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The Incidence of Akathisia in the Treatment of Schizophrenia with Aripiprazole, Asenapine and Lurasidone: A Meta-Analysis

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Abstract: Akathisia is a troubling side effect that leads to non-adherence with antipsychotic regimens. Second generation antipsychotics (SGAs) tend to cause less akathisia than older agents but the risk still exists and rates vary between agents. Little is known about the incidence of akathisia among the newer SGAs. The purpose of this study was to conduct a meta-analysis of akathisia incidence rates for three of the newer SGAs: aripiprazole, asenapine, and lurasidone. Data were drawn from published and unpublished clinical trials comparing the drug of interest to either placebo or another SGA in adults with schizophrenia. Twenty-four studies (11 aripiprazole, 5 asenapine, and 8 lurasidone) provided incidence rates for akathisia and related nervous system events. Data showed that the relative risk (RR) of akathisia was double that of controls, with lurasidone having the highest individual RR at 2.7 [CI: 2-3.6]. Sensitivity analysis changed the RR of akathisia to less than 10%. The RR of akathisia was still elevated (1.75 [1.4-2.1]) when these drugs were compared only to actives (older SGAs). Agitation and anxiety RRs were also higher with the newer SGAs as compared to the older SGAs. Previous theory suggests antagonism of serotonin $(5\text{-HT})_{2A}$ receptors may decrease akathisia risk. Expectations were that aripiprazole, asenapine and lurasidone would have a low incidence of akathisia, as all display strong antagonism at 5-HT_{2A}. However, in this study all three had a significantly higher risk of akathisia compared to placebo or other SGAs. This suggests the pathophysiology of akathisia involves other receptors and is multifactorial.

Keywords: Akathisia, aripiprazole, asenapine, lurasidone.

INTRODUCTION

Akathisia is a movement disorder defined by the DSM-5 as restlessness, fidgeting of the legs, rocking, pacing, and the inability to sit or stand still [1]. It usually occurs during the first few weeks (and up to three months) of initiating or increasing an antipsychotic [2]. These symptoms are grouped into three components including subjective akathisia, distress, and motor phenomena. Subjective akathisia is typically the feeling of restlessness which patients can usually differentiate from agitation or anxiety [3]. Akathisia distress results from the inability to control such feelings of restlessness which at times can be severe and debilitating [4, 5]. Motor phenomenon includes activities such as fidgeting, pacing, or rocking and can sometimes be repressed by the patient, which can affect the diagnosis by the physician [6]. Overall, these symptoms of akathisia can be misdiagnosed as agitation induced by psychosis and or lead to an increase in medication (which will worsen the condition and render a patient helpless). The occurrence of adverse effects is known to be a barrier to medication adherence, and akathisia in particular has been associated with a reluctance to take antipsychotic medication [7].

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While akathisia is more commonly associated with first generation antipsychotics, the side effect does occur in patients taking second generation antipsychotics (SGA), although usually at lower rates [8]. The range of occurrence varies based on the SGA being assessed, the nature of reporting akathisia (*e.g.*, subjective vs. objective), and the different presentations of akathisia being measured. Additionally, the higher the dose of the SGA, the higher the likelihood that akathisia may manifest [3]. Due to parkinsonism commonly associated with SGAs and increased concerns on black box warnings regarding metabolic complications (*e.g.*, increased risk for weight gain, elevations in blood glucose and/or blood pressure) with most SGAs, newer SGAs have been marketed and reported as lower the rates of extrapyramidal symptoms (EPS). However, their rates of akathisia may be a problem since they may lead to non-adherence and suicidal ideations.

Akathisia is a side effect that is usually unaccounted for or receives less emphasis or attention. As a result, it may often be under reported or not thoroughly assessed. While rates of akathisia among SGAs have been previously elucidated in the literature [8], comparative data regarding akathisia among some of the newer SGAs over the past few years are lacking. This may be of concern when choosing a newer SGA since akathisia can be a cause of non-adherence and may be associated with an increased risk of suicidal ideation. Clinician reported data show patients experiencing akathisia had an increased likelihood to be suicidal [9]. In

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one study of approximately 300 patients with first episode schizophrenia, akathisia was seen in 18% of the population [9]. Despite the majority describing the side effect as borderline or mild, clinician–rated akathisia was associated with suicidal ideation (p=0.02).

The purpose of this study was to examine the relative risk of akathisia of three of the newer SGAs: aripiprazole, asenapine, and lurasidone, using data reported in clinical trials. Meta-analysis of akathisia outcomes along with other nervous system events with similar symptoms (*i.e.*, agitation, anxiety, restlessness, dystonia, nervousness, parkinsonism) was used to calculate drug-related risks. This information could aid clinicians in assessing the risks versus benefits of some of the newer antipsychotics.

METHODS

A systematic review of the literature was conducted to identify studies involving adult patients receiving treatment for schizophrenia or a related disorder (*e.g.*, schizoaffective disorder) with one of the following SGAs: aripiprazole, asenapine, or lurasidone. Included studies were randomized, double-blind controlled trials which compared the newer aforementioned SGA with either a placebo or an older SGA. Each study was evaluated for data on treatment emergent akathisia rates in study participants.

