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Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis

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Abstract

Background Negative symptoms are the core of schizophrenia, but whether antipsychotics are efficacious for their treat-ment is unclear. Moreover, there is debate whether patients in relevant trials should have predominant negative symptoms or whether prominent negative symptoms are also acceptable.

Methods We systematically reviewed randomised, blinded antipsychotic drug trials in patients with schizophrenia and either predominant or prominent negative symptoms (last search Dec 12, 2017). Separate pairwise meta-analyses were conducted in these two populations. The primary outcome was negative symptoms. Depressive, symptoms, positive symptoms, and extrapyramidal side-effects were analysed as causes of secondary negative symptoms.

Findings We included 21 randomized-controlled trials with 3451 participants which revealed the following significant differences in the primary outcome: in patients with predominant negative symptoms amisulpride was superior to placebo ($N = 4$; $n = 590$, SMD 0.47, CI 0.23, 0.71), olanzapine was superior to haloperidol in a small trial ($n = 35$) and cariprazine outperformed risperidone ($N = 1$, $n = 456$, SMD − 0.29, CI − 0.48, − 0.11). In patients with prominent negative symptoms, olanzapine and quetiapine were superior to risperidone in single trials. Overall, studies in prominent negative symptoms were potentially more confounded by improvements of secondary negative symptoms.

Interpretation Amisulpride is the only antipsychotic that outperformed placebo in the treatment of predominant negative symptoms, but there was a parallel reduction of depression. Cariprazine was better than risperidone in a large trial that was well-controlled for secondary negative symptoms, but the trial was sponsored by its manufacturer. Future trials should apply scientifically developed definitions such as the deficit syndrome and the persistent negative symptoms concept.

Keywords Deficit syndrome · Deficit schizophrenia · Persistent negative symptoms · Depressive symptoms · Positive symptoms · Study design

Introduction

Eugen Bleuler described negative symptoms in schizophrenia as the core of the disorder. There have been multiple efforts to further conceptualize these symptoms, [1–6]

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such as the type I, type II concept by Crow [3], or the concept by Andreasen and Olsen [5] that distinguishes between positive, negative, and mixed-subtype symptoms of schizophrenia. An elaborate and well-evaluated concept is the deficit syndrome developed by Carpenter et al. [2] and Buchanan et al. [1]. Their definition comprises at least two of five pre-defined negative symptoms, which are not the cause(s) of depression, anxiety, drug effects or environmental deprivation, as well as symptoms persisting for at least 12 months [2]. Moreover, in 2007, Buchanan [7] presented the broader concept of persistent negative symptoms which requires at least moderate negative symptoms, a defined threshold of positive symptoms, and no or low depressives and extrapyramidal symptoms (all defined on validated scales), with demonstrated clinical stability.

Antipsychotic drugs, the mainstay of treatment for schizophrenia, have been shown to be effective for negative symptoms, but it is unclear whether they only improve so-called 'secondary' or also 'primary' negative symptoms [8]. For example, meta-analyses showed that second-generation antipsychotics and haloperidol reduced negative symptoms more than placebo [9]. However, almost all included studies focused on patients with exacerbations of positive symptoms. In such studies, it is possible that improvements of negative symptoms are only secondary to reductions of positive symptoms. Similarly, some second-generation antipsychotics were more efficacious than first-generation antipsychotics in another meta-analysis [10], but these effects might have been due in part to the extrapyramidal side-effects of haloperidol which can mimic negative symptoms.

Therefore, studies in specific populations are needed to determine whether antipsychotic drugs are truly effective for primary negative symptoms. In this context, there is a discussion whether it is sufficient that patients have 'prominent' negative symptoms or whether negative symptoms should also be 'predominant.' While patients with prominent negative symptoms are characterized only as patients with a high degree of negative symptoms, the definition of predominant negative symptoms includes the additional criteria of no-to-little positive symptoms [11]. While the European Medical Agency (EMA) requires predominant negative symptoms in such studies, the United States Food and Drug Agency (FDA) is somewhat less stringent in this regard, and an international expert consensus conference with participants from academia, industry and the EMA did not find an agreement [11].

We, therefore, conducted a systematic review on the effects of antipsychotics in patients with negative symptoms as inclusion criteria. The aims were to determine which antipsychotics are more efficacious than placebo, and whether there are differences between single antipsychotics. Moreover, we evaluated whether studies in prominent or in predominant negative symptom studies could have been more confounded by secondary negative symptoms.

Methods

An a priori written study protocol was registered at PROSPERO under the registration number: CRD42016052060.

Participants and interventions

We included all randomized controlled trials (RCTs) in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder (as defined by any diagnostic criteria) which focussed on patients with negative symptoms according to their in- and exclusion criteria. This means that we excluded studies in which it was described only in the introduction or discussion sections that patients had primarily negative symptoms. We then classified the studies into "predominant" and "prominent" negative symptom studies. As there are no uniformly accepted criteria for this distinction, we followed the broad conceptualisation of the international consensus conference published by Marder et al. [11] (see point 3.2 there). According to this report, predominant negative symptoms can occur in the presence of other symptoms, in particular psychotic symptoms, but these are only relatively mild and well controlled [11]. For prominent negative symptoms, however, it is not necessary that the level of psychotic symptoms is low at the same time as negative symptoms are high [11]. Thus, definitions that were eligible for inclusion in the prominent subgroup had to entail that the patients experienced a considerable degree of negative symptoms regardless of the degree of positive symptoms. Definitions that were eligible for the predominant subgroup had to assure that the patients had more negative symptoms than positive symptoms. In addition, the level of positive symptoms had to be low. Moreover, the minimally necessary degree of negative symptoms and the maximally possible degree of positive symptoms had to be operationalised by scale-derived criteria. As the exact cutoffs varied (see "Discussion"), further refinement was not possible (see "Discussion").

