Published in final edited form as:
J Clin Psychopharmacol. 2008 April ; 28(2): 203–209. doi:10.1097/JCP.0b013e318166c4d5.

Antipsychotic-Induced Extrapyramidal Side Effects in Bipolar Disorder and Schizophrenia:

A Systematic Review

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Abstract

Objectives—Newer atypical antipsychotics have been reported to cause a lower incidence of extrapyramidal side effects (EPS) than conventional agents. This review is to compare antipsychotic-induced EPS relative to placebo in bipolar disorder (BPD) and schizophrenia.

Methods—English-language literature cited in Medline was searched with terms antipsychotics, placebo-controlled trial, and bipolar disorder or schizophrenia and then with antipsychotic (generic/brand name), safety, akathisia, EPS, or anticholinergic use, bipolar mania/depression, BPD, or schizophrenia, and randomized clinical trial. Randomized, double-blind, placebo-controlled, monotherapy studies with comparable doses in both BPD and schizophrenia were included. Absolute risk increase and number needed to treat to harm (NNTH) for akathisia, overall EPS, and anticholinergic use relative to placebo were estimated.

Results—Eleven trials in mania, 4 in bipolar depression, and 8 in schizophrenia were included. Haloperidol significantly increased the risk for akathisia, overall EPS, and anticholinergic use in both mania and schizophrenia, with a larger magnitude in mania, an NNTH for akathisia of 4 versus 7, EPS of 3 versus 5, and anticholinergic use of 2 versus 4, respectively Among atypical antipsychotics, only ziprasidone significantly increased the risk for overall EPS and anticholinergic use in both mania and schizophrenia, again with larger differences in mania, an NNTH for overall EPS of 11 versus 19, and anticholinergic use of 5 versus 9. In addition, risks were significantly increased for overall EPS (NNTH = 5) and anticholinergic use (NNTH = 5) in risperidone-treated mania, akathisia in aripiprazole-treated mania (NNTH = 9) and bipolar depression (NNTH = 5), and overall EPS (NNTH = 19) in quetiapine-treated bipolar depression.

Conclusions—Bipolar patients, especially in depression, were more vulnerable to having acute antipsychotic-induced movement disorders than those with schizophrenia.

The matter of bipolar disorder (BPD) as a risk factor for antipsychotic-induced movement disorders is still inconclusive. Some early studies showed that patients with BPD were more vulnerable to developing tardive dyskinesia (TD) as well as acute extrapyramidal side effects (EPS) than those with schizophrenia,[1-3] but others found that they had a similar risk.[4,5] More recently, in a pooled data analysis, Canvazoni et al[6] reported that haloperidol-treated patients with BPD seemed to be more vulnerable to the development of EPS than those with schizophrenia, but not olanzapine-treated patients with BPD. It remains unclear if

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patients with BPD have a similar degree of vulnerability to developing acute EPS as those with schizophrenia when being treated with other antipsychotics.

Atypical agents have a lower liability for acute EPS and TD than typical agents,[7] but TD has been observed even with the atypicals.[8,9] A number of studies have reported that the development of acute EPS is a significant risk factor for later development of TD in schizophrenia.[10-12] With the increasing use of atypical antipsychotics[13,14] and continuous use of typical agents in BPD,[15,16] the issue of antipsychotic-induced acute EPS in BPD is worth revisiting. In this review, we used randomized, double-blind, placebo-controlled studies of antipsychotics being carried out in both schizophrenia and BPD to compare the risk for antipsychotic-induced acute EPS relative to that of placebo.

METHODS

English-language literature published and cited in Medline through October 31, 2007 was searched using the terms antipsychotics, placebo-controlled trial, and BPD, or mania, or schizophrenia, and then with terms typical antipsychotics, atypical antipsychotics, fluphenazine, haloperidol, perphenazine, pimozide, thiothixene, trifluoperazine, loxapine, molindone, chlorpromazine, mesoridazine, thioridazine, fluspirilene, penfuridol, pipothiazine, flupenthixol, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, or aripiprazole; with safety, tolerability, akathisia, EPS, or anticholinergic use; with bipolar mania or depression, BPD, manic-depressive illness, or schizophrenia; and with randomized, double-blind, controlled clinical trial. Recent studies, especially in BPD, presented at major scientific meetings were also included.