Published and unpublished studies were identified by a search of Medline, EMBASE and ClinicalTrials.gov for publications available up to June 1, 2014. Search terms consisted of the generic names of the medications along with the term "schizophrenia". Searches were limited to randomized controlled trials and English language publications. Studies were included in the analysis if they involved adult patients (age 18 years and older) taking either orally dosed aripiprazole or lurasidone, or sublingual asenapine, as monotherapy for schizophrenia. Studies were excluded if they involved children or patients with concomitant diagnoses for other psychiatric illnesses. Study quality was assessed by two of the three reviewers (JET, CAH) by determining the Jadad scores [10]. Studies with Jadad scores of 3 or less were considered to be of low quality.

Data were independently extracted by at least two of the three reviewers (JET, JC). The primary outcome was the rate of akathisia. Secondary outcomes included rates of agitation, anxiety, dystonia, nervousness, parkinsonism, restlessness, and suicide or suicidal ideation incidence. The meta-analysis was conducted using RevMan 5.2 [11] using the Mantel-Haenzel statistical method with a fixed model for risk ratios at a 95% confidence interval. Heterogeneity was assessed by calculation of the I^2 measure. Combinations of studies were considered to have unacceptable heterogeneity if the I^2 measure was greater than 50%. Sensitivity analyses were conducted to assess both changes in effect size and heterogeneity by exclusion of low quality studies, by specific drug, and by eliminating outlying studies.

RESULTS

The electronic searches yielded a total of 329 publications. Following the initial screening of the references, 63 abstracts were screened for inclusion. After screening the abstracts, 43 of the studies were fully assessed and 23 publications met the inclusion criteria [12-34]. Additionally, one unpublished study was identified with results on clinicaltrials.gov, and included in the analysis [35]. There were 11 studies of aripiprazole [12-22], 5 studies of asenapine [23-27], and 8 studies of lurasidone [28-35]. See Table **1**.

The included studies represent 10,377 patients, the majority of which were male. Most trials were short term lasting from 4 to 6 weeks. The dosage ranges were aripiprazole 10-30 mg/day, asenapine 10-20 mg/day, and lurasidone 40-160 mg/day. The most common scales used to measure movement disorders in the studies were the Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale (SAS), and Abnormal Involuntary Movement Scale (AIMS). One study used the Extrapyramidal Symptom Rating Scale (ESRS) to measure all movement disorders [25], while another study utilized the Udvalg for kliniske Undersogelser Scale (UKU Side Effect Rating Scale) to assess for adverse effects [22].

Primary Outcome: Akathisia

The relative risk of akathisia from aripiprazole, asenapine, and lurasidone was significantly elevated in the combined data from comparative (versus placebo and/or active controls) clinical trials (RR = 2.01 [1.71-2.37], P <0.00001 I^2 = 36%). Lurasidone had the highest relative risk at 2.7 [2.02-3.62]; however, this combination of studies was not homogenous (I^2 = 64%). Aripiprazole had the lowest risk of the three drugs analyzed but it was still 52% higher than the controls. See Fig. **1**.

When compared to older SGAs alone, the risk of akathisia remained elevated for the newer antipsychotics (RR = 1.75 [1.44, 2.14], P <0.00001). Asenapine had the highest risk of akathisia with double the risk of olanzapine (RR = 2.23 [1.45-3.42]). The risk of akathisia remained elevated (49% higher) with aripiprazole as compared to a combination of older SGAs (*i.e.*, olanzapine, risperidone, ziprasidone). Lurasidone showed an elevated risk for akathisia against risperidone and quetiapine but not ziprasidone causing inconsistency in the analysis (I^2 = 62%). See Fig. **2**.

When compared to placebos only, the risk of akathisia was high for the newer antipsychotics (RR = 2.55 [1.92-3.39], P<0.0001) but heterogeneity was high (I^2=55%). Lurasidone had a very high relative risk for akathisia (4.48) which meant that 1 of every 10 patients taking it in the placebo controlled trials had drug-related akathisia. See Fig. **3**.

Sensitivity Analysis of Akathisia Outcome

Re-analysis of the primary outcome of akathisia under various alternative scenarios is presented in Table **2**. Inclusion of only studies of high quality (Jadad score of 4 or 5) increased the risk estimate by 7% (RR = 2.15 versus 2.01) but also increased heterogeneity (I^2 = 50% vs. 36%) in the combined comparators model.

Exclusion of different subgroups of active drug comparators showed that excluding the olanzapine trials decreased the effect size slightly but increased heterogeneity

Table 1. Characteristics of included studies.

