate an effect size. In van Nimwegen et al.

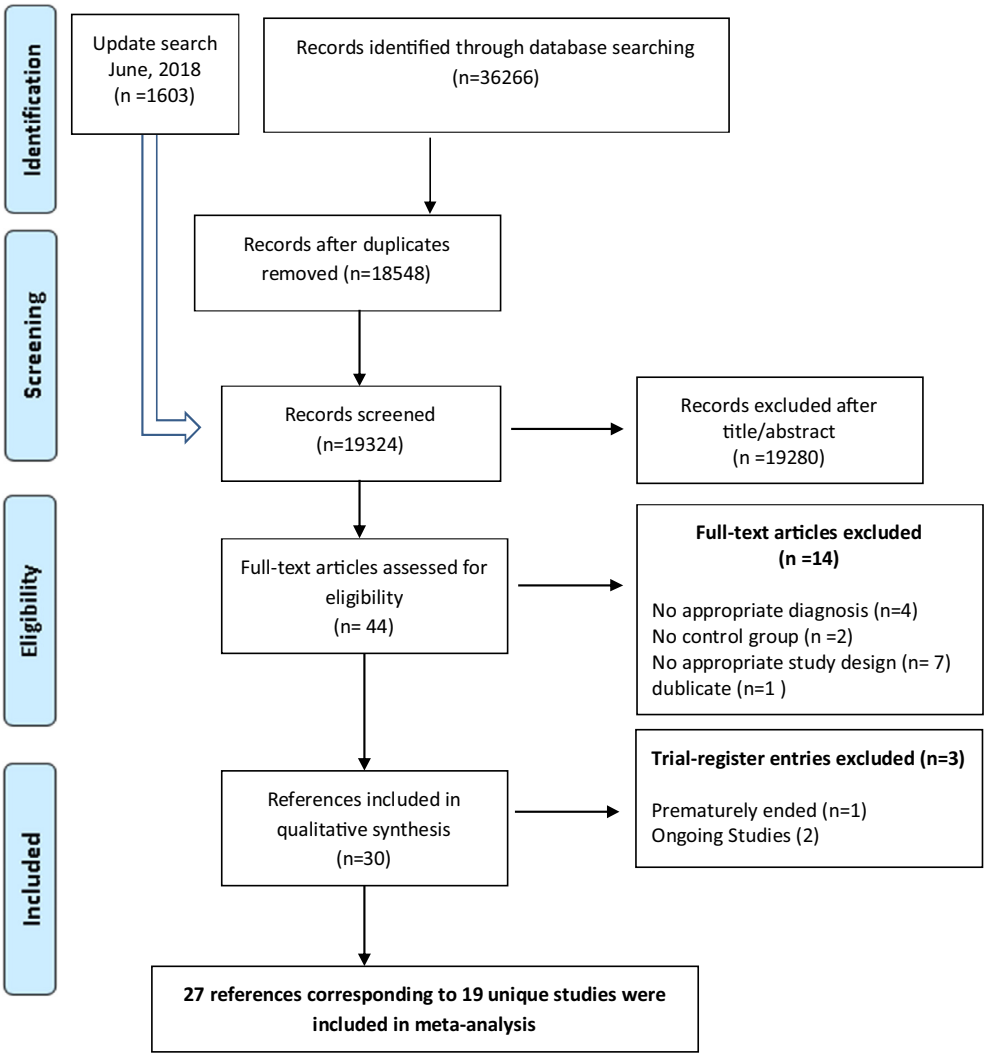

Fig. 1 Flow-chart of study selection.

