# A Review of Sensitivity and Tolerability of Antipsychotics in Patients With Bipolar Disorder or Schizophrenia: Focus on Somnolence

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***Objective:*** This study compared the sensitivity and tolerability of antipsychotics in patients with bipolar disorder or schizophrenia.

***Data Sources:*** English-language literature from January 1966 to December 2006 cited in MEDLINE was searched for the terms *antipsychotics*, *typical antipsychotics*, *atypical antipsychotic*, generic and brand names of antipsychotics, *safety*, *tolerability*, *discontinuation due to adverse events*, *somnolence*, and *bipolar mania*, *bipolar depression*, *bipolar disorder*, *manic-depressive illness*, or *schizophrenia*, *randomized*, *double blind*, and *controlled clinical trial*.

***Study Selection:*** Randomized, double-blind, placebo-controlled, monotherapy studies of antipsychotics in both bipolar disorder and schizophrenia were prioritized.

***Data Extraction:*** Absolute risk increase (ARI) or reduction (ARR) and the numbers needed to treat to harm (NNTH) or benefit (NNTB) for the discontinuation due to adverse events and somnolence relative to placebo were estimated.

***Data Synthesis:*** Ten acute trials in mania, 3 in bipolar depression, and 8 in schizophrenia were identified, along with 2 maintenance studies in bipolar disorder and 2 in schizophrenia. In schizophrenia, ziprasidone caused significantly more discontinuations due to adverse events than placebo, with an NNTH of 19, while aripiprazole caused significantly fewer discontinuations due to adverse events than placebo, with an NNTB of 12. In mania, there was no statistically significant difference in discontinuation due to adverse events between antipsychotics and placebo. However, in bipolar depression, both quetiapine and olanzapine caused more discontinuations due to adverse events than placebo, with NNTHs of 7 and 24, respectively. All atypical antipsychotics caused a significantly greater incidence of somnolence than placebo in mania and depression, with NNTHs from 5 to 8 for mania and 2 to 6 for depression. In schizophrenia, only olanzapine, ziprasidone, and aripiprazole (NNTHs from 5 to 14) caused a significantly higher incidence of somnolence. There was no significant difference between schizophrenia and mania in the discontinuation due to adverse events or somnolence of all studied antipsychotics. However, there was a significantly higher incidence of discontinuation due to adverse events and somnolence caused by quetiapine in bipolar depression than that in schizophrenia or mania.

***Conclusion:*** Patients with bipolar disorder appear more sensitive to antipsychotics, and depressed patients are less tolerant to somnolence than those with either mania or schizophrenia.

*(J Clin Psychiatry 2008;69:302–309)*

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*Support for this manuscript includes grant # P20 MH-66054 (Dr. Calabrese) from the National Institute of Mental Health, Bethesda, Md.*

*Financial disclosure appears at the end of the article.*

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Differences in the phenomenology and neurobiology of schizophrenia and bipolar disorder have been reported,[1–3] although overlap also exists.[4,5] However, it is unclear whether patients with bipolar disorder experience a similar degree of sensitivity and tolerability to antipsychotics as those with schizophrenia or whether patients with bipolar disorder experience differences in sensitivity and tolerability to antipsychotics when they are in a depressed versus a manic state.

In an era of increasingly frequent use of atypical antipsychotics[6–9] and continuous use of typical antipsychotics in bipolar disorder,[10,11] the importance of studying the difference in the sensitivity and tolerability to these agents between patients with schizophrenia and those with bipolar disorder cannot be ignored. Given the lack of head-to-head comparison studies between bipolar disorder and schizophrenia, this review utilized existing placebo-controlled studies of haloperidol and newer atypical antipsychotics in the acute treatment of schizophrenia, mania, and bipolar depression to compare (1) risks for discontinuation due to adverse events and somnolence between

antipsychotics and their respective placebo in 3 psychiatric conditions and (2) the differences in the risk for the discontinuation due to adverse events or somnolence of each individual antipsychotic among the 3 conditions.