Study Name	N	Length (Weeks)	Medication Studied	Comparator	Dose Ranges (mg/day)	Dose Ranges Comparator (mg /day)	Sex (% Male)	Akathisia and EPS Rates Scales
Buchanan 2012 EH [25]	481	26	Asenapine	Olanzapine	10-20	5-20	Unknown	ESRS-A
Buchanan 2012 WH [25]	468	26	Asenapine	Olanzapine	10-20	5-20	Unknown	ESRS-A
Chan 2007 [14]	83	4	Aripiprazole	Risperidone	15	6	54.2	SAS, BARS, AIMS
Citrome 2012 [34]	621	52	Lurasidone	Risperidone	40-120	2-6	68.6	BARS, AIMS, SAS
Fleischhacker 2009 [18]	695	52	Aripiprazole	Olanzapine	15-30	10-20	56.8	SAS, BARS, AIMS
Jindal 2013 [22]	53	6	Aripiprazole	Olanzapine	10-20	10-20	56.7	UKU, SAS
Kane 2002 [12]	307	4	Aripiprazole	Placebo	15-30		71	SAS, BARS, AIMS
Kane 2009 [19]	566	28	Aripiprazole	Olanzapine	10-30	10-20	67.8	SAS, AIMS, BARS
Kane 2010 [24]	340	6	Asenapine	Placebo	10-20		52-68	SAS, BARS, AIMS
Kane 2011 [23]	386	26	Asenapine	Placebo	10-20		57.3	Patient reports, SAS, BARS, AIMS
Loebel 2013 Placebo [29]	367	6	Lurasidone	Placebo	80-160		69.5	SAS, BARS, AIMS
Loebel 2013 Quetiapine [29]	365	6	Lurasidone	Quetiapine	80-160	600	69.9	SAS, BARS, AIMS
McEvoy 2007 [16]	415	6	Aripiprazole	Placebo	10-20		77.6	SAS, BARS, AIMS
McQuade 2004 [20]	317	26	Aripiprazole	Olanzapine	15-30	10-20	72	Patient reports, physical examination
Meltzer 2011 Placebo [30]	353	6	Lurasidone	Placebo	40-120		78.1	SAS, BARS, AIMS
Meltzer 2011 Olanzapine [30]	359	6	Lurasidone	Olanzapine	40-120	15	78.3	SAS, BARS, AIMS
Nakamura 2009 [32]	180	6	Lurasidone	Placebo	80		76.7	SAS, BARS, AIMS
Nasrallah 2013 [31]	496	6	Lurasidone	Placebo	40-120		69.5	SAS, BARS, AIMS
NCT00044044 [35]	281	6	Lurasidone	Placebo	20-80		72.6	Not reported
Newcomer 2008 [21]	173	16	Aripiprazole	Olanzapine	10-30	10-20	64.2	SAS, AIMS
Ogasa 2013 [28]	149	6	Lurasidone	Placebo	40-120		76.5	SAS, BARS, AIMS
Pigott 2003 [13]	306	26	Aripiprazole	Placebo	15		56.1	SAS, AIMS, BARS
Potkin 2003 Placebo [15]	304	4	Aripiprazole	Placebo	20-30		69.5	SAS, BARS, AIMS
Potkin 2003 Risperidone [15]	300	4	Aripiprazole	Risperidone	20-30	6	69.8	SAS, BARS, AIMS
Potkin 2007 Placebo [27]	121	6	Asenapine	Placebo	10		78.5	SAS, BARS, AIMS
Potkin 2007 Risperidone [27]	118	6	Asenapine	Risperidone	10	6	69.5	SAS, BARS, AIMS
Potkin 2011 [33]	301	3	Lurasidone	Ziprasidone	120	160	70.4	SAS, BARS, AIMS
Schoemaker 2010 [26]	1219	52	Asenapine	Olanzapine	10-20	10-20	53.9	BARS, SAS, AIMS
Zimbroff 2007 [17]	253	4	Aripiprazole	Ziprasidone	10-30	80-160	66.8	SAS, BARS, AIMS

ESRS-A= Extrapyramidal Symptom Rating Scale-Abbreviated
SAS= Simpson-Angus Scale
BARS= Barnes Akathisia Rating Scale
AIMS= Abnormal Involuntary Movement Scale
UKU= Udvalg for kliniske Undersogelser Scale (UKU Side Effect Rating Scale)

