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Characterization of the Respiratory Syncytial Virus (RSV) Attachment Protein Mucin Domains

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Medication and Strategy Considerations in the Treatment of Depression

A Thesis

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Introduction

Despite the prevalence and significance of major depressive disorder (MDD), treatment guidance still largely suggests a trial and error method regarding pharmacotherapy intended to produce remission of symptoms. Worldwide, over 300 million individuals have been diagnosed with depression[1] and 16% of individuals will be diagnosed with depression at some point in their lifetime.[2] Depression is also the leading cause of disability and premature death in adults 18-44 years old.[3] Many patients with depression are treated in a primary care setting, accounting for nearly 10% of primary care visits.[2] This prevalence correlates with a significant cost burden; over $210 billion in healthcare costs in the United States can be attributed to the treatment of depression.[4]

The American Psychiatric Association (APA) 2010 clinical practice guidelines for the treatment of MDD offer multiple strategies for effective pharmacotherapy regimens. Following diagnosis, patients begin acute phase treatment aimed at inducing remission of depressive symptoms; this treatment will include pharmacotherapy and/or psychotherapy or electroconvulsive therapy for six to twelve weeks. Among pharmacologic choices, selective serotonin uptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), mirtazapine and bupropion are suggested as first line agents due to improved tolerability compared to older agents such as tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs), but all approved agents have proven efficacy. After symptom improvement in the acute phase, continuation phase using the same agents and doses should be continued for four to nine months to reduce the risk of relapse. Patients with chronic depressive disorder, multiple prior depressive episodes, or high risk of relapse will then enter maintenance phase, continuing the same regimen indefinitely.[5]

Generally, patients are treated with monotherapy unless they do not achieve remission with single agent therapy. Almost two-thirds of patients do not achieve remission after 12-14 weeks of an appropriate antidepressant.[6] Commonly used strategies for pharmacotherapy in these patients are to increase the dose of the initial agent, switch to a different agent, add a second antidepressant of a different class, or add a non-antidepressant augmenting agent.[5] The APA guidelines on this decision-making process and choice of agent is not specific.

Ambulatory care pharmacists in a primary care setting are in a unique position to add benefit to these patients. Much like other chronic disease states, depression requires follow-up for monitoring of symptom improvement and potential medication side effects. APA guidelines recommend follow-up within two weeks of change in antidepressant therapy.[5] Utilizing the well-validated PHQ-9 questionnaire allows a pharmacist to score symptom improvement and additional patient counseling can improve adherence. Up to 43% of patients will self-discontinue their antidepressant within 30 days of starting therapy.[2] In one study, pharmacists were able to provide interventions to 40% of patients surveyed regarding depression treatment.[2] Despite the opportunity to guide therapy as medication experts, practice guidelines to approach choices in therapy are lacking in specificity and have not been recently updated.

This review provides a resource regarding individual medication profiles and choices of treatment strategy for pharmacists treating depression in a primary care setting. When data permits, agents are addressed individually and compared to other agents of the class. Side effect mitigation strategies are included when possible. Treatment strategies are addressed in relation to patient-specific factors.

Medication Considerations

Since all marketed antidepressants have been proven more effective than placebo in reducing symptoms of depression, choice of agent largely depends on comparative side effects and patient-specific parameters. One meta-analysis assessed comparative efficacy and acceptability among 21 different antidepressants (Table 1).[7] All treatments were statistically more effective than placebo at inducing a clinical response (defined as at least 50% reduction in symptoms). Amitriptyline, mirtazapine, and duloxetine provided the largest benefit in symptom relief. Regarding acceptability, only fluoxetine had fewer patient dropouts than placebo, and clomipramine had statistically more patient dropouts than placebo.

Side effect profile, potential drug interactions, and dosing are additional considerations when choosing an antidepressant. Side effects reported in at least 10% of patients receiving second generation antidepressants can be found in Table 2,[8] antidepressants acting as CYP substrates and inhibitors can be found in Table 3,[9] and usual dosing range is included in Table 4.[10]

All antidepressants may take up to six weeks or longer to achieve maximum symptom improvement[5] which may cause patients to discontinue therapy prematurely from a lack of immediate response. Pertinent counseling points across drug classes include continuation of therapy for two to four weeks before expecting noticeable improvement of symptoms and avoiding abrupt discontinuation. Additionally, therapy-induced nausea is most common within the first two weeks of starting therapy and can be ameliorated by administering antidepressants with food and dosing at bedtime.[11]

Selective Serotonin Reuptake Inhibitors

Agents in this class include fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine, although fluvoxamine has only been FDA approved for OCD. When studied,

SSRIs are often grouped as a class of agents. As a class, SSRIs are more well tolerated than older antidepressants but some variation between individual agents does exist.