As we wanted to address whether studies in prominent negative symptoms may be more confounded by positive (and other) symptoms than studies conducted in patients with predominant negative symptoms, the subgroups were examined in two separate meta-analyses.

The interventions were 34 antipsychotic drugs 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 [12] (amisulpride, aripiprazole,

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asenapine, benperidol, brexpiprazole, cariprazine, chlorpromazine, clopenthixol, clozapine, flupenthixol, fluphenazine, fluspirilene, haloperidol, iloperidone, levomepromazine, loxapine, lurasidone, molindone, olanzapine, paliperidone, penfluridol, perazine, perphenazine, pimozide, quetiapine, risperidone, sertindole, sulpiride, thioridazine, thiothixene, trifluoperazine, ziprasidone, zotepine, and zuclopenthixol). We included these drugs at any dose and in any form of administration when compared with another antipsychotic or placebo, and used as monotherapy. Drugs that failed to obtain FDA/EMA approval or which have not been licensed yet were not considered.

Search strategy and selection criteria

We conducted a comprehensive, systematic literature search in MEDLINE, EMBASE, PsycINFO, Cochrane Library, PubMed, Biosis, and ClinicalTrials.gov up to Nov 17, 2016 (eAppendix 2 in the Supplement) and a final PubMed search until Dec 12, 2017. The search terms included the generic names of 34 antipsychotics listed above. The minimum duration of the RCTs was set at 3 weeks. We also inspected the reference lists of the included studies and of the previous systematic reviews [13, 14] and a narrative review [15] about negative symptoms. Citations were screened independently by at least two reviewers (MK, MH, YZ) at both the title/abstract and full-text stages. In the case of crossover studies, we only used the first crossover phase to avoid the problem of carryover effects [16]. We excluded cluster-randomized trials [17]. Studies that demonstrated a high risk for bias for sequence generation or allocation concealment were excluded [18]. If a trial was described as double blind, but randomization was not explicitly mentioned, we assumed that study participants were randomized, and we excluded the trial in a sensitivity analysis. We excluded studies from mainland China to avoid a systematic bias, because many of these studies do not use appropriate randomization procedures, but as their methods usually presented only briefly, it is difficult to evaluate them [19, 20].

Outcome measures and data extraction

The primary outcome was the mean change from baseline to endpoint in negative symptoms of schizophrenia as measured by negative subscales of the Positive and Negative Syndrome Scale [14, 21] (PANSS-negative), the Scale for the Assessment of Negative Symptoms [22] (SANS), or any other validated scale for the assessment of negative symptoms in schizophrenic patients such as the Brief Negative Symptom Scale [23] (BNSS). If change data were not available, we used the mean score at study endpoint of these scales. Intention-to-treat data sets were used whenever available.

Secondary outcomes were depressive and positive symptoms (change from baseline to endpoint or at endpoint) as measured by published rating scales, the number of patients receiving antiparkinson medication at least once, and the number of patients who experienced at least one extrapyramidal side-effect. These outcomes were examined to find out whether effects on negative symptoms might have been confounded by secondary negative symptoms. Other side-effect data were extracted, but not analysed, because there is no reason to believe that they differ from those in patients with exacerbations of positive symptoms for whom many more data were available [24]. Moreover, few side-effect data were available, so that these results would have contributed little.

We used the Cochrane Collaboration's risk-of-bias tool for the assessment of potential bias in terms of randomisation, allocation concealment, blinding, missing outcomes, selective reporting, and other biases [18].

Data extraction and assessment of study quality were performed independently by at least two reviewers (MK, YZ, MH, JS, IB, SL, and PR). We sent emails to the first and corresponding authors of all included studies to request missing data. Missing SDs were estimated from test statistics or substituted by the mean SD of the other included studies using the same scale [25].

Statistical analysis

We originally planned to conduct a network meta-analysis. However, there were only a few eligible studies; thus, the network plot was very poorly connected (see Fig. 1). The design-by-treatment interaction model [26, 27] showed a high degree of statistical inconsistency for the primary outcome (chi^2 (1) = 5.89 and p value > chi^2 = 0.0153). Therefore, we decided to calculate pairwise, random-effects meta-analyses. Moreover, as we aimed to compare studies in predominant and prominent negative symptoms, this approach was more appropriate, because results of individual studies cannot be visualised in network meta-analysis. For continuous outcomes, the effect sizes were calculated as standardized mean differences (SMDs) according to Hedges's g [18]. For binary outcomes, the effect sizes were calculated as odds ratios (ORs). Both types of effect sizes were presented along with their 95% confidence intervals (CIs). We applied the random-effects model by Der-Simonian and Laird [28] to all outcomes. Heterogeneity was assessed with the I^2 statistic [18] and a chi^2-square test for homogeneity. Small trial effects were explored by funnel-plots if at least ten studies were available [18]. As the method is based on symmetry, funnel plots based on fewer trials are not meaningful [18]. The network plots and the analysis of inconsistency were made with the network graphs package in Stata 14 [29]. All other statistical calculations were made with RevMan

