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Medication-induced akathisia with newly approved antipsychotics in patients with a severe mental illness: a systematic review and meta-analysis --Manuscript Draft--

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Full Title:	Medication-induced akathisia with newly approved antipsychotics in patients with a severe mental illness: a systematic review and meta-analysis
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Abstract:	<p>Background</p> <p>Akathisia is a common and distressing movement disorder, characterized by a subjective (inner restlessness) and objective (excessive movements) component. It can have a negative impact on clinical outcome and even lead to treatment discontinuation. Although medication-induced akathisia is more commonly associated with the use of first-generation antipsychotics (FGA), it also occurs with most second-generation antipsychotics (SGA), including the newly approved antipsychotics (NAP) asenapine, lurasidone, iloperidone, cariprazine and brexpiprazole. Until now, no meta-analysis has been published on the risk of akathisia for all NAP, as monotherapy or adjunctive treatment in patients with a severe mental illness.</p> <p>Objective</p> <p>The primary objectives of this systematic review and meta-analysis were (i) to compare prevalence akathisia rates of the NAP, as monotherapy or adjunctive treatment, in adult patients with a severe mental illness (i.e., schizophrenia, bipolar disorder or major depressive disorder), using data from published and unpublished clinical randomized trials and (ii) to examine the role of several study characteristics explaining differences in the prevalence rates of akathisia between studies.</p> <p>Methods</p> <p>A systematic literature search, using the PubMed, Embase and Cochrane Library database (until October 2018), was conducted for placebo- as well as active-controlled clinical trials, including subjective (percentage of patients spontaneously reporting akathisia) and/or scale-defined medication-induced akathisia rates with NAP (as monotherapy or as adjunctive treatment) in adult patients with schizophrenia, bipolar disorder or major depressive disorder. Additional unpublished clinical trials were identified through the clinicaltrials.gov electronic database. Two meta-analyses [prevalence rates and odds ratio, OR (placebo vs. active) of medication-induced akathisia with NAP] were performed to obtain an optimal estimation of akathisia risks of adult patients with an severe mental illness under these treatment conditions and to assess the role of study characteristics.</p> <p>Results</p> <p>Two hundred and thirteen reports were selected as potentially eligible for our meta-analysis. Of these, 48 met the inclusion criteria. Eight records, identified through the clinicaltrials.gov database and cross-reference and fulfilling the inclusion criteria, were added, resulting in a total of 56 records. The estimated weighted mean prevalence rate (with 95%CI) of akathisia was 7.7% (6.5-9.1) with estimates being respectively 3.9% (2.4-6.3) for iloperidone, 6.8% (5.1-9.0) for asenapine, 10.0% (7.4-13.5) for brexpiprazole, 12.7% (10.1-16.1) for lurasidone, and 17.2% (13.4-22.1) for cariprazine. Type of medication ($p<0.0001$), diagnosis ($p=0.02$) and race ($p=0.0003$) significantly explained part of the heterogeneity of the prevalence estimates of akathisia between studies. The estimated weighted OR of akathisia under medication, compared to placebo, was 2.43 (95% CI: 1.91-3.10). The OR was smallest for iloperidone (OR 1.20; 95% CI 0.42-3.45) and increased for, respectively, brexpiprazole (OR 2.04; 95% CI 1.09-3.83), asenapine (OR 2.37; 95% CI 1.32-4.27), lurasidone (OR 3.74; 95% CI</p>

	<p>2.32–6.02) and cariprazine (OR 4.35; 95% CI 2.80–6.75). Only type of medication (p=0.03) explained systematic differences in the OR for akathisia between placebo versus active treatment across studies. After Tukey-adjustment for multiple testing, no significant differences between these ORs were found. The severity of akathisia with NAP generally is mild to moderate, only in a minority of cases (<5%) leading to treatment discontinuation.</p> <p>Conclusions</p> <p>The use of a NAP raises the akathisia risk more than two-fold, when compared to patients receiving placebo. Although distinctions between the different NAP were not clear in placebo controlled trials, generally the results of our meta-analyses and systematic review indicate that these differences more than likely reflect real differences, with iloperidone showing the most benign akathisia profile. Moreover, due to patient characteristics and methodological issues, prevalence rates of akathisia with NAP found in this meta-analysis may even be an underestimation of true prevalence rates.</p>
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Akathisia with newly approved antipsychotics in severe mental illness patients

Medication-induced akathisia with newly approved antipsychotics in patients with a severe mental illness: a systematic review and meta-analysis.

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Compliance with Ethical Standards

Conflicts of Interest

Koen Demyttenaere declares that he has received fees from Lundbeck, Servier, Boehringer Ingelheim, LivaNova, Pfizer, Recordati and Johnson & Johnson in the past 3 years.

Giorgio Racagni declares that he has received personal fees from Servier and Recordati

Johan Detraux and Kristof Vansteelandt have no conflict of interest.

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Abstract

Background

Akathisia is a common and distressing movement disorder, characterized by a subjective (inner restlessness) and objective (excessive movements) component. It can have a negative impact on clinical outcome and even lead to treatment discontinuation. Although medication-induced akathisia is more commonly associated with the use of first-generation antipsychotics (FGA), it also occurs with most second-generation antipsychotics (SGA), including the newly approved antipsychotics (NAP) asenapine, lurasidone, iloperidone, cariprazine and brexpiprazole. Until now, no meta-analysis has been published on the risk of akathisia for all NAP, as monotherapy or adjunctive treatment in patients with a severe mental illness.

Objective

The primary objectives of this systematic review and meta-analysis were (i) to compare prevalence akathisia rates of the NAP, as monotherapy or adjunctive treatment, in adult patients with a severe mental illness (i.e., schizophrenia, bipolar disorder or major depressive disorder), using data from published and unpublished clinical randomized trials and (ii) to examine the role of several study characteristics explaining differences in the prevalence rates of akathisia between studies.

Methods

A systematic literature search, using the PubMed, Embase and Cochrane Library database (until October 2018), was conducted for placebo- as well as active-controlled clinical trials, including subjective (percentage of patients spontaneously reporting akathisia) and/or scale-defined medication-induced akathisia rates with NAP (as monotherapy or as adjunctive treatment) in adult patients with schizophrenia, bipolar disorder or major depressive disorder. Additional unpublished clinical trials were identified through the clinicaltrials.gov electronic database. Two meta-analyses [prevalence rates and odds ratio, OR (placebo vs. active) of medication-induced akathisia with NAP] were performed to obtain an optimal estimation of akathisia risks of adult patients with an severe mental illness under these treatment conditions and to assess the role of study characteristics.

Results

Two hundred and thirteen reports were selected as potentially eligible for our meta-analysis. Of these, 48 met the inclusion criteria. Eight records, identified through the clinicaltrials.gov database and cross-reference and fulfilling the inclusion criteria, were added, resulting in a total of 56 records. The estimated weighted mean prevalence rate (with 95%CI) of akathisia was 7.7% (6.5-9.1) with estimates being respectively 3.9% (2.4-6.3) for iloperidone, 6.8% (5.1-9.0) for asenapine, 10.0% (7.4-13.5) for brexpiprazole, 12.7% (10.1-16.1) for lurasidone, and 17.2% (13.4-22.1) for cariprazine. Type of medication ($p<0.0001$), diagnosis ($p=0.02$) and race ($p=0.0003$) significantly explained part of the heterogeneity of the prevalence estimates of akathisia between studies. The estimated weighted OR of akathisia under medication, compared to placebo, was 2.43 (95% CI: 1.91-3.10). The OR was smallest for iloperidone (OR 1.20; 95% CI 0.42-3.45) and increased for, respectively, brexpiprazole (OR 2.04; 95% CI 1.09-3.83), asenapine (OR 2.37; 95% CI 1.32-4.27), lurasidone (OR 3.74; 95%

CI 2.32–6.02) and cariprazine (OR 4.35; 95 % CI 2.80–6.75). Only type of medication (p=0.03) explained systematic differences in the OR for akathisia between placebo versus active treatment across studies. After Tukey-adjustment for multiple testing, no significant differences between these ORs were found. The severity of akathisia with NAP generally is mild to moderate, only in a minority of cases (<5%) leading to treatment discontinuation.

Conclusions

The use of a NAP raises the akathisia risk more than two-fold, when compared to patients receiving placebo. Although distinctions between the different NAP were not clear in placebo controlled trials, generally the results of our meta-analyses and systematic review indicate that these differences more than likely reflect real differences, with iloperidone showing the most benign akathisia profile. Moreover, due to patient characteristics and methodological issues, prevalence rates of akathisia with NAP found in this meta-analysis may even be an underestimation of true prevalence rates.

Key points

Severe mental illness patients receiving a newly approved antipsychotic are more than twice as likely to suffer from akathisia, compared to those receiving placebo. Despite this, the severity of akathisia with these agents generally is mild to moderate, only in a minority of cases leading to treatment discontinuation.

Although distinctions between the different newly approved antipsychotics are not always clear in placebo controlled trials, with the exception of iloperidone, all these antipsychotics, as monotherapy or adjunctive treatment, likely are associated with moderate (asenapine and brexpiprazole) to high prevalence rates of akathisia (lurasidone and cariprazine) in patients with a severe mental illness.

As the included studies almost exclusively included samples with middle-aged patients and in many cases rely on spontaneous reporting, rather than on scale-defined akathisia to assess prevalence rates, akathisia rates found in this meta-analysis are expected to be an underestimate of actual outcome rates in daily clinical practice.

1 Background

Akathisia, a term derived from the Greek for ‘inability to sit’ (*a* + *kathisis*, without sitting), is a common and distressing movement disorder [1-5]. It is characterized by feelings of inner tension, restlessness and/or discomfort with a compelling urge to move (subjective component), in most cases leading to observable excessive movements (objective component) that are complex, semi-purposeful, and repetitive, such as persistent swinging and crossing and uncrossing of the legs, rocking from foot to foot, pacing incessantly, and inability to sit or stand still [1-12]. According to certain authors [e.g., 4] akathisia should be considered more as a sensorimotor (instead of a movement) disorder, because the sensory component is the defining characteristic of the condition, with motor signs being secondary to the subjective feelings of restlessness and the urge to move. On the basis of the time of onset, pattern of presentation and its duration, several subtypes of akathisia have been described [2,4,7,11] (see **Table 1**).

