International Journal of Emergency Mental Health and Human Resilience, Vol. 17, No.2, pp. 476-480, ISSN 1522-4821

A Review of the Role of Antipsychotics as an Augmentation Agent or Treatment Option for Patients with Treatment Resistant Unipolar Depression

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ABSTRACT: ***Background:*** *Patients with unipolar depression present a unique challenge for physicians who are considering therapeutic drug treatment. Physicians have historically treated patients who present symptoms of unipolar depression with SSRIs or other medications that are commonly prescribed to patients with non-unipolar depression. Many of these medications are ineffective for patients suffering from unipolar disorder. Recently, an exciting new treatment approach for the depressive symptoms related to unipolar disorder has emerged in the form of second-generation atypical antipsychotics. A wealth of empirical support for treating treatment-resistant bipolar depression is becoming increasingly available, but much less is understood regarding the efficacy of atypical psychotics in treating unipolar depression.* ***Methods:*** *An electronic literature review was conducted through PubMed, PsycINFO, the Cochrane Library, Web of Science, and Embase using the following search phrases: depression, unipolar depression, antipsychotics, second-generation antipsychotics, atypical antipsychotics, and depression treatment. There were no restrictions on publication year, type, or language. Meta-analyses and randomized clinical trials (RCTs) were considered. A sensitivity analysis was performed by excluding studies with small sample sizes and a high placebo effect.* ***Discussion:*** *Preliminary evidence for this treatment approach is promising, although additional clinical trials which more clearly elucidate the role of second-generation atypical antipsychotics in treating unipolar depressive symptoms may be warranted. Accordingly, this article discusses the second-generation atypical antipsychotics that have, to date, received empirical support for use in treating patients with unipolar disorder. Proposed mechanisms of action are discussed and current FDA approvals as well as approval status in different countries for usage are reviewed. Indications for future research are also proposed.*

Key words: *Unipolar depression, depression, antipsychotics, second-generation antipsychotics, atypical antipsychotics, depression treatment*

INTRODUCTION

Depression is incredibly common. According to a World Health Organization (WHO) Survey, major depression is prevalent in over 30% of the population in the United States, France, and the Netherlands, 36% in India, and 12% in China (Bromet, Andrade, Hwang et al., 2011). Moreover, approximately 30% of these cases were reported to have severe symptoms. Given its pervasiveness, a large body of research over the last several decades has been devoted to developing effective treatment options for the disorder. While there have been many advances in the field, a disturbingly high percentage of patients do not experience relief from their symptoms of depression, despite multiple interventions (Thase, 2002). Some estimates have even suggested that nearly 30% of patients being treated for major depression will not experience symptom relief through conventional methods (Amsterdam & Hornig-Rohan, 1996; Katzman & Tsirgelis, 2011).

Physicians making initial treatment decisions for patients presenting with unipolar depression can be faced with quite a challenge. Decades of research in the field have paved the way for a wide range of available intervention options. In general, though, first-line treatment recommendations for a patient with unipolar depression is likely to include a selective serotonin reuptake inhibitor (SSRI), selective norepinephrine reuptake inhibitor (SNRI), or norepinephrine and dopamine reuptake inhibitor (NDRI). The rationale for this is that the side effect profiles for these classes of medication are typically regarded as low risk. While many patients do experience significant degrees of symptom improvement from these treatments (between about 60 to 70%) when compared to a placebo-controlled group (McIntyre, Gendron, & McIntyre, 2007), concerns with regard to the divide between statistically-significant and practically-significant improvements still exist. More specifically, a patient can be considered a treatment *responder* simply by exhibiting approximately 50% improvement in their depressive symptoms on a standardized rating scale. However, despite a statistically-significant improvement in symptom presentation in terms of the rating scale, the patient may continue to struggle with clinically concerning symptoms and even experience ongoing functional impairments as a result of their refractory depressive symptoms. This group of unipolar depression patients, which is estimated to be around one third of the overall population of individuals suffering from depression (Rush, Kraemer, Sackeim et al., 2006), warrants possible consideration for augmentation with another treatment or even an alteration in their current treatment plan. Furthermore, difficult-to-treat patients with major depressive disorder are often treated with augmentation therapies that include first-generation antipsychotics, two different antidepressants or the combination of an antidepressant and an anticonvulsant, psychostimulant, lithium, thyroid hormones, or electroconvulsive therapy (ECT) (Bauer, Bschor, Pfennig et al., 2007).