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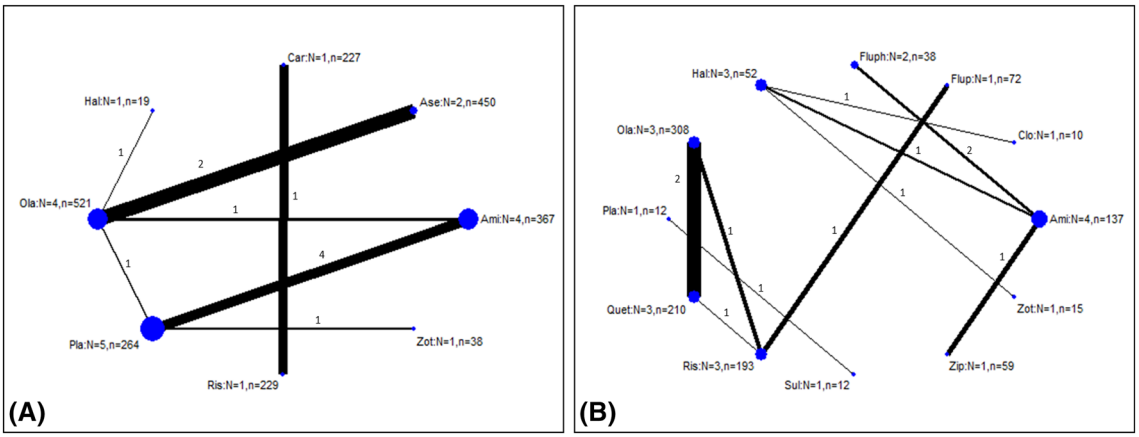

Fig. 1 Network plots for mean change in negative symptoms of schizophrenia. The size of the nodes corresponds to the number of trials that study the treatments. Directly comparable treatments are linked with a line. The number of studies and comparisons can be different, because of multiple-arm studies. **a** Network plot for the subgroup of patients with predominant negative symptoms. **b** Network plot for the subgroup of patients with prominent negative symptoms. *N* Number of studies, *n* number of participants. *Ami* amisulpride, *Ase* asenapine, *Cari* cariprazine, *Cloz* clozapine, *Flup* flupentixol, *Fluph* fluphenazine, *Hal* haloperidol, *Ola* olanzapine, *Pla* placebo, *Quet* quetiapine, *Ris* risperidone, *Zip* Ziprasidone, *Zot* zotepine

version 5.3 [30], *p* values lower than 0.05 were considered to be statistically significant.

Results

Description of included studies

We identified 43 references from 21 [31–50] unique RCTs with 3451 unique participants published from 1989 to 2017. The PRISMA flowchart is shown in eFigure 1. Of the 15 excluded studies, four studies may be noteworthy, because they somehow described their patients as having mainly negative symptoms in the "Introduction" or "Discussion" [51–54]. However, as negative symptoms were not defined by inclusion/exclusion criteria, these studies were excluded (see eAppendix 3). Details of all included studies are presented in Table 1. Of 3352 patients with gender indicated, 2245 were men (67%). The mean age of participants was 39 and 83 years. The median trial duration was 12 weeks (range 6–52 weeks). The assessment for risk of bias is presented in eAppendix 4 in the Supplement. The trial reports often did not provide clear details about randomization procedures (> 50%) and allocation concealment (60%). The blinding of patients and personnel was unclear in 30% of the studies and showed a high risk for unsufficient blinding (10%). The risk of bias for blinding of outcome assessment was similar with 30% unclear and 5% high risk. The rates of high risk of bias for missing outcomes and selective reporting were 20 and 50%, respectively.

Figure 1 shows the network of eligible comparisons for the primary outcome. The identified studies included the drugs amisulpride, sulpiride, asenapine, cariprazine, clozapine, flupentixol, fluphenazine, haloperidol, olanzapine, placebo, quetiapine, risperidone, ziprasidone, and zotepine. Nine of the 21 included studies met our criteria for patients with predominant negative symptoms and included the treatments (one study [34] had three arms): amisulpride ($N=4$), asenapine ($N=2$), cariprazine ($N=1$), haloperidol ($N=1$), olanzapine ($N=4$), placebo ($N=5$), risperidone ($N=1$), and zotepine ($N=1$). The other 12 studies included patients with schizophrenia and prominent negative symptoms and investigated the following drugs: amisulpride ($N=4$), sulpiride ($N=1$) clozapine ($N=1$), flupentixol ($N=1$) fluphenazine ($N=2$), haloperidol ($N=2$), olanzapine ($N=3$), quetiapine ($N=3$), risperidone ($N=3$), sulpiride ($N=1$), ziprasidone ($N=1$), zotepine ($N=1$).

Outcome results

One aim of our systematic review was to judge qualitatively whether reduction of negative symptoms may be secondary to effects on depressive symptoms or positive symptoms. To facilitate this judgement, the results of these three outcomes are presented in parallel in panel figures (Figs. 2, 3). Figure 2 summarizes the main results for the predominant negative symptom subgroup, Fig. 3 those of the prominent negative symptom subgroup. eFigures 5 and 6 present results on "use of antiparkinson medication at least once" for patients with predominant negative symptoms, respectively, prominent negative symptoms, and eFigure 7 and eFigure 8 present the same for the outcome "at least one extrapyramidal symptom (EPS)."

Table 1 Characteristics of included studies

Study	Study groups/number of participants	Trial duration (weeks)	Mean antipsychotic doses (mg/days)	Diagnosis	Key-operationalisation criteria to defined predominant negative symptoms	Study design	Sponsors
Boyer et al. [31]	Ami 100: $n=34$ Ami 300: $n=36$ Pla: $n=34$	6	Ami: 100 Ami: 300	Schizophrenia predominant negative symptoms (DSM-III)	SANS total ≥ 75 and SAPS total ≤ 60	DB-RCT	Sanofi Aventis
Buchanan et al. [32]	Ase: $n=244$ Ola: $n=224$	26	Ase: 14.5 Ola: 14	Schizophrenia (DSM-IV-TR)	PANSS negative subscale score ≥ 20 and ≤ 4 on at least two PANSS positive items, stable for at least 5 months before screening and 1 month observation period	DB-RCT	Merck
Buchanan et al. [32]	Ase: $n=241$ Ola: $n=240$	26	Ase: 14.4 Ola: 12.5	Schizophrenia (DSM-IV-TR)	PANSS negative subscale score ≥ 20 and ≤ 4 on at least two PANSS positive items, stable for at least 5 months before screening and 1 month observation period	DB-RCT	Merck
Danion et al. [33]	Ami 50: $n=84$ Ami 100: $n=75$ Pla: $n=83$	12	Ami: 50 Ami: 100	Schizophrenia of residual type (DSM-III-R)	SANS total > 60 and SAPS total < 50	DB-RCT	Synthelabo
Lecrubier et al. [34]	Ola 5: $n=70$ Ola 20: $n=70$ Ami 150: $n=70$ Pla: $n=34$	26	Ola: 5 Ola: 20 Ami: 150	Schizophrenia, residual, disorganised or catatonic (DSM-IV)	SANS summary > 10 and PANSS Positive symptoms ≤ 4 for PANSS-positive single items	DB-RCT	Eli Lilly

