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“Efficacy of second generation antipsychotics as an adjunct therapy for major depressive disorder”

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Efficacy of second generation antipsychotics as adjunct therapy for major depressive disorder

Abstract

INTRODUCTION: Major depressive disorder is a debilitating mental health condition for many US adults. Traditional therapies may not be effective for many patients. The purpose of this paper is to evaluate the effectiveness of brexpiprazole, a second generation antipsychotic medication, as an adjunctive treatment for resistant MDD.

METHODS: PubMed was searched with a specific search strategy using key terms "brexpiprazole" and "major depressive disorder." This search resulted in 21 results in which four articles were chosen based on the availability of free full text and the included content. Of the articles selected, three were a systemic review and meta-analyses, and one was just a meta-analysis.

RESULTS: Two systematic reviews/meta-analyses and one meta-analysis compared the efficacy of various second generation antipsychotics to a placebo. One systematic review and meta-analysis studied only brexpiprazole and its efficacy and side effect profile.

DISCUSSION: All the articles reviewed showed brexpiprazole to improve symptoms of depression, though significant results are mixed. The downside to using SGAs as adjunct treatment is the various adverse effects. Brexpiprazole had one of the largest side effect profiles and highest discontinuation rates.

Efficacy of second generation antipsychotics as adjunct therapy for major depressive disorder

INTRODUCTION

Major depressive disorder (MDD) is a chronic mental health condition that affects more than 20% of adults in the US.[1] Major depressive disorder is defined by the DSM 5 criteria as five or more symptoms, with at least one being depressed mood or anhedonia, that lasts for more than two weeks.[2,3] The symptom criteria include sleep disturbances, anhedonia, feelings of guilt or worthlessness, lack of energy, poor concentration, appetite, and weight changes, psychomotor agitation or retardation, or suicidal thoughts.[3] MDD most commonly results from a combination of biological, environmental, and psychosocial events that are endured daily. Adverse life events, excessive alcohol or drug use, inactivity, or pre-existing comorbidities are examples of risk factors.[2,3] The pathophysiology of depression is abnormalities in the neurotransmitters serotonin, norepinephrine, and dopamine.[3] Typically, patients with MMD lack these neurotransmitters at the synaptic cleft because they are being reabsorbed too quickly.

MDD is a clinical diagnosis that is made when patients fit the DSM-5 criteria, however, tests such as CBC, CMP, TSH, vitamin D, urinalysis, and toxicology, amongst others, are performed to try and identify underlying causes.[3] A comprehensive history and mental status exam are also performed. Self-reporting questionnaires like the Patient Health Questionaire-2 and 9 (PHQ-2 and PHQ-9) are used as screening and treatment monitoring tools.[3]

Treatment for MDD combines psychotherapy and medications. PHQ-9 screening scores help determine if patients need single or combined therapy as first-line treatment, although combination therapy is typically recommended.[1,3,4,5,6] Cognitive behavioral therapy is the most common type patients start with, and it focuses on rewiring a patient's negative thought

processes.[4] First-line pharmacologic management are selective serotonin reuptake inhibitors (SSRI) and serotonin/norepinephrine reuptake inhibitors (SNRI).[1,3] These medications act to allow the neurotransmitters serotonin and norepinephrine to stay in the synaptic cleft longer by preventing their reuptake.

Although these classes of medications are intended for first-line use and are typically combined with therapy, 30% of patients still experience symptoms of depression after trying multiple medications in each of the two drug classes.[6] Patients with MDD have a higher suicide rate than those without the disease.[1,6] Approximately 10 to 20 percent of patients diagnosed with MDD attempt to commit suicide at least once in their lifetime.[8] Other medications can be used as add-on therapy to SSRIs or SNRIs that could aid in treatment resistance. One class of medications that is being researched is second generation or atypical antipsychotics (SGA). SGAs work by blocking dopamine receptors along with serotonin receptors. Low dopamine levels can contribute to depression, and blocking receptors can allow more dopamine to stay in the synaptic cleft.[3,7]

Since many patients are refractory to treatment with SSRIs and SNRIs, it is important to research other possible treatment options to try and reduce the risk of serious complications. The purpose of this review is to investigate the efficacy of using second generation antipsychotics as adjunct therapy to antidepressants.