Consequently, researchers in the field continue to wrestle with the underlying mechanisms that may explain why so many unipolar depression patients do not respond to these types of traditional interventions. As new evidence continues to be uncovered, other

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treatment options are also being developed. Perhaps among the most promising of these are the early findings on using atypical antipsychotic medications with patients whose unipolar depression has been unresponsive to other treatments (Chun-Yuan, Guochuan, Hon-Song et al., 2014). Thus, this article provides a discussion of the use of atypical antipsychotics for treating patients with unipolar depression. Side effects and monitoring recommendations will also be discussed. See Table 1 for a summary of side effects and FDA approvals.

METHODS

Data Sources and Search Strategy

Five electronic databases (PubMed, PsycINFO, the Cochrane Library, Web of Science, and Embase) were searched from inception to February 2014 by using the following headings and keywords: (depression OR depression treatment) AND (unipolar depression OR major depressive disorder) AND (antipsychotics OR second-generation antipsychotics OR atypical antipsychotics). There were no restrictions on publication year, type, or language. Meta-analyses and randomized clinical trials (RCTs) were considered. A sensitivity analysis was performed by excluding studies with small sample sizes of less than 20 subjects. Additional studies were searched from the reference list of all publications that were identified, including relevant meta-analyses, RCTs, and systematic reviews. Data were independently extracted by two reviewers.

Over 100 studies were found, 50 were considered, and 26 were subsequently chosen based on criteria such as: being a pilot study, an open-label, or a double-blind placebo trial of 20 or more subjects. Of the 26 studies that were chosen, 16 showed positive effects for atypical antipsychotics as an adjunctive treatment of unipolar depression, three showed effects that were similar to monotherapy with SSRIs, and two showed no significant effect.

DISCUSSION

Atypical Antipsychotics Currently Receiving Support in the Treatment of Unipolar Depression

A number of studies exist, which have explored the role of various second-generation antipsychotics in the treatment of unipolar depression (Chun-Yuan et al., 2014; Selle et al., 2014; Shelton & Papakostas, 2008). A review that investigated the effectiveness of second-generation antipsychotic augmentation treatment with aripiprazole, olanzapine, quetiapine, or risperidone for major depressive disorder used data from the National Health Insurance Research Database (NHIRD) in Taiwan (Chun-Yuan L, Guochuan TE, Hon-Song et al., 2014). The data included information from over 180,000 patients who received inpatient psychiatric treatment between 1996 and 2007, and their follow-up health care data until December 2011.

According to the findings, the proportion of continuous 8-week atypical antipsychotic augmentation therapy was about 9.3%, with augmentation in major depressive disorder patients steadily increasing after 1999. The average daily dosage of aripiprazole, olanzapine, quetiapine, and risperidone was 5.38 mg, 4.60 mg, 103.41 mg, and 1.46 mg, respectively; with olanzapine, quetiapine, and risperidone being prescribed more widely than aripiprazole in Taiwan. Furthermore, in comparison to the psychiatric treatment the year before atypical antipsychotic augmentation therapy, the total days of psychiatric hospitalizations and emergency room visits was reduced by 9.9% and 54.7%, respectively (n = 993). The subgroup analysis also demonstrated significant reductions in the number of psychiatric hospitalizations for patients receiving olanzapine (–38.5%, P = 0.003), aripiprazole (−67.9%, P<0.0001), quetiapine (–49.6%, P<0.0001), and risperidone (–73.7%, P<0.0001) (Chun-Yuan L, Guochuan TE, Hon-Song et al., 2014). Finally, it was observed that many major depressive disorder patients being prescribed second-generation antipsychotics were typically older and sicker than patients who had never been treated with atypical antipsychotics. Overall, the results of this study indicate that second-generation antipsychotics yield favorable outcomes in clinical settings for patients with moderate to severe major depressive disorder.