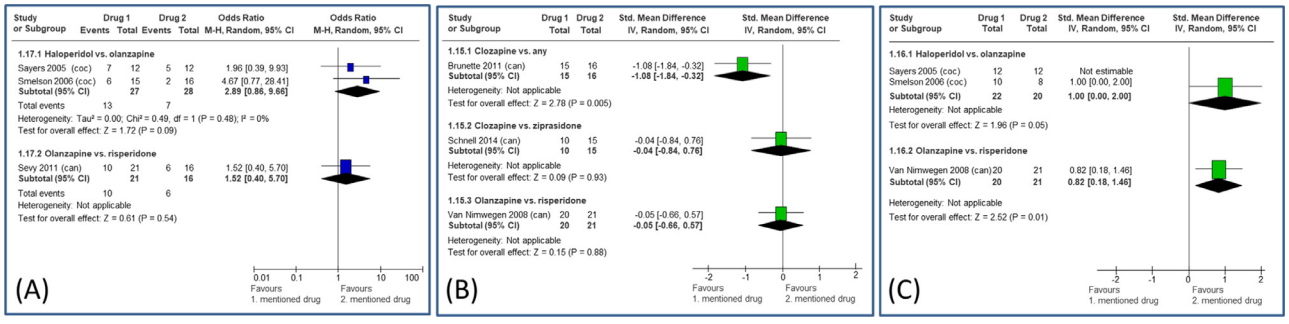

Fig. 2 Forest-plots for substance use disorder related outcomes – A: Number of drug users, B: Mean drug use and C: Mean craving for drugs.

Forest plots of pairwise meta-analyses for patients with drug abuse. The size of squares reflects the weight attributed to each study for every separate pairwise meta-analysis (per comparison). Error bars indicate 95% CI. An odds ratio smaller than one means that patients taking the first mentioned drug use fewer substances during the study period. A standardized mean difference smaller than zero means that the first mentioned drug is better for the reduction of mean drug use, mean craving, respectively.

A number of substance users, **B** mean substance use and **C** mean craving for drugs.

(can) = cannabis, (coc) = cocaine.

Table 1 Study characteristics.

Study	Drug/number of participants	Mean doses (Range) mg/days	Duration (weeks)	Inpatient or outpatient	Blinding type	Diagnostic term	Definition of comorbidity	Countries study sites
Akerele, 2007	Olanzapine: $n = 14$ Risperidone: $n = 14$	O: 5–20 R: 3–9	12	out	DB-RCT	DSM-IV schizophrenia or schizoaffective disorder	Patients met DSM-IV criteria for current cocaine and/or marijuana abuse or dependence	USA
Beresford, 2017	Aripiprazole: $n = 22$ Perphenazine: n=22	A: (15–30) P: 12–24	8	out	DB-RCT	DSM-IV diagnoses of schizophrenia or schizoaffective disorder	Current, co-occurring cocaine dependence	USA
Berk, 1999	Olanzapine: $n = 15$ Haloperidol: $n = 15$	O: 10 H: 10	4	in	DB-RCT	DSM-IV cannabis-induced psychotic disorder	DSM-IV criteria for cannabis -induced psychotic disorder.	South Africa
Berk, 2000	Haloperidol: $n = 15$ Risperidone: $n = 15$	H: 10 R: 6	4	in	DB-RCT	DSM-IV cannabis-induced psychotic disorder	DSM-IV criteria for cannabis-induced psychotic disorder	South Africa
Brunette, 2011	Clozapine: $n = 15$ TAU: $n = 16$	C: 341,45 (400–550)	12	out	SB-RCT	DSM-IV schizophrenia or schizoaffective disorder	Current cannabis use disorder	USA
Farnia, 2014	Aripiprazole: $n = 26$ Risperidone: $n = 27$	A: 15 R: 4	6	in	DB-RCT	DSM-IV amphetamine-induced psychotic disorder	DSM-IV criteria for amphetamine-induced psychotic disorder	Iran
Green, 2004	Olanzapine: $n = 126$ Haloperidol: $n = 126$	O: 10,2 (5–20) H: 4,8 (2–20)	12	n.a.	DB-RCT	DSM-IV schizophrenia, schizoaffective disorder or schizophreniform disorder	Substance abuse disorder, Alcohol abuse disorder, Cannabis use disorder	North America, Western Europe
Green, 2015	Risperidone LAI: $n = 49$ Risperidone Oral: $n = 46$	R LAI: 4,3 R oral: 33,8 (25–50)	26	n.a.	SB-RCT	DSM-IV-TR Schizophrenia	Co-occurring alcohol use disorder	USA
Machielsen, 2014	Risperidone: $n = 20$ Clozapine: $n = 16$	R: 3,8 C: 302,6	4	both	OL-RCT	DSM-IV schizophrenia, schizophreniform or schizoaffective disorder	Cannabis use disorder	Netherlands
Noordsy, 2010	Clozapine: $n = 7$ Risperidone: $n = 7$	C: 75 R: 3,1	24	n.a.		DSM-IV schizophrenia	DSM-IV criteria for cannabis abuse or dependence	USA
Sayers, 2005	Haloperidol: $n = 12$ Olanzapine: $n = 12$	H: 10–20 O = 10–20	26	both	DB-RCT	DSM-IV schizophrenia	Current cocaine abuse	USA
Schnell, 2014	Ziprasidone: $n = 16$ Clozapine: $n = 14$	Z: 200 C: 225	52	in	OL-RCT	DSM-IV schizophrenia, schizophreniform or schizoaffective disorder	DSM - IV criteria for cannabis abuse or dependence	Germany