## METHOD

English-language literature published and cited in MEDLINE from January 1966 to December 2006 was searched for the terms *antipsychotics*, *typical antipsychotics*, *atypical antipsychotic*, *fluphenazine*, *haloperidol*, *perphenazine*, *pimozide*, *thiothixene*, *trifluoperazine*, *loxapine*, *molindone*, *chlorpromazine*, *mesoridazine*, *thioridazine*, *fluspirilene*, *penfluridol*, *pipothiazine*, *flupenthixol*, *clozapine*, *olanzapine*, *risperidone*, *quetiapine*, *ziprasidone*, *aripiprazole*, *safety*, *tolerability*, *discontinuation due to adverse events*, *somnolence*, and *bipolar mania*, *bipolar depression*, *bipolar disorder*, *manic-depressive illness*, or *schizophrenia*, *randomized*, *double-blind*, and *controlled clinical trial*. Randomized, double-blind, placebo-controlled, monotherapy studies of antipsychotics in both bipolar disorder and schizophrenia were prioritized.

After reviewing all relevant articles from the MEDLINE search, we found that there was no unified approach to reporting side effects in bipolar disorder or schizophrenia studies. Most side effects were reported only for some antipsychotics or in some studies but not in others. However, the incidences of discontinuation due to adverse events and somnolence were reported in the majority of studies. In addition, somnolence was the main reason for the discontinuation due to adverse events in bipolar depression.[12–14] Therefore, comparing discontinuation due to adverse events and somnolence in schizophrenia, mania, and bipolar depression could shed light on the differential sensitivity and tolerability of various patient populations to antipsychotics. Because there was no separate reporting of somnolence from sedation in the majority of these studies, in this review, *somnolence* refers to somnolence and sedation.

In the studies of schizophrenia, multiple fixed doses were used. Some of these dosages, such as aripiprazole 2 mg/day, olanzapine 2.5 mg/day, risperidone 2 mg/day, quetiapine 75 mg/day, or ziprasidone 10 mg/day, were low. On the other hand, most studies in bipolar disorder were flexible dosed and the mean doses were targeted to the maximal doses recommended for schizophrenia. To make the comparison as close as possible, the doses of antipsychotics in a schizophrenia study that were most closely matched to the mean doses of a corresponding mania study were chosen as follows: aripiprazole 30 mg/day, haloperidol 10–12 mg/day, olanzapine 11.6–16.3 mg/day, quetiapine 600 mg/day, risperidone 6 mg/day, and ziprasidone 120–160 mg/day. For the bipolar depression studies involving quetiapine, 600 mg/day was used to match the mania studies involving quetiapine.

The absolute risk reduction (ARR) or increase (ARI) and the numbers needed to treat to harm (NNTH) or benefit (NNTB) were used for measuring the difference in occurrence of the discontinuation due to adverse events or somnolence between antipsychotics and placebo. The ARR or ARI equals placebo event rate minus antipsychotic event rate, and the NNTH or NNTB equals 1/ARI or ARR and the reciprocal of ARI or ARR. These measures are believed to provide more clinically relevant information than relative risk reduction or odds ratios[15] and have been advocated to be used for systematic reviews.[16,17] Another advantage of using NNTH or NNTB is that clinicians can easily tell how many patients need to be treated to have 1 patient for an event, benefit or harm, according to the outcome of a treatment relative to a control.[16–18] In this review, the assumption was that an antipsychotic would cause a greater occurrence of discontinuation due to adverse events or somnolence than would placebo. Therefore, a negative value, presented with an NNTH and an ARI, was indicative of a higher risk for discontinuation due to adverse events or somnolence with an antipsychotic than with placebo. On the other hand, a positive value, presented with an NNTB and an ARR, was indicative of a lower risk for discontinuation due to adverse events or somnolence with an antipsychotic than with placebo.