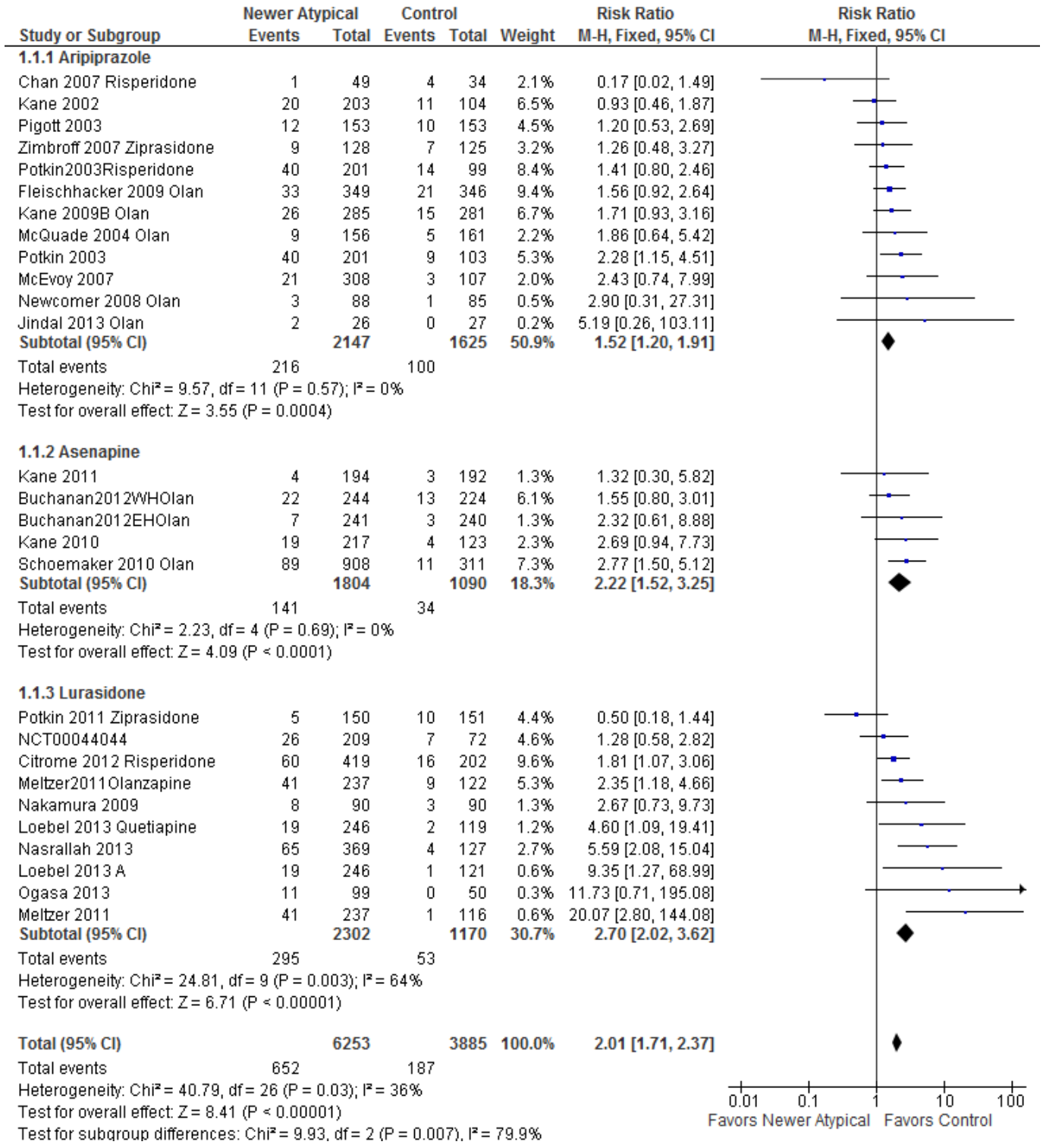

Fig. (1). Relative risk of akathisia (placebo and SGA comparators).

to an unacceptable level (I^2 = 55%). Elimination of risperidone or ziprasidone increased the risk estimate (RR = 2.15 and 2.11 from 2.01, respectively) with small decreases in heterogeneity. Trimming the ends, or removing the studies reporting the smallest and largest relative risks reduced the risk estimate to 1.94 but also reduced heterogeneity (as expected).

Other Nervous System Adverse Events

Combined Controls (Placebo and Active) Model

The risk of agitation was not elevated by the newer antipsychotics (RR = 1.07 [0.91-1.28]). Lurasidone, but not the other drugs or the group, had a significantly higher risk

