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Number Needed to Treat to Harm for Discontinuation Due to Adverse Events in the Treatment of Bipolar Depression, Major Depressive Disorder, and Generalized Anxiety Disorder With Atypical Antipsychotics

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Abstract

Objective—To estimate the number needed to treat to harm (NNTH) for discontinuation due to adverse events with atypical antipsychotics relative to placebo during the treatment of bipolar depression, major depressive disorder (MDD), and generalized anxiety disorder (GAD).

Data Sources—English-language literature published and cited in MEDLINE from January 1966 to May 2009 was searched with the terms *antipsychotic, atypical antipsychotic*, generic and brand names of atypical antipsychotics, *safety, tolerability, discontinuation due to adverse events, somnolence, sedation, weight gain, akathisia*, or *extrapyramidal side effect*; and *bipolar depression, major depressive disorder*, or *generalized anxiety disorder*, and *randomized, placebo-controlled clinical trial*. This search was augmented with a manual search.

Study Selection—Studies with a cumulative sample of ≥ 100 patients were included.

Data Extraction—The NNTHs for discontinuation due to adverse events, somnolence, sedation, ≥ 7% weight gain, and akathisia relative to placebo were estimated with 95% confidence intervals to reflect the magnitude of variance.

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Drug names; aripiprazole (Abilify), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), risperidone (Risperdal and others), quetiapine (Seroquel), ziprasidone (Geodon).

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Data Synthesis—Five studies in bipolar depression, 10 studies in MDD, and 4 studies in GAD were identified. Aripiprazole and olanzapine have been studied in bipolar depression and refractory MDD. Only quetiapine extended release (quetiapine-XR) has been studied in 3 psychiatric conditions with different fixed dosing schedules. For aripiprazole, the mean NNTH for discontinuation due to adverse events was 14 in bipolar depression, but was not significantly different from placebo in MDD. For olanzapine, the mean NNTHs were 24 in bipolar depression and 9 in MDD. The risk for discontinuation due to adverse events during quetiapine-XR treatment appeared to be associated with dose. For quetiapine-XR 300 mg/d, the NNTHs for discontinuation due to adverse events were 9 for bipolar depression, 8 for refractory MDD, 9 for MDD, and 5 for GAD.

Conclusions—At the same dose of quetiapine-XR, patients with GAD appeared to have a lower tolerability than those with bipolar depression or MDD, Due to flexible dosing, the risk for discontinuation due to adverse events in the treatment of bipolar depression, MDD, or GAD with other atypical antipsychotics could not be compared.

Our previous studies[1,2] have shown that patients with schizophrenia, bipolar mania, or bipolar depression have different sensitivities and tolerabilities to atypical antipsychotics and haloperidol as well as different vulnerabilities to antipsychotic-induced extrapyramidal side effects. During the treatment of generalized anxiety disorder (GAD) with fluspirilene, a typical antipsychotic, patients who experienced a side effect had a poor clinical outcome.[3] Some previous studies[4,5] have also shown that patients with a mood disorder and comorbid anxiety were more likely to discontinue the study due to adverse events and more likely to report having a greater side effect burden. Atypical antipsychotics have been increasingly used in different psychiatric conditions, such as bipolar disorder, major depressive disorder (MDD), and anxiety disorders.[6–10] It is unclear if patients with MDD or GAD have the same degree of tolerability to atypical antipsychotics as those with bipolar depression. Such information will guide clinicians to use atypical antipsychotics more properly.

To compare tolerability, in this review, the number needed to treat to harm (NNTH) for discontinuation due to adverse events of atypical antipsychotics relative to placebo was estimated during the treatment of bipolar depression, MDD, and GAD. Similarly, the NNTHs of reported somnolence, sedation, ≥ 7% weight gain, and akathisia of atypical antipsychotics relative to placebo were also estimated, which may shed light on whether there is any difference in sensitivity to atypical antipsychotics among patients with these different psychiatric conditions.

METHOD

English-language literature published and cited in MEDLINE from January 1966 to May 2009 was searched with the terms *antipsychotic, atypical antipsychotic, aripiprazole/Abilify, olanzapine/Zyprexa, risperidone/Risperdal, quetiapine/Seroquel, ziprasidone/Geodon, safety, tolerability, discontinuation due to adverse events, somnolence, sedation, weight gain, akathisia*, or *extrapyramidal side effect*; and *bipolar depression, major depressive disorder*, or *generalized anxiety disorder*; and *randomized, placebo-controlled clinical trial*. A manual search of references from published articles was conducted. Studies presented in major scientific meetings were also included.

All relevant articles were reviewed. Discontinuations due to adverse events, an overall indicator of safety and tolerability, were reported in all studies. Similarly, data on reported somnolence, a main reason for discontinuations due to adverse events in bipolar depression, MDD, and GAD, were also available in all acute studies. Data on reported sedation and ≥7% weight gain were available in some studies, but not in others. Akathisia as a side effect was reported in aripiprazole studies, but was reported with the change in Barnes Akathisia

Rating Scale score in other studies. Because reported somnolence, sedation, akathisia, and weight gain were the main reasons for discontinuations due to adverse events, these variables were also used for comparison.

For antipsychotics with more than 1 clinical trial with a similar study design, the values of these variables were recalculated based on a pooled sample. As they were not the focus of the original studies, these variables were not used for sample size calculation. Therefore, studies with a small sample size might not have enough power to detect the difference in these variables between active treatments and their placebo. To minimize such potential limitation, only studies with a cumulative sample of ≥ 100 were included.