(*continued on next page*)

Table 1 (*continued*)

Study	Drug/number of participants	Mean doses (Range) mg/days	Duration (weeks)	Inpatient or outpatient	Blinding type	Diagnostic term	Definition of comorbidity	Countries study sites
Sevy, 2011	Risperidone: $n=21$ Olanzapine: $n=28$	R: 1-6 O: 2,5-20	16	in	OL-RCT	DSM-IV schizophrenia, schizophreniform disorder, or schizoaffective disorder	DSM-IV criteria for a lifetime history of cannabis abuse or dependence.	USA
Smelson, 2002	Risperidone: $n=8$ Conventional: $n=10$	R: 2-6 C: 522,9 CPZ (equivalent)	6	out	OL-RCT		DSM-IV diagnosis for cocaine dependence	USA
Smelson, 2006	Haloperidol: $n=16$ Olanzapine: $n=15$	H: 10 (5-20) O: 10 (5-20)	6	out	DB-RCT	DSM-IV Schizophrenia	DSM-IV diagnostic criteria for cocaine dependence"	USA
Smelson, 2006b	Conventional: $n=85$ Risperidone: $n=76$ Olanzapine: $n=75$	R: 4,84 O: 13,26	52	both	OL-RCT	DSM-IV schizophrenia, or schizoaffective or schizophreniform disorders	Co-occurring substance use	No usable outcome data
Swartz, 2008	Perphenazine: $n=83$ Risperidone: $n=124$ Ziprasidone: $n=142$ Quetiapine: $n=137$ Olanzapine: $n=157$	P: 20,4 (8-24) R: 3,8 (1,5-6) Z: 113,3 (40-160) Q: 515 (200-800) O: 20 (7,5-30)	72	both	DB-RCT	DSM-IV schizophrenia	Illicit drug use	USA
Tsuang, 2002	Haloperidol: $n=2$ Olanzapine: $n=2$	H: 7,5 (5-10) O: 17,5 (15-20)	24	out	DB-RCT	DSM-IV schizophrenia	DSM-IV criteria for cocaine abuse.	USA
Van Nimwegen, 2008	Olanzapine: $n=66$ Risperidone: $n=72$	O: 10,95 (5-20) R: 3 (1-5)	6	both	DB-RCT	DSM-IV-R schizophrenia, schizoaffective disorder, schizophreniform disorder	“craving for cannabis in patients with schizophrenia”	Netherlands

DB-RCT: double blind randomized controlled trial; SB-RCT: single blind randomized controlled trial; OL-RCT: open label randomized controlled trial; n.a.: not available; in: inpatients; out: outpatients; both: study included inpatients and outpatients.