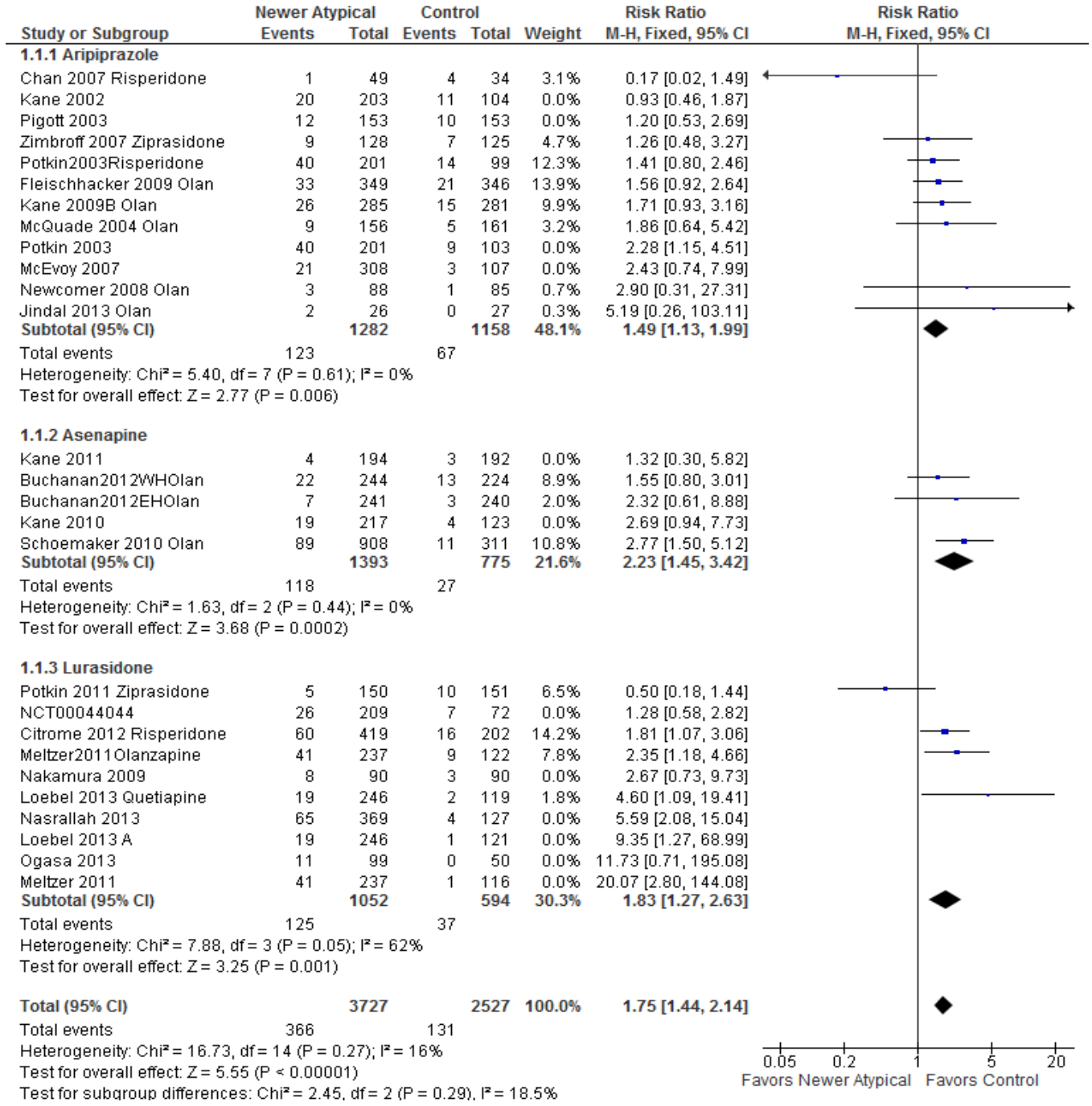

Fig. (2). Relative risk of akathisia (SGA comparators).

for anxiety versus comparators (RR = 1.36 [1.01-1.85]). The newer SGAs had a higher risk of dystonia (combined RR = 1.61 [1.05, 2.48]). Asenapine had the highest relative risk (2.67) of dystonia but sample size was too small to detect a significant difference. Dystonia risk from lurasidone was significantly elevated (RR = 1.81[1.07-3.08]). It is possible that aripiprazole (RR = 0.40[0.12-1.31] reduces the risk of dystonia but the sample size was too small to fully evaluate it as only two studies reported it.

Parkinsonism was elevated by the newer antipsychotics (combined RR = 1.61 [1.19-2.17]). However, lurasidone was responsible for most of this risk and the combination of lurasidone studies was not consistent (I^2 = 61%). Aripiprazole may have a lower risk but only one study reported it. Risk of nervousness and restlessness could not be estimated due to lack of data. See Table **3**.

Active Controls Model

When compared to the older SGAs alone, the newer agents did show an increased risk of agitation (RR = 1.34 [1.04-1.71]). Asenapine had the highest risk of agitation (RR = 1.66) but was only compared to olanzapine due to