"Number needed to treat is defined as the number of patients one would expect to treat with *T*[reatment] to have one more success (or one less failure) than if the same number were treated with *C*[ontrol]."[11] Therefore, according to the outcome of success or failure relative to control, the number needed to treat can be estimated as number needed to treat to benefit (NNTB) or harm (NNTH). Mathematically, NNTB = 1/absolute risk reduction and NNTH = 1/absolute risk increase (ARI). The use of number needed to treat (NNT) has been advocated for systematic reviews of clinical studies.[12,13] An NNT estimate can provide more clinically relevant information for clinicians to make a decision than absolute risk reduction or increase, or relative risk estimate.[12] The American Medical Association recommends that NNT comparisons be used for treatment assessments in different disease conditions with the same outcome of interest.[13]

The focus of this study was to estimate the NNTH for discontinuation due to adverse events, which is likely to reflect overall tolerability. Reported somnolence, sedation, akathisia, and ≥ 7% weight gain are more likely to provide information on sensitivity to atypical antipsychotics. Therefore, the NNTH for each of these variables was calculated as 1/ARI (experimental event rate-control event rate).[11,14] Such calculations were based on the assumption that antipsychotic treatments caused more discontinuations due to adverse events and had higher rates of reported somnolence, sedation, ≥ 7% weight gain, and akathisia than the control/placebo. Since ARI estimates can be presented with decimals, this measure was calculated first at an α level of .05. If there was a significant difference as shown by an increased risk between a control and a treatment arm, then an NNTH was estimated with a 95% confidence interval to reflect the magnitude of variance.

RESULTS

Five randomized, double-blind, placebo (active)-controlled, monotherapy or adjunctive therapy trials of atypical antipsychotics in the acute treatment of bipolar depression,[15–21] 10 in MDD,[22–31] and 4 in GAD[32–35] were identified (Table 1).

Discontinuation Due to Adverse Events in Bipolar Depression, MDD, or GAD

In bipolar depression studies, patients treated with aripiprazole, olanzapine, quetiapine immediate release (quetiapine-IR), and quetiapine extended release (quetiapine-XR) had significantly increased risks for discontinuation due to adverse events compared to their placebo-treated counterparts; NNTHs were 14 (95% CI, 1–35) for aripiprazole, 24 (95% CI, 13–224) for olanzapine, 24 (95% CI, 14–83) for quetiapine-IR 300 mg/d, 11 (95% CI, 8–18)for quetiapine-IR 600 mg/d, and 9 (95% CI, 6–20) for quetiapine-XR 300 mg/d. However, patients treated with the combination of olanzapine and fluoxetine (OFC) had a similar risk for discontinuation due to adverse events compared to those treated with placebo (Table 1).

In MDD studies, olanzapine monotherapy or OFC in the acute treatment of refractory MDD caused significantly higher risks for discontinuation due to adverse events compared to fluoxetine monotherapy; NNTHs were 9 (95% CI, 7–14) for olanzapine monotherapy and 12 (95% CI, 8–22) for OFC. Similarly, in the treatment of refractory MDD, patients receiving quetiapine-XR 150 mg/d and 300 mg/d had significantly higher risks of discontinuation due to adverse events compared to placebo; NNTHs were 16 (95% CI, 10–35) for quetiapine-XR 150 mg/d and 8 (95% CI, 6–12) for quetiapine-XR 300 mg/d. In the treatment of nonrefractory MDD, there was a similar increased risk with quetiapine-XR 150 mg/d and 300 mg/d for discontinuation due to adverse events relative to placebo, with an NNTH of 9 (95% CI, 6–15) for both dosages, but no increased risk with quetiapine-XR 50 mg/d compared to placebo (Table 1). Patients receiving aripiprazole and risperidone therapy adjunctive to antidepressants also did not have an increased risk for discontinuation due to adverse events (Table 1).

In the acute treatment of GAD, quetiapine-XR 50 mg/d, 150 mg/d, and 300 mg/d significantly increased the risk for discontinuation due to adverse events relative to placebo, with NNTHs of 12 (95% CI, 8–21), 9 (95% CI, 7–12), and 5 (95% CI, 4–7), respectively. In the treatment of refractory GAD, adjunctive therapy of quetiapine-XR 50 to 300 mg/d to antidepressant monotherapy or antidepressant with benzodiazepine also increased the risk for discontinuation due to adverse events relative to placebo, with an NNTH of 11 (95% CI, 7–21) (Table 1).

Reported Somnolence in Bipolar Depression, MDD, or GAD

In bipolar depression studies, patients treated with olanzapine, quetiapine-IR, and quetiapine-XR had significantly increased risks for reported somnolence compared to their placebo-treated counterparts; NNTHs were 6 (95% CI, 5–10) for olanzapine monotherapy, 12 (95% CI, 5–326) for OFC, 6 (95% CI, 5–8) for quetiapine-IR 300 mg/d, 7 (95% CI, 5–9) for quetiapine-IR 600 mg/d, and 4 (95% CI, 3–7) for quetiapine-XR 300 mg/d. However, patients treated with aripiprazole had a similar risk for reported somnolence compared to those treated with placebo (Table 2).

In MDD studies, olanzapine monotherapy or OFC in the acute treatment of refractory MDD caused significantly higher risks for reported somnolence compared to fluoxetine monotherapy, with NNTHs of 15 (95% CI, 8–82) for olanzapine monotherapy and 8 (95% CI, 5–17) for OFC. Similarly, in the acute treatment of refractory MDD, patients treated with quetiapine-XR 150 mg/d and 300 mg/d had significantly higher risks of reported somnolence compared to placebo; NNTHs were 6 (95% CI, 5–9) for quetiapine-XR 150 mg/d and 5 (95% CI, 4–6) for quetiapine-XR 300 mg/d. In the treatment of nonrefractory MDD, all 3 dosages of quetiapine-XR, 50 mg/d, 150 mg/d, and 300 mg/d, had significant risks for reported somnolence relative to placebo, with NNTHs of 11 (95% CI, 6–30), 8 (95% CI, 5–13), and 5 (95% CI, 4–7), respectively (Table 2). Aripiprazole and risperidone as adjunctive therapy to antidepressants did not result in increased risk for reported somnolence (Table 2).