In addition, a meta-analysis, conducted in 2009, discusses the usefulness of atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) as an adjunctive treatment for resistant unipolar depression and provides a description of the manner in which these antipsychotics have been studied through clinical trials (DeBattista & Hawkins, 2011). Each of these drugs are discussed in more detail below.

Olanzapine

Olanzapine is a serotonin-dopamine antagonist that has been studied more extensively than any other antipsychotic for the treatment of depression. While the chemical structure of olanzapine is similar to clozapine, it is a much more potent antipsychotic than clozapine. Olanzapine works by blocking dopamine 2 receptors, which both reduces the positive symptoms of psychosis and acts to stabilize affective symptoms. The drug also blocks serotonin 2A receptors, which has positive impacts on affective symptoms.

Table 1.
Atypical Antipsychotic Side Effects and FDA Approval

Drug	Effect	FDA Approval	Side Effects
Olanzapine	Superior to SSRIs when used as an adjunctive treatment	FDA approved for adjunctive treatment	Dizziness, sedation, dry mouth, constipation, dyspepsia, weight gain, peripheral edema, joint pain, chest pain, back pain, pain in the extremities, abnormal gait, ecchymosis, tachycardia, and orthostatic hypotension; increased risk of diabetes mellitus and dyslipidemia
Aripiprazole	Effective as an augmentation agent for resistant depression	FDA approved for treatment augmentation	Dizziness, insomnia, akathisia, activation, nausea, vomiting, orthostatic hypotension (infrequently and only during initial dosing), constipation, headache, asthenia, and sedation
Quetiapine	Effective adjunctive treatment for depression	FDA approved for monotherapy and adjunctive treatment	Dizziness, sedation, dry mouth, constipation, dyspepsia, abdominal pain, weight gain, tachycardia, and orthostatic hypotension (typically only during the initial phase of dose titration); increased risk of diabetes mellitus and dyslipidemia
Risperidone	Efficacious both in augmentation treatment for depression and adjunctive maintenance	Off-label use for depression; not FDA approved	Dizziness, insomnia, headache, anxiety, sedation, nausea, constipation, abdominal pain, weight gain, sexual dysfunction, tachycardia, and orthostatic hypotension (very rare and typically only during initial dose titration phase); increased risk of diabetes mellitus, dyslipidemia, extrapyramidal symptoms, and hyperprolactinemia
Ziprasidone	Effective as an augmentation agent for resistant depression	Off-label use for depression; not FDA approved	Dizziness, sedation, dystonia, nausea, dry mouth, asthenia, skin rash, and, in rare instances, tardive dyskinesia; increased risk of experiencing extrapyramidal symptoms

Further, olanzapine is preferred in instances of refractory unipolar depression because of its antagonist actions at 5HT2C receptors, which is believed to also contribute to the positive effects the drug has on affective symptoms. This effect can be strengthened by combining olanzapine with fluoxetine, which also blocks the reuptake of serotonin. The combination treatment of olanzapine and fluoxetine has been thoroughly studied and approved by the FDA for the treatment of treatment-resistant depression in adults (Shelton et al., 2001; Shelton et al., 2005; Corya et al., 2006; Thase et al., 2007). One of the first double-blind, clinical trials reported that 28 patients who were resistant to SSRI treatment alone, responded positively to the combination of olanzapine and fluoxetine as early as one week after starting the combined treatment (Shelton, Tollefson, Tohen et al., 2001). Improvement was demonstrated through a significant decrease in the Montgomery-Asberg Depression Rating Scale (MADRS) scores for the combination-treated patients in comparison to the single-therapy patients. Several subsequent clinical trials (Shelton et al., 2005; Corya et al., 2006; Thase et al., 2007), one of which involved over 600 patients (Thase, Corya, Osuntokun et al., 2007), reported similar results. Olanzapine is approved in the European Union (EU) including countries such as Ireland, Germany, Finland, Denmark, and Norway under the name Zypadhera for the treatment of schizophrenia.