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Table 1 (continued)

Study	Study groups/number of participants	Trial duration (weeks)	Mean antipsychotic doses (mg/days)	Diagnosis	Key-operationalisation criteria to defined predominant negative symptoms	Study design	Sponsors
Lindenmayer et al. [35]	Hal: $n=19$ Ola: $n=16$	12	Hal: 17.11 Ola: 18.44	Schizophrenia and predominant negative symptoms (DSM-IV-TR)	PANSS negative subscale score of ≥ 20 and PANSS positive subscale score of ≤ 20, moreover patients met the criteria of the deficit syndrome	DB-RCT	Eli Lilly
Loo et al. [36]	Ami: $n=69$ Pla: $n=72$	26	Ami: 100	Schizophrenia with predominant negative symptoms (DSM-III-R)	SANS total ≥ 60 and SAPS total ≤ 50	DB-RCT	Synthelabo
Möller et al. [37]	Pla: $n=46$ Zot: $n=39$	8	Zot: 131	Residual schizophrenia with stable primary negative symptoms (ICD-10)	Min three items of PANSS negative >3 and max two items of PANSS positive >3, stable symptoms for at least 6 months	DB-RCT	Aventis Pharma
Nemeth et al. [38]	Cari: $n=230$ Ris: $n=231$	26	Cari: 4.2 Ris: 3.8	Schizophrenia (DSM-IV-TR)	PANSS-FSNS >24 and PANSS-FSPS ≤ 19, predominant negative symptoms for at least 6 months	DB-RCT	Gedeon Richter Plc

Study	Study groups/number of participants	Trial duration (weeks)	Mean antipsychotic doses (mg/days)	Diagnosis	Key-operationalisation criteria to defined prominent negative symptoms	Study design	
Alvarez et al. [39]	Ola: $n=124$ Ris: $n=123$	52	Ola: 12.2 Ris: 4.9	Schizophrenia with prominent negative symptoms (DSM-IV)	≥ 10 SANS summary score, no hospitalisation in the last 3 months	OL-RCT	Eli Lilly

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Table 1 (continued)

Study	Study groups/number of participants	Trial duration (weeks)	Mean antipsychotic doses (mg/days)	Diagnosis	Key-operationalisation criteria to defined prominent negative symptoms	Study design	
Barnas et al. [40]	Hal: $n=15$ Zot: $n=15$	7	Hal: 4.2 Zot: 94.4	Schizophrenia, residual type (DSM-III-R)	SANS total > 50	DB-RCT	No sponsor stated
Buchanan et al. [41]	Cloz: $n=10$ Hal: $n=11$	10	Cloz: 405 Hal: 24.1	Schizophrenia or schizoaffective disorder (DSM-III-R)	SANS total ≥ 20, patients met the criteria of the deficit syndrome	DB-RCT	No sponsor stated
Kinon et al. [42]	Ola: $n=171$ Quet: $n=175$	26	Ola: 15.6 Quet: 455.8	Schizophrenia or schizoaffective disorder (DSM-IV)	PANSS negative ≥ 4 on at least three, of seven items, PANSS negative ≥ 5 on at least two of seven items	DB-RCT	Eli Lilly
Pichot et al. [43]	Ami: $n=34$ Fluph: $n=28$	6	Ami: 210 Fluph: 9.6	Chronic schizophrenia (DSM-III)	DSAS ≥ 7	DB-RCT	No sponsor stated
Riedel et al. [44]	Quet: $n=22$ Ris: $n=22$	12	Quet: 589.7 Ris: 4.9	Schizophrenia (DSM-IV, ICD-10)	PANSS negative ≥ 21 and at least 1 point higher than PANSS positive	DB-RCT	Astra Zeneca
Ruhrmann et al. [45]	Flu: $n=76$ Ris: $n=77$	24	Flu: 6.68 Ris: 3.51	Chronic schizophrenia (ICD-10)	PANSS negative ≥ 4, stable (maintenance treatment started)	DB-RCT	Bayer Vital GmbH
Saletu et al. [46]	Ami: $n=19$ Fluph: $n=21$	6	Ami: 100 Fluph: 4	Unproductive schizophrenia (ICD-9)	Unproductive schizophrenia	DB-RCT	Sanofi (Synthelabo)
Sirota et al. [47]	Ola: $n=21$ Quet: $n=19$	12	Ola: 16 Quet: 637.2	Schizophrenia (DSM-IV)	Assessed for the deficit syndrome at baseline, PANSS negative > 15, SANS total > 60	SB-RCT	AstraZeneca

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Table 1 (continued)