In the acute treatment of GAD, quetiapine-XR 50 mg/d, 150 mg/d, and 300 mg/d significantly increased the risk for reported somnolence relative to placebo, with NNTHs of 7 (95% CI, 5–10), 5 (95% CI, 4–6), and 5 (95% CI, 4–6), respectively. In the treatment of refractory GAD, quetiapine-XR 50 to 300 mg/d adjunctive to antidepressant monotherapy or antidepressant therapy with a benzodiazepine also increased the risk for reported somnolence relative to placebo, with an NNTH of 10 (95% CI, 6–32) (Table 2).

Reported Sedation in Bipolar Depression, MDD, or GAD

In bipolar depression studies, aripiprazole treatment resulted in a significantly higher risk of sedation relative to placebo, with an NNTH of 32 (95% CI, 16–320). Both quetiapine-IR 300 mg/d and 600 mg/d resulted in significantly higher risks of sedation, with NNTHs of 8 (95% CI, 7–12) and 8 (95% CI, 6–10), respectively. In refractory MDD studies, patients treated with quetiapine-XR 150 mg/d and 300 mg/d had significantly higher risks for sedation; NNTHs were 9 (95% CI, 6–14) and 7 (95% CI, 5–10), respectively. In nonrefractory MDD studies, quetiapine-XR 50 mg/d, 150 mg/d, and 300 mg/d resulted in significantly higher risks for sedation, with NNTHs of 5 (95% 4–7), 3 (95% CI, 3–4), and 4 (95% CI, 3–5), respectively. In GAD studies, quetiapine-XR 50 mg/d, 150 mg/d, and 300 mg/d resulted in significantly higher risks for sedation, with NNTHs of 9 (95% CI, 6–17), 6 (95% CI, 4–8), and 5 (95% CI, 4–6), respectively. In the treatment of refractory GAD, quetiapine-XR 50–300 mg/d adjunctive to antidepressant monotherapy or antidepressant therapy with a benzodtazepine also increased the risk for reported sedation relative to placebo, with an NNTH of 10 (95% CI, 7–20) (Table 3).

Weight Gain ≥ 7% in Bipolar Depression, MDD, or GAD

In bipolar depression studies, patients treated with olanzapine, quetiapine-IR, and quetiapine-XR had significantly increased risks for ≥ 7% weight gain compared to their placebo-treated counterparts; NNTHs were 5 (95% CI, 4–7) for olanzapine monotherapy, 5 (95% CI, 3–8) for OFC, 28 (95% CI, 18–71) for quetiapine-IR 300 mg/d, 17 (95% CI, 12–27) for quetiapine-IR 600 mg/d, and 14 (95% CI, 8–39) for quetiapine-XR 300 mg/d. However, patients treated with aripiprazole had a similar risk for ≥ 7% weight gain compared to those treated with placebo (Table 4).

In MDD studies, olanzapine monotherapy and OFC in the acute treatment of refractory MDD caused significantly higher risks for ≥ 10% weight gain compared to fluoxetine monotherapy, with NNTHs of 24 (95% CI, 11–141) for olanzapine monotherapy and 13 (95% CI, 8–30) for OFC.[24] In the acute treatment of refractory MDD with quetiapine-XR, only quetiapine-XR 300 mg/d resulted in significantly higher risks of ≥ 7% weight gain compared to placebo, with an NNTH of 24 (95% CI, 13–85). In the treatment of nonrefractory MDD, both quetiapine-XR 150 mg/d and 300 mg/d significantly increased the risk of ≥ 7% weight gain relative to placebo, with NNTHs of 47 (95% CI, 22–773) and 30 (95% CI, 17–91), respectively (Table 4).

In the acute treatment of GAD, quetiapine-XR 150 mg/d and 300 mg/d significantly increased the risk for ≥ 7% weight gain relative to placebo, with NNTHs of 38 (95% CI, 22–121) and 41 (95% CI, 21–218), respectively. In the treatment of refractory GAD, adjunctive therapy of quetiapine-XR 50 to 300 mg/d to antidepressant monotherapy or antidepressant with a benzodiazepine also increased the risk for ≥ 7% weight gain relative to placebo, with an NNTH of 30 (95% CI, 14–3,036) (Table 4).

Reported Akathisia in Bipolar Depression and MDD

Only aripiprazole studies in bipolar depression and MDD reported akathisia as a common side effect. Aripiprazole monotherapy in bipolar depression and adjunctive therapy to antidepressants in refractory MDD resulted in significantly higher risks for akathisia relative to placebo, with NNTHs of 5 (95% CI, 4–6) in bipolar depression and 5 (95% CI, 4–7) in MDD (Table 5).

DISCUSSION

To our knowledge, this is the first review to use the NNTH for discontinuation due to adverse events to compare the tolerability of atypical antipsychotics in patients with bipolar depression, MDD, or GAD. This review provides an estimate for clinicians on how many patients need to be treated for one to discontinue the treatment due to intolerable adverse events. That the majority of NNTHs for discontinuation due to adverse events relative to placebo are ≥ 9 suggests that all atypical antipsychotics at studied doses are as relatively well tolerated as placebo in the acute treatment of bipolar depression, MDD, and GAD. However, with the exception of the quetiapine studies, the relationships between the NNTH for discontinuation due to adverse events and different doses of aripiprazole, olanzapine, and risperidone could not be established due to their flexible dosing schedules.