The features that characterize olanzapine as an atypical antipsychotic include, rare occurrences of severe sedation, no effect on prolactin levels, and it is not known to cause EPS symptoms. Olanzapine is, however, associated with an increased risk in weight gain owning to its antagonist properties in terms of H1-histaminic and 5HT2C. Common side effects of olanzapine include dizziness, sedation, dry mouth, constipation, dyspepsia, weight gain, peripheral edema, joint pain, chest pain, back pain, pain in the extremities, abnormal gait, ecchymosis, tachycardia, and orthostatic hypotension (typically only during the initial phase of dose titration). In addition, it is believed that olanzapine may increase the risk for developing diabetes mellitus and dyslipidemia. Nonetheless, clinical findings have been fairly consistent in demonstrating the usefulness of olanzapine for treatment-resistant unipolar depression.

Aripiprazole

Aripiprazole is the first antipsychotic that received FDA approval as an adjunctive treatment for major depression (DeBattista & Hawkins, 2009). It works as a partial dopamine 2 agonist and this is believed to reduce the output of dopamine when concentration levels of dopamine are high, thereby reducing the positive symptoms of psychosis. This action is also believed to increase dopamine output when concentration levels of dopamine are high, thereby improving the patient's mood symptoms. The drug also blocks serotonin 2A receptors, which has positive impacts on affective symptoms. Several clinical studies have indicated that combination treatment with aripiprazole can improve symptoms of resistant unipolar depression (Berman et al., 2007; Marcus et al., 2008; Pae et al., 2011). In particular, two double-blind, placebo controlled trials demonstrated that aripiprazole augmentation for resistant depression resulted in significant decreases in MADRS scores and dramatic improvements in overall function on the Sheehan Disability Scale in comparison to placebo treatments (Berman et al., 2007; Marcus et al., 2008). Furthermore, aripiprazole is one of the few atypical antipsychotics that have received FDA approval as an adjunctive treatment for major depressive disorder. In Europe Aripiprazole is approved for the treatment of moderate to severe manic episodes of bipolar disorder.

Aripiprazole is associated with the lowest risk for weight gain of the atypical antipsychotics, and is also accompanied by the lowest rate of sedation effects. Common side effects of aripiprazole include dizziness, insomnia, akathisia, activation, nausea, vomiting, orthostatic hypotension (infrequently and only during initial dosing), constipation, headache, asthenia, and sedation.

Quetiapine

Quetiapine is the first drug that was approved by the FDA as a monotherapy treatment for bipolar depression and research is ongoing regarding its usefulness as a monotherapeutic agent for unipolar depression (DeBattista & Hawkins, 2009). It works by blocking dopamine 2 receptors, which both reduces the positive symptoms of psychosis and acts to stabilize affective symptoms. The drug also blocks serotonin 2A receptors, which has positive impacts on affective symptoms. Further, quetiapine is preferred in instances of refractory bipolar disorder because of its actions at 5HT1A receptors, which is believed to also contribute to the positive effects the drug has on affective symptoms. A number of existing clinical studies have supported quetiapine as an augment agent in the treatment of treatment-resistant depression and it has been implicated to improve quality of sleep as well as depressive symptoms (DeBattista & Hawkins, 2009; Sagud et al., 2006). An open-label, 20-week trial involving quetiapine augmentation demonstrated significant decreases in Hamilton Depression Rating Scale (HDRS) scores as well as anxiety and insomnia by week four of the treatment (Sagud, Mihaljevic-Peles, Muck-Seler et al., 2006). The results from large randomized controlled trials are lacking at this time as are long-term efficacy and tolerability data. In the EU Quetiapine is approved under the name Seroquel for the treatment of schizophrenia and moderate to severe manic episodes in patients with bipolar disorder.

Quetiapine is associated with an increased risk in weight gain owning to its antagonist properties in terms of H1-histaminic. Common side effects of quetiapine include dizziness, sedation, dry mouth, constipation, dyspepsia, abdominal pain, weight gain, tachycardia, and orthostatic hypotension (typically only during the initial phase of dose titration). In addition, it is believed that quetiapine may increase the risk for developing diabetes mellitus and dyslipidemia.