Citations generated by the Medline search were examined for the original placebo-controlled trials of antipsychotics in BPD or schizophrenia. Only antipsychotics with studies in both BPD and schizophrenia were included for further examination. Studies designed for schizoaffective disorder or prodromal psychosis were excluded for analyses. With only a few maintenance studies of antipsychotics in BPD, maintenance studies were also excluded for further examination. Among acute treatment studies, dosing schedule and dosages of antipsychotics varied substantially. In acute schizophrenia studies, multiple fixed doses of antipsychotics were used. Some of these dosages, such as aripiprazole 2 mg/d, olanzapine 2.5 mg/d, risperidone 2 mg/d, quetiapine 75 mg/d, or ziprasidone 10 mg/d, were low and less likely to be clinically useful. On the other hand, most studies in BPD were flexibly dosed, but the mean doses of most of these atypical antipsychotics were targeted to the maximal doses recommended for schizophrenia. To make a comparison as fair as possible, the incidences of the movement disorders of the closest dose(s) of an antipsychotic in a schizophrenia study to the mean dose of a corresponding mania study was chosen: aripiprazole 30 mg/d for mania and 15–20 mg/d for bipolar depression, haloperidol 8 to 12 mg/d, olanzapine 12 to 16 mg/d, quetiapine 600 mg/d, risperidone 6 mg/d, and ziprasidone 120 to 160 mg/d. For quetiapine bipolar depression studies, 600 mg/d was used to match the quetiapine mania study. Studies in schizophrenia with either a lower or a higher dose than those defined above were excluded for analysis.

In terms of the outcome variables for EPS, the EPS was reported by the incidence of occurrence, the use of anticholinergic agents, and/or the change in rating scales. The occurrence of akathisia was reported separately in most studies. Therefore, comparisons of the risk for akathisia, overall EPS, and anticholinergic use would cover a spectrum of antipsychotic-induced movement disorders. For this review, the number needed to treat to benefit (NNTB) or harm (NNTH) and the absolute risk reduction (ARR) or increase (ARI) were used to measure the differences.[17] The NNTB or NNTH = 1/ARR or ARI and the ARR or ARI = placebo event rate – antipsychotic event rate. The calculation was based on the

assumption that an antipsychotic would cause a greater occurrence of the EPS than placebo. Therefore, a negative value was indicative of a higher risk of an antipsychotic than placebo, presented with an NNTH and an ARI. A positve value was indicative of a lower risk of an antipsychotic than placebo presented with an NNTB and an ARR.

The type I error rate for significance tests between antipsychotics and placebo was set at $\alpha = 0.05$. Confidence intervals (CI) were presented as mean ± 1.96 standard error.[18] For antipsychotic-placebo comparison, statistical significance was declared when a CI did not include zero. For between-condition comparisons, nonoverlapping CIs were considered to be an indicator of statistical significance. Overlapping CIs were interpreted to indicate lack of statistical significance. Although this conservative interpretation might miss statistical significance,[19] the NNTB or NNTH and the degree overlap of CIs can help clinicians to determine the degree of clinical significance. For antipsychotics with more than one clinical trial of a similar study design, the values of these variables were recalculated based on a pooled sample.

RESULTS

The Medline search generated 1003 citations for schizophrenia and 128 for BPD. An initial examination of these citations revealed that only haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone had placebo-controlled studies in both BPD and schizophrenia. Among the acute treatment studies, 9 in schizophrenia,[20-28] 11 monotherapy trials in the acute treatment of mania,[29-39] and 4 in bipolar depression[40-43] met the inclusion criteria for analysis (Tables 1-3).

Akathisia in Schizophrenia, Mania, or Bipolar Depression

In schizophrenia, there was a higher risk for akathisia with haloperidol than placebo with an NNTH of 7 (95% CI: −12 to −5). There was no higher risk for akathisia with aripiprazole, olanzapine, quetiapine, or ziprasidone compared with their respective placebo (Table 1). In mania, there is also no higher risk with quetiapine or ziprasidone compared with placebo, but there was higher risk with haloperidol or aripiprazole compared with placebo with an NNTH of 4 (95% CI: −6 to −3) for haloperidol and 9 (95% CI: −16 to −6) for aripiprazole. In bipolar depression, there was a significantly higher risk with aripiprazole compared with placebo with an NNTH of 5 (95% CI: −6 to −4). There was no overlap between the ARIs of aripiprazole in bipolar depression and aripiprazole 15 to 20 mg/d in schizophrenia. However, the CIs of other antipsychotics in BPD and schizophrenia or the CIs of aripiprazole in mania and bipolar depression overlapped (Table 1).