In bipolar depression studies, all 95% CIs of the ARI for discontinuation due to adverse events relative to placebo overlapped to some extent. However, the lack of statistical significance should not obscure the clinical importance. For example, the NNTH for discontinuation due to adverse events was 11 for quetiapine-IR 600 mg/d, but it was 24 for quetiapine-IR 300 mg/d. Although there was no significant difference between these 2 treatments in statistical terms, it does indicate that double the number of patients treated with quetiapine-IR 600 mg/d would experience discontinuation due to adverse events relative to those treated with quetiapine-IR 300 mg/d. In the treatment of MDD, the majority of 95% CIs of the ARI did not overlap with those of aripiprazole, suggesting that the risk for discontinuation due to adverse events from aripiprazole was significantly lower than from other treatments. Similar to bipolar depression studies, among the remaining treatments studied in MDD, a majority of the 95% CIs of the ARIs for discontinuation due to adverse events overlapped with either different medications in the same psychiatric condition or the same medication at different doses or in different psychiatric conditions. Again, this may not be statistically significant, but the differences from a clinical standpoint cannot be ignored.

The results from the quetiapine studies suggest that a lower dose is better tolerated than a higher dose in the treatment of bipolar depression (Table 1). This dose-dependent tolerability also extended to patients with MDD, which is supported by the fact that there was no significant difference between quetiapine-XR 50 mg/d and placebo in the risk of discontinuation due to adverse events, but the risk for discontinuation due to adverse events was significantly increased with quetiapine-XR 150 mg/d and quetiapine-XR 300 mg/d, with an NNTH of 9 for both. The efficacy data of quetiapine-XR in the treatment of GAD showed that only the 150-mg/d dose yielded consistent results in both primary and secondary outcome measures, although the doses of 50 mg/d and 300 mg/d had superiority to placebo in some primary and secondary outcome measures.[30–32] Clearly, these efficacy and safety data pose a challenge for clinicians to select a dose with a minimal risk for discontinuation due to adverse events without compromising efficacy. Thus far, except for quetiapine-XR in MDD and GAD,[26–30,32–34] no dose-efficacy data are available for other drugs or in other psychiatric conditions.

The finding of lower tolerability in patients with “pure” GAD from our study is consistent with some previous studies in patients with comorbid anxiety and mood disorders[4,5] in which patients with anxiety were more likely to discontinue the study due to adverse events and more likely to report having side effects. In terms of sensitivity as measured by reported somnolence and sedation, patients with GAD were quite similar to those with bipolar depression and MDD (Tables 2 and 3). Taking the tolerability and sensitivity data together, it is suggested that patients with GAD might have a similar sensitivity to atypical antipsychotics as patients with bipolar depression and MDD, but are less tolerant to side effects including somnolence and sedation than those with bipolar depression and MDD.

The cause of the high sensitivity and low tolerability in patients with anxiety is unclear. It was speculated that premature discontinuation from study in patients with anxiety was due to the distortion of severity of side effects.[3]

Sensitivity was also dose-related, but the magnitude of the difference in sensitivity related to different doses was much smaller compared with that of tolerability related to different doses. For instance, in the treatment of GAD, the NNTHs for somnolence were 7 for quetiapine-XR 50 mg/d and 5 for both quetiapine-XR 150 mg/d and quetiapine-XR 300 mg/d. However, the NNTHs for discontinuation due to adverse events were 12 for 50 mg/d, 9 for 150 mg/d, and 5 for 300 mg/d. Compared to relatively large NNTHs for discontinuation due to adverse events (Table 1), the NNTHs for reported somnolence, sedation, and akathisia were relatively small (Tables 2, 3, and 5). Clearly, there is a disjoint between the risk for discontinuation due to adverse events (tolerability) and the risk for reported somnolence, sedation, and akathisia and weight gain (sensitivity). Undoubtedly, these tolerable side effects cannot be ignored. The question that remains is how to address those with tolerable side effects. The timeline of the occurrence of adverse events from the reviewed studies was unavailable. Clinicians may have to negotiate and discuss with patients who are experiencing side effects to prevent premature discontinuation. However, a previous study showed that patients with GAD who experienced side effect(s) from a typical antipsychotic had a poor outcome compared to those without a side effect.[3] The relationship between tolerable side effects and treatment outcome is worthy of further exploration.

In terms of ≥ 7% weight gain, olanzapine monotherapy and OFC had the smallest NNTHs, 5 for both (Table 4). The lack of overlap of the 95% CIs of ARI from olanzapine and OFC in the treatment of bipolar depression with the majority of other 95% CIs suggests that at the currently studied doses, olanzapine and OFC significantly increased the risk for ≥ 7% weight gain in patients with bipolar depression compared to other treatments in patients with bipolar depression, MDD, or GAD. On the other hand, our finding that, for quetiapine and aripiprazole treatments, the majority of NNTHs were ≥ 22 or showed no significant difference relative to placebo suggests that the weight gain may not be a major concern at currently studied doses of these 2 medications. An increased risk for ≥ 7% weight gain that was generally dose-dependent, though not always, was observed in quetiapine-treated patients with bipolar depression, MDD, or GAD (Table 4). The quetiapine studies also suggest that the dose threshold of quetiapine for significant weight gain relative to placebo may be different in different psychiatric conditions. For instance, patients with MDD or GAD, but not those with refractory MDD, had a significantly higher rate of ≥ 7% weight gain at the quetiapine-XR dose of 150 mg/d than placebo. However, at above “threshold” doses, the differences of different doses of quetiapine-XR relative to placebo in the same or different psychiatric conditions were relatively small (Table 4). In a long-term study of patients with schizophrenia, Brecher and colleagues[36] reported that patients treated with quetiapine < 200 mg/d had the lowest weight gain compared to patients treated with 200–399 mg/d, 400–599 mg/d, or ≥ 600 mg/d, but no clear dose relationship was found. The quetiapine studies further suggest that the magnitude of difference in weight gain at the same dose may differ in different psychiatric conditions. For instance, at the dose of quetiapine-XR 300 mg/d, patients with bipolar depression had the smallest NNTH of 14; in contrast, patients with GAD had the largest NNTH of 41 (Table 4). Clearly, a study comparing weight gain in different psychiatric conditions with the same or different antipsychotics is warranted.