Table 1: Subtypes of akathisia [2-14]

Acute akathisia: akathisia occurring within 6 weeks (usually within 2 or 3 weeks) of either initiating an antipsychotic medication, increasing the antipsychotic medication dose, or switching to a high-potency antipsychotic medication. The duration of symptoms and signs of acute akathisia do not exceed 3 months.

Chronic akathisia: akathisia that has been present for a long time (usually for more than 3 months).

Tardive akathisia: akathisia occurring late (usually after 3 months or more) during the course of treatment with antipsychotics. It is provoked or exacerbated by dose reduction or may even emerge after antipsychotic medication discontinuation. It often improves or attenuates, at least temporarily, when the dose is increased, but it may also persist for months or years even after the antipsychotic medication is discontinued. Tardive akathisia is indistinguishable in clinical appearance from acute akathisia.

Withdrawal akathisia: akathisia occurring within 2-6 weeks following dose reduction or cessation of an antipsychotic medication, or following dose reduction or discontinuation of an anticholinergic medication. It is considered to be phenomenologically indistinguishable from acute akathisia and generally disappears within about 6 weeks. If the akathisia persists for

more than 6 weeks, it is no longer considered withdrawal akathisia but instead should be classified as tardive akathisia.

Persistent akathisia: akathisia that is particularly disabling and often refractory to treatment.

Pseudo-akathisia: this term has been used for the condition in which a patient exhibits the objective signs of akathisia in the absence of awareness of the typical subjective experience such a restlessness. It is not clear if pseudo-akathisia should actually be considered a “pseudo” form of the disorder, because many patients experience discomfort that they are unable to understand or express clearly. This form of akathisia therefore probably reflects a late stage of chronic akathisia, where the patient is either unable to verbalize the subjective dysphoria or this component has faded over time, or is a variant of tardive dyskinesia.

Subjective akathisia: akathisia that is essentially an abnormal subjective state. This is particularly evident in milder cases, as the signs of motor restlessness are not invariably present.

Bing-Sicard akathisia: akathisia occurring in parkinsonian disorders such as Parkinson’s disease and post-encephalitic parkinsonism.

Hemi-akathisia: akathisia affecting only one side of the body.

Spontaneous akathisia: akathisia occurring in untreated patients.

When mild to moderate in severity, akathisia predominantly affects the lower extremities from the hips to the ankles [2,4,7]. With increasing severity, however, akathisia can involve the entire body [4].

Akathisia can have a negative impact on clinical outcome [13]. It may be disturbing for the patient and increase the risk of suicidal ideation and impulsive behavior, in extreme cases leading to suicide or aggressive behavior (homicide) [7,15,16]. Moreover, akathisia can become a cause of poor medication adherence and even treatment discontinuation [4,16].

Medication-induced akathisia generally appears to be dose-related: the risk of this adverse drug reaction is greater in case of rapid dose increase, high-dose strategies or polypharmacy [17-22]. Medication-naïve patients are more sensible for this side effect [1,3,4,13]. Other risk factors may include negative symptoms, cognitive dysfunction, traumatic brain injury, cancer, a prior presence of substance abuse (especially cocaine), iron deficiency, prior akathisia, and concomitant parkinsonism. It also appears that patients with

mood disorders, particularly bipolar disorder, may actually be at higher risk for medication-induced akathisia. Although chronic and tardive akathisia may be associated with advanced age and female gender, there is no clear evidence that these factors are associated with a higher risk of acute akathisia [4,8,10,13].

Currently, medication-induced akathisia is a diagnosis made purely by patient report and clinical observation [4]. Most studies, providing safety data for medications, mention the percentage of patients spontaneously reporting akathisia. They also provide in many cases data from rating scales that have been developed to identify and score the severity of akathisia [2]. The most widely used rating scale for the measurement of akathisia symptoms is the Barnes Akathisia Rating Scale (BARS) [2,4,5,11]. This 4-item scale includes a subjective (awareness of the presence of restlessness and any associated subjective distress) and objective assessment of akathisia, as well as a global clinical assessment of akathisia. The instrument is easy to administer and score, with established reliability, validity, and clinical utility [1,2]. Most studies using this rating scale define treatment-emergent akathisia as a total BARS score of 2 or more at (any) post-baseline assessment (assuming a total score of less than 2 at baseline). Another rating scale used in research is the Extrapyramidal Symptom Rating Scale (ESRS). This scale includes one item on the symptoms of akathisia, one item assessing objective signs of akathisia, and a Clinical Global Impression of Severity (CGI-S) of akathisia [1].

Although several medications across a number of categories, including antidepressants [particularly selective serotonin receptor inhibitors (SSRIs), such as paroxetine], calcium channel blockers, antibiotics (e.g., azithromycin), antiemetics (e.g., metoclopramide), and even illicit drugs (e.g., cocaine) can induce akathisia [1,3-5,7,10,12,23-27], it is principally seen in association with antipsychotic medication [2,3,5].

1 In 2009 and 2010, three new antipsychotics were approved by the U.S. Food and Drug
2 Administration (FDA): asenapine (SaphrisTM), iloperidone (FanaptTM), and lurasidone
3 (LatudaTM). Later, in 2015, brexpiprazole (RexultiTM) and cariprazine (VraylarTM) have been
4 added to the pantheon of antipsychotic medications. To get a fuller picture of the relationship
5 between these antipsychotics and akathisia risk and because, at this moment, no meta-analysis
6 has been published about this risk for all these agents as monotherapy, as well as adjunctive
7 treatment in patients with severe mental illness, we have conducted a systematic review and
8 meta-analysis on this topic.
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23 **2 Objective**

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29 The purpose of this systematic review was to examine the risk of akathisia with the
30 newly approved antipsychotics (NAP) asenapine, iloperidone, lurasidone, brexpiprazole, and
31 cariprazine, using data reported in randomized (placebo and/or active) controlled trials. A
32 meta-analysis of akathisia outcomes was conducted to calculate drug-related risk. This
33 information could aid clinicians in assessing the akathisia risks of the NAP and place them
34 against the risk with the other available second generation antipsychotics (SGA).
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47 **3 Methods**

48 **3.1 Literature Search**

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57 A systematic search of the PubMed, Embase, Cochrane Library and clinicaltrials.gov
58 electronic databases from their inception to October 2018 was conducted to synthesize the
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results concerning the current state of knowledge about akathisia and its relationship to the NAP in adult patients with a severe mental illness (schizophrenia, bipolar disorder or major depressive disorder). Following key words were used in various combinations:

‘schizophrenia’, ‘bipolar disorder’, or ‘major depressive disorder/major depression’, ‘akathisia’, and ‘asenapine’, ‘iloperidone’, ‘lurasidone’, ‘brexpiprazole’, or ‘cariprazine’.

References of the identified studies and reviews were carefully cross-checked for additional relevant studies. We performed this systematic review in accordance with the ‘Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)’ guidelines.

3.2 Trial Selection

For the meta-analysis we selected randomized controlled (placebo-controlled and/or active-controlled) trials. Individual clinical studies were included if:

- 1: they were written in English;
- 2: they included patients who were diagnosed with a schizophrenia spectrum or other psychotic disorder, bipolar disorder, or major depressive disorder;
- 3: they included at least one of the following outcome measures for akathisia:
 - prevalence of akathisia
 - percentage of patients spontaneously reporting akathisia. In this meta-analysis, the terms ‘akathisia’ and ‘restlessness’ will be referred to only as ‘akathisia’. For clinical studies with a record of both akathisia and restlessness, only the percentage of patients spontaneously reporting akathisia was considered.
 - percentage of patients with scale-defined medication-induced akathisia: an objective assessment of akathisia using the BARS Global Clinical

Assessment of Akathisia (item 4) score, with scores ≥ 2 describing the objective diagnosis of akathisia (0 = absent, 1 = questionable, 2 = mild akathisia, 3 = moderate akathisia, 4 = marked akathisia, 5 = severe akathisia).

- mean/median time to onset (i.e. the first time point at which akathisia was reported);
- mean/median duration: the duration (days/weeks) of akathisia;
- severity of akathisia: akathisia can be described as mild, moderate or severe;
- discontinuation rates: rates of discontinuation that were specifically due to akathisia.

3.3 Statistical Analysis

Two meta-analyses were conducted on the basis of the available studies. A first analysis was performed to obtain an optimal estimation of the prevalence of akathisia. Although the proportion was used as effect size (ES), all proportions were converted into logits as the mean proportion across studies underestimates the size of the confidence interval (CI) around the mean proportion (due to the compression of the standard error as p approaches 0 or 1) and overestimates the degree of heterogeneity across ESs [28]. The logit method circumvents these problems and therefore was the preferred method, especially given our interest in between study differences. For ease of interpretation, all final results were back-converted into proportions after analysis. Next, a second meta-analysis was performed to obtain an optimal estimate of the risk for akathisia under placebo *versus* active treatment conditions. In this meta-analysis, the Odds Ratio (OR) was the used ES to compare both groups is. We refrained from using the proportion difference because simulation studies have showed that this ES results in an

underestimation of the CI around the mean proportion difference and a consistent overestimation of the amount of heterogeneity across ESs between studies [28]. However, because the OR has the inconvenient form of being asymmetrically centered around 1 rather than 0, it is common practice to perform analyses on the natural Log of the OR (LOR), which is normally distributed. For ease of interpretation, all final results and CIs were back-converted into ORs after analysis.

To examine the homogeneity of the ES distribution in both meta-analyses, visual inspection and the Q-statistic were used [28]. When the 0-hypothesis is rejected by the Q-statistic, the ES distribution is not homogeneous, implying that the variability in the ESs between studies is larger than can be expected on the basis of sampling error (the error associated with the fact that the estimated ESs in the individual studies are based on different samples of subjects). In this case, we conducted a mixed random effects model implying that the observed variance stems from three sources: (a) variance due to subject-level sampling error, (b) variance from study characteristics that we could identify, (c) and variance from other systematic random or unmeasured sources. In both meta-analyses, several study characteristics were incorporated including (a) type of (active) medication (iloperidone, asenapine, lurasidone, brexpiprazole, cariprazine), (b) diagnosis (schizophrenia vs. bipolar mania vs. major depression), (c) time of follow-up assessment (expressed in weeks), (d) titration time (expressed in days), (e) dosing (fixed versus flexible), and (f) race/ethnicity (proportion of Caucasians in the study).

To examine the possibility of publication bias, we used the Begg-Mazumder and Egger's bias test.