For antipsychotics with more than 1 clinical trial of a similar study design, the values of the outcome measures were recalculated based on a pooled sample. Significance tests between antipsychotics and placebo were set at $\alpha = .05$ and presented with confidence intervals (95% CI = mean ± 1.96 standard error). The rationale for the use of CI, instead of p value, is that the CI not only can provide a more quantifiable comparison, but it can also help to interpret the result, especially when there is no statistical significance.[19,20] For antipsychotic-placebo comparison, a statistical significance was claimed when a CI did not include 0. For comparisons between schizophrenia and mania or depression, a statistical significance was claimed when there was no overlap between the CIs. Such conservative interpretation might miss statistical significance,[21–23] but the NNTH or NNTB and the degree of the CI overlaps can help clinicians determine the degree of clinical significance. Forest plots were created with risk differences between treatment and placebo (95% CI = mean ± 1.96 standard error). For the maintenance studies, the results were integrated into the discussion without further analysis.

## RESULTS

Ten randomized, double-blind, placebo-controlled, monotherapy trials in acute mania,[24–33] 3 in bipolar depression,[12–14] and 8 in schizophrenia[34–41] were identified (Table 1), with an additional 2 maintenance studies in bipolar disorder[42,43] and 2 in schizophrenia.[44,45]

**Table 1. Discontinuation Due to Adverse Events and Reported Somnolence Between Antipsychotics and Placebo in the Acute Treatment of Schizophrenia, Mania, or Bipolar Depression[a]**

| | | | Discontinuation Due to Adverse Events | | | Somnolence | | |
|---|---|---|---|---|---|---|---|---|
| Trial | Treatment Arm | Duration, wk | Patients, % | ARR or ARI, Mean (95% CI), % | NNTB or NNTH, Mean (95% CI) | Patients, % | ARR or ARI, Mean (95% CI), % | NNTB or NNTH, Mean (95% CI) |
| Schizophrenia | | | | | | | | |
| Haloperidol | | | | | | | | |
| Kane et al[34] | Haloperidol, 10–12 mg/d (N = 155) | 4–6 | 9.7 | 2.3 (–4.4 to 9.5) | 39 (10 to –23) | 10.3 | –5.2 (–11.1 to 0.8) | –19 (131 to –9) |
| Arvanitis et al[36] | Placebo (N = 155) | | 12.3 | | | 5.2 | | |
| Aripiprazole | | | | | | | | |
| Kane et al[34] | Aripiprazole, 15–30 mg/d (N = 201) | 4 | 8.0 | 8.5 (2.2 to 14.8)* | 12 (7 to 46)* | 14.4 | –7.2 (–13.2 to –1.2)* | –14 (–85 to –8)* |
| Potkin et al[35] | Placebo (N = 207) | | 16.4 | | | 7.2 | | |
| Olanzapine | | | | | | | | |
| Beasley et al[37] | Olanzapine, 12–16 mg/d (N = 133) | 6 | 3.8 | 6.5 (–1.4 to 14.5) | 15 (7 to –73) | 34.6 | –18.4 (–30.3 to –6.5)* | –5 (–15 to –3)* |
| | Placebo (N = 68) | | 10.3 | | | 16.2 | | |
| Quetiapine | | | | | | | | |
| Arvanitis et al[36] | Quetiapine, 600 mg/d (N = 51) | 6 | 0.0 | 3.9 (–1.4 to 9.3) | 26 (11 to –71) | 9.8 | –2.0 (–13.0 to 9.0) | –51 (11 to –8) |
| | Placebo (N = 51) | | 3.9 | | | 7.8 | | |
| Risperidone | | | | | | | | |
| Chouinard et al[38] | Risperidone, 6 mg/d (N = 185) | 4–8 | 7.4 | 7 (–0.8 to 14.6)[b] | 14 (7 to –130) | 8.5 | –2.0 (–7.7 to 3.6)[c] | –49 (27 to –13) |
| Marder and Meibach[39] | Placebo (N = 191) | | 14.4 | | | 6.5 | | |
| Potkin et al[35] | | | | | | | | |
| Ziprasidone | | | | | | | | |
| Keck et al[40] | Ziprasidone, 120–160 mg/d (N = 151) | 4–6 | 5.3 | –5.3 (–10.1 to –1.6)* | –19 (–63 to –10)* | 15.9 | –9.5 (–16.6 to –2.4)* | –11 (–42 to –6)* |
| Daniel et al[41] | Placebo (N = 140) | | 0.0 | | | 6.4 | | |
| Mania | | | | | | | | |
| Haloperidol | | | | | | | | |
| Smulevich et al[30] | Haloperidol, 8 mg/d (N = 144) | 3 | 2.8 | 2.2 (–2.3 to 6.7) | 45 (15 to –44) | 2.1 | –1.4 (–4.1 to 1.4) | –73 (74 to –24) |
| | Placebo (N = 140) | | 5.0 | | | 0.7 | | |
| Aripiprazole | | | | | | | | |
| Keck et al[24] | Aripiprazole, ~28 mg/d (N = 260) | 3 | 11.0 | 1 (–6.3 to 4.2) | –97 (24 to –16) | 20.2 | –12.1 (–18.0 to –6.2)* | –8 (–16 to –6)* |
| Sachs et al[25] | Placebo (N = 263) | | 10.0 | | | 8.1 | | |
| Olanzapine | | | | | | | | |
| Tohen et al[26,27] | Olanzapine, 15–16.4 mg/d (N = 125) | 3–4 | 1.6 | 0.7 (–2.7 to 4.1) | 138 (24 to –37) | 35.2 | –22.0 (–32.2 to –11.8)* | –5 (–8 to –3)* |
| | Placebo (N = 129) | | 2.3 | | | 13.2 | | |
| Quetiapine | | | | | | | | |
| Vieta et al[28] | Quetiapine, ~600 mg/d (N = 208) | 12 | 5.8 | –0.6 (–5.1 to 3.8) | –156 (26 to –20) | 16.3 | –12.2 (–17.9 to –6.5)* | –8 (–15 to –6)* |
| | Placebo (N = 195) | | 5.1 | | | 4.1 | | |
| Risperidone | | | | | | | | |
| Hirschfeld et al[29] | Risperidone, 4.1–5.6 mg/d (N = 434) | 3 | 4.6 | –0.5 (–3.2 to 2.3) | –221 (43 to –31) | 15.6 | –11.9 (–16.6 to –7.1)*[d] | –8 (–14 to –6)* |
| Smulevich et al[30] | Placebo (N = 409) | | 4.2 | | | 3.8 | | |
| Khanna et al[31] | | | | | | | | |
| Ziprasidone | | | | | | | | |
| Keck et al[32] | Ziprasidone, 112–147 mg/d (N = 268) | 3 | 6.1 | –3.2 (–7.1 to 0.8) | –32 (119 to –14) | 29.8 | –20.2 (–27.5 to –12.9)* | –5 (–8 to –4)* |
| Potkin et al[33] | Placebo (N = 131) | | 2.9 | | | 9.6 | | |