Data from the quetiapine-XR MDD studies suggest that patients with refractory MDD had a higher tolerability than those with nonrefractory MDD (Table 1). In terms of sensitivity, patients with refractory MDD had a similar or lower sensitivity than those with nonrefractory MDD (Tables 2 and 3). This suggests that patients with refractory MDD

might be less sensitive and more tolerant to atypical antipsychotics than those with nonrefractory MDD.

Limitations

This study is limited by the study designs of original studies in which different coding systems for adverse events were used and criteria for discontinuation might have been different. Therefore, the comparison of 1 medication at different doses in the same psychiatric condition or at the same dose in different psychiatric conditions would be more accurate and meaningful than the comparison of different medications in the same psychiatric condition. Quetiapine-XR was the only drug to be investigated in 3 psychiatric conditions using a fixed dosing schedule. Therefore, the results of aripiprazole and olanzapine studies in bipolar depression and MDD should be interpreted with caution. The mean doses of aripiprazole and olanzapine in the treatment of MDD were lower than those used in bipolar depression. Because equivalent doses among the atypical antipsychotics have not been established, accurate and fair comparisons between atypical antipsychotics are impossible. The independent variables used in this study were not the focus of the original studies. More importantly, these data may not be generalizable to routine clinical settings, since all of these studies were carried out in relatively “pure” populations of patients with each disorder. Therefore, the use of atypical antipsychotics as monotherapy or adjunctive therapy in patients with bipolar depression, MDD, or GAD should be carefully justified. In addition, some results used in this analysis have not been published and subject to peer review.

CONCLUSIONS

From quetiapine studies, patients with GAD were less tolerant to atypical antipsychotics compared to those with bipolar depression and MDD, although they appeared to have similar sensitivity. Patients with refractory MDD appeared less sensitive and more tolerant to atypical antipsychotics than those with nonrefractory MDD. Quetiapine studies also showed that the tolerability was related to dosing. In most cases, lower doses were better tolerated than higher doses regardless of psychiatric conditions. However, due to flexible dosing of other atypical antipsychotics, comparisons of the sensitivity and tolerability of these antipsychotics in different psychiatric conditions and at different doses were not available.

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Table 1

Risk Estimates for Discontinuation Due to Adverse Events of Atypical Antipsychotics Relative to Placebo in the Treatment of Bipolar Depression, Major Depressive Disorder, and Generalized Anxiety Disorder

Antipsychotic	Diagnosis	Duration (wk)	Treatment Arms[a]	No. of Patients, Total	No. of Patients With Discontinuation Due to Adverse Events	Absolute Risk Increase (%)		NNTH, Mean (95% CI)
						Mean (95% CI)	Pearson *P*	
Bipolar depression								
Aripiprazole[15]	Bipolar I depression	8	Aripiprazole 5–30 mg/d (17.6 mg/d in study 1, 15.5 mg/d in study 2)	373	50	7.0 (2.8 to 11.4)	.0012	14 (1 to 35)
			Placebo	376	24			
Olanzapine[16]	Bipolar I depression	8	Olanzapine 5–20 mg/d (9.7 mg/d)	370	34	4.2 (4.5 to 8.0)	.0124	24 (13 to 224)
			Olanzapine/fluoxetine	86	2	−2.7 (−5.9 to ∞ to 3.3)	.2750	NS
			Placebo	377	19			
Quetiapine-IR[17–20]	Bipolar I or II depression	8	Quetiapine-IR 300 mg/d	861	91	4.1 (1.2 to 6.9)	.0060	24 (14 to 83)
			Quetiapine-IR 600 mg/d	861	131	8.8 (5.6 to 11.8)	<.0001	11 (8 to 18)
			Placebo	606	39			
Quetiapine-XR[21]	Bipolar I or II depression	8	Quetiapine-XR 300 mg/d	140	17	10.7 (5.0 to 17.2)	.003	9 (6 to 20)
			Placebo	140	2			
Major depressive disorder								
Aripiprazole[22,23]	Refractory MDD	6	Aripiprazole 2–20 mg/d (11.0–11.8 mg/d)	373	13	1.8 (−0.5 to ∞ to 4.4)	.1129	NS
			Placebo	366	6			
Olanzapine[24,25]	Refractory MDD	8	Olanzapine 6–18 mg/d (8.3–8.7 mg/d)	343	46	10.8 (6.9 to 15.0)	<.0001	9 (7 to 14)
			Olanzapine/fluoxetine (8.5/48.8 mg/d)	346	37	8.1 (4.5 to 12.0)	<.0001	12 (8 to 22)
			Fluoxetine 25–50 mg/d (35.8–49.5 mg/d)	348	9			
Quetiapine-XR[26,27]	Refractory MDD	6	Quetiapine-XR 150 mg/d	311	27	6.4 (2.9 to 10.3)	.0004	16 (10 to 35)
			Quetiapine-XR 300 mg/d	315	46	12.3 (8.2 to 16.8)	<.0001	8 (6 to 12)
			Placebo	309	7			

J Clin Psychiatry. Author manuscript; available in PMC 2012 September 25.