Overall EPS in Schizophrenia, Mania, or Bipolar Depression

In schizophrenia, there was no higher risk with aripiprazole, quetiapine, or risperidone compared with placebo. However, there was higher risk with haloperidol and ziprasidone compared with placebo with an NNTH of 5 (95% CI: −8 to −3) for haloperidol and 19 (95% CI: −203 to −10) for ziprasidone (Table 2). In mania, the higher risk with haloperidol and ziprasidone compared with placebo continued with an NNTH of 3 (95% CI: −4 to −3) for haloperidol and 11 (95% CI: −67 to −6) for ziprasidone. In addition, there was also higher risk with risperidone compared with placebo with an NNTH of 5 (95% CI: −8 to −4). In depression, there was higher risk with quetiapine compared with placebo with an NNTH of 19 (95% CI: −72 to −11) (Table 2). There was no overlap between the CI of ARI of risperidone in schizophrenia and the CI in mania. All other CIs of overall EPS overlapped (Table 2).

Anticholinergic Use in Schizophrenia, Mania, or Bipolar Depression

In schizophrenia, there was a higher risk with haloperidol compared with placebo in anticholinergic use with an NNTH of 4 (95% CI: −7 to −3). There was also a higher risk with olanzapine and ziprasidone compared with their respective placebo with an NNTH of 9 (95% CI: −33 to −5) for ziprasidone and 8 (95% CI: −78 to −4) for olanzapine. In mania, the higher risks with haloperidol and ziprasidone compared with placebo continued with an NNTH of 2 (95% CI: −4 to −2) for haloperidol and 5 (95% CI: −12 to −4) for ziprasidone. In addition, there was a higher risk with risperidone compared with placebo with an NNTH of 5 (95% CI: −7 to −4). All CIs of ARI in mania and schizophrenia overlapped. The CIs overlap was small with haloperidol as well as with risperidone (Table 3).

DISCUSSION

This first systematic review of the antipsychotic-induced acute EPS in BPD and schizophrenia has found that patients with BPD were more vulnerable to developing akathisia and other EPS than those with schizophrenia. Although only a few comparisons between these 2 disorders reached the conservative interpretation of statistical significance, the NNTH for akathisia, overall EPS, and/or anticholinergic use of each antipsychotic in BPD was much smaller than that in schizophrenia. In addition, the lower doses of haloperidol, risperidone, and ziprasidone used in BPD than those in schizophrenia further support these findings (Tables 1-3).

Seemingly, bipolar depressed patients were even more sensitive to antipsychotics than those in mania, which was at least supported by quetiapine and aripiprazole studies.[20,21,31,32,40-42] A naturalistic report of aripiprazole augmentation in refractory bipolar depression also found that 42% (5/12) of patients developed akathisia.[44] However, olanzapine did not show a higher risk for overall EPS than placebo in depression[43] as well as in mania, although a higher risk was observed in schizophrenia.[24] It remains unclear whether the increased EPS in quetiapine-treated bipolar depression is a state-dependent phenomenon or an individual antipsychotic-dependent phenomenon or both.

The impact of this higher vulnerability to antipsychotic-induced acute EPS on the development of TD in BPD is yet to be determined. However, the uncertainty of the effect of acute EPS on TD in BPD should not minimize the importance of reducing the occurrence of acute EPS. One strategy is to select an antipsychotic with low EPS liability. From this review, haloperidol had the highest risk for movement disorders. These results are consistent with head-to-head comparison studies of haloperidol versus atypical agents in BPD[45,46] and schizophrenia.[47,48] However, it is also possible that the unnecessarily high doses of haloperidol being used in these studies might play a role. Neuroimaging studies have shown that the occurrence of EPS was positively correlated to doses of haloperidol.[49,50] The doses of haloperidol in bipolar studies varied from 3 to 15 mg/d (most around 10 mg/d), and those in schizophrenia were even higher, mostly 10 to 20 mg/d.

Among the atypical antipsychotics, aripiprazole, ziprasidone, and risperidone were more likely to cause EPS (Tables 1-3). However, the results have been challenged by an observational study, in which Ghaemi et al[51] assessed 51 individual patient trials of atypical antipsychotics in 37 patients with BPD and found that 63% of trials resulted in moderate to severe EPS. The EPS and discontinuation frequencies were similar between high-potency (risperidone/ziprasidone/aripiprazole) and low-potency (quetiapine/olanzapine) agents.

Another strategy is to use lower doses of antipsychotics. However, most studies in BPD are flexibly dosed and the dose-efficacy or dose–side effect data are not available. Therefore,

the balance between efficacy and side effects including EPS in the treatment of BPD should be evaluated individually.