Study	Study groups/number of participants	Trial duration (weeks)	Mean antipsychotic doses (mg/days)	Diagnosis	Key-operationalisation criteria to defined prominent negative symptoms	Study design	
Speller et al. [48]	Ami: $n=29$ Hal: $n=31$	52	Ami:not stated Hal:not stated	Chronic schizophrenia (DSM-III-R)	> 4 on the sum of the items: the flatness of affect and poverty of speech (Manchester Scale)	DB-RCT	No sponsor stated
Olie et al. [49]	Ami: $n=63$ Zip: $n=60$	12	Ami: 144.7 Zip: 118	Chronic schizophrenia (DSM-III-R)	Baseline PANSS negative had to exceed the PANSS positive by ≥ 6, no acute exacerbation for 12 weeks	DB-RCT	Pfizer
Soni et al. [50]	Sul: $n=12$ Pla: $n=12$	12	Sul: 400 Pla	Chronic schizophrenia (DSM-III)	> 3 on the sum of the items: the flatness of affect and poverty of speech (Manchester Scale)	SB-RCT	Squibb

Ami amisulpride, *Ase* asenapine, *Cari* cariprazine, *Cloz* clozapine, *Flup* flupentixol, *Fluph* fluphenazine, *Hal* haloperidol, *Ola* olanzapine, *Pla* placebo, *Quet* quetiapine, *Ris* risperidone, *Sul* sulpiride, *Zip* ziprasidone, *Zot* zotepine, *DB-RCT* double blind randomized controlled trial, *SB-RCT* single blind randomized controlled trial, *OL-RCT* open label randomized controlled trial, *n* number of participants

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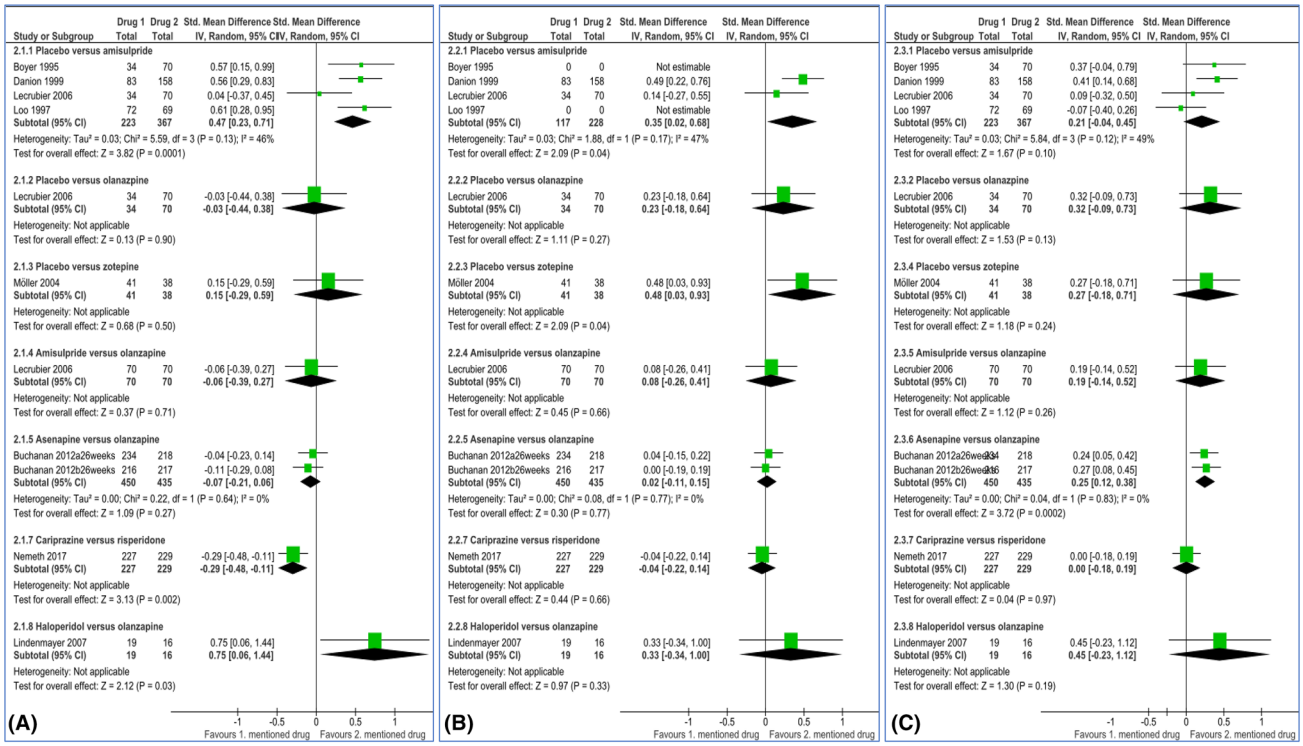

Fig. 2 Forest plots of pairwise meta-analyses for patients with predominant negative symptoms. The size of squares reflects the weight attributed to each study for every separate pairwise meta-analysis (per comparison). Error bars indicate 95% CI. A standardized mean difference smaller than zero means that the first mentioned drug is better for the reduction of specific symptoms. **a** negative symptoms, **b** depressive symptoms, and **c** positive symptoms. 'Not estimable' means that there were no useable data for this outcome

Patients with predominant negative symptoms: effects on psychopathology

Three drugs were compared with placebo (see Fig. 2). For amisulpride, four placebo-controlled trials were available. Amisulpride was significantly better than placebo for negative symptoms ($N=4$; $n=590$, SMD 0.47, CI 0.23, 0.71) and depression ($N=4$, $n=345$, SMD 0.35, CI 0.02, 0.68), while the effect size for positive symptoms was not significant (see Fig. 2). Based on a single trial, olanzapine was not significantly more efficacious than placebo in neither negative symptoms, nor depression nor positive symptoms, and again, based on a single study, zotepine outperformed placebo only in depressive symptoms ($N=1$, $n=79$, SMD 0.48, CI 0.03 to 0.93).