Antipsychotic	Diagnosis	Duration (wk)	Treatment Arms[a]	No. of Patients, Total	No. of Patients With Discontinuation Due to Adverse Events	Absolute Risk Increase (%)		NNTH, Mean (95% CI)
						Mean (95% CI)	Pearson *P*	
Quetiapine-XR[28,29]	MDD	6	Quetiapine-XR 50 mg/d	181	15	2.4 (−2.0 to ∞ to 7.7)	.8954	NS
			Quetiapine-XR 150 mg/d	330	57	11.4 (6.8 to 16.3)	.0023	9 (6 to 15)
			Quetiapine-XR 300 mg/d	331	57	11.3 (6.5 to 16)	.0024	9 (6 to 15)
			Placebo	338	20			
Quetiapine-XR[30]	MDD	8	Quetiapine-XR 150 or 300 mg/d	152	13	6.0 (0.8 to 11.7)	.0221	17 (9 to 131)
			Placebo	155	4			
Risperidone[31]	Refractory MDD	6	Risperidone 1–2 mg/d	137	8	3.5 (−1.5 to ∞ to 9.0)	.2190	NS
			Placebo	131	3			
Generalized anxiety disorder								
Quetiapine-XR[32–34]	GAD	8	Quetiapine-XR 50 mg/d	452	63	8.2 (4.7 to 12.0)	<.0001	12 (8 to 21)
			Quetiapine-XR 150 mg/d	673	116	11.5 (8.2 to 14.9)	<.0001	9 (7 to 12)
			Quetiapine-XR 300 mg/d	444	110	19.1 (14.8 to 23.5)	<.000l	5 (4 to 7)
			Placebo	665	38			
Quetiapine-XR[35]	Refractory GAD	8	Quetiapine-XR 50–300 mg/d	209	24	9.5 (4.7 to 14.7)	.0001	11 (7 to 21)
			Placebo	200	4			

[a]Mean doses at study end are shown in parentheses.

Abbreviations: GAD = generalized anxiety disorder, IR = immediate release, MDD = major depressive disorder, NNTH = number needed to treat to harm, NS = nonsignificant, XR = extended release.

J Clin Psychiatry. Author manuscript; available in PMC 2012 September 25.

Table 2

Risk Estimates for Reported Somnolence With Atypical Antipsychotics Relative to Placebo in the Treatment of Bipolar Depression, Major Depressive Disorder, and Generalized Anxiety Disorder

Antipsychotic	Diagnosis	Duration (wk)	Treatment Arms[a]	No. of Patients, Total	No. of Patients With Reported Somnolence	Absolute Risk Increase (%)		NNTH, Mean (95% CI)
						Mean (95% CI)	Pearson *P*	
Bipolar depression								
Aripiprazole[15]	Bipolar I depression	8	Aripiprazole 5–30 mg/d (17.6 mg/d in study 1, 15.5 mg/d in study 2)	360	27	3.4 (0 to ∞ to 7.0)	.1010	NS
			Placebo	367	15			
Olanzapine[16]	Bipolar I depression	8	Olanzapine 5–20 mg/d (9.7 mg/d)	370	104	15.6 (10 to 21.3)	<.0001	6 (5 to 10)
			Olanzapine/fluoxetirie	86	18	8.5 (0.3 to 19.7)	.0414	12 (5 to 326)
			Placebo	377	47			
Quetiapine-IR[17–20]	Bipolar I or II depression	8	Quetiapine-IR 300 mg/d	853	193	16.3 (12.8 to 19.7)	<.0001	6 (5 to 8)
			Quetiapine-IR 600 mg/d	859	184	15.1 (11.7 to 18.4)	<.0001	7 (5 to 9)
			Placebo	602	38			
Quetiapine-XR[21]	Bipolar I or II depression	8	Quetiapine-XR 300 mg/d	137	40	23.5 (14.8 to 32.0)	<.0001	4 (3 to 7)
			Placebo	140	8			
Major depressive disorder								
Aripiprazole[23]	Refractory MDD	6	Aripiprazole 2–20 mg/d (11.0–11.8 mg/d)	189	13	3.2 (−1.5 to ∞ to 8.l)	.1643	NS
			Placebo	190	7			
Olanzapine[24]	Refractory MDD	8	Olanzapine (8.7 mg/d)	199	24	6.7 (1.2 to 12.5)	.0161	15 (8 to 82)
			Olanzapine/fluoxetine (8.6/48.8 mg/d)	200	35	12.2 (6.1 to 18.5)	<.0001	8 (5 to 17)
			Fluoxetine 50 mg/d (49.5 mg/d)	206	11			
Quetiapine-XR[26,27]	Refractory MDD	6	Quetiapine-XR 150 mg/d	311	61	16.4 (11.6 to 21.4)	<.0001	6 (5 to 9)
			Quetiapine-XR 300 mg/d	316	80	22.1 (16.9 to 27.4)	<.0001	5 (4 to 6)
			Placebo	309	10			