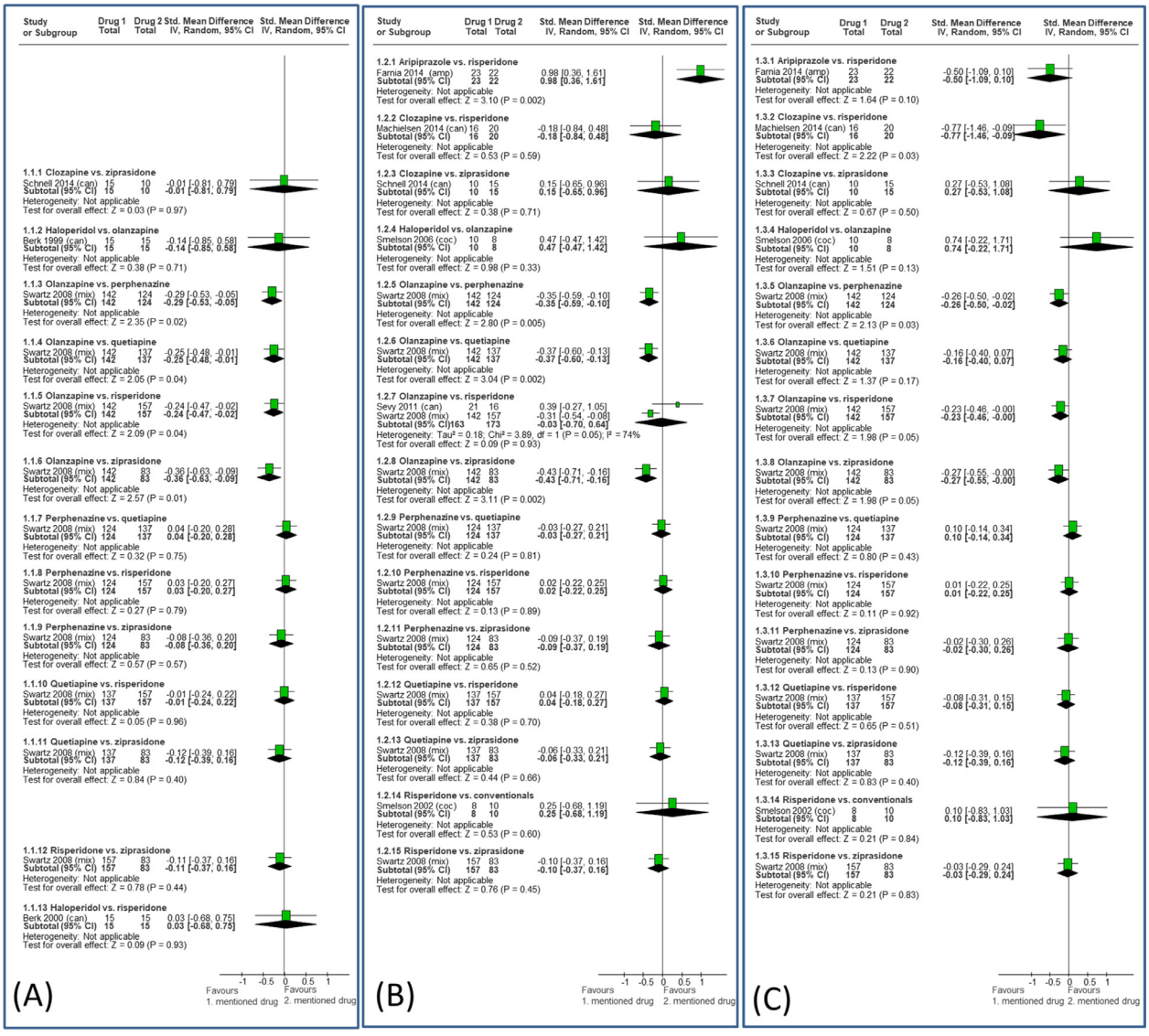

Fig. 3 Forest-plots for reduction in symptoms of schizophrenia – A: Overall symptoms, B: Positive symptoms, and C: Negative symptoms.
Forest plots of pairwise meta-analyses for patients with drug abuse. The size of squares reflects the weight attributed to each study for every separate pairwise meta-analysis (per comparison). Error bars indicate 95% CI. A standardized mean difference smaller than zero means that the first mentioned drug is better for the reduction of specific symptoms.
A overall symptoms, **B** positive symptoms and **C** negative symptoms.
(can) = cannabis, (coc) = cocaine, (amp) = amphetamine, (mix) = different substances.

(2008) risperidone reduced craving significantly more than olanzapine ($n = 41$, SMD 0.82, CI 0.18–1.46).