Risperidone

Risperidone is one of the oldest second-generation atypical antipsychotic medications available on the market, and it also one of the cheapest. Risperidone works by blocking dopamine 2 receptors, which both reduces the positive symptoms of psychosis and acts to stabilize affective symptoms. The drug also blocks serotonin 2A receptors, which has positive impacts on affective symptoms. Risperidone also possesses alpha 2 antagonist properties, which are believed to explain the drug's antidepressant properties. Findings from previous clinical studies have supported the use of risperidone in the treatment of unipolar depression, particularly in instances where the patient has not responded to SSRIs alone (Rapaport et al., 2006; Reeves et al., 2008; Keitner et al., 2009). One of the largest double-blind studies that evaluated risperidone for treatment-resistant depression demonstrated that patients who were partial or non-responders to citalopram responded positively to risperidone augmentation (Rapaport, Gharabawi, Canuso et al., 2006). The majority of the patients treated through risperidone augmentation had longer periods of depressive symptom relapse in comparison to those who continued to take citalopram with an adjunctive placebo. Risperidone is approved in the EU for the treatment of schizophrenia, manic episodes associated with bipolar disorder, and moderate to severe Alzheimer's dementia.

Common side effects of risperidone include dizziness, insomnia, headache, anxiety, sedation, nausea, constipation, abdominal pain, weight gain, sexual dysfunction, tachycardia, and orthostatic hypotension (very rare and typically only during the initial phase of dose titration). It is believed that risperidone may increase the risk for developing diabetes mellitus and dyslipidemia. In addition, patients taking risperidone are at increased risk for developing extrapyramidal symptoms depending on the patient's dosage. There is also some increased risk for the development of hyperprolactinemia

among patients taking risperidone, which also appears to be linked to the dosage.

Ziprasidone

Ziprasidone works by blocking dopamine 2 receptors, which both reduces the positive symptoms of psychosis and acts to stabilize affective symptoms. The drug also blocks serotonin 2A receptors, which has positive impacts on affective symptoms. Ziprasidone interacts with 5HT2C, 5HT1A, 5HT1D, as well as serotonin, norepinephrine, and dopamine transporters (particularly in high doses), which may also account for the positive effects noted in terms of affective symptoms. Findings from clinical research have supported the use of ziprasidone in the treatment of unipolar depression, particularly in instances where the patient has not responded to SSRIs alone (Sachs, Ice, Chappell et al., 2011). As an adjunctive therapy, ziprasidone has demonstrated usefulness in improving depressive symptoms. Ziprasidone is approved in Sweden for the treatment of schizophrenia, but has not been approved as of yet in the entire EU.

Common side effects of ziprasidone include dizziness, sedation, dystonia, nausea, dry mouth, asthenia, skin rash, and, in rare instances, tardive dyskinesia. In addition, patients taking ziprasidone are at increased risk for developing extrapyramidal symptoms depending on the patient's dosage.

Monitoring for Patients Being Prescribed Atypical Antipsychotics

While the effects of these drugs on symptoms of psychosis and mania can be experienced within a week, it generally can take between 4 and 6 weeks for the patient to experience any improvements in terms of their affective symptoms. In some cases, these positive effects aren't noted for 16 to 20 weeks. When beginning a patient on an atypical antipsychotic, it is recommended that the prescribing physician monitor the patient's BMI monthly for the first three months and quarterly thereafter. For patients who are at risk for metabolic complications, it is recommended that the prescribing physician monitor fasting triglycerides monthly for the first several months. This should also be done in patients who are just starting a trial of antipsychotics or who are switching antipsychotics. It is recommended that prescribing physicians monitor blood pressure, fasting plasma glucose, and fasting lipids within three months of starting an antipsychotic and then annually thereafter. In patients with diabetes or who have gained greater than 5% of their initial weight, it is recommended that this be done earlier and more frequently.