Antipsychotic	Diagnosis	Duration (wk)	Treatment Arms[a]	No. of Patients, Total	No. of Patients With Reported Somnolence	Absolute Risk Increase (%)		NNTH, Mean (95% CI)
						Mean (95% CI)	Pearson *P*	
Quetiapine-XR[28,29]	MDD	6	Quetiapine-XR 50 mg/d	181	33	9.4 (3.3 to 16.1)	.0018	11 (6 to 30)
			Quetiapine-XR 150 mg/d	330	72	12.9 (7.5 to 18.4)	<.0001	8 (5 to 13)
			Quetiapine-XR 300 mg/d	331	93	19.2 (13.5 to 24.9)	<.0001	5 (4 to 7)
			Placebo	338	30			
Quetiapine-XR[30]	MDD	8	Quetiapine-XR 150 or 300 mg/d	152	31	15.2 (7.9 to 22.8)	<.0001	7 (4 to 13)
			Placebo	155	8			
Risperidone[31]	Refractory MDD	6	Risperidone 1–2 mg/d	137	5	2.1 (−2.3 ∞ to 6.9)	.2760	NS
			Placebo	131	2			
Generalized anxiety disorder								
Quetiapine-XR[32–34]	GAD	8	Quetiapine-XR 50 mg/d	452	114	15.0 (10.4 to 19.7)	<.0001	7 (5 to 10)
			Quetiapine-XR 150 mg/d	672	211	21.2 (17.0 to 25.3)	<.0001	5 (4 to 6)
			Quetiapine-XR 300 mg/d	444	145	22.4 (17.5 to 27.4)	<.0001	5 (4 to 6)
			Placebo	665	68			
Quetiapine-XR[35]	Refractory GAD	8	Quetiapine-XR 50–300 mg/d	209	47	10.5 (3.2 to 17.7)	.0051	10 (6 to 32)
			Placebo	200	24			

[a]Mean doses at study end are shown in parentheses.

Abbreviations: GAD = generalized anxiety disorder, IR = immediate release. MDD = major depressive disorder, NNTH = number needed to treat to harm., NS = nonsignificant, XR = extended release.

Table 3

Risk Estimates for Reported Sedation With Atypical Antipsychotics Relative to Placebo in the Treatment of Bipolar Depression, Major Depressive Disorder, and Generalized Anxiety Disorder

Antipsychotic	Diagnosis	Duration (wk)	Treatment Arms	No. of Patients, Total	No. of Patients With Reported Sedation	Absolute Risk Increase (%)		NNTH, Mean (95% CI)
						Mean (95% CI)	Pearson *P*	
Bipolar depression								
Aripiprazole[15]	Bipolar I depression	8	Aripiprazole 5–30 mg/d (mean = 17.6 mg/d in study 1, 15.5 mg/d in study 2)	360	19	3.1 (0.3 to 6.1)	.0272	32 (16 to 320)
			Placebo	367	8			
Quetiapine-IR[17–20]	Bipolar I or II depression		Quetiapine-IR 300 mg/d	851	151	11.9 (8.7 to 15.1)	<.0001	8 (7 to 12)
		8	Quetiapine-IR 600 mg/d	861	161	12.9 (9.6 to 16.1)	<.0001	8 (6 to 10)
			Placebo	602	38			
Major depressive disorder								
Quetiapine-XR[26,27]	Refractory MDD	6	Quetiapine-XR 150 mg/d	311	47	11.6 (7.1 to 16.2)	<.0001	9 (6 to 14)
			Quetiapine-XR 300 mg/d	316	57	14.5 (9.8 to 19.5)	<.0001	7 (5 to 10)
			Placebo	309	11			
Quetiapine-XR[28,29]	MDD	6	Quetiapine-XR 50 mg/d	181	48	20.9 (14.3 to 28.1)	<.0001	5 (4 to 7)
			Quetiapine-XR 150 mg/d	330	122	31.4 (25.5 to 37.0)	<.0001	3 (3 to 4)
			Quetiapine-XR 300 mg/d	331	111	27.9 (22.2 to 33.5)	<.0001	4 (3 to 5)
			Placebo	338	19			
Quetiapine-XR[30]	MDD	8	Quetiapine-XR 150 or 300 mg/d	152	33	20.4 (13.7 to 27.7)	<.0001	5 (4 to 7)
			Placebo	155	2			
Generalized anxiety disorder								
Quetiapine-XR[32–34]	GAD	8	Quetiapine-XR 50 mg/d	232	42	11.0 (5.7 to 16.8)	<.0001	9 (6 to 17)
			Quetiapine-XR 150 mg/d	455	114	17.9 (13.2 to 22.6)	<.0001	6 (4 to 8)
			Quetiapine-XR 300 mg/d	444	127	21.5 (16.6 to 26.3)	<.0001	5 (4 to 6)
			Placebo	448	32			

Antipsychotic	Diagnosis	Duration (wk)	Treatment Arms	No. of Patients, Total	No. of Patients With Reported Sedation	Absolute Risk Increase (%)		NNTH, Mean (95% CI)
						Mean (95% CI)	Pearson *P*	
Quetiapine-XR[35]	Refractory GAD	8	Quetiapine-XR 50–300 mg/d	209	26	9.9 (5.0 to 15.3)	.0001	10 (7 to 20)
			Placebo	200	5			

Abbreviations: GAD = generalized anxiety disorder, IR = immediate release, MDD = major depressive disorder, NNTH = number needed to treat to harm, NS = nonsignificant, XR = extended release.