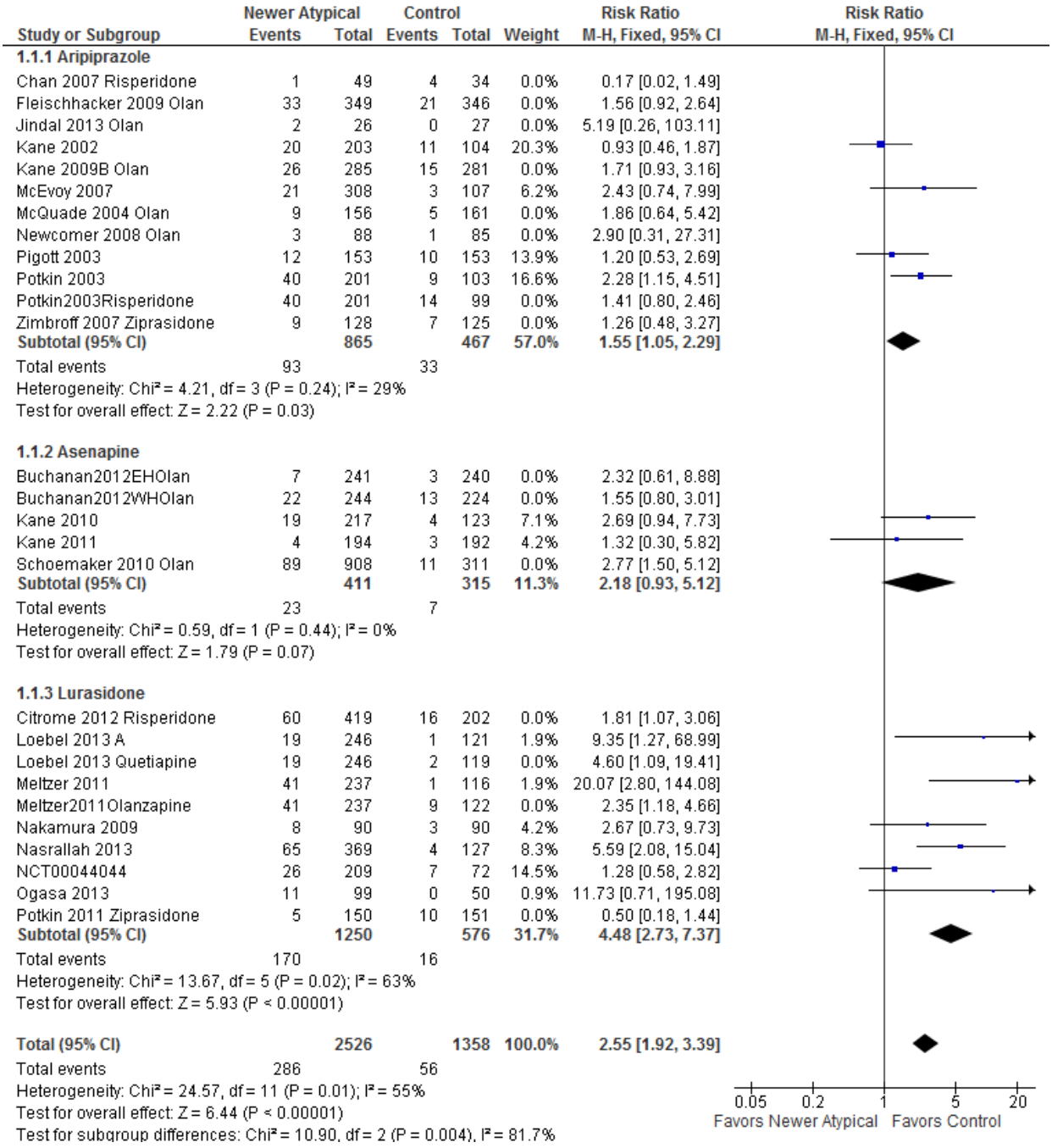

Fig. (3). Relative risk of akathisia (placebo comparators).

Table 2. Sensitivity analysis of akathisia outcome (combined comparators model).

Scenario	Relative Risk	Confidence	P	Studies Cut	I^2
Included only high quality studies	2.15	1.77,2.62	<0.00001	11	50
Trim olanzapine studies	1.97	1.59, 2.43	<0.00001	9	55
Trim risperidone studies	2.15	1.79, 2.57	<0.00001	3	35
Trim ziprasidone studies	2.11	1.78, 2.49	<0.00001	2	30
Trim ends (smallest and largest)	1.94	1.64, 2.29	<0.00001	2	19

Table 3. Relative risk of nervous system events (all comparators).

Adverse Event	Drug	Relative Risk (RR)	Confidence	P	Studies	I^2 %
Agitation	Aripiprazole	1.02	0.83, 1.26	0.83	6	43
	Asenapine	0.98	0.70, 1.38	0.93	5	59
	Lurasidone	1.33	0.90, 1.95	0.15	4	28
	Combined	1.07	0.91, 1.26	0.42	15	42
Anxiety	Aripiprazole	1.02	0.87, 1.20	0.81	10	5
	Asenapine	1.13	0.85, 1.50	0.40	5	0
	Lurasidone	1.36	1.0,1.85	0.05	6	19
	Combined	1.10	0.97, 1.25	0.13	21	0
Dystonia	Aripiprazole	0.4	0.12, 1.31	0.14	2	49
	Asenapine	2.67	0.90, 7.98	0.07	3	0
	Lurasidone	1.81	1.07, 3.08	0.03	6	61
	Combined	1.61	1.05, 2.48	0.03	11	48
Nervousness	Aripiprazole	1.0	0.37, 2.74	1.0	1	NE*
	Asenapine	NE				
	Lurasidone	NE				
	Combined	NE**				
Parkinsonism	Aripiprazole	0.92	0.50, 1.71	0.80	1	NE*
	Asenapine	1.16	0.68, 1.96	0.59	4	0
	Lurasidone	2.50	1.56, 4.02	0.0002	4	73
	Combined	1.61	1.19, 2.17	0.002	9	51
Restlessness	Aripiprazole	NE				
	Asenapine	NE				
	Lurasidone	1.66	0.78, 3.50	0.19	3	0
	Combined	NE**				

NE = not estimable, no comparative studies; NE*=had only 1 study; NE**=had only 1 drug group

lack of data versus other SGAs. The risk of anxiety was also slightly elevated among the newer SGAs as compared to the older ones (RR = 1.19 [1.01-1.41]) with lurasidone posing the highest risk (RR = 1.48 [0.99-2.23]. Risk of dystonia or parkinsonism did not differ in the three newer versus the older SGAs. Nervousness and restlessness could not be evaluated due to lack of data. See Table **4**.