Sexual dysfunction may be experienced in up to 50% of patients on SSRIs, occurring slightly more with SSRIs than with SNRIs.[11] This side effect typically does not subside over time and may require dose reduction or switching to a different agent to improve patient quality of life. According to one meta-analysis, escitalopram and paroxetine have higher rates of sexual dysfunction than other second-generation antidepressants.[12]

GI bleeds may happen with any SSRI (RR=3.0 compared to placebo).[13] This risk is doubled when an SSRI is co-administered with an NSAID, although addition of an acid-suppressing agent significantly reduces the risk.[8] Antidepressants with no serotonin reuptake activity do not increase the risk of GI bleed and may be an alternative option.

Risk of QTc prolongation is an uncommon but serious adverse effect associated with citalopram and, to a lesser extent, escitalopram. While the risk is low at therapeutic doses, the FDA provides dosing recommendations to limit QTc prolongation with citalopram. Citalopram should not be used if a patient is also receiving another QT interval prolonging medication, or has congenital long-QT syndrome, persistent QTc>500ms, bradycardia, hypokalemia, hypomagnesemia, recent acute MI, or uncompensated HF.[14] A reduced maximum dose of 20mg daily of citalopram is suggested if a patient is older than 60, has hepatic impairment, is a poor CYP2C19 metabolizer, or receives a concomitant CYP2C19 inhibitor. The FDA has no restrictions regarding escitalopram; however, the British regulatory body, the MHRA, provides the same recommendations for escitalopram as citalopram.[14] Of the SSRIs, only paroxetine has not been shown to prolong QTc, even in overdose scenarios.[14]

Falls and fractures as well as hyponatremia have been associated with the use of SSRIs particularly in the elderly.[8] The risk of a fall increases at least two-fold in this population.[5] Hyponatremia, though rare, occurred more frequently with citalopram (0.08%) and escitalopram (0.09%) than other agents.[15]

GI intolerance can be a significant cause for early discontinuation of SSRIs. Fluoxetine in particular has been associated with more nausea, vomiting, and diarrhea than other SSRIs[13] and sertraline associated with more diarrhea.[16] These adverse effects are dose dependent and typically subside within several weeks.

Headaches and migraines, much like GI intolerance, generally improve within the first few weeks of treatment. Over time, SSRIs may actually help prevent migraines.[5]

Safety in overdose is a significant benefit of SSRIs over TCAs. The rate ratio of case fatality (defined as mortality rate/self-poisoning rate) for SSRIs is 0.5 compared to a rate ratio of 13.8 for TCAs.[13] Among the SSRIs, case fatality risk is lowest with paroxetine (rate ratio=0.3) and fluoxetine (rate ratio=0.3) and highest with citalopram (RR=1.1).[13]

Serotonin and Norepinephrine Reuptake Inhibitors

Agents in this class include venlafaxine, desvenlafaxine, duloxetine, milnacipran and, approved most recently, levomilnacipran. SNRIs share many side effect similarities with SSRIs, particularly at lower doses, but tend to add norepinephrine-related side effects at higher doses.

Nausea and vomiting was noted particularly with venlafaxine (RR=1.53 compared to SSRIs) among the SNRIs in one meta-analysis.[16] For venlafaxine, nausea is more common with IR than XR formulations.[17]

Compared to SSRIs, the norepinephrine reuptake inhibition component of SNRIs contributes additional side effects that may include increased heart rate and blood pressure, dry mouth, and constipation.[5] Increased blood pressure is more prevalent with venlafaxine than duloxetine or desvenlafaxine.[5] Blood pressure increase is dose-related and may be improved with decreased doses of SNRIs. For venlafaxine, elevated blood pressure is rare at doses below 225mg/day but up to 13% in doses 300mg/day or higher.[17]

Hepatotoxicity is more associated with SNRIs than with SSRIs. In particular, two European studies found milnacipran and duloxetine to have the highest odds ratios of hepatotoxicity among second generation antidepressants.[18,19] Duloxetine should be avoided in patients with significant liver disease and patients should have periodic ALT/AST monitoring due to this risk.[17]