4 Results

4.1 Literature Search

The original search in the PubMed, Embase and Cochrane Library databases yielded a total of 1,534 reports (asenapine: 369; iloperidone: 221; lurasidone: 473; brexpiprazole: 203; cariprazine: 268). Of these, 1,045 duplicate reports were removed (see Fig. 1). Overall, 213 references of published studies were selected as potentially eligible, of which 48 original records, identified on the basis of 68 publications, met the inclusion criteria. Six unpublished studies with results identified through the clinicaltrials.gov database, and 2 records identified through cross-reference and fulfilling the inclusion criteria, were added, resulting in a total of 56 original records (70 publications) [16-21, 29-97] (see supplementary online material for further details). The different studies of McIntyre et al. [35-38], Schoemaker [43,44] , Landbloom and Durgam [48, 49] and Loebel [91,92] were each counted as one as their pivotal or core study was followed by one or several extension trials containing patients from the original study. Table 1 (see electronic supplementary material) gives an overview of study characteristics and results of the included placebo and/or active-controlled records.

Figure 1: Prisma Checklist Flow Diagram

4.2 Meta-Analytic Results of Prevalence Rates of Medication-Induced Akathisia with Newly Approved Antipsychotics

Based on a meta-analysis involving 56 (placebo-and active controlled) studies with 16,302 unique patients, the estimated weighted mean prevalence rate of akathisia is 9.5% (95% CI: 9.0-10.0). In Figure 2, the distribution of the estimated prevalence rates with 95% CIs of akathisia for each individual study, ordered from small to large, is depicted together with the weighted mean prevalence rate with 95% CI for the Fixed Effects Model (FEM) (assuming only

sampling error) and Random Effects Model (REM) (assuming variance from sampling error and other systematic random sources). The Q-statistic indicated that the distribution of akathisia prevalence rates of individual studies was not homogeneous ($\chi^2(55)=419.46, p<0.0001$), implying that the variability in the prevalence rates of akathisia between studies is larger than can be expected on the basis of sampling error. Therefore, we estimated a Random Effects Model (REM), assuming that the variance of the prevalence rates of individual studies is due to subject-level sampling error and other (unknown) sources of systematic variation. As can be seen in this figure, the estimated prevalence rate of akathisia in the REM is 7.7% (95% CI: 6.5-9.1). Consequently, in a next step, we examined the potential role of several study characteristics to explain systematic differences in prevalence rates of akathisia between studies.

Figure 2: Distribution of estimated prevalence rates with 95% CIs of akathisia for each individual study

Table 2. Prevalence rates of akathisia with newly approved antipsychotics

Newly approved antipsychotic	Prevalence rate of akathisia	95% CI
Iloperidone ^a	3.9 %	2.4 %-6.3 %
Asenapine ^{ab}	6.8 %	5.1 %-9.0 %
Brexpiprazole ^{bc}	10.0 %	7.4 %-13.5 %
Lurasidone ^{cd}	12.7 %	10.1 %-16.1 %
Cariprazine ^d	17.2 %	13.4 %-22.1 %

Note: ^{abcd} Prevalence rates that do not share the same subscript are statistically significantly different after Tukey adjustment for multiple comparisons

Results indicate that type of medication, ($F(4,32.6)=15.02$, $p<0.0001$), diagnosis, ($F(2,30.2)=4.37$, $p=0.02$) and race ($F(1,30.9)=16.82$, $p=0.0003$), significantly explained part of the heterogeneity of the prevalence estimates of akathisia between the included studies.

As can be seen in Table 2, the estimated prevalence rates (with 95% CI) of akathisia, ordered from low to high, are respectively 3.9% (2.4–6.3) for iloperidone, 6.8% (5.1–9.0) for asenapine, 10% (7.4–13.5), for brexpiprazole, 12.7% (10.1–16.1) for lurasidone, and 17.2% (13.4–22.1) for cariprazine. After Tukey-adjustment for multiple testing, the prevalence rate of

akathisia was significantly ($p<0.05$) lower in iloperidone compared to brexpiprazole, lurasidone, and cariprazine. In addition, the prevalence rate of akathisia was significantly ($p<0.05$) lower in asenapine compared to lurasidone and cariprazine. Finally, the prevalence rate of akathisia was significantly ($p<0.05$) lower for brexpiprazole compared to cariprazine (see Table 2). Next, with respect to diagnosis, the estimated prevalence of akathisia (with 95% CIs) is respectively 6.6% (5.7-7.7) in schizophrenia, 9.2% (6.8-12.5) in bipolar mania, and 11.7% (8.2-16.8) in major depression. After Tukey adjustment for multiple comparisons, there is a significantly ($p<0.05$) difference in prevalence of akathisia between schizophrenia and major depression. Further, the prevalence rate of akathisia decreases significantly ($p<0.05$) as a function of race with the estimated prevalence rate of akathisia being lower in studies in which the proportion of Caucasians is higher. Finally, it should be noted that differences in prevalence rates of akathisia between studies could not be explained by differences in time of follow-up assessment [$F(1,25.2)=0.67$, $p=0.42$], titration time [$F(1,25.7)=1.90$, $p=0.18$], or dosing [$F(1,38.2)=1.55$, $p=0.22$].

Akathisia was predominantly reported as mild to moderate and generally time-limited. Treatment discontinuation rates with the NAP were low ($<5\%$).

With respect to publication bias Begg and Mazumdar's rank correlation (using Kendall's tau) ($z=-0.34$, $p=0.0007$), as well as Egger's regression intercept were significant, [$t(46)=3.82$, $p=0.0004$], suggesting that there is evidence for publication bias.

4.2 Meta-Analytic Results of Odds Ratio (Placebo vs. Active) of Medication-Induced Akathisia with Newly Approved Antipsychotics

Based on a meta-analysis involving 48 (placebo-controlled) studies with 7,132 unique patients in the placebo condition and 12,722 unique patients in the active medication condition, an estimated weighted OR of 2.24 [95% CI:1.93–2.62] was found, indicating that the odds of akathisia are 2.24 times higher for patients receiving a NAP, compared to those in the placebo condition. In Figure 3, the distribution of the estimated ORs with 95% CI for each individual study, ordered from smallest to largest, is presented together with the weighted OR for the FEM and REM. Further, the Q-statistic indicated that the distribution of the LORs of individual studies is not homogeneous ($\chi^2(47)=102.22$, $p<0.0001$), implying that the variability in LORs between studies is larger than can be expected on the basis of sampling error. Therefore, we estimated a REM, assuming that the variance of the LORs of individual studies is due to subject-level sampling error and other (unknown) sources of systematic variation. As can be seen in this figure, the estimated weighted OR from the REM is 2.43 (95% CI: 1.91-3.10), indicating that the odds of having akathisia are 2.4 times higher for patients in the active treatment condition compared to those in the placebo condition.

Figure 3: Distribution of estimated odds ratios with 95% CIs of akathisia for each individual study

When examining the potential role of several study characteristics to explain systematic differences in the ORs for akathisia between placebo versus treatment conditions across studies, results revealed that part of this heterogeneity can be explained by medication type, $F(4,24.4)=3.36$, $p=0.03$.

The ORs for the different medication groups are shown in Table 3. Note that all ORs are significantly different from 1 with the exception of the OR for iloperidone (for which 1 is included within the 95 % CI interval). However, after Tukey-adjustment for multiple testing, there were no significant ($p<0.05$) differences between these ORs. Finally, there were no effects found for diagnosis [$F(2,32.8)=0.68$, $p=0.52$], time of follow-up assessment [$F(1,38)=0.04$, $p=0.84$], titration time [$F(1,31.1)=0.39$, $p=0.54$], dosing [$F(1,38)=0.32$, $p=0.57$] and race [$F(1,27)=0.09$, $p=0.77$].

Table 3. Odds Ratio for akathisia comparing medication with placebo conditions

Newly approved antipsychotic	Odds Ratio	95% CI
Iloperidone	1.20	0.42-3.45
Brexipiprazole	2.04	1.09-3.83
Asenapine	2.37	1.32-4.27
Lurasidone	3.74	2.32-6.02
Cariprazine	4.35	2.80-6.75

With respect to publication bias, Begg and Mazumdar's rank correlation (using Kendall's tau) was not significant ($z=-0.34$, $p=0.0007$), whereas Egger's regression intercept was significant [$t(38)=2.49$, $p=0.02$]. In summary, these results rather suggest that there is no evidence for publication bias.

5. Discussion

Within the class of antipsychotics, the risk of akathisia is greater with (particularly high-potency) first-generation antipsychotics (FGA) (e.g., haloperidol and fluphenazine) than with SGA [3,4,98]. Prevalence rates of akathisia with FGA vary between 8% and 76% across studies [4,8,10]. It was commonly thought that akathisia was not a significant problem with SGA [4]. However, despite the fact that, as a group, SGA are generally reported to be more benign than FGA [11,13,98-102], the prevalence rate of akathisia with certain SGA can be quite high [4,103]. Moreover, polypharmacy with SGA can be associated with even higher prevalence rates of akathisia [100]. Nevertheless, although several reports state that the prevalence rate of akathisia with intermediate (e.g., perphenazine) and low-potency (e.g., chlorpromazine) FGA is not necessarily higher than that seen with certain SGA [3,102,104], a recent overview of Cochrane reviews and meta-analyses [103] showed that none of the SGA showed a higher prevalence figure than chlorpromazine.

With respect to the NAP, our first meta-analysis yielded prevalence estimates ranging from 3.9% (iloperidone) to 17.2% (cariprazine). Even after Tukey-adjustment for multiple testing, statistically significant differences ($p < 0.05$) were found between prevalence rates for several of these agents, with iloperidone showing a better akathisia profile than brexpiprazole, lurasidone and cariprazine, and with asenapine being associated with a significant lower prevalence rate of akathisia than lurasidone and cariprazine. Finally, the prevalence rate of akathisia was significantly lower for brexpiprazole, compared to cariprazine. The severity of akathisia with these agents generally seems to be mild to moderate, only in a minority of cases ($< 5\%$) leading to treatment discontinuation. Our second meta-analysis demonstrated that, in general, the propensity of NAP to cause akathisia was more than two-fold (OR 2.43, 95% CI: 1.91-3.10) higher than placebo. However, after Turkey adjustment for multiple testing no statistically significant differences ($p < 0.05$) in terms of medication type were found between the ORs. The fact that we found significant differences in prevalence rates of akathisia between NAP (first meta-analysis) but no significant differences in ORs for akathisia under medication conditions versus placebo (second meta-analysis) may be explained by the fact that patients under placebo conditions also report akathisia which may result in less pronounced differences between NAP.