Limitations

First, the ideal for indirect comparison should be to compare interventions of equivalent intensity or dose, in the same condition, at similar disease severity, using the same outcomes, and during the same period of time.[52] Clearly, these requirements were not met in this review. Second, for each antipsychotic, the studies were pooled based on the diagnosis. Although incidences of EPS at the closest dose from each study were used, the heterogeneity within and between the original studies could not be controlled. The results could be biased by original study designs, including inclusion and exclusion criteria, sample sizes, study durations, medication doing schedule and dosages, or concomitant treatments such as benzodiazepines that could mask or prevent EPS from emerging. Third, only published studies were reviewed. Although the occurrence of EPS was unlikely to cause publication bias, it remains unclear whether the efficacy-related publication bias had any effect on the outcomes of adverse events including EPS. Fourth, the severity of EPS and doses or number of times an anticholinergic drug was administered could not be systematically reviewed because most studies did not report these results.

CONCLUSIONS

Overall, patients with BPD, especially when in a depressive phase, are more vulnerable to developing antipsychotic-induced acute EPS than those with schizophrenia. Compared with haloperidol, atypical antipsychotics are less liable for inducing acute EPS in BPD, although each individual antipsychotic has a differential liability. The relationship between acute EPS and TD in BPD is worthy of further exploration.

Acknowledgments

AUTHOR DISCLOSURE INFORMATION

Dr Calabrese has also received grant support and honoraria from Abbott, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Lilly, Pfizer, and Janssen. Dr Gao received honoraria and/or grant support from Abbott, AstraZeneca, GSK, and NARSAD. Dr Gajwani received grant support and/or honoraria from Abbott Laboratories, AstraZeneca, Bristol Myers Squibb, Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, and Pfizer. Dr Kemp received educational grants from Abbott and Bristol-Myers Squibb and research support from GlaxoSmithKline.

Support for this study included NIMH P20 MH-66054 (J.R.C.).

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J Clin Psychopharmacol. Author manuscript; available in PMC 2012 November 05.

TABLE 1

Comparison of Akathisia Between Antipsychotics and Placebo in the Acute Treatment of Schizophrenia, Mania, or Bipolar Depression

			Akathisia		
				ARR or ARI, %	NNTB or NNTH
Agents and Trials	**Treatment Arms**	**Duration, wk**	**No. Patients**	**Mean (95% CI)**	**Mean (95% CI)**
Antipsychotics in schizophrenia					
Haloperidol					
Kane et al[20]	HAL 8–12 mg/d (n = 222)	4–8	57	−15.2 (−22.1 to −8.1)	−7 (−12 to −5)*
Arvanitis et al[21]	PBO (n = 228)		24		
Zimbroff et al[22]					
Aripiprazole					
Kane et al[20]	ARIP 30 mg/d (n = 201)	4	31	−5.8 (−12.3 to 0.7)	−17 (142 to −8)
Potkin et al[23]	PBO (n = 207)		20		
Kane et al[20]	ARIP 15–20 mg/d (n = 203)	4	28	−4.1 (−10.5 to 2.2)	−24 (46 to −10)
Potkin et al[23]	PBO (n = 207)		20		
Olanzapine					
Beasley et al[24]	OLZ 12–16 mg/d (n = 133)	6	9	−5.3 (−11.0 to 1.8)	−19 (54 to −9)
	PBO (n = 68)		1		
Quetiapine					
Arvanitis et al[21]	QTP 600 mg/d (n = 51)	6	1	5.9 (−3.7 to 16.7)	17 (6 to −27)
	PBO (n = 51)		4		
Ziprasidone					
Keck et al[27]	ZIP 120–160 mg/d (n = 151)	4–6	14	−2.8 (−9.3 to 3.6)	−35 (28 to −11)
Daniel et al[28]	PBO (n = 140)		9		
Antipsychotics in bipolar mania					
Haloperidol					
McIntyre et al[29]	HAL 2–8 mg/d (n = 99)	12	33	−27.4 (−37.7 to −16.7)	−4 (−6 to −3)*
	PBO (n = 101)		6		
Aripiprazole					
Keck et al[30]	ARIP ≈ 28 mg/d (n = 260)	3	38	−11.0 (−16.0 to −6.2)	−9 (−16 to −6)*