Suicides and Suicide Ideation

The risk of suicide or suicide ideation was not significantly elevated among patients taking the newer SGAs (RR = 0.76 [0.37-1.57]. However, only six studies, 2 in each drug subgroup reported these events. Four of the six studies were comparisons versus olanzapine, one versus risperidone, and one versus placebo. Only 35 events were reported total among the 3,341 patients in those six studies.

DISCUSSION

It has been suggested that antagonism of 5-HT_{2A} receptors may decrease the risk of akathisia, as SGAs generally have a lower incidence of akathisia than first-generation agents [36, 37]. Serotonin (5-HT)$_{2A}$ antagonists have even been suggested as a potential treatment option for akathisia [38]. Therefore, it would be expected that asenapine, aripiprazole, and lurasidone would have a low incidence of akathisia, as all of these agents display strong binding affinity and antagonism at 5-HT_{2A} receptors. However, all three of the newer agents appear to increase the risk of akathisia significantly when compared to placebo or other SGAs. This suggests that the pathophysiology of akathisia involves other receptors and is multifactorial. The pathophysiology of akathisia appears to be complex involving several neurotransmitters including dopamine,

Table 4. Relative risk of nervous system events (SGA comparators).

Adverse Event	Drug	Relative Risk	Confidence	P	Studies	I^2
Agitation	Aripiprazole	1.21	0.89, 1.65	0.23	4	0
	Asenapine	1.66	0.97, 2.81	0.06	3	67
	Lurasidone	1.42	0.73, 2.78	0.30	2	0
	Combined	1.34	1.04, 1.71	0.02	9	9
Anxiety	Aripiprazole	1.09	0.88, 1.35	0.43	6	0
	Asenapine	1.26	0.88, 1.83	0.21	3	0
	Lurasidone	1.48	0.99, 2.23	0.06	4	8
	Combined	1.19	1.01, 1.41	0.06	13	0
Dystonia	Aripiprazole	0.29	0.07, 1.23	0.09	2	67
	Asenapine	1.95	0.58, 6.53	0.28	2	0
	Lurasidone	0.99	0.50, 1.94	0.97	2	84
	Combined	0.95	0.56, 1.60	0.84	6	60
Nervousness	Aripiprazole	NE				
	Asenapine	NE				
	Lurasidone	NE				
	Combined	NE				
Parkinsonism	Aripiprazole	0.92	0.50, 1.71	0.80	1	NE*
	Asenapine	1.14	0.57, 2.28	0.71	2	0
	Lurasidone	1.23	0.71, 2.12	0.46	2	64
	Combined	1.10	0.78, 1.57	0.58	5	0
Restlessness	Aripiprazole	NE				
	Asenapine	NE				
	Lurasidone	1.66	0.78, 3.50	19	3	0
	Combined	NE**				

NE = not estimable, no comparative studies; NE*=had only 1 study; NE**=had only 1 drug group

acetylcholine, y-aminobutyric acid (GABA), norepinephrine, serotonin, and neuropeptides [3].

The pharmacology of the newer SGAs is also complex with all of them having some impact on multiple pathways in the brain and rest of the body. Aripiprazole displays high affinity at dopamine $(D)_2$ and $(D)_3$ receptors, as well as 5-HT_{1A} and 5-HT_{2A} receptors [39, 40]. Additionally, it exhibits moderate affinity for 5-HT_{2C} and 5-HT_7, D_4, adrenergic $(\alpha)_1$ receptors, and histamine $(H)_1$ receptors [39]. It is thought that the therapeutic effect of aripiprazole is due to its action as a partial agonist at D_2 and 5-HT_{1A} receptors and antagonism at 5-HT_{2A} receptors. However, study results have been conflicting, and there is also evidence that aripiprazole may act as a partial agonist at 5-HT_{2A} receptors [41-43]. There are also data which suggest that aripiprazole may generally act as an antagonist at D_2 receptors in the presence of excess dopamine, and this mixed agonism-antagonism may decrease the incidence of EPS (*e.g.*, parkinsonism, dystonia) [44]. However, the serotonergic theory does not elucidate why the risk for akathisia was significantly higher for aripiprazole versus other active agents (mostly olanzapine, risperidone, ziprasidone) in our analysis. It appears that the sedating properties of other agents may be somewhat responsible for attenuating the effects of akathisia and its related complications (*e.g.*, agitation).