Moreover, some important remarks have to be made. The prevalence rates reported in this meta-analysis may be an underestimation of true prevalence rates. A substantial proportion of the included studies reported rates of akathisia and restlessness separately. This introduces the possibility that a proportion of the patients in the restless category actually belong to those with medication-induced akathisia, instead of those who have illness-related restlessness (due, for example, to anxiety or depression). Moreover, prevalence rates in this analysis have been based on the percentage of patients spontaneously reporting akathisia. Although the majority of the included studies used an objective instrument (in most cases the

1 BARS) to measure the mean change from baseline to endpoint in severity of akathisia, most
2 of these studies relied on spontaneous reporting, rather than on scale-defined akathisia to
3 assess prevalence rates. As the use of these objective measurements almost consistently
4 resulted in higher rates of akathisia in studies that included such a measurement, a meta-
5 analysis based on scale-defined akathisia rates would generate higher figures. Finally, patients
6 included in our analysis typically were middle-aged (mean age: 40.8 years) patients who have
7 been treated before. However, some populations not included in our analysis, such as patients
8 with delirium or antipsychotic-naïve patients can be particularly sensitive to the development
9 of antipsychotic-induced akathisia, even with a different pattern for the antipsychotics
10 medications [3]. Prevalence rates found in this meta-analysis therefore must be interpreted
11 cautiously.
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27 Despite this, our results suggest a distribution of akathisia prevalence rates across 4
28 main groups: the most benign akathisia profile is represented by iloperidone and comparable
29 to that of quetiapine, followed by asenapine and brexpiprazole, having a risk comparable to
30 that of olanzapine (although the latter may be somewhat more benign regarding this side-
31 effect than brexpiprazole), and finally lurasidone and cariprazine, both comparable to the
32 profile of risperidone. In accordance with this classification, head-to-head comparisons of
33 older SGA and NAP have found that in patients with schizophrenia the risk of akathisia with
34 lurasidone and cariprazine seems to be higher than with olanzapine and asenapine [105-108].
35 The risk of akathisia with quetiapine extended-release and iloperidone has been found to be
36 not statistically significant different from, or even to be lower than with placebo [105].
37 Former analyses indicated that brexpiprazole seems to cause significant less akathisia than
38 aripiprazole [14,109], somewhat comparable with the risk for ziprasidone [107], both having
39 akathisia profiles that are similar to that of olanzapine [103].
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Akathisia is the most common reported treatment-emergent adverse event in cariprazine-treated patients with schizophrenia [22,54,55,60,80,97,102,110-116], as well as in patients with bipolar mania, depression or mixed episodes [53,56,58,59,61,115,117,118] or major depressive disorder, where cariprazine is used as an adjunctive treatment [52]. However, the severity of these adverse events are generally mild to moderate [52,53,58-61,102] and $\leq 1\%$ of patients with schizophrenia [22,102] and $< 5\%$ of patients with bipolar disorder [53,56,59,61,119] overall discontinue cariprazine due to akathisia, suggesting that akathisia in patients treated with cariprazine is manageable for most of them [60,119]. The literature generally reports a lower rate of akathisia with cariprazine in patients with schizophrenia, compared with bipolar mania patients. This is in line with the higher prevalence rate of akathisia that has been found in our analysis for patients with bipolar mania, compared to patients with schizophrenia treated with NAP (although this difference disappeared after correction for multiple comparisons). This may be related to between-trial differences in doses (the recommended dose range for patients with schizophrenia treated with cariprazine is 1.5 to 6 mg once daily, while this for manic or mixed episodes associated with bipolar I disorder is 3 to 6 mg once daily), faster titration schedules applied in the bipolar mania studies, the underlying symptomatology of bipolar mania, or the greater sensitivity to antipsychotic-induced adverse events of some patients with bipolar mania or depression [22,61,119-121]. Most new cases of akathisia with cariprazine are reported during the first 2-6 weeks of treatment; the number of new cases decreases dramatically thereafter [22,60,61,102,119].

Higher rates of akathisia are equally observed in individuals with schizophrenia receiving lurasidone, in comparison to most other SGA [122,123]. An analysis of pooled patient data from four randomized, placebo-controlled, 6-week premarketing studies of lurasidone (20-160 mg/day) in adult patients with schizophrenia (n=1,508) found a percentage

of 12.9% (versus 3% for placebo-treated patients) for all doses combined [122,124]. Akathisia with lurasidone in the schizophrenia studies seems to be dose-related [17-20,122], with a percentage of 22% for lurasidone 120 mg/day [122]. A recent meta-analysis of 8 randomized controlled short-term (6-week) trials, including 2,373 patients with acute schizophrenia, found the number needed to harm for lurasidone (20-160 mg/day) to be 11 (95% CI: 8-17, $p<0.00001$) [125]. The rates of akathisia reported by patients in long-term (6-months to 2-year) schizophrenia studies of lurasidone (between 10.7% and 14.3%) are similar and consistent with those reported in short-term studies. Despite this, rates of discontinuation because of akathisia remain low (between 0.4% and 1.6%) in lurasidone treatment groups [92,93,126,127]. There are indications that evening administration of lurasidone may be associated with lower rates of akathisia [91,127]. Switching from olanzapine to lurasidone seems to result in a modest increase in the incidence of akathisia [127,128].

Across available (systematic) reviews, based on randomized controlled trials, akathisia is equally consistently mentioned among the most commonly reported adverse events with lurasidone in the treatment of bipolar depression, as monotherapy, or as adjunctive therapy with lithium or valproate [129-135]. In patients with bipolar depression a percentage of 9.4% and 10.8% (all doses combined, versus 2.4% and 4.8% for placebo-treated patients) was noted in patients receiving lurasidone monotherapy or adjunctive therapy, respectively, both at daily doses ranging from 20 to 120 mg [122,124]. Among adults with bipolar I depression, lurasidone monotherapy, compared with placebo, has a NNH for akathisia of 15 (NNH=18 for lurasidone 20-60 mg/day and NNH=12 for lurasidone 80-120 mg/day) [133,136] and a NNH for akathisia of 30 (not statistically significant) as adjunctive therapy with lithium or valproate [133]. The incidence of akathisia is higher in patients with bipolar depression associated with mixed features [137].

Compared to all other currently available D2/5HT2A antagonist antipsychotics, iloperidone has the most favorable akathisia profile [138,139]. Studies have shown that iloperidone has a very low propensity to cause akathisia that is generally similar to or even lower than with placebo [16,32,33,105,138-140]. Our analysis also showed that iloperidone (OR=1.20, 95% CI: 0.42-3.45) had the lowest risk of all NAP, a risk that is comparable to placebo. This favorable akathisia profile of iloperidone is seen across the entire therapeutic dose range, and the need for anticholinergics or other anti-akathisia treatments is relatively infrequent [16,33,141,142]. A post-hoc analysis of pooled patient data from four Phase III, placebo- and active controlled 4- or 6-week, fixed- or flexible-dose studies, found no statistically significant association with akathisia for iloperidone at any dose [3.6%, NNH=113 (iloperidone 4-8 mg/day), 1.7%, NNH=94 (iloperidone 10-16 mg/day), 2.3%, NNH=236 (iloperidone 20-24 mg/day) vs. 2.7% (placebo)] [30,32,33,143]. The low akathisia burden is sustained during long-term treatment [16,140] and the majority of patients taking iloperidone experience no change or improvement in akathisia BARS and ESRS scores [140]. Switching from antipsychotics with a higher propensity to cause akathisia (such as aripiprazole or risperidone) to iloperidone by either gradual or an immediate method can be an appropriate option for patients who experience suboptimal therapy due to the burden of akathisia, as this switch can be done without any clinically significant differences in ratings of overall efficacy [138].

Although displaying a high affinity for and antagonism at 5-HT2A receptors [144], akathisia is one of the most frequently reported adverse events with asenapine during acute treatment in adults with schizophrenia or manic or mixed episodes associated with bipolar I disorder [145-147]. This suggests that the pathophysiology of akathisia involves other than dopaminergic and serotonergic receptors and is multifactorial [106] (see further).

Akathisia with newly approved antipsychotics in severe mental illness patients

According to an analysis of pooled patient data from four short-term placebo-controlled premarketing trials (a pool of three 6-week fixed-dose trials and one 6-week flexible-dose trial) in adult patients with acute schizophrenia (n=572), akathisia (including hyperkinesia) occurs at greater incidence with treatment with sublingual asenapine 5 or 10 mg BID (4% and 11%, respectively) than with placebo (3 %) (n=378) [148]. This effect appears to be dose-related [145,148]. Compared with olanzapine, asenapine is more likely to cause akathisia [106,149]. A meta-analysis focusing on akathisia in patients with schizophrenia treated with asenapine, aripiprazole or lurasidone found that asenapine had a double higher risk of akathisia than placebo or other older SGA, with double the risk of olanzapine (Relative Ratio=2.23, 95% CI 1.45-3.42) [106]. Pooled results from two randomized multicenter trials in stable patients with persistent negative symptoms in schizophrenia (n=949) showed that switching to asenapine from other antipsychotic agents is associated with a higher percentage of patients reporting akathisia during the first 28 days of the switch period, compared with patients who were switched to olanzapine (3.6% versus 1.9%) [150].

Another analysis of pooled patient data from three short-term placebo-controlled premarketing trials (a pool of two 3-week flexible-dose trials and one 3-week fixed-dose trial) in adult patients with bipolar mania (n=620), showed that akathisia equally occurs at greater incidence with treatment with sublingual asenapine 5 or 10 mg BID (6%) than with placebo (2 %) in these patients (n=329). Again, the effect appears to be dose-related [148].

Akathisia is also one of the most commonly reported adverse events in long-term studies of asenapine in the treatment of schizophrenia [42,43,49] and bipolar disorder [37]. In a double-blind 40-week extension study in patients with bipolar disorder, the most commonly reported extrapyramidal symptom (EPS) was akathisia, occurring in 11.4% of asenapine-treated patients and 10.3% of olanzapine patients [37]. As rates of akathisia were higher in asenapine-treated patients in this extension study, compared to the rates that have been found in the

initial short-term studies [35,36,38], this indicates that some cases of acute akathisia with asenapine persist for months, and thus become chronic, and tardive cases of akathisia emerged. This, however, has not been found in another extension study with schizophrenic patients, where cases of akathisia disappeared with continued use of asenapine (2.5 mg BID and 5 mg BID) [49].