*(continued)*

Table 1 (continued). Discontinuation Due to Adverse Events and Reported Somnolence Between Antipsychotics and Placebo in the Acute Treatment of Schizophrenia, Mania, or Bipolar Depression[a]

| | | | Discontinuation Due to Adverse Events | | | Somnolence | |
|---|---|---|---|---|---|---|---|
| Trial | Treatment Arm | Duration, wk | Patients, % | ARR or ARI, Mean (95% CI), % | NNTB or NNTH, Mean (95% CI) | Patients, % | ARR or ARI, Mean (95% CI), % | NNTB or NNTH, Mean (95% CI) |
| Bipolar I (olanzapine) or I and II (quetiapine) depression | | | | | | | | |
| Olanzapine | | | | | | | | |
| Tohen et al[12] | Olanzapine, 9.7 mg/d (N = 351) | 8 | 9.2 | –4.2 (–7.8 to –0.5)* | –24 (–213 to –13)*[e] | 28.1 | –15.6 (–21.3 to –10)* | –6 (–10 to –5)* |
| | Placebo (N = 355) | | 5.0 | | | 12.5 | | |
| Quetiapine | | | | | | | | |
| Calabrese et al[13] | Quetiapine, 600 mg/d (N = 348) | 8 | 19.0 | –13.9 (–18.7 to –9.1)* | –7 (–11 to –5)*[e] | 60.3 | –43.6 (–49.8 to –36.9)* | –2 (–3 to –2)* |
| Thase et al[14] | Placebo (N = 347) | | 5.2 | | | 16.7 | | |

