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Second Generation Antipsychotic Use in Major Depressive Disorder

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Background

In the United States, major depressive disorder (MDD) is a chief contributor to disability and the tenth leading cause of death.[1-3] MDD is defined as a history of one or more major depressive episodes (characterized by 2 or more consecutive weeks with depressed mood or loss of interest alongside other depressive symptoms) without previous mania. Annually, about 7% of U.S. adults report at least 2 weeks of depressed mood or loss of pleasure in daily activities.[4,5] The annual rate is higher in adults treated in rural and urban primary care clinics (estimates range from 10%-29%).[4] About two-thirds of these episodes are accompanied by severe impairment that interferes with daily activities and interpersonal relationships.[5] The increasing incidence of MDD is also associated with a rising number of patients being prescribed second generation antipsychotics (SGA) as part of a treatment regimen for MDD. SGAs reduce symptoms of anxiety and personality disorders that are often concomitant with MDD. This newsletter will review the evidence for the use of SGAs as adjunctive therapy for MDD.

When cognitive therapy alone is unable to improve symptoms of depression, initiation of pharmacotherapy is recommended.[1] Second generation antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs]), are recommended first-line based on similar efficacy and improved adverse effect profiles over first generation antidepressants.[2] According to the American Psychiatry Association (APA), the goals of antidepressant treatment are to achieve remission (defined as ≥3 weeks with the absence of both sad mood and reduced interest and ≤3 remaining symptoms of the major depressive episode), improve functionality, and increase quality of life.[3]

It is estimated that one-third to one-half of patients fail initial antidepressant therapy.[4] Patients who are nonresponsive to initial therapy should be considered for the following: optimization of the dose of current treatment, depression-focused psychotherapy or switch to a different antidepressant.[3] A trial that examined a sequential approach to antidepressant treatment failure found about two-thirds of patients failed initial treatment and required either a change to a different antidepressant or addition of adjunctive therapy.[6] Therapy changes continued based on failure of response, up to a fourth treatment stage.[7] After one year, two-thirds of patients were in remission; however, the rate of remission decreased each time therapy was changed.[6,7]

Augmentation Therapy

There is limited evidence to guide optimal adjunctive treatment; however, augmentation therapy is considered appropriate for patients with two or more treatment failures.[2] The APA MDD guidelines describe several different strategies for patients who require adjunctive therapy, including the addition of another antidepressant (from a different pharmacological class) or non-antidepressant such as lithium, thyroid hormone or a SGA.[3] Guideline recommendations from the Veterans Administration (VA) suggest that SGAs should be considered only after failure of other treatment options due to significant potential for adverse events.[8]

Four SGAs have Food and Drug Administration (FDA) approval for MDD and two are used off-label. Cost comparisons of treatment options used for augmentation therapy are presented in Table 1.[3,9]

Table 1. Cost of SGAs used as Augmentation Therapy for MDD[3,9]

Medication[3]	Daily Dose	30 Day Supply
Risperidone*	2 mg	$1
Buspirone*	15 mg	$2
Mirtazapine	30 mg	$2
Lithium*	300 mg	$3
Quetiapine	200 mg	$3
Trazodone	150 mg	$3
Bupropion SR	150 mg	$11
Ziprasidone*	60 mg	$12
Aripiprazole	15 mg	$16
Quetiapine ER	200 mg	$30
Olanzapine/ Fluoxetine (Symbyax™)	6 mg/50 mg	$401
Olanzapine + fluoxetine	5 mg + 40 mg	$4
Brexpiprazole (Rexulti®)	2 mg	$974
Cariprazine (Vraylar®)	3 mg	$1,155

Oregon Health Authority Average Actual Acquisition Costs (2/13/18)
* Treatments used off-label for MDD

Evidence for Augmentation with SGAs

A high quality systematic review and meta-analysis done by the Agency for Healthcare Research and Quality (AHRQ) identified 26 trials lasting 4-9 weeks that evaluated off-label uses of atypical antipsychotics for use in MDD.[10] There was insufficient evidence on direct comparisons of SGAs used for MDD.

- There was moderate quality evidence of efficacy, compared to placebo, for aripiprazole, quetiapine and risperidone when used adjunctively with SRRIs or SNRIs for the treatment of MDD (Table 2).
- Quetiapine extended release (ER) monotherapy demonstrated moderate evidence of efficacy in MDD based on Montgomery-Åsberg Depression Rating Scale (MADRS) remission rates (relative risk [RR] 1.43; 95% CI, 1.07 – 1.91; number needed to treat [NNT] 13) and MADRS response rates (RR 1.49; 95% CI, 1.23 to 1.81; NNT 6).[10]
- Active treatment comparisons found that the addition of an SGA to SSRI or SNRI resulted in improvement in symptoms compared to either a SSRI or SNRI alone. Combinations that were studied were: olanzapine/fluoxetine, ziprasidone/sertraline, quetiapine/paroxetine or quetiapine/venlafaxine.[10]

Table 2. SGA Augmentation in MDD[10]