			Akathisia		
				ARR or ARI, %	NNTB or NNTH
Agents and Trials	**Treatment Arms**	**Duration, wk**	**No. Patients**	**Mean (95% CI)**	**Mean (95% CI)**
Sachs et al[31]	PBO (n = 263)		9		
Quetiapine					
Vieta et al[32]	QTP ≈ 600 mg/d (n = 209)	12	7	2.7 (−1.6 to 7.3)	37 (14 to −65)
	PBO (n = 198)		12		
Ziprasidone					
Keck et al[38]	ZIP 112–147 mg/d (n = 279)	3	28	−4.9 (−9.8 to 1.0)	−20 (98 to −10)
Potkin et al[39]	PBO (n = 136)		7		
Antipsychotics in bipolar depression					
Marcus et al[40]	ARIP 15.5–17.6 mg/d (n = 360)	8	88	−20.6 (−25.6 to −15.8)	−5 (−6 to −4) *
	PBO (n = 367)		14		

* Significant difference from placebo at $\alpha = 0.05$ level.

ARI indicates absolute risk increase; ARIP, aripiprazole; ARR, absolute risk reduction; CI, confidence interval; HAL, haloperidol; NNTB, number needed to treat to benefit; NNTH, number needed to treat harm; OLZ, olanzapine; PBO, placebo; QTP, quetiapine; ZIP, ziprasidone.

J Clin Psychopharmacol. Author manuscript; available in PMC 2012 November 05.

TABLE 2

Comparison of Overall EPS Between Antipsychotics and Placebo in the Acute Treatment of Schizophrenia, Mania, or Bipolar Depression

				EPS	
				ARR or ARI, %	NNTB or NNTH
Agents and Trials	**Treatment Arms**	**Duration, wk**	**No. Patients**	**Mean (95% CI)**	**Mean (95% CI)**
Antipsychotics in schizophrenia					
Haloperidol					
Kane et al[20]	HAL 8–12 mg/d (n = 222)	4–8	93	−21.3 (−29.3 to −13.0)	−5 (−8 to −3) *
Arvanitis et al[21]	PBO (n = 228)		51		
Zimbroff et al[22]					
Aripiprazole					
Kane et al[20]	ARIP 30 mg/d (n = 201)	4	21	−0.8 (−6.8 to 5.2)	−127 (19 to −15)
Potkin et al[23]	PBO (n = 207)		20		
Kane et al[20]	ARIP 15–20 mg/d (n = 203)	4	24	−1.2 (−7.4 to 5.0)	−84 (20 to −13)
Potkin et al[23]	PBO (n = 207)		22		
Quetiapine					
Arvanitis et al[21]	QTP 600 mg/d (n = 51)	6	4	9.8 (−3.6 to 23.3)	10 (4 to −28)
	PBO (n = 51)		9		
Risperidone					
Potkin et al[23]	RIS 6 mg/d (n = 185)	4–8	12	−0.7 (−5.9 to 4.3)	−137 (23 to −17)
Chouinard et al[25]	PBO (n = 191)		11		
Marder et al[26]					
Ziprasidone					
Keck et al[27]	ZIP 120–160 mg/d (n = 151)	4–6	10	−5.2 (−10.4 to −0.5)	−19 (−203 to −10) *
Daniel et al[28]	PBO (n= 140)		2		
Antipsychotics in bipolar mania					
Haloperidol					
McIntyre et al[29]	HAL 2–8 mg/d (n = 243)	3	93	−30.8 (−37.6 to −23.8)	−3 (−4 to −3) *
Smulevich et al[35]	PBO (n = 241)		18		
Quetiapine					

				EPS	
				ARR or ARI, %	NNTB or NNTH
Agents and Trials	**Treatment Arms**	**Duration, wk**	**No. Patients**	**Mean (95% CI)**	**Mean (95% CI)**
Vieta et al[32]	QTP ≈ 600 mg/d (n = 209)	12	27	0.2 (−6.4 to 6.9)	470 (15 to −16)
	PBO (n = 198)		26		
Risperidone					
Smulevich et al[35]	RIS 4.1–5.6 mg/d (n = 300)	3	77	−18.3 (−24.1 to −12.4)	−5 (−8 to −4)*
Khanna et al[37]	PBO (n = 284)		21		
Ziprasidone					
Potkin et al[39]	ZIP 112–147 mg/d (n = 139)	3	15	−9.3 (−15.7 to −1.5)	−11 (−67 to −6)*
	PBO (n = 66)		1		
Antipsychotics in bipolar depression					
Quetiapine					
Calabrese et al[41]	QTP 600 mg/d (n = 348)	8	33	−5.2 (−9.1 to −1.4)	−19 (−72 to −11)*
Thase et al[42]	PBO (n = 347)		15		

*Significant difference from placebo at $\alpha = 0.05$ level.