Somatic symptoms such as chronic pain often accompany depression symptoms. As a class, SNRIs have proven benefit for alleviating somatic symptoms associated with depression.[8] In particular, SNRIs are helpful in reducing hot flashes and chronic pain.[5] Duloxetine has FDA approval for treating diabetic neuropathy, fibromyalgia, and musculoskeletal pain and milnacipran has FDA approval for fibromyalgia.[17]

Novel Antidepressants

Bupropion, mirtazapine, trazodone, nefazodone, vilazodone, and vortioxetine are among first line agents but have different mechanisms of action and side effect profiles than the SSRI or SNRIs and generally cause much lower rates of sexual dysfunction.[8]

Bupropion was the only antidepressant associated with weight loss both acutely (12-14 weeks) and long-term (>4 months) in one meta-analysis.[20] Patients averaged 1.13kg weight loss acutely and 1.87kg weight loss in maintenance phase of treatment. In an overdose setting, bupropion has significant seizure potential. Bupropion IR doses greater than 450mg cause a 10-fold increase in seizure incidence.[13] APA guidelines recommend avoiding bupropion in patients with preexisting seizure disorders, history of anorexia nervosa or bulimia nervosa, or concomitant CYP2B6 inhibitors due to increased risk of drug accumulation causing seizures.[5] Bupropion may be of particular benefit in patients with Parkinson's disease due to dopamine agonist effects.[5]

Mirtazapine has been shown to cause more weight gain and sedation than SSRIs.[5] After four or more months on therapy, patients gained an average of 2.59kg.[20] For these reasons, it may be an optimal choice for patients who present with insomnia or weight loss associated with depression, and is ideally administered at night. In an overdose setting, the rate ratio of case fatality was 1.9 (95% CI 1.1-2.9) which was higher than SSRIs but much lower than TCAs.[13]

Trazodone most commonly causes sedation,[16] and much like mirtazapine is optimally administered at night to patients with insomnia. Less commonly, it has been associated with orthostasis, particularly in older adults.[5] Although sexual side effects occur less commonly with trazodone than with serotonergic agents, erectile dysfunction and priapism may occur, particularly within the first month of treatment or after dose increases.[21]

Nefazodone, like trazodone, is sedating and may cause orthostasis; however, unlike trazodone, nefazodone has very low rates of sexual dysfunction and does not cause priapism. When compared to sertraline, nefazodone caused almost three-times less sexual dysfunction (76% vs 26%, $p<0.001$).[22]

Vilazodone and vortioxetine are the most recently approved antidepressants. Vilazodone must be taken with food for absorption. The dose is titrated from 10mg up to 40mg to avoid GI upset.[8] Because of its mechanism as an SSRI plus partial serotonin agonist, vilazodone was initially proposed to have a more rapid onset of action but that added benefit has yet to be proven.[23] Similarly to SSRIs and SNRIs, vilazodone may increase risk of GI bleeds. Vortioxetine may have particular cognitive benefit, and has proven efficacy in elderly adults.[10,23] Nausea was the most commonly reported side effect with vortioxetine but occurred less compared to duloxetine (23% vs 35%).[23] Between the two, vortioxetine has more long-term remission data than vilazodone.

Tricyclic Antidepressants

Agents in this class include amitriptyline, nortriptyline, protriptyline, imipramine, desipramine, doxepin, and trimipramine. TCAs are no longer favored agents for the treatment of depression largely because of poor tolerability compared to newer agents. APA guidelines suggest restricting their use to patients who do not respond to other treatment.[5]

TCAs are associated with cardiovascular risk, even at therapeutic doses.[13] Because of this risk, a baseline ECG is recommended for patients over 50 years old and those with cardiac risk factors when starting TCA therapy.[5] Patients who also require antiarrhythmic therapy and patients with prolonged QT intervals should be closely followed for risk of arrhythmia. In addition to

arrhythmic potential, TCAs can also cause tachycardia and orthostasis, though nortriptyline may have the lowest risk of the class.[5]

In an overdose, TCAs have much higher case fatality (RR=13.8) than SSRIs. Within the class, amitriptyline is the safest (RR=8.6) and doxepin is the least safe (RR=22.5).[13] Doses as low as 10mg/kg may cause fatality, which means a patient may only need to take a week's worth of doses for an overdose to cause death.[24]

Anticholinergic effects such as constipation, dry mouth, dizziness, sweating, and blurred vision occur in higher rates among TCAs compared to SSRIs. This may be clinically significant for heart rate increases in cardiac disease, cognitive decline in dementia, bladder obstruction in benign prostatic hypertrophy, and worsening of glaucoma. Among TCAs, desipramine and nortriptyline have less anticholinergic activity.[5] Due to anticholinergic effect, the Beers Criteria list recommends avoiding TCAs in older adults.