METHODS

PubMed was searched using the terms “brexpiprazole” and “major depressive disorder.” MeSH terms and Boolean operators were added to produce a final search of “brexpiprazole” AND “major depressive disorder.” Search filters were applied for meta-analysis, randomized controlled trials, and systematic reviews. The dates were restricted to no earlier than the last five

years, and the language was restricted to English. This produced 21 results. A total of four articles, three systematic reviews and meta-analysis and one meta-analysis were chosen for review. These four articles were chosen because they all compared the efficacy and safety of SGAs to a placebo, and brexpiprazole was included as one of the studied medications in each article. They were also picked based on what free full texts were available.

RESULTS

Vasquez et al[9] conducted a systematic review and meta-analysis of 43 peer-reviewed reports of randomized, normally double-blinded, short-term placebo controlled trials. Inclusion criteria for these reviews included selected agents being compared with lithium as an adjunct to antidepressants for adults only with criteria diagnosed unipolar major depressive episodes. Out of the 43 peer-reviewed reports, there was a total of 49 drug-placebo pairs that were compared. The goal of this article was to compare efficacy as odds ratio versus placebo, NNT, and NNH of add-on second generation antipsychotics to antidepressants in adults with unipolar major depressive episodes.

Twenty-eight of the drug-placebo trials were for second generation antipsychotics. A total of 8104 patients were selected at random, 4030 combined with an SGA and 4074 combined with a placebo. NNT, NNH, LHH, and all other measures are reported as means with a confidence interval of 95%. The SGAs present in these studies are aripiprazole, brexpiprazole, cariprazine, olanzapine + fluoxetine combination, quetiapine, risperidone, and ziprasidone. The addition of SGA yielded an odds ratio of 1.59 with CI 1.44 – 1.75, a z score of 9.16 and p less than 0.0001. SGA showed to be more effective than adding a placebo to a patient who is already taking an antidepressant for unipolar major depressive episodes.

NNT values were recorded for all SGAs and each one specifically, all with a 95% CI. For all SGAs 11 [9-15] was reported and for brexpiprazole specifically 16 [10-34] was reported. Brexpiprazole had the highest NNT compared to all other SGA's individually. NNH values were also recorded to assess the relative adverse events associated with adjunctive treatments. Each SGA was compared separately due to their individual side effect profiles. Brexpiprazole resulted in akathisia, olanzapine/fluoxetine in weight gain, cariprazine in akathisia, risperidone/ziprasidone/quetiapine in sedation/somnolence, and aripiprazole in extrapyramidal symptoms/akathisia. NNH value for brexpiprazole specifically was 19 [14-29] which was the highest of all SGAs.

Kishi et al[10] conducted a systematic review and meta-analysis of 9 double-blind, randomized, placebo-controlled trials that looked at the effects of brexpiprazole in patients with MDD that had been refractory to treatment with at least one antidepressant. A total of 3391 patients were included in the analysis, 1815 of which were given brexpiprazole and 1576 who were given a placebo. Primary efficacy of brexpiprazole was defined by a greater than or equal to 50% reduction from baseline Montgomery-Asberg depression rating scale (MADRS) score. Secondary efficacy, or remission, was defined by MADRS score less than or equal to 10 and a greater than or equal to 50% reduction form baseline. The observational periods were different in each study ranging from 6 weeks, to 30 and 24 weeks. The studies chosen compared 1.5 +/- 0.5 mg/d, 1mg/d, and 3mg/d dose of brexpiprazole to the placebo.

Efficacy was measured as a relative risk (RR) ratio with a confidence interval of 95%. Response rate for brexpiprazole at any of the included doses at weeks 1 through 6 are as follows respectively: 1.00 (0.96-1.05), 0.96 (0.93-0.99), 0.95 (0.91-0.99), 0.88 (0.80-0.96), 0.92 (0.86-0.99), and 0.93 (0.89-0.97). The remission rates for weeks 1-6 respectively are as follows: 1.00

(0.98-1.03), 0.99 (0.95-1.02), 0.96 (0.93-1.00), 0.91 (0.85-0.98), 0.95 (0.88-1.02), and 0.95 (0.93-0.98). At doses of greater than 2 mg/d and less than or equal to 2mg/d response rate was 0.96 (0.93-1.00) and 0.89 (0.84-0.95) respectively. The remission rate was 0.98 (0.95-1.01) and 0.94 (0.90 – 0.98). The MADRS score at dose greater than 2 was reported at -0.15 (-0.28, -0.2) and -0.26 (-0.37, 0.16). The SDS or Sheehan Disability Scale was analyzed to be -0.09 (-0.22, 0.04) and -0.19 (-0.30, -0.09). Data was also collected for safety outcomes of brexpiprazole. The RR for discontinuation due to adverse events was 2.36 (1.46-3.82). Further data was reported for individual side effects.