[a]For discontinuation due to adverse events or somnolence, a negative value means ARI relative to placebo or NNTH, and a positive value means ARR relative to placebo or NNTB.
[b]Two studies were available: Potkin et al.[35] and Chouinard et al.[38] (risperidone, N = 121; placebo, N = 125).
[c]Two studies were available: Potkin et al.[35] and Marder and Meibach[39] (risperidone, N = 163; placebo, N = 169).
[d]Two studies were available: Hirschfeld et al.[29] and Smulevich et al.[30] (risperidone, N = 288; placebo, N = 265).
[e]Somnolence was the most common reason for discontinuation due to adverse events.
*Significant difference compared to placebo at $\alpha = .05$ level.
Abbreviations: ARI = absolute risk increase, ARR = absolute risk reduction, CI = confidence interval, NNTB = number needed to treat to benefit, NNTH = number needed to treat to harm.

## Discontinuation Due to Adverse Events in Schizophrenia, Mania, and Bipolar Depression

***Schizophrenia.*** There were no significant differences between haloperidol, olanzapine, quetiapine, or risperidone and their respective placebo in the discontinuation due to adverse events (Table 1, Figure 1). However, there was a higher risk with ziprasidone compared with placebo, with an ARI of 5.3% (95% CI = –10.1 to –1.6) and an NNTH of 19 (95% CI = –63 to –10). The causes of discontinuation due to adverse events were rash (N = 3), allergic reaction (N = 1), dizziness (N = 1), insomnia (N = 1), hallucination (N = 1), and extrapyramidal side effect and sedation (N = 1). On the contrary, there was a lower risk with aripiprazole than with placebo, with an ARR of 8.5% (95% CI = 2.2 to 14.8) and an NNTB of 12 (95% CI = 7 to 46).

***Mania.*** Similarly, all newer atypical antipsychotics and haloperidol appeared to be well tolerated in mania. There was no significant difference in the discontinuations due to adverse events between atypical antipsychotics or haloperidol and their respective placebo in any of the studies in mania (Table 1, Figure 1).

***Bipolar depression.*** Of the only 2 atypical antipsychotics investigated in acute bipolar depression,[12–14] there was a higher risk for discontinuation due to adverse events with olanzapine or quetiapine than with placebo (Table 1, Figure 1). The mean ARI and NNTH values were 4.2% (95% CI = –7.8 to –0.5) and 24 (95% CI = –213 to –13) for olanzapine and 13.9% (95% CI = –18.7 to –9.1) and 7 (95% CI = –11 to –5) for quetiapine, respectively. The most frequent cause for the discontinuation of olanzapine due to adverse events was somnolence.[12] The most common causes for the discontinuation of quetiapine due to adverse events were somnolence (8.3%), dizziness (2.3%), fatigue (1.1%), and dry mouth (0.9%).[13,14]

***Comparison of individual antipsychotics in 3 conditions.*** Of all studied antipsychotics, there was no significant difference in the discontinuation of each individual antipsychotic due to adverse events between schizophrenia and mania because the CIs overlapped (Table 1, Figure 1). However, the CI of quetiapine in depression did not overlap with that of mania or schizophrenia. For olanzapine, the CI of depression overlapped with that of mania or schizophrenia to some extent (Table 1, Figure 1), but it is of clinical importance that olanzapine will certainly increase risk for discontinuation due to adverse events (mean NNHT = 24) in depression but not in mania or schizophrenia.