3.5. Overall symptoms

Four studies (Berk et al., 2000,1999; Schnell et al., 2014; Swartz et al., 2008) reported usable outcome data about the reduction of overall symptoms (see Fig. 3A).

There was no significant difference between clozapine and ziprasidone ($n = 25$, SMD −0.01, CI −0.81 to 0.79), haloperidol and olanzapine ($n = 30$, SMD −0.14, CI −0.85 to 0.58), and haloperidol versus risperidone ($n = 30$, SMD 0.03, CI −0.68 to 0.75), all effect sizes were based on single trials (Berk et al., 2000,1999; Schnell et al., 2014). Moreover, in the multi-arm study by Swartz et al. (2008), olanzapine was significantly better than risperidone ($n = 294$, SMD −0.24, CI −0.47 to −0.02), quetiapine ($n = 261$, SMD −0.25, CI −0.48 to −0.01), perphenazine ($n = 266$, SMD −0.29, CI −0.53 to −0.05), and ziprasidone ($n = 225$, SMD −0.36, CI −0.63 to −0.09). In the same study there were no significant differences between perphenazine, quetiapine, risperidone and ziprasidone.

3.6. Positive symptoms

Seven studies (Farnia et al., 2014; Machielsen et al., 2014; Schnell et al., 2014; Sevy et al., 2011; Smelson et al., 2006b,2002; Swartz et al., 2008) reported usable outcome data for the mean reduction of positive symptoms (see Fig. 3B).

Risperidone was significantly better compared to aripiprazole (Farnia et al., 2014) ($n=$, SMD 0.98, CI 0.36-1.61). Olanzapine was associated with a significantly higher reduction of positive symptoms compared to perphenazine ($n=266$, SMD −0.35, CI −0.59 to −0.10), ziprasidone ($n=225$, SMD −0.43, CI −0.71 to −0.16) and quetiapine ($n=279$, SMD −0.37, CI −0.60 to −0.13), but not compared to risperidone and haloperidol. The latter effects were based on the same multi-arm study (Swartz et al., 2008; Sevy et al., 2011). There were no significant differences between perphenazine and quetiapine, risperidone and ziprasidone in the same study (Swartz et al., 2008). Moreover, there were no significant differences between clozapine and risperidone, clozapine and ziprasidone and risperidone versus conventional antipsychotics, again based on single studies each (Machielsen et al., 2014; Schnell et al., 2014; Smelson et al., 2002).

3.7. Negative symptoms

Six studies (Farnia et al., 2014; Machielsen et al., 2014; Schnell et al., 2014; Smelson et al., 2006b,2002; Swartz et al., 2008) reported usable outcome data for the mean reduction of negative symptoms (see Fig. 3C).

Olanzapine was associated with a significantly higher reduction of negative symptoms compared to perphenazine ($n=266$, SMD −0.26, CI −0.50 to −0.02), and it trended to be better than risperidone ($n=299$, SMD −0.23, CI −0.46 to −0.00) and ziprasidone ($n=225$, SMD −0.27, CI −0.55 to −0.00). Moreover, clozapine was significantly better than risperidone ($n=36$, SMD −0.77, CI −1.46 to −0.09), but not compared to ziprasidone. Other comparisons involved the antipsychotics aripiprazole, perphenazine, quetiapine, risperidone, ziprasidone, and conventional antipsychotics and found no important differences between groups. All effects were based on a single study each.

3.8. Depressive symptoms

Only two studies reported usable outcome data for depressive symptoms (Akerele and Levin, 2007; Schnell et al., 2014) (see eFig. 3).

There was neither a significant difference between clozapine and ziprasidone, nor between olanzapine and risperidone.

3.9. Responder rates

Three studies (Green et al., 2004; Sayers et al., 2005; Sevy et al., 2011) reported the number of patients who responded to treatment based on various criteria. The meta-analysis showed neither a significant difference between haloperidol and olanzapine, nor between risperidone and olanzapine (see eFig. 4).