CONCLUSION AND FUTURE DIRECTIONS

Atypical antipsychotics have emerged as an exciting new avenue for the treatment of refractory depression. In particular, the inhibitory effects of second-generation antipsychotics on the noradrenaline and serotonin transporters are less intrusive than those which are observed with SSRIs and SNRIs (DeBattista & Hawkins, 2009). Furthermore, clinical trials have provided compelling support for the use of atypical antipsychotics in the treatment of resistant unipolar depression (Shelton et al., 2001; Berman et al., 2007; Sagud et al., 2006, Rapaport et al., 2006, Sachs et al., 2011).

Previous clinical research has shown that some patients experience significant symptom improvement from treatments including dual antidepressants, mood stabilizers, and ECT when compared to a placebo-controlled group (McIntyre et al., 2007; Bauer et al., 2007), but a number of patients continue to report serious clinical concerns regarding their symptoms that warrants further treatment. Moreover, patients are often labeled as responders simply by exhibiting approximately 50% improvement of their moderate or severe unipolar depressive symptoms on a standardized rating scale. Such patients may experience heightened health outcomes through treatment with second-generation antipsychotics. The atypical antipsychotics that were evaluated (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) have strong implications as an optimal approach or augmentation treatment for patients with moderate to severe unipolar depression that does not respond to conventional interventions alone or are responders of 50% or less. Nonetheless, a very large percentage of individuals suffering from depression do not receive appropriate treatment.

In actuality, estimates suggest that nearly 80% of individuals suffering from symptoms of depression may not receive adequate treatment (Gonzalez, Vega, Williams et al., 2010). Indeed, this is concerning as previous studies have suggested that these are the individuals who ultimately commit suicide (Sher, Mann, Traskman-Bendz et al., 2006). It has been estimated that as many as 15% of patients suffering from depression will ultimately commit suicide (Murphy, 1994). Additional health concerns regarding weight gain, metabolic and cardiac effects, and extrapyramidal symptoms also limit the effectiveness of antipsychotics as a long-term depression treatment. Therefore, more work is necessary on the role of antipsychotics in the treatment of depression, particularly with regard to cases of treatment-resistant depression.

For instance, direct comparisons between these atypical antipsychotic medications have not been conducted in order to identify whether one drug is more effective than another. Similarly, studies identifying characteristics of patients who are most likely to benefit from atypical antipsychotics are limited. Although, according to the NHIRD study, major depressive disorder patients who receive inpatient treatment demonstrate better treatment responses and reductions in disease progression, suicidal crisis, function deterioration, and relapse (Chun-Yuan L, Guochuan TE, Hon-Song et al., 2014). Nonetheless, it will be important for additional studies to establish an optimal length for augmentation with antipsychotics.

For the NHIRD study, tests were performed to examine the risk of cardiometabolic diseases within one year from the day when the 8-week second-generation antipsychotic augmentation therapy was initiated. There was no statistical difference in the rate of newly onset diabetes mellitus, hypertension, ischemic heart diseases, and disorders of lipoid metabolism (Chun-Yuan L, Guochuan TE, Hon-Song et al., 2014). However, this was attributed to the short duration of the therapy. Previous clinical trials have shown that the rate of treatment discontinuation due to adverse side effects from second-generation antipsychotics occurs at a higher rate than that of a placebo (Nelson & Papakostas, 2009). In addition, the FDA issued a black box warning in 2008 regarding the risks of combining first- and second-generation antipsychotics, which is seen among elderly patients who have dementia (Dorsey, Rabbani, Gallagher et al., 2010). Moreover, there is little research about the long-term safety of atypical antipsychotics. Therefore, the use of second-generation antipsychotic augmentation therapy is restricted for elderly patients and those who have a history of cardiovascular disease (Spielmans, Berman, Linardatos et al., 2013). Similarly, the long-term risk for tardive dyskinesia has yet to be established. Currently, atypical antipsychotics are gaining support as an effective adjunctive treatment for resistant unipolar depression and as research continues, the long-term risk-to-benefit ratio may eventually be elucidated.

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