In terms of direct comparisons between antipsychotics, there were no significant differences between amisulpride and olanzapine, and between asenapine and olanzapine, except that asenapine was inferior compared to olanzapine for positive symptoms. Olanzapine was significantly better than haloperidol for negative symptoms in a small trial ($N=1$, $n=35$, SMD 0.75, CI 0.06–1.44); the SMDs for depression and positive symptoms were not statistically significant. The largest trial ($n=456$) found a significant superiority of cariprazine compared to risperidone ($N=1$, $n=456$, SMD −0.29, CI −0.48 to −0.11). In this comparison, there were virtually no differences between drugs in terms of depressive and positive symptoms (see Fig. 2).

Patients with prominent negative symptoms: effects on psychopathology

There were no placebo-controlled studies for this subgroup except one study in which sulpiride tended to be less efficacious (see Fig. 3). In terms of direct comparisons between antipsychotics, there was no significant difference in negative symptoms between amisulpride versus fluphenazine, amisulpride versus haloperidol, and amisulpride versus ziprasidone. In all three comparisons, only one study [43] provided useable data for another outcome—depressive symptoms—where amisulpride was significantly superior to fluphenazine ($N=1$, $n=48$, SMD −0.78, CI −1.37 to −0.19).

There was no significant difference between risperidone and flupenthixol in terms of negative symptoms, positive symptoms, and depressive symptoms. A single study showed a superiority of olanzapine compared to risperidone in terms of both negative symptoms ($N=1$, $n=235$, SMD −0.30,

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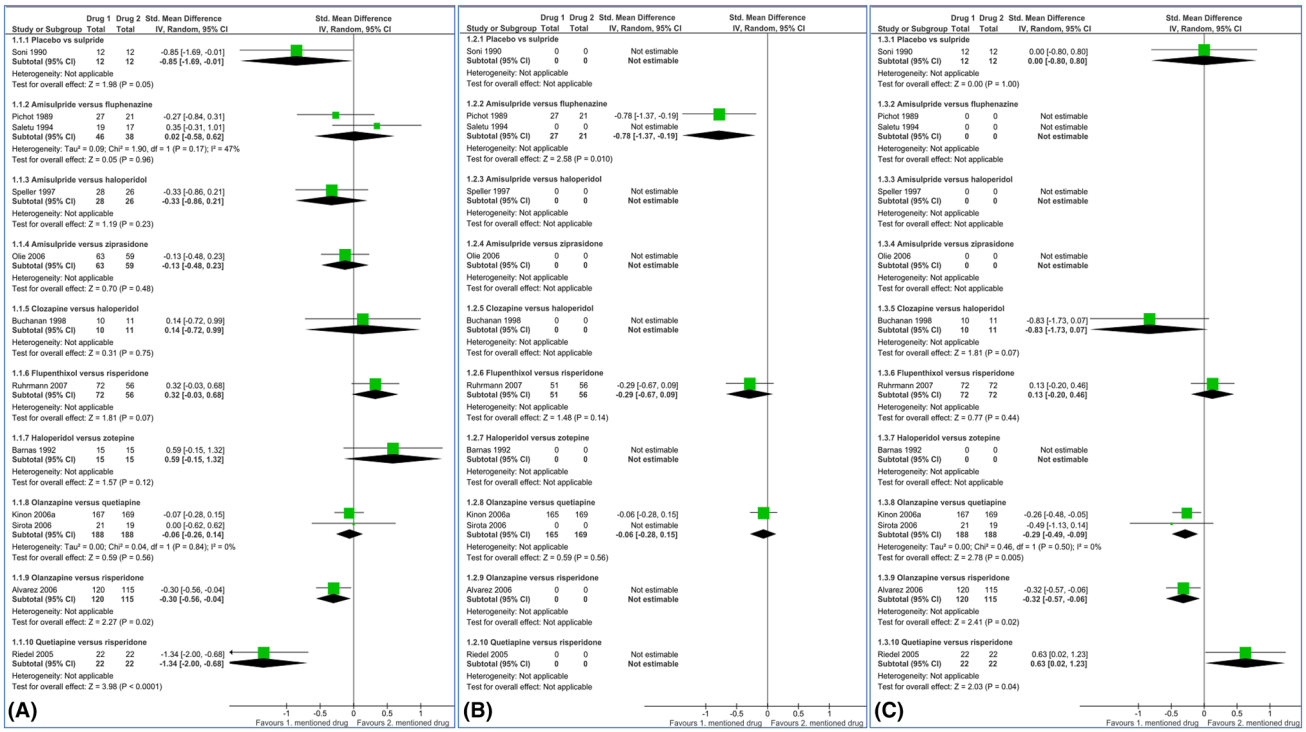

Fig. 3 Forest plots of pairwise meta-analyses for patients with prominent negative symptoms. The size of squares reflects the weight attributed to each study for every separate pairwise meta-analysis (per comparison). Error bars indicate 95% CI. A standardized mean difference smaller than zero means that the first mentioned drug is better for the reduction of specific symptoms. **a** negative symptoms, **b** depressive symptoms, and **c** positive symptoms. 'Not estimable' means that there were no useable data for this outcome

CI −0.04 to −0.56) and positive symptoms ($N=1$, $n=235$, SMD −0.32, CI −0.06 to −0.57).

While there was no significant difference between olanzapine and quetiapine for the reduction of negative and depressive symptoms, olanzapine was significantly better for the treatment of positive symptoms ($N=2$, $n=376$, SMD −0.29, CI −0.49 to −0.09).

In a small single study, quetiapine was superior compared to risperidone in the treatment of negative symptoms ($N=1$, $n=44$, SMD −1.34, CI −2.00 to −0.68), while the effect size for positive symptoms was significant in the opposite direction ($N=1$, $n=44$, SMD 0.63, CI 0.02–1.23).