3.10. All-cause discontinuation (indicates compliance)

Fifteen studies reported usable outcome data for the outcome “treatment discontinuation for any reason.. The meta-analysis showed no significant differences between evaluated drugs (see eFig. 5).

3.11. Dropouts due to inefficacy

Five studies reported usable outcome data for dropouts due to inefficacy (Akerele and Levin, 2007; Noordsy et al., 2010; Schnell et al., 2014; Tsuang et al., 2002; van Nimwegen et al., 2008). There were significantly less dropouts due to inefficacy for clozapine compared to ziprasidone ($n=30$, OR 0.04, CI 0.00-0.86). There were no significant differences between olanzapine and risperidone (See eFig. 6).

3.12. Dropouts due to adverse events

Four studies reported dropouts due to adverse events (Akerele and Levin, 2007; Schnell et al., 2014; Tsuang et al., 2002; van Nimwegen et al., 2008). One study (Schnell et al., 2014) showed a significant superiority for ziprasidone compared to clozapine ($n=30$, OR 12.60, CI 2.00-79.44). There was neither a significant difference between haloperidol and olanzapine nor between olanzapine and risperidone in the remaining studies (see eFig. 7).

3.13. Quality of life

Two studies reported quality of life (Machielsen et al., 2014; van Nimwegen et al., 2008). There were neither significant differences between clozapine and risperidone nor between olanzapine and risperidone (see eFig. 8a).

3.14. Social functioning

Two studies reported social functioning (Berk et al., 1999; Schnell et al., 2014). There were neither significant differences between clozapine and ziprasidone nor between haloperidol and olanzapine (see eFig. 8b).

3.15. Weight gain

One study reported usable outcome data for weight gain (Sevy et al., 2011). In this study risperidone was associated with significantly less weight gain compared to olanzapine ($n=37$, SMD 0.81, CI 0.13-1.49) (see eFig. 9A).

3.16. Sedation

Two studies reported usable outcome data for sedation (Akerele and Levin, 2007; Brunette et al., 2011). The only significant difference was an inferiority of clozapine compared to a group which included different antipsychotics ($n = 31$, OR 10.50 CI 1.72–63.91) (see eFig. 9b). There was no significant difference between olanzapine and risperidone.

3.17. Use of antiparkinsonian medication

One study reported usable data for the "use of at least one antiparkinson medication" (Machielsen et al., 2014). There was no significant difference between clozapine and risperidone (see eFig. 9C).

3.18. Assessment of heterogeneity and small trial bias

We did not detect significant heterogeneity in any outcome, but since there were very few studies for most of the comparisons, heterogeneity cannot be well estimated. Funnel plots to detect small trial/publication bias were not meaningful, because the maximum number of trials available for a comparison was five, not enough to decide on asymmetry of the plots.

3.19. Subgroup analyses

We a priori planned subgroup analyses evaluating separately populations with different substance use disorders. If there was only one type of substance use available for a comparison (drug A vs. drug B), we did not report the results again. We refer to Figs. 2, 3 and eFigs. 3–9, in which the type of substance use in question is reported beside the name of each study.

In case those different types of substance use had been pooled in the primary analysis, we re-analysed the data for each type separately. These results can be summarized such that in terms of dropouts due to any reason there was no significant difference ($n = 59$, OR 1.04, CI 0.30–3.66) between haloperidol and olanzapine after pooling the three trials conducted in patients with cocaine-related disorders. In the same outcome there were no significant differences between olanzapine and risperidone for patients using mixed substances ($n = 327$, OR 1.31, CI 0.32–5.35).

Finally, to give an overview about the most relevant results for each type of substance use disorder, Table 2 shows all significant effects for each substance.

3.20. Sensitivity analysis

We also performed a sensitivity analysis excluding studies with substance induced psychotic disorder (Berk et al., 2000, 1999; Farnia et al., 2014) which was only relevant for the comparison, haloperidol versus olanzapine, in terms of dropouts total. The exclusion of one small study (Berk et al., 1999) showed only a small difference in effect

Table 2 Significant effects for all outcomes grouped by type of substance.