## Reported Somnolence in Schizophrenia, Mania, and Bipolar Depression

***Schizophrenia.*** There was no significant difference between haloperidol, quetiapine, or risperidone and their respective placebo in the risks for somnolence. However,

**Figure 1. A Forest Plot of Risk Differences in the Discontinuation Due to Adverse Events Between Treatment and Placebo in Schizophrenia, Mania, and Bipolar Depression**

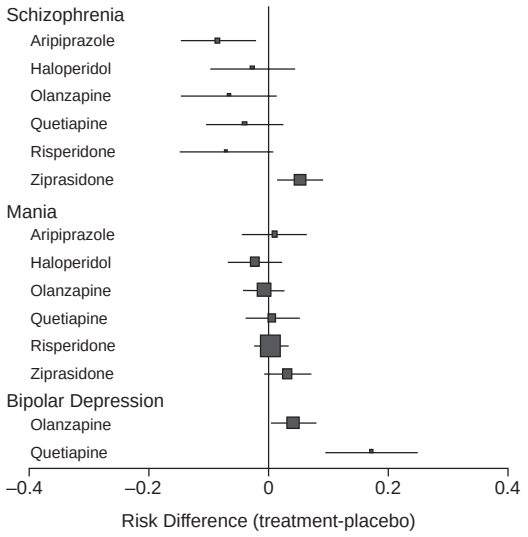
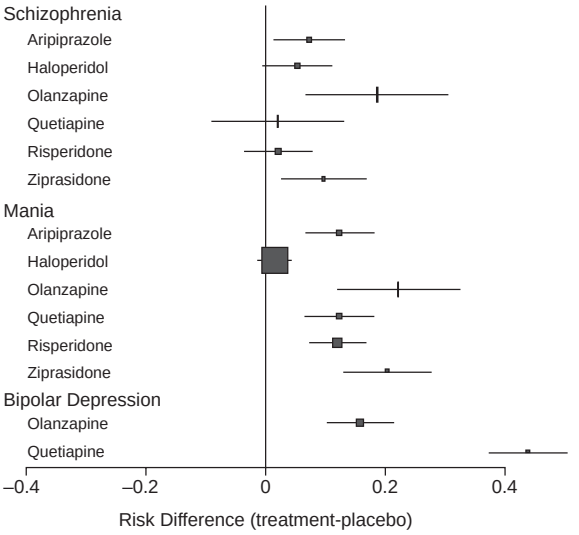



**Figure 2. A Forest Plot of Risk Differences in the Reported Somnolence Between Treatment and Placebo in Schizophrenia, Mania, and Bipolar Depression**




there was a higher risk with aripiprazole, ziprasidone, and olanzapine than with placebo (Table 1, Figure 2). The mean ARI value was 7.2% (95% CI = –13.2 to –1.2) for aripiprazole, 9.5% (95% CI = –16.6 to –2.4) for ziprasidone, and 18.4% (95% CI = –30.3 to –6.5) for olanzapine. Conversely, the mean NNTH value was 14 (95% CI = –85 to –8) for aripiprazole, 11 (95% CI = –42 to –6) for ziprasidone, and 5 (95% CI = –15 to –3) for olanzapine.

***Mania.*** There was also no significant difference between haloperidol and placebo in the risk for somnolence. However, there was a higher risk with risperidone, aripiprazole, quetiapine, ziprasidone, or olanzapine than placebo (Table 1, Figure 2). The mean ARI value was 11.9% (95% CI = –16.6 to –7.1) for risperidone, 12.1% (95% CI = –18.0 to –6.2) for aripiprazole, 12.2% (95% CI = –17.9 to –6.5) for quetiapine, 20.2% (95% CI = –27.5 to –12.9) for ziprasidone, and 22% (95% CI = –32.2 to –11.8) for olanzapine. The mean NNTH value was 8 for risperidone (95% CI = –14 to –6), aripiprazole (95% CI = –16 to –6), and quetiapine (95% CI = –15 to –6) and 5 for ziprasidone (95% CI = –8 to –4) and olanzapine (95% CI = –8 to –3).

***Bipolar depression.*** Both olanzapine and quetiapine had higher risks for somnolence than their respective placebo. The mean ARI value was 15.6% (95% CI = –21.3 to –10) for olanzapine and 43.6% (95% CI = –49.8 to –36.9) for quetiapine. The NNTH was 6 (95% CI = –10 to –5) for olanzapine and 2 (95% CI = –3 to –2) for quetiapine.