Brexpiprazole is a dopamine partial agonist antipsychotic in the same class as aripiprazole. However, with less intrinsic activity than aripiprazole at the D2 receptor, stronger antagonistic activity at serotonin 5-HT_{2A} and noradrenergic α _{1B} receptors, and stronger agonistic activity at serotonin 5-HT_{1A} receptors, the pharmacological properties of brexpiprazole would suggest a more tolerable side effect profile with regard to akathisia [70,72,76,107,109,151,152].

The analysis of pooled patient data from two randomized, placebo-controlled, 6-week fixed-dose, premarketing studies of brexpiprazole (1-4 mg/day) in adult patients with schizophrenia (n=852) found a percentage of 5.2% (all doses combined) versus 4.6% for placebo-treated patients [71,80,151,153]. Other short-term randomized controlled (6 weeks) [71,72], as well as long-term open-label (52 weeks) extension studies confirmed this relatively favorable safety profile [70]. In long-term, open-label extension studies (brexpiprazole 1-4 mg/day, 52 weeks) akathisia rates remained low (between 4.6% and 8.5%) [70,154,155]. In patients receiving brexpiprazole treatment during periods longer than one year, activating side effects, such as akathisia, seem to be generally resolved [69]. Thus, over time, the incidence of akathisia events may reduce with continued brexpiprazole use [76]. An overview of short (fixed and flexible dose)- and long-term safety data of brexpiprazole showed the incidence of akathisia in short-term trials was similar in the brexpiprazole 2-4 mg (n=822), pooled brexpiprazole (< 2 mg - > 4mg) (n=1,256) and placebo groups (5.7%, 5.8% vs. 4.5%, respectively), although it increased profoundly with doses > 4 mg (15.1%) (this higher

incidence, however, is seen in studies when brexpiprazole is started without titration) [70].

The onset of akathisia in schizophrenia trials mostly occurred during the first 3 weeks of treatment (peak incidence between days 8 and 11 of treatment) and is dose-related. Akathisia tends to be mild to moderate and discontinuations due to akathisia with brexpiprazole are uncommon [$\leq 1\%$ in both short-term (0.1%) and long-term studies (0.4%-1.1%)] [70,71,80,81,107,152,153,155,156]. The NNH for akathisia in the short-term studies has been estimated 84 for the brexpiprazole 2-4 mg group, which is higher (and thus more promising) than these for aripiprazole (NNH=34), risperidone (NNH=15) and olanzapine (NNH=25) [70,112]. Adequately powered studies comparing brexpiprazole with other antipsychotics are not available. In an open-label 6-week trial comparing brexpiprazole 3mg/day with aripiprazole 15 mg/day, the incidence of akathisia was lower in patients treated with brexpiprazole (9.4%) than aripiprazole (21.2%) [72].

Akathisia is nevertheless a common treatment-emergent adverse effect with brexpiprazole as an antidepressant adjunct for major depressive disorder [151,157]. For brexpiprazole NNH values for akathisia have been found to be lower (thus more problematic) for the treatment of major depressive disorder than for schizophrenia [105]. In short-term (6 weeks) placebo-controlled and long-term (52 weeks) open-label studies, reported percentages of akathisia with adjunctive brexpiprazole (1-3 mg/day for short-term studies) were 8.6% (versus 1.7% for placebo) and 10.0%, respectively [78]. In premarketing, fixed-dose, clinical trials, the incidence of akathisia events for brexpiprazole (1-3 mg/day) + antidepressant-treated patients was 9% versus 2% for placebo + antidepressant-treated patients [151]. The risk of akathisia was found to be higher in the brexpiprazole group than in the placebo group, with a pooled risk ratio of 3.39 (95% CI 2.08-5.51, $p < 0.00001$) [79].

The incidence of akathisia with brexpiprazole in patients with major depressive disorder, however, remains lower than that reported in randomized studies with adjunctive aripiprazole

(24.8% versus 4.4% for placebo) [77,78,105,158,159], but higher than with other antipsychotics approved for adjunctive treatment of major depressive disorder [quetiapine extended release (2.1% versus 1% for placebo) or the combination of olanzapine with fluoxetine (3.3% versus 2.7% for placebo)] for treatment-resistant major depressive disorder [78,105,158]. The NNH for akathisia during adjunctive treatment was found to be 15 (95% CI: 11-23) for brexpiprazole, versus 5 (95% CI: 4-7) for aripiprazole, 91 (not statistically significant) for quetiapine extended release, and >100 (not statistically significant) for the olanzapine/fluoxetine combination [105,158].

Akathisia with brexpiprazole usually occurs 2-4 weeks after treatment initiation, and appears to be dose-related, with higher incidences of akathisia for doses of more than 2 mg [78,79]. The median duration of akathisia seems to be similar across the brexpiprazole doses, ranging from 20 to 22.5 days. The majority of akathisia adverse events are assessed by the investigator as mild or moderate in severity [78].

It is known that rapid antipsychotic titration has the potential to increase the risk of akathisia. However, titration time in our analysis did not explain differences in prevalence rates of akathisia between studies. Although slow initiation of antipsychotics may be preferable when performing an antipsychotic switch, a recent meta-analysis [160] found no significant difference in akathisia rates between the slow vs. rapid initiation group for relatively stable patients with schizophrenia (Risk Ratio 0.69; 95% CI: 0.43-1.11, $p=0.13$). Patients included in our analysis were relatively stable, middle-aged patients with a longer disease history. These patient features therefore can explain why we didn't find a significant result for this study characteristic. Results also indicated that Caucasians may be statistically significantly ($p<0.01$) less vulnerable for medication-induced akathisia, compared to other ethnic groups. Although ethnicity has been identified as an important risk factor associated

with tardive dyskinesia (with Caucasians having a lower risk) [161], the literature seems to be less clear regarding the association of akathisia with ethnicity [162].

Although the pathophysiology of akathisia is still unclear, it seems likely that a complex interplay of several neurotransmitter systems are involved in its pathophysiology. Dopaminergic and serotonergic receptor activities seem to play a major role. In addition, acetylcholine, gamma-aminobutyric acid (GABA), and noradrenergic receptor activities, as well as mechanisms related to neuro-inflammation have also been suggested to play a role in the emergence of akathisia [2,3,4,7,106,121,163].

Since akathisia is predominantly induced by dopamine receptor antagonist antipsychotics, blockade of dopamine D₂ receptors is believed to be an important factor in the pathophysiology of akathisia. Dopaminergic D₂ receptors are particularly found in high concentration in the basal ganglia (playing a critical role in motor control) [164]. Studies have shown that EPS, including akathisia, is associated with dopamine deficiency in the basal ganglia, caused by an excessive blockade of dopamine D₂ receptors (>75-80%) [165-169].

Recently, it has been suggested that antipsychotic agents capable of blocking striatal D₁ and D₂ receptors might be less likely to induce EPS than those acting selectively on either D₁ or D₂ receptors [170]. A study, that examined the long-term effects of multiple doses of iloperidone on dopamine D₁, D₂, D₃, and D₄ receptor subtypes in rats, has found that the upregulation of striatal D₁ receptors after treatment with 5 mg/kg iloperidone might offset the EPS associated with striatal D₂ receptor upregulation, possibly offering one (although not the most important) explanation for the lower incidence of akathisia with iloperidone [170].

Antagonism of serotonin 5-HT_{2A} receptors may decrease the risk of akathisia as SGA, as a group, have a lower incidence of akathisia than FGA by blocking these receptors [106,167].

Blockade of cortical 5-HT_{2A} receptors may stimulate dopamine release in the striatum that

partially reverses the D2 dopamine receptor blockade there (reducing the D2 receptor binding below 80% to more like 60%), which should minimize the incidence of akathisia [166,171].

Therefore, it would be expected that iloperidone and asenapine would have a lower incidence of akathisia, as these agents display more potent antagonist activity at 5-HT_{2A} than dopamine D2 receptors, compared to lurasidone, brexpiprazole and cariprazine, displaying relatively equivalent binding at both sites [172]. This serotonergic receptor activity mechanism also explains why SSRIs (having no affinity for the dopamine D2 receptor) may induce akathisia. These agents stimulate 5-HT_{2A} receptors, which results in inhibition of dopamine release [167].

In addition to serotonin 5-HT_{2A} receptor antagonism, observations that the use of anticholinergics, benzodiazepines and β -adrenergic blockers may alleviate symptoms of akathisia, suggest a role for other neurotransmitters as well [3,10,121]. Of these adrenergic receptor activity may be particular important. Indeed, the pharmacologic action that distinguishes iloperidone most from other SGA is its potent antagonism of α ₁ adrenergic receptors. Moreover, this property is the most potent of all pharmacologic actions of iloperidone. Alpha-1 adrenergic antagonism hypothetically causes downstream release of striatal dopamine [166]. Thus, the low incidence of akathisia associated with iloperidone may be linked to its unique binding profile of high affinity antagonism of both α ₁ adrenergic receptors and serotonin 5HT_{2A} receptors, and its simultaneous antagonism of D1 and D2 receptors. Asenapine, having a low-to-moderate akathisia risk, will also very likely cause significant blockade at the α ₁ adrenergic receptors [173]. One exception to the α ₁ adrenergic hypothesis is that risperidone, which has relatively high α ₁ receptor binding, nevertheless has higher rates of akathisia [166,173].

Once developed, akathisia should prompt reassessment of treatment, with reduction in dose, discontinuation of the causative agent, or switching to a SGA with low akathisia

potential (including iloperidone and quetiapine), all of which, however, incur the risk of psychotic exacerbation or relapse [1,2,4,8,10]. Therefore, the addition of an anti-akathisia agent may be necessary [2]. If the akathisia worsens during dose reduction or a medication switch, tardive akathisia may be present. The general treatment guidelines for this condition, however, follow those of acute akathisia, with the exception that, when severe, tardive akathisia can be suppressed with a reinstitution of the offending antipsychotic at the previous dose [4]. In cases of refractory akathisia, clozapine can be considered [2].

The actual evidence base for treatments of akathisia is very small, and many of the recommendations are based on clinical experience, case reports, and reports from studies of drugs where akathisia was not a primary concern [4].