Type of disorder	Mean drug use (Fig. 2b)	Craving (Fig. 2c)	Overall Symptoms (Fig. 3a)	Positive symptoms (Fig. 3b)	Negative symptoms (Fig. 3c)	Weight gain (eFig. 7c)	Sedation (eFig. 7b)
Cannabis	$n = 31$, CLO vs. ANY: −1.08 (−1.84,−0.32)	$n = 41$, OLA vs. RIS: 0.82 (0.18,1.46)			$n = 36$, CLO vs. RIS: −0.77 (−1.46, −0.09)	$n = 37$, OLA vs. RIS: 0.81 (0.13, 1.49)	$n = 31$, CLO vs. ANY: 10.50 (1.72, 63.91)
Amphetamine				$n = 45$, ARI vs. RIS: 0.98 (0.36, 1.61)			
Mixed			$n = 266$, OLA. vs. PER: −0.29 (−0.53,−0.05) $n = 279$, OLA vs. QUE: −0.25 (−0.48, −0.01) $n = 299$, OLA vs. RIS: −0.24 (−0.47, −0.02) $n = 225$, OLA vs. ZIP: −0.36 (−0.63, −0.09)	$n = 266$, OLA. vs. PER: −0.35 (−0.59, −0.10) $n = 279$, OLA vs. QUE: −0.37 (−0.60, −0.13) $n = 299$, OLA vs. RIS: −0.31 (−0.54, −0.08) $n = 225$, OLA vs. ZIP: −0.43 (−0.71, −0.16)	$n = 266$ OLA vs PER: −0.26 (−0.50, −0.02)	

The table summarizes all significant effects of included single studies grouped by type of substance use disorder.
ANY = any antipsychotic, CLO = clozapine, OLA = olanzapine, PER = perphenazine, QUE = quetiapine, RIS = risperidone, ZIP = ziprasidone, n = number of patients.

size ($N = 5$, $n = 340$, OR 1.39, CI 0.87-2.22 versus $N = 4$, $n = 310$, OR 1.41, CI 0.80-2.47).

4. Discussion

With 19 RCTs including 1742 participants we present the up-to-date most comprehensive systematic review on the effects of antipsychotic drugs in people with schizophrenia and comorbid substance use. Concerning substance use related outcomes, we find superiority of clozapine compared to 'any other antipsychotic' in terms of mean cannabis use, and of risperidone compared to olanzapine in terms of craving for cannabis. Both results were based on one small trial each. With regards to symptoms of schizophrenia in Swartz et al. (2008), a subgroup analysis of the CATIE trial (Lieberman et al., 2005), reported a superiority of olanzapine compared to risperidone, quetiapine, perphenazine and ziprasidone for overall symptoms of schizophrenia, which was paralleled in part by superiority for positive and negative symptoms. Moreover, risperidone outperformed aripiprazole for positive symptoms in people with amphetamine use disorder, and clozapine outperformed risperidone in people with cannabis use disorder, again, both based on one small trial each. If differences in side-effects were significant they followed known patterns. There were no significant differences in terms of all-cause discontinuation.

Our systematic review has strengths. It is part of a publicly funded project titled "The next step in evidence-based treatment of schizophrenia. Individualizing the care for important patient subgroups," in which we aim to summarize the randomized evidence of the effects of antipsychotic drugs in special patient subgroups of people with schizophrenia (first episode; Zhu et al., 2017, children/adolescents; Krause et al., 2018b), elderly (Krause et al., 2018a), primary negative symptoms (Krause et al., 2018c), and patients with a substance-related comorbidity), four of which have already been published. We stringently followed the methodology required by the PRISMA statement (Liberati et al., 2009) including an a priori published protocol on PROSPERO (Krause et al., 2016). The meta-analysis is clearly more comprehensive than previous (systematic) reviews which did not apply meta-analysis (Hjorthoj et al., 2009; Koola et al., 2012; Smelson et al., 2008), included fewer studies (Hjorthoj et al., 2009; Koola et al., 2012; Smelson et al., 2008), focused on single antipsychotics (Koola et al., 2012), (Temmingh et al., 2018), focused on a specific substance (Sabioni et al., 2013) or were clearly out of date (Wobrock et al., 2008).