***Comparison of individual antipsychotics in 3 conditions.*** Similar to discontinuation due to adverse events, of all studied antipsychotics, there was no statistically significant difference in risk for somnolence with each individual antipsychotic between schizophrenia and mania because the CIs overlapped (Table 1, Figure 2). However, the degree of the overlaps varied, from the largest CI overlap with olanzapine to the smallest with risperidone. In spite of these overlaps, the differences are still clinically relevant in most cases. Risperidone or quetiapine will certainly increase the risk for somnolence in mania, but it is unlikely to increase in schizophrenia, with a mean NNTH of 8 (95% CI = –14 to –6) versus 49 (95% CI = 27 to –13) for risperidone and 8 (95% CI = –15 to –6) versus 51 (95% CI = 11 to –8) for quetiapine. For aripiprazole and ziprasidone, both will certainly increase the risk for somnolence in mania and in schizophrenia, but a much higher risk exists in mania, with an NNTH of 8 versus 14 for aripiprazole and 5 versus 11 for ziprasidone.

The CI of quetiapine in depression did not overlap with those in mania or schizophrenia. On the contrary, the CI of olanzapine in depression overlapped with those in mania and schizophrenia to a large extent (Table 1, Figure 2).

## DISCUSSION

This review represents the first comparison of discontinuation due to adverse events and somnolence with antipsychotics in the treatment of bipolar disorder and schizophrenia. Overall, haloperidol and newer atypical

antipsychotics are as well tolerated as placebo in the acute treatment of mania or schizophrenia as reflected by a lack of significant difference between antipsychotics (except for ziprasidone in schizophrenia) and placebo in the rate of discontinuation due to adverse events. However, olanzapine and quetiapine were not as well tolerated as placebo in bipolar depression as indicated by significantly higher risks for discontinuation due to adverse events with these 2 agents than with placebo.[12–14] The significantly higher risk for discontinuation due to adverse events with quetiapine in depression than in mania or schizophrenia suggests that patients with bipolar depression may have a lower tolerability to antipsychotics.

A lower tolerability to antipsychotics in patients with bipolar disorder than in those with schizophrenia was also suggested by maintenance studies,[42–45] in which olanzapine caused significantly higher incidences of discontinuation due to adverse events than did placebo in bipolar disorder (7.6% vs. 0%, $p < .001$)[42] but showed the opposite in schizophrenia (0.9% vs. 11.8%, $p < .001$).[44] Similarly, aripiprazole caused discontinuation (361 out of 567 patients, with 22% of those discontinued due to adverse events) during open-label treatment in bipolar disorder[43] but not in schizophrenia.[45]

The reason for the different tolerabilities is unclear. Some may argue that the insignificance of discontinuation due to adverse events between antipsychotics and placebo in schizophrenia or mania were simply an artifact of a well-controlled inpatient environment. This argument is not supported, at least, by the quetiapine mania study,[28] in which patients could only stay in the hospital 1 week during a 12-week study period. Others may suggest that the increased risk for discontinuation due to adverse events in bipolar depression was simply due to a longer duration of trials compared to that found in mania studies: 8 weeks versus 3 to 4 weeks. This assumption is also not supported by the 12-week quetiapine mania study.

Like the atypicals, haloperidol was well tolerated, although higher rates of extrapyramidal side effects were consistently reported in the haloperidol-treated patients compared with placebo-treated or atypical antipsychotic–treated patients.[34,36–40,46–52] However, the results of discontinuations of atypical agents versus haloperidol due to adverse events (especially extrapyramidal side effects) from the head-to-head comparison studies in mania[47,48] or schizophrenia[49–53] were inconsistent. Some showed that haloperidol had similar rates of discontinuation due to adverse events as the atypicals,[47,49,50] but others showed that haloperidol had significantly higher rates of discontinuation due to adverse events than the atypicals.[48,51–53]

In addition to the lower tolerability, patients with bipolar disorder, especially in depression, are more sensitive to most antipsychotics than are those with schizophrenia. This observation is strongly supported by the quetiapine studies,[13,14,28,36] in which the ARI for somnolence was significantly higher in depression than in mania or schizophrenia and the ARI for somnolence in mania was significantly higher than in schizophrenia (Table 1, Figure 2). Other evidence, such as the finding of only 3 agents associated with a significantly higher risk than placebo for somnolence in schizophrenia compared to 5 agents in mania, is also suggestive of a higher sensitivity to side effects in bipolar disorder than in schizophrenia. In addition, with the exception of olanzapine, a higher risk for somnolence was consistently found in mania than in schizophrenia.