β -adrenergic antagonists have been effective in some studies, although their use is limited by the risk for hypotension, bradycardia, sleep disturbances, and medical contraindications (e.g., patients with comorbid diabetes) [2,8,10]. Moreover, results from meta-analyses have reported that the efficacy of β -adrenergic antagonists in the treatment of akathisia is poor at best [174]. The therapeutic action of β -adrenergic antagonists is linked to their purported action in blocking noradrenergic/serotonergic input into the dopaminergic pathways [2]. The non-selective β -adrenergic antagonist propranolol (40-80 mg/day BID) should be the first-choice option if adjunctive medication (rather than dose lowering or antipsychotic switching) is required for the treatment of akathisia, as this agent has the most robust evidence to support its use for subjective and objective symptoms of akathisia [1,2]. There are no reports of worsening psychosis associated with propranolol use [1]. However, this medication should only be given after reviewing contraindications and associated precautions (cf. *supra*) on a per-patient basis. Moreover, due to the short duration of studies it is difficult to decide how long propranolol, if helpful, should be continued [1]. Another adrenergic antagonist studied is metoprolol (although evidence to support its use is extremely limited) [1,2].

Anticholinergics are traditionally used to treat antipsychotic-induced EPS. The anticholinergic medications benztropine and biperiden should not be routinely used for the treatment of medication-induced akathisia, due to the extremely limited available evidence for its use in antipsychotic-induced akathisia (with inconsistent findings among studies) and the risk of cognitive and anticholinergic adverse effects with these drugs [1,2,175]. Their limited efficacy also makes them relatively unsuitable for long-term use [2]. Some older data [176,177] suggest that anticholinergics may be preferentially helpful in patients with akathisia and co-existing parkinsonism [1,8,10]. Despite the lack of controlled data supporting this approach, anticholinergics are still often recommended for this kind of patients [2].

As antipsychotics with high 5-HT_{2A} antagonist activity relative to D₂ antagonistic activity are associated with reduced risk for EPS, serotonergic 5-HT_{2A} antagonists, such as mianserin, mirtazapine, trazodone and cyproheptadine, have been assessed for their anti-akathisia effects [1,2,8,10]. Once again, although findings suggest that 5-HT(2A) antagonists are effective in the treatment of medication-induced akathisia [178], evidence remains limited to support the use of 5-HT_{2A} antagonists for the treatment of akathisia. Moreover, sedation is the most common adverse effect with mianserin and mirtazapine [1]. Only when propranolol is contraindicated, ineffective, or not tolerated and long-term pharmacological management of akathisia is anticipated, the use of a serotonin-based strategy for akathisia may be considered [1,2].

Benzodiazepines, considered as second-line treatment for akathisia [2], have been useful owing to their anxiolytic and sedative properties [8,10]. However, long-term use of benzodiazepines should be avoided because of the risk of dependence, drowsiness (and risk of fall) and cognitive side effects. After the disappearance of akathisia clinicians should consider gradual tapering of the benzodiazepine [1,2].

The role of antihistamines remains controversial with some studies suggesting reduction in akathisia and other studies reporting that antihistamines worsened akathisia. Moreover, antihistamines can also be associated with serious adverse events [2].

In patients failing to respond to alternative treatments for persistent antipsychotic-induced akathisia, short-term therapy with vitamin B6 may be considered. However, extremely limited evidence for its use exist and long-term use of vitamin B6 can cause an irreversible and severe neuropathy [1].

Many other medications have been assessed as potential treatments for antipsychotic-induced akathisia, including amantadine (acting as a dopamine reuptake inhibitor through it antagonism of the glutamate receptor), apomorphine, clonidine, gabapentin, and pregabalin [1,2,10]. Some are promising but the evidence available on the potential risks and benefits for these agents (e.g., the emergence of psychosis associated with the use of amantadine) as treatments for akathisia limits their utility in akathisia [1,2].

6 Conclusion

The results of our first meta-analysis showed different prevalence rates of akathisia for different NAP. These differences disappeared when prevalence rates of akathisia were compared under medication versus placebo conditions after correction for multiple comparisons. This may be due to the fact that patients under placebo condition also spontaneously report akathisia. Moreover, due to patient characteristics and methodological issues, prevalence rates with NAP may be an underestimation of true prevalence rates so that trend differences between medications in our second meta-analysis actually represent real differences. A meta-analysis based on objectives measurements, including younger and/or non-Caucasian patients with a severe mental illness other than schizophrenia, would probably

generate even higher figures. Taken all the above into consideration, one can assume that iloperidone probably has a very low propensity to cause akathisia, that is generally similar to or even lower than with placebo, while the other NAP have a less benign akathisia profile, varying from a moderate (asenapine and brexpiprazole) to a higher (lurasidone and cariprazine) akathisia risk. Nevertheless, the severity of akathisia with these agents generally is mild to moderate, only in a minority of cases (<5%) leading to treatment discontinuation, meaning that this adverse effect with the NAP appears to be manageable.

7 References

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Figure 1: Prisma Checklist Flow Diagram

Supplementary material: Characteristics of studies with newly approved antipsychotics included in the meta-analysis

Newly Approved Antipsychotic	Study characteristics	Prevalence of akathisia	Mean/median time to onset	Median/median duration	Severity of akathisia in most cases	Discontinuation rate due to akathisia
ILOPERIDONE						
Weiden et al. (2016) NCT01291511	RCT with PBO (26w) Patients with SZ (n=301) ILO 4-12 mg BID (after 24w stabilization on ILO 4-12 BID)	1% (ILO 4-12 mg BID, n=1/151), 0% (PBO, n=0/150)	NR	NR	NR	NR
Potkin et al. (2013)	RCT with active control (4w) Patients with SZ or SZA (n=188) ILO 16-24 mg/d QUE 375 mg BID ZIPRA 80 mg BID	6% (ILO 8 mg BID), 11% (ILO 12 mg BID), 6% (ILO 24 mg QD), 12% (ZIPRA 80 mg BID), 3% (QUE 375 mg BID)	NR	NR	NR	NR
Weiden et al. (2008) Potkin et al. (2008) ILP3000ST ILP3004ST ILP3005ST	Pooled analysis of 3 Phase III RCT with PBO and active control (6w) Acute or subacute exacerbation of SZ or SZA (n=1,943) ILO 4-24 mg/d RIS 4-8 mg/d HAL 15 mg/d	3.7% (ILO 4-8 mg/d, n=463), 1.5% (ILO 10-16 mg/d, n=456), 4.8% (ILO 20-24 mg/d, n=125), 13.6% (HAL 15 mg/d, n=118), 6.9% (RIS 4-8 mg/d, n=306) vs. 3.6% (PBO, n=440)	NR	NR	NR	NR
Cutler et al. (2008) VP-VYY-683-3101	RCT with PBO and active control (Phase III) (4w) Acute exacerbation of SZ (n=593) ILO 24 mg/d ZIPRA 160 mg/d	1% (ILO 24 mg/d, n=1/300), 7% (ZIPRA 160 mg/d, n=11/150) vs. 0% PBO (n=0/147),	NR	NR	mild to moderate	NR
Kane et al. (2008)	Pooled analysis of 3 RCT (6w) Patients with SZ or SZA (n=1,634) ILO 4-16 mg/d (n=1,231) HAL 5-20 mg/d (n=403)	3.5% (ILO 4-16 mg/d, n=43/1231), 18.6% (HAL 5-20 mg/d, n=75/403)	NR	NR	NR	NR
ASENAPINE						
Szegedi et al. (2018) NCT01396291	RCT with PBO (26w) (following a 12- to 16 week open-label period with flexible doses) Acute manic or mixed episodes BP-I (n=253) ASE 10-20 mg/d	1.6% (ASE 10-20 mg/d, n=2/126) vs. 0.8% (PBO, n=1/126)	NR	NR	NR	NR
Landbloom et al. (2017) NCT01617187	RCT with PBO and active control (6w) Acute exacerbation of SZ (n=311) ASE 2.5-5 mg BID OLZ 15 mg/d	No statistically significant differences between ASE groups and PBO or OLZ and PBO: 3.1% (ASE 2.5 mg BID, n=3/97), 4.4% (ASE 5 mg BID, n=5/113), 2.2% (OLZ 15 mg/d, n=1/46) vs. 5% (PBO) (n=5/101) BARS: 1.1% (ASE 2.5 mg BID, n=1/94), 2.7% (ASE 5 mg BID, n=3/113), 2.4% (OLZ 15 mg/d, n=1/42) vs. 3.1% (PBO, n=3/98)	NR	NR	mild to moderate	NR
Landbloom et al. (2016) NCT00764478	RCT with PBO (Phase IIb) (3w) Acute manic or mixed episodes BP-I (n=367) ASE 5-10 mg BID	4.1% (ASE 5 mg BID, n=5/122), 15.1% (ASE 10 mg BID, n=18/119) vs. 0.8% (PBO, n=1/126) There was a higher percentage of patients with a BARS global score ≥ 2 in both ASE groups compared with	NR	NR	mild to moderate	NR