One study comparing clozapine with haloperidol did not show a difference in terms of negative and positive symptoms (see Fig. 3).

Use of antiparkinson medication and at least one extrapyramidal side-effect

In studies on patients with predominant negative symptoms, use of antiparkinson medication at least once was only reported for the comparisons between amisulpride and placebo and for asenapine versus olanzapine. In neither analysis, there was a significant difference (see eFigure 5).

In studies on prominent negative symptoms, significantly, more fluphenazine-treated patients received antiparkinson medication frequently than did those on amisulpride ($N=1$, $n=102$, OR 0.11 CI 0.01–1.01), flupenthixol-treated patients received it more frequently than those on risperidone ($N=1$, $n=153$, OR 2.80 CI 1.40–5.60), and risperidone-treated patients more frequently than those on quetiapine ($N=1$, $n=44$, OR 0.14 CI 0.03–0.78). The other results were not statistically significant, but the trend was always to the disadvantage of the more dopaminergic compounds (see eFigure 6).

Very few studies reported the outcome "at least one extrapyramidal side effect". The effects were comparable to use of at least one antiparkinson medication. The only relevant additional information was that in a single study of patients with prominent negative symptoms, risperidone produced significantly more EPS than olanzapine ($N=1$, $n=246$, OR 2.50, CI 1.48–4.24, see supplemental eFigure 8).

Assessment of heterogeneity and small trial bias

We did not detect significant heterogeneity in any outcome. As there were very few studies for most of the comparisons, heterogeneity might not be well estimated. Funnel plots

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to detect small trial/publication bias were not meaningful, because the maximum number of trials available for a comparison was four, not enough to decide on asymmetry of the plots.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis regarding the effects of antipsychotics in people with schizophrenia and negative symptoms as inclusion criteria. The main findings were that in terms of predominant negative symptoms, amisulpride was more efficacious than placebo. Moreover, based on a large trial [38], cariprazine was superior to risperidone, and based on a small trial [35], olanzapine was superior to haloperidol. In terms of prominent negative symptoms, only olanzapine and quetiapine significantly outperformed risperidone, again, each based on a single study (247 [39] and 44 [44] participants, respectively). Possible confounding due to parallel effects on depression, positive symptoms or EPS occurred in many studies, albeit more frequently in prominent negative symptoms studies.

In patients with predominant negative symptoms, amisulpride was the only antipsychotic that was significantly more efficacious than placebo. This result can be considered rather robust, because it was based on four studies with 590 participants who is recommended. The effectiveness of amisulpride for negative symptoms is explained, since amisulpride is a selective dopamine D2/D3 receptor antagonist. Previous studies have proposed that hypodopaminergic tone in prefrontal cortex may underlie some of the pathophysiology of negative symptoms and that amisulpride which at low doses (here 50–300 mg/day) binds to presynaptic receptors in the frontal cortex may enhance dopamine transmission in this area. However, there was also a significant superiority of amisulpride for depressive symptoms. Indeed, it has been shown that amisulpride is also a 5-HT7 antagonist which can explain its antidepressant effects [55], and amisulpride has an official indication for dysthymia in some European countries [56]. As depressive and negative symptoms overlap, it is difficult to say whether amisulpride reduces primary or only secondary negative symptoms. Moreover, with the exception of the only negative study [34], all studies were conducted by the manufacturer of amisulpride. Actually, 17 out of 21 included studies (81%) were sponsored by pharmaceutical companies, see Table 1. In head-to-head comparisons of antipsychotics, there were only two statistically significant differences between compounds. The single study showing a superiority of olanzapine over haloperidol was relatively small ($n=35$), so that a replication is needed [35]. The superiority of cariprazine compared to risperidone was more convincing [38]. The sample size was large ($n=461$), there was a run-in phase confirming that negative symptoms were stable, and there was virtually no effect on either depressive symptoms or positive symptoms, and no differential effects on extrapyramidal side-effects (see Fig. 2 and the original publication [38]). Greater affinity to D3 than D2 dopamine receptors in addition to preferential limbic action has been discussed as potential mechanisms of action [57]. However, this study was sponsored by the manufacturer of cariprazine and placebo-controlled evidence is lacking.

The problem in several studies of patients with prominent negative symptoms was that the effect sizes for positive symptoms were either identical or higher than those for negative symptoms. This renders the possibility of confounding by secondary effects more likely. Concretely, in the comparisons of risperidone with flupenthixol, of olanzapine with quetiapine, and of clozapine with haloperidol, only the SMDs for positive symptoms were significant and they were higher than those for negative symptoms (see Fig. 3). In the single study comparing olanzapine with risperidone, the effect sizes for negative and positive symptoms were virtually identical. The results of the single study comparing quetiapine with risperidone are difficult to interpret, because quetiapine was significantly better for negative symptoms, but less efficacious for positive symptoms. Perhaps, this can be explained in part by quetiapine being a norepinephrine reuptake inhibitor [58, 59] which is FDA-approved for the treatment of major depressive disorder [60]. However, significant effects in opposite directions are unusual in antipsychotic trials, and the study was relatively small. Amisulpride was not significantly better than fluphenazine for negative symptoms, but was for depression. Finally, in its only small study, sulpiride tended to be less efficacious than placebo, but this effect was due to the fact that negative symptoms were lower in the placebo group at baseline. When the original authors corrected for this baseline imbalance, sulpiride was more efficacious than placebo [50], in contrast to what Fig. 3 suggests.