It must also be noted that individual antipsychotics have different liabilities for causing somnolence. Haloperidol was not shown to have an increased risk for somnolence compared with placebo in either mania or schizophrenia. On the other hand, olanzapine was associated with a significantly increased risk for somnolence over placebo across studies of schizophrenia, mania, and bipolar depression. However, the remaining agents demonstrated different risks for somnolence based upon the primary psychiatric diagnosis. This is illustrated most convincingly in the quetiapine studies, which showed the rates of somnolence with quetiapine to be lowest in schizophrenia, higher in mania, and highest in depression.

These short-term data should be interpreted with caution and cannot necessarily be extrapolated to long-term use. For instance, somnolence was a major cause of discontinuation due to adverse events in the olanzapine depression study,[12] but it was not a factor for discontinuation due to adverse events in the maintenance study.[42] On the other hand, olanzapine-related weight gain was not the primary reason for discontinuation due to adverse events in the acute studies, but it became a main factor for discontinuation due to adverse events during the maintenance treatment of bipolar depression[42] as well as schizophrenia.[53] These short-term findings may help clinicians to select an appropriate antipsychotic early in treatment, and they indicate that using lower initial doses of antipsychotics than the ones employed in trials of schizophrenia may be useful to improve initial tolerability in bipolar mania and, more importantly, bipolar depression.

**Limitations**

This review is limited by the computer search parameters, which included only English-language publications and primarily focused on randomized, placebo-controlled trials and used only discontinuation due to adverse events and somnolence for comparison. Although placebo was used as a direct comparator to each antipsychotic among the different psychiatric conditions, it could still be confounded by the original study designs, including the inclusion and exclusion criteria (inpatient vs. outpatient); sample sizes; study durations; medication dosages; or concomitant use of other psychotropic agents.

## CONCLUSIONS

Patients with bipolar disorder, regardless of whether in a manic or depressed phase, are more sensitive to antipsychotics when compared to patients with schizophrenia, although patients with acute mania appear to be more tolerant to side effects than those with depression. For patients with bipolar depression, a lower initial antipsychotic dose may reduce discontinuations related to adverse events.

***Drug names:*** aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

***Financial disclosure:*** **Dr. Gao** has received grant/research support from GlaxoSmithKline, Abbott, AstraZeneca, and National Alliance for Research on Schizophrenia and Depression and has received honoraria from and served on speakers or advisory boards for AstraZeneca. **Dr. Gajwani** has been a consultant to Solvay; has received grant/research support from Pfizer and Bristol-Myers Squibb; has received honoraria from AstraZeneca; and has served on speakers or advisory boards for Pfizer, Forest, Abbott, AstraZeneca, and Cyberonics. **Dr. Muzina** has been a consultant to AstraZeneca and GlaxoSmithKline; has received grant/research support from Abbott, Eli Lilly, GlaxoSmithKline, Novartis, and Repligen; has received honoraria from AstraZeneca, GlaxoSmithKline, and Pfizer; and has served on speakers or advisory boards for AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, and Pfizer. **Dr. Kemp** has been a consultant to Abbott and Bristol-Myers Squibb and has received research support from GlaxoSmithKline. **Dr. Calabrese** has received federal funding from U.S. Department of Defense, Health Resources Services Administration, and National Institute of Mental Health; has received grant/research support from Cleveland Foundation, National Alliance for Research on Schizophrenia and Depression, Repligen, Stanley Medical Research Institute, Abbott, AstraZeneca, GlaxoSmithKline, Janssen, and Lilly; has served on advisory boards for Abbott, AstraZeneca, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Solvay, and Wyeth; and has been a faculty of CME activities for AstraZeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Solvay, and Wyeth. **Dr. Ganocy** reports no financial affiliation or other relationship relevant to the subject of this article.

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