		PBO				
Kinoshita et al. (2016) NCT01098110	RCT with PBO (6w) Patients with acute exacerbation of SZ (n=530) ASE 5-10 mg BID	11.4% (ASE 5 mg BID, n=20/175), 10.5% (ASE 10 mg BID, n=19/181), vs. PBO (5.2%, n=9/174)	NR	NR	NR	NR
Buchanan et al. (2012)	RCT with active control (n=949) Eastern [EH] (n=481) and Western Hemisphere [WH] (n=468) study Patients with persistent negative symptoms of SZ (2w) ASE 10-20 mg/d OLZ 5-20 mg/d	4.5% (ASE 10-20 mg/d) vs. 1.2% (OLZ 5-20 mg/d) [EH] study	NR	NR	mild to moderate	0%
Szegedi et al. (2012)	RCT with PBO (12w) Acute manic or mixed episodes BP-I (n=324) ASE 5-10 mg BID	3.2% (ASE 5-10 mg BID, n=5/158) vs. 5.4% (PBO, n=9/166)	NR	NR	NR	NR
Schoemaker et al. (2010) NCT00212784	RCT with active control (52w) Patients with SZ or SZA (n=1,225) ASE 5-10 mg BID OLZ 10-20 mg/d	8% (ASE 5-10 mg BID, n=76/908), 4% (OLZ 10-20 mg/d, n=11/311)	NR	NR	usually mild	NR
Kane et al. (2011) A7501012 NCT00150176	RCT with PBO (26w) after 26w stabilization Stable SZ (n=386) ASE 10 mg BID	2.1% (ASE 10 mg BID, n=4/194) vs. 1.6% (PBO, n=3/192)	NR	NR	NR	1.3%
Kane et al. (2010b) HERA041023 NCT00156104	Double-blind RCT with PBO and active control (6w) Acute exacerbation of SZ (n=458) ASE 5-10 mg BID HAL 14 mg BID	5% (ASE 5 mg BID, n=6/111), 12% (ASE 10 mg BID, n=13/106), 15% (HAL 14 mg BID, n=17/115) vs. 3% (PBO, n=4/123)	NR	NR	NR	NR
McIntyre et al. (2010b) ARES 7501004 NCT00159744	RCT with PBO and active control (3w) Acute manic or mixed episodes BP-I (n=488) ASE 5-10 mg BID OLZ 5-20 mg/d	5.4% (ASE 5-10 mg BID, n=10/185), 4.9% (OLZ 5-20 mg/d, n=10/205), vs. 3.1% (PBO, n=3/98) BARS: 8.5% (ASE 5-10 mg BID, n=15/177), 3.7% (OLZ 5-20 mg/d, n=7/188), vs. 6.5% (PBO, n=6/93)	NR	NR	mild to moderate	NR
McIntyre et al. (2009a) ARES 7501005 NCT00159796	RCT with PBO and active control (3w) Acute manic or mixed episodes BP-I (n=488) ASE 5-10 mg BID OLZ 5-20 mg/d	2.6% (ASE 5-10 mg BID, n=5/194), 5.8% (OLZ 5-20 mg/d, n=11/189), vs. 1.9% (PBO, n=2/105) BARS: 7.4% (ASE 5-10 mg BID, n=14/188), 7.9% (OLZ 5-20 mg/d, n=14/178), vs. 5.2% (PBO, n=5/96)	NR	NR	mild to moderate	NR
LURASIDONE						
Suppes et al. (2016b) NCT01423240	RCT with PBO (6w) Patients with MDD with mixed features (n=209) LURA 20-60 mg/d	3.7% (LURA 20-60 mg/d, n=4/109) vs. 2% (PBO, n=2/100)	NR	NR	mild to moderate	NR
Suppes et al. (2016a) NCT01284517	RCT with PBO (6w) BP-I depression (n=356) LURA 20-120 mg/d as adjunctive therapy with LI or VAL	14.1% (LURA 20-120 mg/d + LI/VAL, n=25/177) vs. 5.3% (PBO + LI/VAL, n=9/171)	NR	NR	NR	NR

Loebel et al. (2016) NCT01821378	RCT with PBO (6w) Acute exacerbation of SZ (n=412) LURA 20-160 mg/d	5% (LURA 20 mg/d, n=5/101), 16% (LURA 80 mg/d, responders) 3.6% (LURA 80 mg/d, non-responders, n=2/55), 7% (LURA 160 mg/d, n=3/43), vs. 1.8% (PBO, n=2/112) Patients whose dose was increased from 80 to 160 mg/d reported a greater incidence of akathisia BARS changes small and not clinically meaningful in all treatment groups	NR	NR	NR	NR
Potkin et al. (2015)	RCT with PBO and active control (Phase II) (6w) Acute exacerbation of SZ (n=353) LURA 20-80 mg/d HAL 10 mg/d	12.4% (LURA overall), 5.6% (LURA 20 mg/d, n=4/71), 13.4% (LURA 40 mg/d, n=9/67), 18.3% (LURA 80 mg/d, n=13/71), 19.4% (HAL 10 mg/d, n=14/72) vs. 9.7% (PBO, n=7/72) Dose-relationship for akathisia was apparent	NR	NR	mild to moderate	Discontinuation because of EPS or akathisia: 9.7% (HAL 10 mg/d), 0.5% (LURA across all dose groups) vs. 0% (PBO)
Loebel et al. (2014a) NCT00868699	RCT with PBO (6w) Patients with BP-I depression (n=505) LURA 20-120 mg/d	7.9% (LURA 20-60 mg/d, n=13/164), 10.8% (LURA 80-120 mg/d, n=18/167) vs. 2.4% (PBO, n=4/168)	NR	NR	mild to moderate	NR
Loebel et al. (2014b) NCT00868452	RCT with PBO (6w) Patients with BP-I depression (n=348) LURA 20-120 mg/d as adjunctive therapy with LI or VAL	7.7% (LURA + LI, 897.2 mg/d/VAL, 1058.3 mg/d, n=14/183), 4.3% (PBO + LI, 947.3 mg/d /VAL 1117.8 mg/d, n=7/163)	NR	NR	mild to moderate	NR
Ogasa et al. (2013)	RCT with PBO (6w) Acute exacerbation of SZ (n=149) LURA 40-120 mg/d	11.1% (LURA overall, n=11/99), 8% (LURA 40 mg/d, n=4/50), 14.3% (LURA 120 mg/d, n=7/49) vs. 0% (PBO, n=0/50)	NR	NR	mild to moderate	Discontinuation because of EPS or akathisia: 2% (LURA 40 mg/d), 4.1% (LURA 120 mg/d)
Loebel et al. (2013a) NCT00790192 D1050233	RCT with PBO and active control (6w) Acute exacerbation of SZ (n=486) LURA 80-160 mg/d QUE XR 600 mg/d	8.0% (LURA 80 mg/d, n=10/125), 7.4% (LURA 160 mg/d, n=9/121), 1.7% (QUE XR 600 mg/d, n=2/119) vs. 0.8% (PBO, n=1/121)	NR	NR	mild to moderate	1.6% (LURA 80 mg/d), 0.8% (LURA 160 mg/d), 0% (QUE XR 600 mg/d and PBO)
Nasrallah et al. (2013) NCT00549718 D1050229	RCT with PBO (6w) (Phase III) Acute exacerbation of SZ (n=495) LURA 40-120 mg/d	17.6% (LURA overall), 11.3% (LURA 40 mg/d, n=14/124), 17.4% (LURA 80 mg/d, n=21/121), and 24.2% (LURA 120 mg/d, n=30/124) vs. 3.1% (PBO, n=4/127)	NR	NR	mild to moderate Akathisia was rated as mild in 7.6% of patients receiving LURA, moderate in 8.9% of patients, and severe in 1.1% of patients. Scores in the	1.6% (LURA 40 mg/d), 0.8% (LURA 80 mg/d), 2.4% (LURA 120 mg/d)

					moderate to severe range on the BARS Global Clinical Assessment (scores ≥ 3): 2.5% (LURA 40 mg/d), 2.5% (LURA 80 mg/d), and 4.0% (LURA 120 mg/d) vs. 0% (PBO).	
Citrome et al. (2012a) NCT00641745	RCT with active control (52w) Stable outpatients with SZ (n=629) LURA 40-120 mg/d RIS 2-6 mg/d	14.3% (LURA 40-120 mg/d, n=60/419), 7.9% (RIS 2-6 mg/d, n=16/202)	NR	NR	mild to moderate	1% (LURA 40-120 mg/d), 1.5% (RIS 2-6 mg/d)
Meltzer et al. (2011) NCT00615433 D1050231	RCT with PBO and active control (6w) Acute exacerbation of SZ (n=478) LURA 40-120 mg/d OLZ 15 mg/d	11.8% (LURA 40 mg/d, n=14/119), 22.9% (LURA 120 mg/d, n=27/118), 7.4% (OLZ 15 mg/d, n=9/122) vs. 0.9% (PBO, n=1/116)	NR	NR	mild to moderate	Discontinuation due to EPS: 0% (LURA 40 mg/d, OLZ 15 mg/d, PBO), 1.7% (LURA 120 mg/d)
Potkin et al. (2011)	RCT with active control (3w) Patients with SZ or SZA (n=301) ZIPRA 160 mg/d LURA 120 mg/d	3.3% (LURA 120 mg/d, n=5/150), 6.6% (ZIPRA 160 mg/d, n=10/151)	NR	NR	mild to moderate	NR
Nakamura et al. (2009) NCT00088634 D1050196	RCT with PBO (Phase II) (6w) Patients with acute exacerbation of SZ (n=180) LURA 80 mg/d	8.9% (LURA 80 mg/d, n=8/90) vs. 3.3% (PBO, n=3/90)	NR	NR	mild to moderate (one event of akathisia in LURA group rated as severe)	2.2% (LURA 80 mg/d) vs. 0% (PBO)
NCT01358357	RCT with PBO (Phase III) Patients with BP-I with or without rapid cycling and/or psychotic features (n=496) LURA 20-80 mg/d as adjunctive therapy with LI or VAL	3.66% (LURA 20-80 mg/d, n= 9/246) vs. 3.20% (PBO, n=8/250)	NR	NR	NR	NR
NCT00044044	RCT with PBO and active control (Phase II) (6w) Patients with acute exacerbation of SZ (n=353) LURA 20-80 mg/d HAL 10 mg/d	5.63% (LURA 20 mg/d, n=4/71), 13.43% (LURA 40 mg/d, n=9/67), 18.31% (LURA 80 mg/d, n=13/71), 19.44% (HAL 10 mg/d, n=14/72) vs. 9.72% (PBO, n=7/72)	NR	NR	NR	NR
BREXIPRAZOLE						
Ishigooka et al. (2018) NCT01451164	RCT with PBO (Phase II/III) (6w) Acute exacerbation of SZ (n=459) BREX 1-4 mg/d	1.7% (BREX 1 mg/d, n=2/115), 3.5% (BREX 2 mg/d, n=4/114), 5.3% (BREX 4 mg/d, n=6/113) vs. 6.9% (PBO, n=8/116)	Most frequently during first 3w	NR	mild to moderate	0%
Hobart (2018a) NCT02196506	RCT with PBO (6w) Patients with MDD (n=394)	8.3% (AD+BREX 2 mg/d, n=16/192) vs. 5% (AD+PBO)	NR	NR	mild to moderate	NR