The efficacy of asenapine is thought to be due to its action as a primarily antagonist at D_2 and 5-HT_{2A} receptors [45], with a higher binding affinity for serotonin compared to dopamine receptors [46, 47]. Additionally, asenapine acts as an antagonist at multiple serotonin receptors, including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6, and 5-HT_7 [45, 47]. Asenapine is also an antagonist at H_1 receptors, α_1 and α_2 receptors, and D_1, D_2, D_3, and D_4 receptors [47]. Studies suggest asenapine causes an up-regulation of D_1-like

receptors [48], which is noteworthy because there is evidence that the up-regulation of both D_1 and D_2 receptors may decrease the probability of causing EPS-related effects [49]. However, in our analysis, asenapine doubled the risk of akathisia and also appears to cause more agitation than olanzapine. While the reasons for this are unknown, olanzapine has been shown to cause somnolence in approximately 26-29% patients [50], while asenapine has a lower incidence of around 13% [45]. Therefore, as previously mentioned, it may be that olanzapine has higher sedative properties that may reduce the risk for agitation and perhaps mask the symptoms of akathisia.

Lurasidone is an antagonist at 5-HT_{2A}, 5-HT_7, and D_2 receptors, while having little to no binding at H_1 or M_1 receptors [51]. Lurasidone also acts as an antagonist at α_{2A} and α_{2C} receptors, and is a partial agonist at 5-HT_{1A} receptors [51-53]. Lurasidone showed an elevated risk for akathisia against risperidone, olanzapine, and quetiapine but not ziprasidone. One study showed ziprasidone had an increased risk of akathisia compared to lurasidone (6.6% vs. 3.3%); however, despite these low values more data are needed to make definitive conclusions [33]. Lurasidone also appears to increase the risk of anxiety but not agitation. In this case, the higher risk of akathisia with lurasidone cannot be explained since lurasidone has a sedation rate of approximately 20%, which is similar to that of olanzapine and quetiapine [50, 51, 54].

When comparing the newer SGAs to the older SGAs, it was found that the newer agents had an increased risk of agitation and anxiety. While the feelings of restlessness that are associated with akathisia can be differentiated from agitation and anxiety by most patients, it may be possible that akathisia may be overlooked in some patients and confused for agitation or anxiety. Therefore, the higher incidence of agitation and anxiety may actually represent a greater number of patients experiencing akathisia, particularly if the akathisia is less severe, and the patient is able to suppress restless movements while being evaluated for akathisia. Additionally, there is evidence that akathisia is often associated with anxiety.

LIMITATIONS

There is obvious publication bias in this meta-analysis since only a small number of published studies were found for asenapine and lurasidone and few active comparator studies were identified other than those examining olanzapine. Studies are being conducted as listed at clinical trials.gov but publication of results is not forthcoming.

Many publications did not include data about the incidence of akathisia or other related adverse effects. Additionally, the publications used different cut-offs for determining which adverse effects to report. While the majority of the publications reported on all adverse effects that were seen in at least 5% of one of the study groups, other publications included data on less common adverse effects [25, 33], and at least one study only reported on adverse effects that occurred in at least 10% of one of the study groups [27]. This may have led to underreporting of akathisia and related adverse effects, and may lead one to underestimate the prevalence of these symptoms. While the majority of the studies used the BARS scale to assess for akathisia, a few studies used different scales such as ESRS or UKU, or relied on patient self-report, all of which could have resulted in differences in reported rates of akathisia.

While the majority of studies did not allow for the use of anticholinergic medications unless symptoms of EPS arose, most studies did allow for the use of benzodiazepines throughout the study duration. This may have led to an underestimation of the prevalence of anxiety and agitation. Very few publications stated whether participants were allowed to use beta-blockers such as propranolol during the study. This is important, as the use of these medications for other disease states, such as hypertension, anxiety or sleep disorders, may potentially have decreased the incidence of akathisia in these patients. Additionally, many of the studies in this analysis excluded participants who were thought to be at a higher risk of suicide, which may have influenced the prevalence of suicidal ideation observed in study participants.

Another limitation of this meta-analysis is that the results are based on studies in adult populations with schizophrenia. Therefore, the results should not be generalized to children and adolescents, or populations using these medications for other indications, such as bipolar disorder. There is evidence that patients with bipolar disorder, particularly those in a depressive phase, are more susceptible to developing antipsychotic-induced movement disorders than patients with schizophrenia. Therefore, greater care must be noted when treating such patients [55]. Also, 33% of the studies in our analysis also included patients with schizoaffective disorder [12, 14, 15, 17, 21, 26, 33, 34], which may display a greater risk for motor symptoms. However, the sample of these studies ranged between 4-32% of the total population with most studies averaging approximately 20%.

CONCLUSION

Despite the limitations, this study does illustrate that the newer SGAs (*i.e*., aripiprazole, asenapine, lurasidone) appear to have higher risks for akathisia than some of the older SGAs. The risks of anxiety and agitation were also found to be higher with the newer SGAs. The reasons why these newer agents may have a higher incidence of akathisia are not clear, as the pathophysiology of akathisia appears to involve multiple receptors. However, akathisia is a troubling adverse effect for many patients taking newer SGAs, which should be monitored for any patient beginning therapy with one of these agents.

CONFLICT OF INTEREST

The authors report no conflict of interest and attest to the integrity of this work.

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