We believe that the results can be interpreted qualitatively in the sense that it is less stringent to evaluate negative symptoms in patients with prominent negative symptoms than in patients with predominant negative symptoms. In the former group, the effects are even more difficult to disentangle from effects on other symptoms, in particular, positive symptoms. In three [39, 42, 47] of six studies measuring both negative and positive symptoms, the effect size for positive symptoms was equal or higher than that for negative symptoms (Fig. 3). In the subgroup, predominant negative symptoms, this was the case in only one study [37] (Fig. 2), although as discussed above, even many of these studies were not ideal.

Moreover, there was no overlap in the categories, and comparisons were either available for the predominant or the prominent subgroup (e.g., all amisulpride versus placebo

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studies fell in the predominant subgroup). Thus, if we had not applied this distinction, the results for each drug would have been the same.

We did not examine differences between second-generation and first-generation antipsychotics as classes, because this classification has been replaced with "Neuroscience Based Nomenclature (NbN)" by societies such as the European and the American Colleges of Neuropsychopharmacology [59]. However, the analysis of 'antiparkinson medication use' and 'at least one EPS' showed that it is difficult to compare compounds that produce many extrapyramidal side-effects (in particular, D2 receptor antagonists such as haloperidol, but also risperidone) with antipsychotics which are not very prone to extrapyramidal side-effects (e.g., D2/5-HT2 receptor antagonists and norepinephrine reuptake inhibitors such as quetiapine [59]). Such comparisons often could be biased by the higher frequency of extrapyramidal side-effects in the former group, mimicking negative symptoms (see eFigures 7 and 8). Prophylactic antiparkinson medication could mitigate the phenomenon, however, only Lindenmayer et al. [35] and Buchanan et al. [41] have applied this strategy.

How do these results mesh with what we know about the efficacy of other pharmacological treatments for negative symptoms? A comprehensive meta-analysis of 168 RCTs found significant effects on negative symptoms for antidepressants, second-generation antipsychotics, psychological treatments, glutamatergic medication, and the combination of pharmacological agents [14]. In an overview of reviews, 12 out of 26 pharmacological cotreatments added to antipsychotics significantly outperformed controls [61]. However, in both reviews, the study populations were not restricted to patients with prominent/predominant negative symptoms. Thus, effects on secondary negative symptoms, again, could not be ruled out. A subgroup analysis of patients with predominant negative symptoms in a meta-analysis on the effects of antidepressants added to antipsychotics revealed a significant positive effect ($N = 17$, $N = 729$; SMD -0.58, CI -0.94 to -0.21) [62]. Therefore, the addition of antidepressants to antipsychotics is an evidence-based treatment for negative symptoms in schizophrenia, [63] with the caveat that the inclusion criteria of these studies were not as stringent as in the current review. All definitions of the original authors were accepted without further operationalisation in this previous systematic review [63].

The present meta-analysis is not without limitations. While a previous meta-analysis in patients with exacerbations of positive symptoms included 167 placebo-controlled studies [8], we identified only six placebo-controlled and 16 active-controlled studies (one study had two active treatments and one placebo group) in the negative symptom population, and for many comparisons, only one study was available. This is not an objection to systematically present and review their effect sizes (which primarily depend on sample size and not on number of studies). This procedure helps to present the data graphically in a standardized way (effect sizes and their statistical significance). In addition, we systematically present which studies are available to date. However, it is imaginable that some comparisons could show significant effects if statistical power was increased. Figure 2,3 and eFigures 7, 8 show that data on depressive symptoms, positive symptoms, and extrapyramidal side effects often were not presented in the original studies, thus making it difficult to evaluate the secondary effects. A systematic reporting of these outcomes should be a prerequisite for future studies on negative symptoms. The major issue is the lack of consensus about how to exactly define inclusion criteria in such studies [11], so that the criteria in the individual studies varied substantially. Moreover, while we addressed the predominant/prominent negative symptom distinction which had been discussed at a recent conference and is important for the FDA and EMA, this distinction is not the same as the validated concepts of the deficit syndrome [2] and of 'persistent negative symptoms' described in the introduction. These definitions have been developed scientifically, but rarely applied so far. The "deficit syndrome" has only been used in three [34, 35, 41], out of 21 studies and the "persistent negative symptoms" concept has only been explicitly used in two studies by Buchanan et al. [32, 64], and a few other studies came close. Therefore, it was not possible to examine these constructs in more detail. However, one key aspect of these criteria and also stressed by the NIMH consensus [65], persistence of negative symptoms, recommended for at least 6 months by Buchanan 2007 [7], was considered by only six trials (see Table 1). Finally, the scores of rating scales to measure negative symptoms are difficult to interpret clinically. Equipercentile linking analyses such as one that compared SANS scores with clinical global impressions of the raters [66] also would be useful for other scales.

Taken together, our findings showed that the inclusion criterion 'predominant negative symptoms' probably provides a better safeguard against secondary effects than the criterion 'prominent negative symptoms.' Amisulpride is the best-examined antipsychotic for predominant negative symptoms compared to placebo, but this superiority is difficult to disentangle from that on depression. A single, though large, trial ($n = 461$) demonstrated a superiority of cariprazine compared to risperidone, where effects on depressive symptoms, positive symptoms, and extrapyramidal side-effects were controlled, [38], but placebo-controlled evidence is lacking and the trial was sponsored by cariprazine's manufacturer. Future trials should apply scientifically developed definitions such as the deficit syndrome [1] and the persistent [7, 67] negative symptoms concept.

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Compliance with ethical standards

Conflict of interest In the last 3 years, Stefan Leucht has received honoraria for consulting from LB Pharma, Lundbeck, Otsuka, Teva Pharmaceutical Industries Ltd, LTS Lohmann, Geodon Richter, Recordati, Boehringer Ingelheim, and for lectures from Janssen, Lilly, Lundbeck, Otsuka, SanofiAventis and Servier.

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