Antipsychotic	Remission	Response
Aripiprazole*	RR 1.57 (95% CI: 1.24-2.00)/ NNT NP	RR 1.66 (95% CI: 1.37-2.01) / NNT 7
Quetiapineɬ	RR 2.76 (95% CI: 1.21-6.28) / NNT 5	RR 2.30 (95% CI: 1.35-3.92) / NNT 3
Risperidoneɬ	RR 2.10 (95% CI: 1.43-3.09) / NNT 8	RR 1.50 (95% CI: 1.20-1.87) / NNT 7

Abbreviations: CI – confidence interval, NNT – number needed to treat, NP – not provided, RR – relative risk
*Key: * Based on MADRS scale , ɬ Based on HAM-D Scale*

New SGAs for MDD Augmentation

Brexpiprazole – Brexpiprazole is the most recently FDA-approved SGA indicated for adjunctive treatment of MDD. Approval was based on two, phase 3, 6-week, double-blind studies in adult patients with a history of inadequate response to 1-3 previous antidepressants.[11,12] Both studies were funded by industry. In the first study, 379 patients were randomized to brexpiprazole 2 mg/day plus an antidepressant or placebo plus an antidepressant (36% SNRIs and 64% SSRIs).[11] Results are most applicable to patients similar to trial participants with the following characteristics: mean MADRS score of 27 (moderate depression), mean age 45 years, 70% women, 87% Caucasian.

The MADRS scale has 10 items associated with major depression with a range of 0-6 points for each item. Response is often defined as a 50% or greater decrease in MADRS from baseline and remission is a MADRS score of 10 or less.[13]

Study findings did not demonstrate a clinically relevant improvement for the primary outcome of reduction in MADRS total score. There was a mean reduction of -8.36 with brexpiprazole and –5.15.[11] With a mean MADRS score at baseline of 27, a decrease of around 8 points is unlikely to be clinically meaningful.

In the second study, patients (n=677) were given brexpiprazole 3mg/day, brexpiprazole 1 mg/day or placebo in addition to an assigned antidepressant (47% SNRIs and 53% SSRIs).[12] Included patients had a mean MADRS score of 26.5 (moderate depression), mean age of 47 years and 68% of patients were women. The brexpiprazole 3 mg/day group was found to lower MADRS scores more than placebo, but not to a clinically significant degree (95% CI, -3.39 to -0.51).[12] Changes for brexpiprazole 1 mg were not statistically different from placebo (-7.64 vs. -6.33), respectively.

With such a small effect on MADRS scores, it is unlikely that brexpiprazole has a clinical impact on depression symptoms. Common adverse events in both studies were weight gain and akathisia.

Cariprazine – Cariprazine is an SGA approved by the FDA in 2015 for schizophrenia and bipolar I disorder that has also been studied off-label for MDD. Cariprazine was studied in a randomized, placebo-controlled, double-blind trial lasting only 8-weeks in adult patients (n=808) with MDD and inadequate antidepressant response (baseline mean MADRS total score of 29).[14] Patients were a mean age of 46 years, 71% were women and 87% were Caucasian. Cariprazine 1-2 mg/day or 2-4.5 mg/day was given as an adjunct to SSRI or SNRI therapy and compared with placebo added to SSRI or SNRI treatment.

Results from augmentation with doses of 1-2 mg/day cariprazine were not statisttically significantly different from placebo. Response rates for cariprazine, based on changes in MADRS scores, were not clinically significantly different.[14] Adverse events occurring in greater than or equal to 10% of patients treated with cariprazine were akathisia, insomnia and nausea.

Overall, the evidence suggests that these new SGAs are not effective as adjunctive therapy in MDD. Both treatments are limited by small, short-term studies in patients with moderate depression.

Adverse Events

Common adverse events associated with all SGAs are weight gain, fatigue, sedation, akathisia and extrapyramidal symptoms. Additionally, specific SGAs are associated with a higher incidence of certain adverse reactions (Table 3).

Table 3. Select SGA Adverse Events [10,15]

Antipsychotic	Major Side Effect	NNH
Aripiprazole	Akathesia/Parkinsonism	7
Olanzapine	Weight gain	3
Quetiapine	Sedation	11
Risperidone	Increased risk of stroke in elderly	53
All SGAs (pooled)	Increased risk of death in elderly	87

Abbreviations: NNH – number needed to harm, SGA – second generation antipsychotic

Conclusions

- Aripiprazole, quetiapine and risperidone, when used for augmentation with SSRIs or SNRIs, have demonstrated the strongest evidence as augmentation therapy in patients with MDD who have failed other treatments. **Risperidone and quetiapine are both preferred treatments for Oregon Health Plans fee-for-service patients.**
- Newer SGAs are costlier and offer no efficacy advantage over generic options. There is insufficient long-term evidence for second generation antipsychotics as augmentation therapy for MDD.
- Second generation antipsychotics can have significant adverse events not associated with second generation anti-depressants.

For these reasons, SGAs should be considered for MDD augmentation only after exploring other treatment options.

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