Table 4

Risk Estimates for ≥ 7% Weight Gain With Atypical Antipsychotics Relative to Placebo in the Treatment of Bipolar Depression, Major Depressive Disorder, and Generalized Anxiety Disorder

Antipsychotic	Diagnosis	Duration (wk)	Treatment Arms[a]	No. of Patients, Total	No. of Patients With ≥ 7% Weight Gain	Absolute Risk Increase (%)		NNTH, Mean (95% CI)
						Mean (95% CI)	Pearson *P*	
Bipolar depression								
Aripiprazole[15]	Bipolar I depression	8	Aripiprazole 5–30 mg/d (15.5–17.6 mg/d)	360	17	1.5 (−1.5 to ∞ to 4.5)	.317	NS
			Placebo	367	12			
Olanzapine[16]	Bipolar I depression	8	Olanzapine 5–20 mg/d (9.7 mg/d)	347	65	18.5 (14.5 to 22.9)	<.0001	5 (4 to 7)
			Olanzapine/fluoxetine combination	82	16	19.2 (12.0 to 29.1)	<.0001	5 (3 to 8)
			Placebo	355	1			
Quetiapine-IR[17–20]	Bipolar I or II depression	8	Quetiapine-IR 300 mg/d	851	53	3.6 (1.4 to 5.7)	.0016	28 (18 to 71)
			Quetiapine-IR 600 mg/d	861	75	6.1 (3.7 to 8.4)	<.0001	17 (12 to 27)
			Placebo	602	16			
Quetiapine-XR[21]	Bipolar I or II depression	8	Quetiapine-XR 300 mg/d	137	11	7.3 (2.6 to 13.1)	.0027	14 (8 to 39)
			Placebo	140	1			
Major depressive disorder								
Aripiprazole[22,23]	Refractory MDD	6	Aripiprazole 2–20 mg/d (11.0–11.8 mg/d)	371	19	4.6 (1.3 to 7.3)	.0001	22 (14 to 44)
			Placebo	366	2			
Olanzapine[24],*b*	Refractory MDD	8	Olanzapine 6–12 mg/d (8.5 mg/d)	144	6	4.2 (0.7 to 8.8)	.0146	24 (11 to 141)
			Olanzapine/fluoxetine (8.5/35.6 mg/d)	146	11	7.5 (3.3 to 13.0)	.0009	13 (8 to 30)
			Fluoxetine 25–50 mg/d (35.8 mg/d)	142	0			
Quetiapine-XR[26,27]	Refractory MDD	6	Quetiapine-XR 150 mg/d	315	9	1.2 (−1.3 to ∞ to 3.9)	.296	NS
			Quetiapine-XR 300 mg/d	312	18	4.2 (1.2 to 7.5)	.0061	24 (13 to 85)
			Placebo	309	5			
Quetiapine-XR[28,29]	MDD	6	Quetiapine-XR 50 mg/d	181	1	0.0 (−1.6 to ∞ to 2.5)	.9551	NS

J Clin Psychiatry. Author manuscript; available in PMC 2012 September 25.

Antipsychotic	Diagnosis	Duration (wk)	Treatment Arms[a]	No. of Patients, Total	No. of Patients With ≥ 7% Weight Gain	Absolute Risk Increase (%)		NNTH, Mean (95% CI)
						Mean (95% CI)	Pearson *P*	
			Quetiapine-XR 150 mg/d	330	9	2.1 (0.1 to 4.6)	.0301	47 (22 to 773)
			Quetiapine-XR 300 mg/d	331	13	3.3 (1.1 to 6.1)	.0035	30 (17 to 91)
			Placebo	338	2			
Quetiapine-XR[30]	MDD	8	Quetiapine-XR 150 or 300 mg/d	152	2	0.0 (3.5 to ∞ to −3.5)	.9843	NS
			Placebo	155	2			
Risperidone[31]	Refractory MDD	6	Risperidone 1–2 mg/d	137	NA			
			Placebo	131	NA			
Generalized anxiety disorder								
Quetiapine-XR[32–34]	GAD	8	Quetiapine-XR 50 mg/d	452	14	1.4 (0.4 to ∞ to −3.6)	.1112	NS
			Quetiapine-XR 150 mg/d	673	29	2.6 (0.8 to 4.6)	.0044	38 (22 to 121)
			Quetiapine-XR 300 mg/d	441	18	2.4 (0.5 to 4.8)	.0137	41 (21 to 218)
			Placebo	663	11			
Quetiapine-XR[35]	Refractory MDD	8	Quetiapine-XR 50–300 mg/d	209	9	3 (0 to 7.1)	.0388	30 (14 to 3036)
			Placebo	200	2			

[a] Mean doses at study end are shown in parentheses.

[b] ≥ 10% weight gain was used in this study.

Abbreviations: GAD = generalized anxiety disorder, IR = immediate release, MDD = major depressive disorder, NA = not available, NNTH = number needed to treat to harm, NS = nonsignificant, XR = extended release.

Table 5

Risk Estimates for Reported Akathisia With Aripiprazole Relative to Placebo in the Treatment of Bipolar Depression and Major Depressive Disorder

Antipsychotic	Diagnosis	Duration (wk)	Treatment Arms[a]	No. of Patients, Total	No. of Patients With Reported Akathisia	Absolute Risk Increase (%)		NNTH, Mean (95% CI)
						Mean (95% CI)	Pearson *P*	
Bipolar depression								
Aripiprazole[15]	Bipolar I depression	8	Aripiprazole 5–30 mg/d (15.5–17.6 mg/d)	373	88	21.2 (16.3 to 26.2)	<.0001	5 (4 to 6)
			Placebo	376	14			
Major depressive disorder								
Aripiprazole[22,23]	Refractory MDD	6	Aripiprazole 2–20 mg/d (11.0–11.8 mg/d)	373	91	19.6 (14.7 to 24.7)	<.0001	5 (4 to 7)
			Placebo	366	18			

[a]Mean doses at study end are shown in parentheses.

Abbreviations: MDD = major depressive disorder, NNTH = number needed to treat to harm.