Kishimoto et al[7] conducted a meta-analysis of 32 RCTs with a sample size of 8349. The primary efficacy was defined as a treatment response of greater than or equal to 50% improvement in depressive symptom scale scores from baseline. Secondary efficacy was evaluated through MADRS score, Hamilton Depression Scale (HAM-D), and remission. Remission was defined by a score of less than or equal to 7 on the 17 item HAM-D or less than or equal to 10 on the MADRS.

Efficacy was measured using RR with 95% confidence intervals. RR greater than 1 indicated superiority of the adjunct treatment for positive outcomes, and less than 1 for negative outcomes. Clinical benefit and harm were also measured using NNT and NNH. Treatment response was recorded for multiple SGA as adjuncts. Brexpiprazole specifically had a RR of 1.41 with 95% CI 1.21-1.66. The NNT was 14 with a 95% CI 9-27. Intolerability-related discontinuation for SGAs and placebo were also recorded. RR for discontinuation of placebo was 2.39 with 95% CI 1.69-3.38 and a NNH value 37 with 95% CI 27-73. Discontinuation data for brexpiprazole was RR of 3.24 with 95% CI 1.54-6.79 and an NNH of 57 with 95% CI 22-232. Data for secondary outcomes for brexpiprazole is as follows. RR for at least one adverse

effect was 1.24 with a 95% CI 1.24-1.22 and a NNH 10(6-22). RR for akathisia was 2.97 with 95% CI 1.94-4.55 and a NNH 17 (10-36). RR for restlessness was 4.13 (1.24-13.77) and an NNH 31 (8-392). RR for somnolence was 4.25 (1.56-11.6) and an NNH 26 (8-147). RR for weight gain of greater than or equal to 7% was 2.31 (1.24-4.31) and an NNH 45 (18-247). RR for increased appetite 3.81 (1.43-10.2) and an NNH 28 (9-185). RR for suicidal ideation was 0.58 (0.32-1.05) and NNH was non deducible. RR for suicidal attempt was also non deducible.

Wang et al[6] conducted a systemic review and meta-analysis of 56 studies that looked at the efficacy and safety of four atypical antipsychotics as an additional therapy to antidepressants in patients with treatment resistant MDD. These studies were chosen based on PRISMA guidelines. The average sample size of the reviewed studies was 189, all participants were adults over 18 that met the DSM-5 criteria for MDD, and each trial lasted at least 6 weeks or longer. The primary efficacy outcome was defined by a depressive symptom score, and the secondary efficacy outcome was measured as response and remission rate. Response rate had to be at least 50% reduction of symptoms from baseline, and remission rate was at least 75% reduction or a MADRS score less than or equal to 7. The primary safety outcome was defined by acceptability (patients who withdrew from study for any reason) and tolerability (patients who stopped due to adverse reactions). Four

The four atypical antipsychotics studied in this review were quetiapine (qtp), olanzapine (ola), aripiprazole (ari), and brexpiprazole (bre). Each drug was added on as treatment to an antidepressant medication and results were compared with a placebo. Primary efficacy outcomes were as follows respectively, qtp (SMD = −0.40; 95% CI, −0.68 to −0.12), ola (SMD = −0.35; 95% CI, −0.59 to −0.11), ari (SMD = −0.28; 95% CI, −0.47 to −0.09), and bre (SMD = −0.25; 95% CI, −0.42 to −0.07). The secondary efficacy outcomes based on response rate were

qtp (SMD = 0.85; 95% CI, 0.79 to 0.91), ola (SMD = 0.79; 95% CI, 0.74 to 0.83), ari (SMD = 0.64; 95% CI, 0.57 to 0.73), and bre (SMD = 0.72; 95% CI, 0.61 to 0.84). The result of safety in terms of probability was qtp (RR = 0.24; 95% CI,0.11–0.53), ola (RR = 0.30; 95% CI, 0.10–0.55), ari (RR = 0.39; 95% CI,0.22–0.69), and bre (RR = 0.37; 95% CI, 0.18–0.75). Safety in terms of acceptability was qtp (RR = 1.12; 95% CI, 0.58-2.16), ola (RR = 1.10; 95% CI, 0.61-1.99), ari (RR = 1.10; 95% CI, 0.73-1.67), and bre (RR = 0.92; 95% CI, 0.56-1.51).