ARI indicates absolute risk increase; ARIP, aripiprazole; ARR, absolute risk reduction; CI, confidence interval; HAL, haloperidol; NNTB, number needed to treat to benefit; NNTH, number needed to treat harm; OLZ, olanzapine; PBO, placebo; QTP, quetiapine; RIS, risperidone; ZIP, ziprasidone.

J Clin Psychopharmacol. Author manuscript; available in PMC 2012 November 05.

TABLE 3

Comparison of Anticholinergic Use Between Antipsychotics and Placebo in the Acute Treatment of Schizophrenia, Mania, or Bipolar Depression

			Anticholinergic Use		
				ARR or ARI, %	NNTB or NNTH
Agents and Trials	**Treatment Arms**	**Duration, wk**	**No. Patients**	**Mean (95% CI)**	**Mean (95% CI)**
Antipsychotics in schizophrenia					
Haloperidol					
Kane et al[20]	HAL 8–12 mg/d (n = 222)	4–8	56	−23.4 (−31.3 to −15.2)	−4 (−7 to −3) *
Arvanitis et al[21]	PBO (n = 228)		19		
Zimbroff et al[22]					
Aripiprazole					
Kane et al[20]	ARIP 30 mg/d (n = 101)	4	15	−3.3 (−12.8 to 6.1)	−30 (16 to −8)
	PBO (n = 104)		12		
Kane et al[20]	ARIP 15 mg/d (n = 101)	4	8	3.6 (−4.8 to 12.1)	28 (8 to −21)
	PBO (n = 104)		12		
Olanzapine					
Beasley et al[24]	OLZ 12–16 mg/d (n = 133)	6	33	−13.1 (−22.8 to −1.28)	−8 (−78 to −4) *
	PBO (n = 68)		8		
Quetiapine					
Arvanitis et al[21]	QTP 600 mg/d (n = 51)	6	6	2.0 (−11.6 to 15.5)	51 (6 to −9)
	PBO (n = 51)		7		
Risperidone					
Chouinard et al[25]	RIS 6 mg/d (n = 86)	4–8	20	−2.8 (−15.0 to 9.5)	−36 (11 to −7)
Marder et al[26]	PBO (n = 88)		18		
Ziprasidone					
Keck et al[27]	ZIP 120–160 mg/d (n = 151)	4–6	35	−11.8 (−20.3 to −3.0)	−9 (−33 to −5) *
Daniel et al[28]	PBO (n = 140)		16		
Antipsychotics in bipolar mania					
Haloperidol					
McIntyre et al[29]	HAL 2–8 mg/d (n = 99)	3	52	−40.6 (−51.4 to −28.2)	−2 (−4 to −2) *

			Anticholinergic Use		
				ARR or ARI, %	NNTB or NNTH
Agents and Trials	Treatment Arms	Duration, wk	No. Patients	Mean (95% CI)	Mean (95% CI)
	PBO (n = 101)		12		
Quetiapine					
Vieta et al[32]	QTP ≈ 600 mg/d (n = 208)	12	21	0 (−5.9 to 6.1)	1881 (16 to −17)
	PBO (n = 195)		20		
Risperidone					
Hirschfeld et al[36]	RIS 4.1–5.6 mg/d (n = 280)	3	82	−20.7 (−27.0 to −14.4)	−5 (−7 to −4)*
Khanna et al[37]	PBO (n = 269)		23		
Ziprasidone					
Potkin et al[39]	ZIP 112–147 mg/d (n = 136)	3	35	−19.1 (−27.8 to −8.4)	−5 (−12 to −4)*
	PBO (n = 66)		4		
Antipsychotics in bipolar depression					
Olanzapine					
Tohen et al[43]	OLZ 9.7 mg/d (n = 351)	8	12	0.6 (2.3 to −3.4)	−177 (46 to −30)
	PBO (n = 355)		14		

*Significant difference from placebo at $\alpha = 0.05$ level.

ARI indicates absolute risk increase; ARIP, aripiprazole; ARR, absolute risk reduction; CI, confidence interval; HAL, haloperidol; NNTB, number needed to treat to benefit; NNTH, number needed to treat harm; OLZ, olanzapine; PBO, placebo; QTP, quetiapine; RIS, risperidone; ZIP, ziprasidone.

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