(SIRIUS trial)	Adjunctive BREX 2 mg/d					
Hobart (2018b) NCT01727726 (DELPHINUS trial)	RCT with PBO and active control (6w) Patients with MDD (n=503) Adjunctive BREX 2-3 mg/d QUE XR 150-300 mg/d	6.1% (AD+BREX 2-3 mg/d, n=12/197), 3% (AD+QUE XR 150-300 mg/d, n=3/100) vs. 1.9% (AD+PBO, n=4/206)	NR	NR	mild to moderate	NR
Fleischhacker et al. (2017) NCT01668797 (EQUATOR trial)	RCT with PBO (52w) (Phase III) Acute exacerbation of SZ (n=201) BREX 1-4 mg/d	1% (BREX 1-4 mg/d, n=1/97) vs. 1% (PBO, n=1/104)	NR	NR	mild to moderate	0%
Correll (2016b)/ NCT00905307 STEP 203	RCT with PBO and active control (6w) Acute exacerbation of SZ (n=459) BREX 0.25-6 mg/d ARIPI 10-20 mg/d	2.4% (BREX 0.25 mg/d, n=1/42), 6.7% (BREX 1±0.5 mg/d, n=6/89), 5.6% (BREX 2.5±0.5 mg/d, n=5/90), 15.1% (BREX 5±1 mg/d, n=14/93), 4% (ARIPI 10-20 mg/d, n=2/50) vs. 4.2% (PBO, n=4/95)	NR	NR	NR	NR
Citrome et al. (2016) NCT02054702	RCT with active control (6w) (Phase IIIb) Acute exacerbation of SZ (n=97) BREX 1-4 mg/d ARIPI 10-20 mg/d	9.4% (BREX 1-4 mg/d, n=6/64), 21.2% (ARIPI 10-20 mg/d, n=7/33)	NR	NR	mild to moderate	NR
Correll et al. (2015a) NCT01396421 (VECTOR trial)	RCT with PBO (Phase III) (6w) Acute exacerbation of SZ (n=636) BREX 0.25-4 mg/d	0% (BREX 0.25 mg/d, n=0/90), 4.4% (BREX 2 mg/d, n=8/182), 7.2% (BREX 4 mg/d, n=13/180) vs. 2.2% (PBO, n=4/184)	Most often during first 3 weeks of treatment	NR	mild to moderate	0%
Kane et al. (2015b) NCT01393613 (BEACON trial)	RCT with PBO (Phase III) (6w) Acute exacerbation of SZ (n=674) BREX 1-4 mg/d	4.2% (BREX 1 mg/d, n=5/120), 4.8% (BREX 2 mg/d, n=9/186), 6.5% (BREX 4 mg/d, n=12/184) vs. 7.1% (PBO, n=13/184) *patients presenting with severe akathisia at baseline were excluded from the study, possibly explaining the low levels of akathisia	Mostly during first 3 weeks of treatment	NR	mild to moderate	0%
Thase et al. (2015a) (POLARIS trial) NCT01360632	RCT with PBO (Phase III) (6w) Patients with MDD (n=677) BREX 1-3 mg/d	4.4% (BREX 1 mg/d, n=10/226), 13.5 % (BREX 3 mg/d, n=31/229) vs. 2.3% (PBO, n=5/220)	NR	NR	mild to moderate	2.2% (BREX 3 mg/d)
Thase et al. (2015b) (PYXIS trial) NCT01360645	RCT with PBO (Phase III) (6w) Patients with MDD (n=379) BREX 2 mg/d	7.4 % (BREX 2 mg/d, n=14/188) vs. 1% (PBO, n=2/191)	NR	NR	mild to moderate	0.5% (BREX 2 mg/d)
NCT01810380 (LIGHTHOUSE trial) (cited in Marder et al., 2017)	RCT with PBO and active control (6w) Acute exacerbation of SZ (n=311) BREX 2-4 mg/d QUE XR 400-800 mg	6% (BREX 2-4 mg, n=9/150) vs. 2.5% (PBO, n=4/161)	NR	NR	NR	0%
NCT00797966	RCT with PBO (Phase II) (14w) Patients with MDD (n=429) AD+BREX 1-4 mg/d	6.5% (BREX 0.15 mg/d, n=4/62), 5% (BREX 0.5±0.25 mg/d, n=6/120), 8.3% (BREX 1.5±0.5 mg/d, n=10/121) vs. 3.2% (PBO, n=4/126)	NR	NR	NR	NR

NCT01052077 STEP-D222 Cited in Yoon (2017)+Nelson (2016)	RCT with PBO (6w) Patients with MDD (n=372) AD+BREX 1-3 mg/d	11.9% (AD+BREX 1-3 mg/d, n=22/185) vs. 4.81% (AD+PBO, n=9/187)	NR	NR	NR	NR
CARIPRAZINE						
Németh et al. (2017)	RCT with PBO and active control (26w) (Phase IIb) SZ with predominant negative symptoms (n=461) CARI 3-6 mg/d RIS 3-6 mg/d	12% (CARI overall, n=19/230), 9% (RIS overall, n=12/230)	NR	NR	mild to moderate	NR
Durgam et al. (2016a) NCT01396447	RCT with PBO (8w) BP-I depression (n=571) CARI 0.75-3 mg/d	2.8% (CARI 0.75 mg/d, n=4/141), 4.8% (CARI 1.5 mg/d, n=7/146), 14.4% (CARI 3 mg/d, n=21/146) vs. 1.4% (PBO, n=2/145)	NR	NR	mild to moderate (94%)	3% (CARI 3 mg/d)
Durgam et al. (2016b) NCT01469377	RCT with PBO (8w) Patients with MDD (n=819) AD+CARI 1-4.5 mg/d	6.6% (AD+CARI 1-2 mg/d, n=18/273), 22.3% (AD+CARI 2-4.5 mg/d, n=61/273) vs. 2.3% (AD+PBO, n=6/266)	NR	NR	mild to moderate	0.4% (AD+CARI 1-2 mg/d), 4.8% (AD+CARI 2-4.5 mg/d)
Durgam et al. (2016c) NCT00404573 RGH-MD-03	RCT with PBO (6w) Acute exacerbation of SZ (n=392) CARI 1.5-12 mg/d	10.2% (CARI 1.5-4.5 mg/d, n=13/127), 9% (CARI 6-12 mg/d, n=12/133) vs. 0.8% (PBO, n=1/129)	NR	NR	mild to moderate	0.8% (CARI 1.5- 4.5 mg/d) and 2.3% (CARI 6-12 mg/d) vs. 0% (PBO)
Durgam et al. (2016d) NCT01412060	RCT with PBO (46w) Patients with SZ (n=200) CARI 3-9 mg/d	5% (CARI 3-9 mg/d, n=5/101) vs. 3% (PBO, n=3/99)	NR	NR	mild to moderate (>98%)	0% (CARI 3-9 mg/d)
Durgam et al. (2015a) NCT00488618	RCT with PBO (phase II) (3w) Acute manic or mixed episodes BP-I (n=236) CARI 3-12 mg/d (3w)	18.6% (CARI 3-12 mg/d, n=22/118) vs. 5.9% (PBO, n=7/118)	NR	NR	mild to moderate	1.7% (CARI 3-12 mg/d) vs. 0% (PBO)
Durgam et al. (2015b) NCT01104766 RGH-MD-04	RCT with PBO and active control (6w) Acute exacerbation of SZ (n=617) CARI 3-6 mg/d ARIPI 10 mg/d	7.1% (CARI 3 mg/d, n=11/155), 14.6% (CARI 6 mg/d, n=23/157), 7.2% (ARIPI 10 mg/d, n=11/152) vs. 4.6% (PBO, n=7/153)	NR	NR	mild to moderate	1.9% (CARI 3 mg/d), 0.6% (CARI 6 mg/d), 0% (ARIPI 10 mg/d)
Sachs et al. (2015) NCT01058096	RCT with PBO (Phase III) (3w) Acute manic or mixed episodes BP-I (n=312) CARI 3-12 mg/d	22.2% (CARI 3-12 mg/d, n=35/158) vs. 4.5% (PBO, n=7/154)	NR	NR	mild to moderate	3.2% (CARI 3-12 mg/d) vs. 0% (PBO)
Kane et al. (2015b) NCT01104779 RGH-MD-05	RCT with PBO (Phase III) (6w) Acute exacerbation of SZ (n=446) CARI 3-9 mg/d	15.9% (CARI 3-6 mg/d, n=24/151), 16.9% (CARI 6-9 mg/d, n=25/148) vs. 3.4% (PBO, n=5/147)	NR	NR	mild to moderate (100%)	None of the patients from the CARI 3-6 mg/d

						group and only 1 patient from the CARI 6-9 mg/d group discontinued due to akathisia
Calabrese et al. (2015) NCT01058668	RCT with PBO (Phase III) (3w) Acute manic or mixed episodes BP-I (n=497) CARI 3-12 mg/d	17.4% (CARI 3-6 mg/d, n=29/167), 21.9% (CARI 6-12 mg/d, n=37/169) vs. 3.7% (PBO, n=6/161)	NR	NR	mild to moderate	2% (CARI 3-6 mg/d), 3% (CARI 6-12 mg/d) vs. 0% (PBO)
Durgam et al. (2014) NCT00694707 RGH-MD-16	RCT with PBO and active control (6w) Acute exacerbation of SZ (n=617) CARI 1.5-4.5 mg/d RIS 4 mg/d	9% (CARI 1.5 mg/d, n=13/145), 9.6% (CARI 3 mg/d, n=14/146), 7.5% (CARI 4.5 mg/d, n=11/147), 8.6% (RIS 4 mg/d, n=12/140) vs. 4.6% (PBO, n=7/151)	NR	NR	mild (approximately 70% in each group)	Less than 2 patients discontinued due to akathisia
NCT00852202	RCT with PBO (Phase II) (8w) Bipolar depression (n=234) CARI 0.25-3 mg/d	2.7% (CARI 0.25-0.75 mg/d, n=2/75), 17.3% (CARI 1.5-3 mg/d, n=13/75) vs. 6.5% (PBO, n=5/77)	NR	NR	NR	NR

AD: Antidepressant; ARIPI: Aripiprazole; ASE: Asenapine; BARS: Barnes Akathisia Rating Scale; BID: Twice Daily; BP-I: Bipolar I Disorder; BREX: Brexpiprazole; CARI: Cariprazine; D: Days; EPS: Extrapyramidal Symptoms; HAL: Haloperidol; ILO: Iloperidone; LI: Lithium; LURA: Lurasidone; MDD: Major Depressive Disorder; NR: Not Reported; OLZ: Olanzapine; PBO: Placebo; QUE: Quetiapine; QUE XR: Quetiapine Extended-Release; RCT: Randomized Controlled Trial; RIS: Risperidone; SZ: Schizophrenia; SZA: Schizoaffective Disorder; VAL: Valproate; W: Weeks; ZIPRA: Ziprasidone.

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Consulting fees or honorarium	X		
Support for travel to meetings for the study, manuscript preparation or other purposes	X		
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