DISCUSSION

The four studies in this review provide overall strong results to support the use of brexpiprazole for the improvement of MDD, however, data suggests that it may not be the best option due to its overall negative side effect profile and discontinuation rate. The study conducted by Vazquez et al supports the use of second generation antipsychotics as an adjunct treatment to antidepressants for MDD in adults. Overall, the use of SGAs was 1.59 times more likely to result in a positive outcome compared to treatment with the placebo. Brexpiprazole specifically di not report as effective. Out of all the SGAs it had the highest NNT and NNH. SGAs are effective adjuncts as they significantly increase the likelihood of symptom improvement of major depressive disorder as compared to the placebo. Brexpiprazole showed a higher NNT and NNH, concluding it was the least effective, with a higher risk of adverse effects, specifically akathisia. The limitations of this study include the use of older antidepressants, specifically tricyclics. There was also a lack of consistency when reporting adverse effects of treatment.

The study conducted by Kish et al suggests that brexpiprazole shows mild to uncertain improvement of depressive symptoms when compared to placebo. The response rate and remission rate both are close to 1.00 indicating that brexpiprazole may not have a significant

effect compared to the placebo. This study also tested different doses of brexpiprazole. Higher doses greater than or equal to 2 mg/d show to be slightly more effective, but the data was not significant. Another finding was the high discontinuation rate. Patients were 2.36 times more likely to discontinue the medication due to its higher side effect profile. Limitations of this report include but are not limited to publication bias, patient characteristics, compatibility with antidepressants, and sponsorship bias. Few studies included in the analysis were unpublished. The unpublished work showed brexpiprazole to have more efficacy than the published studies, however. All participants in the study were adults, but they were of different races, ethnicity, and geographical region. Brexpiprazole may affect each population differently. The study also did not specify which antidepressants were used in conjunction with brexpiprazole. Lastly, the study was sponsored by industry which can raise the risk of bias.

Kishimoto et al conducted a study in which results showed that brexpiprazole was 41% more likely to improve depressive symptoms compared to placebo. Data showed that there was a higher risk of discontinuation due to intolerability for brexpiprazole as opposed to placebo. Brexpiprazole had a NNH of 57 indicating that for every 57 patients, one would stop treatment. There was a very wide confidence interval with this, however, suggesting much variability with this outcome. The data also resulted in a 24% increased likelihood that one in ten patients being treated with brexpiprazole will experience one adverse effect. The adverse effects experienced were akathisia, restlessness, somnolence, weight gain greater than or equal to 7%, and increased appetite. There was also a trend of reduced risk of suicide, however, the confidence interval indicated these findings may not be significant. Limitations of this study include a small sample size. There was also a limited time frame of only 6-8 weeks which may not be long enough to see the effects of SGAs.

The results of the study conducted by Wang et al suggest that the addition of SGAs to antidepressants for MDD does improve symptoms and treatment outcome compared to the placebo. Brexpiprazole did show to have the least effect compared to all four SGAs studied. Data also revealed that the adjunct therapies were safe, but not as safe compared to the placebo. Brexpiprazole did have one of the higher RR values for tolerability, indicating that it had a lower safety profile than the other medications tested. Some of the adverse effects seen were akathisia, weight gain, and fatigue. All four SGAs had similar acceptability profiles. Limitations of this study include a lack of bias reported in some studies that were used and a shorter duration of treatment time. Most of the studies chosen had a treatment time of 6-8 weeks, thus limiting data on the outcome of long-term effects of SGAs.

CONCLUSION

Overall findings suggest that SGAs are effective. Brexpiprazole specifically has mixed data, including higher discontinuation rates and side effects. Future research should be conducted to investigate the side effect profiles of SGAs. Since these medications are showing the ability to reduce symptoms of MDD, it could be worth further investigating the severity of the adverse effects and potential ways to treat those.

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