Our review also has limitations. Nineteen RCTs with 1742 participants represent a substantial body of evidence. However, only one study was available for most comparisons, and most of the included studies had small sample sizes. This means that usually, the forest plots could only display the results of one or two studies. We emphasize that this is not a limitation of the methods of our review. The aim of a systematic review is to retrieve all relevant studies and to display their results in a uniform way, irrespective of how many studies there are. As an extreme example, Cochrane reviews even gets published when there are no studies on a question, because "no evidence" is an important finding (Higgins, 2011). It is important to communicate to the research community that there is a research gap to stimulate research. Clinicians also need to be informed about such a deficiency. One reason why not many data could be extracted from the 19 studies is that they were poorly reported. Sometimes we had to deal with abstracts from conference reports. It is possible that these analyses did not get fully published, because some were analyses on patient subgroups with comorbid substance use of larger studies. For example, the report by Swartz et al. (2008) is a subgroup of the CATIE study (Lieberman et al., 2005) which only had symptoms of schizophrenia, but not reduction of substance use as an outcome. We emphasize that it is a requirement of high-quality systematic reviews (Higgins, 2011) to include "grey literature" (conference abstracts, etc.) and that these limitations of the original studies are documented in our risk of bias assessment. As we expected, the included studies evaluated patients with various substance related comorbidities and several included patients with any substance use irrespective of the type (see Table 1). We therefore marked the type of substance use in the forest plots (Figs. 2 and 3) and summarized the key findings in Table 2. We did not identify studies on long-acting injectable antipsychotics (LAIs), except Green 2015, which compared oral versus long-acting injectable risperidone (Green et al., 2015). Non-adherence may be even more frequent in this subgroup than in the general population of people with schizophrenia, so that LAIs could be a good option. All cause discontinuation (dropout due to any reason) combines efficacy and safety and therefore has been used as a proxy measure for acceptability of treatments. Moreover, to some extent, it can be considered as a measure of non-adherence, but the meta-analysis revealed no significant difference between antipsychotics.

What are the implications of our findings for clinicians and guidelines? While the current version of the NICE-guideline (National Institute for Health and Care Excellence (UK), 2014) makes no recommendations concerning the choice of antipsychotics for this subgroup, the British Association for Psychopharmacology (BAP) and the World Federation of Societies of Biological Psychiatry (WFSBP) included a section about the treatment of patients with schizophrenia and comorbid substance use disorder in their guidelines (Barnes, 2011; Hasan et al., 2015). The British Association of Psychopharmacology (Barnes, 2011) recommends clozapine in patients with persistent substance misuse, but this recommendation was based only on case reports, naturalistic surveys or retrospective case reviews which had not been reviewed systematically. The guidelines of the WFSBP (Hasan et al., 2015) recommend clozapine (in particular for alcohol use disorder), but also other antipsychotics and LAIs for adherence. The level of the recommendations was low due to the limited evidence. However, based on our review of 19 randomized trials the best we can say is that clozapine and risperidone showed some superiority for reduction on substance use and craving, and that olanzapine, clozapine and risperidone showed some superiority for symptom reduction compared to some other drugs. Nevertheless, this evidence is not good enough to make strong clinical recommendations for this very frequent, but understudied population.

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Conflict of interest

In the last 3 years, Stefan Leucht has received honoraria for consulting or lectures from LB Pharma, Lundbeck, Otsuka, TEVA, LTS Lohmann, Geodon Richter, Recordati, Boehringer Ingelheim, Sandoz, Janssen, Lilly, SanofiAventis, Servier and Sunovion. MH has received speaker's honoraria from Janssen and Lundbeck. The other authors declare no competing interests.

Contributors

All authors had full access to all of the data in the study. The corresponding author takes responsibility for the integrity of the data and the accuracy of the data analysis. SL was the principal investigator who obtained funding. SL and MK designed this study. MK, MH, JS, IB, KG, PR, SB, YZ, TA, NP, HR, CR, SW, CD and SL extracted the data. MK and SL contacted trial investigators for additional data. MK analyzed the data and interpreted them with SL. KG and MK created figures and tables. MK and SL wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2018.11.1103.

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