Seizures may occur in overdose settings with TCAs, especially clomipramine and maprotiline.[5] When compared to other agents in one systematic review, TCAs caused seizures to a lesser extent than clozapine but more frequently than bupropion.[25] APA guidelines caution the use of these agents in patients with a history of seizure disorder.

Fall risk among TCAs is similar to that of SSRIs. One study found that within two weeks of starting a TCA, OR for hip fracture was 4.76 (95% CI 3.06-7.41) and the risk was dose-dependent.[26]

Monoamine Oxidase Inhibitors

Agents in this class include phenelzine, tranylcypromine, isocarboxazid, moclobemide, and transdermal selegiline. APA guidelines suggest restricting the use of MAOIs to patients who do not respond to other treatments, particularly patients who have failed a TCA.[5]

Hypertensive crisis can occur with MAOIs when taken with foods or medications that contain tyramine. Patients may experience headache, nausea, neck stiffness, palpitations, confusion and even stroke or death in instances of too much tyramine ingestion.[27] A mild reaction occurs after 6-10mg of tyramine ingestion, and a severe reaction with 10-25mg.[28] Patients should avoid foods that contain >6mg/serving, which includes aged cheese or meats, fermented products, yeast extracts, draft beers and excessive caffeine or chocolate. Selegiline, unlike other MAOIS, selectively inhibits MAO-B at lower doses and is available transdermally. As a result, patients do not need to adhere to a low-tyramine diet when taking selegiline at lower doses (6mg/24hrs).[28]

Drug interactions, in addition to food interactions, tend to be more significant for MAOIs than other antidepressants because of the risk for hypertensive crisis or serotonin syndrome. Frequency of drug interaction is a significant reason MAOIs are no longer a favored treatment option. Contraindicated agents due to hypertensive crisis include amphetamines, meperidine, bupropion, TCAs, buspirone, cocaine, and sympathomimetics. Contraindicated agents due to serotonin syndrome include amphetamines, meperidine, methadone, pentazocine, propoxyphene, tramadol, linezolid, SSRIs, SNRIs, TCAs, antiepileptics, anti-parkinson agents, buspirone, dextromethorphan, and St. John's wort.[28]

Similar to other antidepressants, MAOIs may also cause orthostasis, weight gain, sexual dysfunction and headaches. Transdermal selegiline, at doses of 6mg/24hrs, did not cause sexual dysfunction compared to placebo.[29]

Strategy Considerations

Analyzing Response

Follow-up monitoring for symptom improvement is essential in achieving response and remission of depression symptoms. Since onset of efficacy is not immediate with antidepressants, an adequate trial period of four to six weeks is needed before determining a patient's level of response to therapy. The PHQ-9 questionnaire is a well-validated nine question patient-rated scoring method that may be used to monitor response.

The PHQ-9 questionnaire considers a decrease of five or more points from baseline a complete response to treatment, with the appropriate next step being continued treatment with periodic follow-up;[3] however, more than 40% of patients fail to respond to initial antidepressant therapy, and more than half do not have sustained remission after multiple therapies.[6] A PHQ-9 score improvement of two to four points indicates a partial response. For these patients, accurate diagnosis and comorbidities should be considered. A dose increase or addition of a second agent may be appropriate.[3] While a partial response is a positive direction, the presence of mild residual symptoms is a strong predictor of relapse to another major depressive episode.[11] A PHQ-9 score improvement of less than two points indicates non-response. Diagnosis and comorbidities should again be considered, and adjustments to therapy may include adding an augmenting agent, switching medication, psychiatric consultation, or psychologic counseling.[3] The term "clinical response" is often used as an efficacy endpoint in studies and defined as at least 50% reduction in symptoms.

In addition to score improvement trends, the PHQ-9 score itself suggests treatment strategy. A score less than five is complete remission of symptoms and requires no action. Scores of five to

nine are mild symptoms that require watchful waiting and periodic screening. Scores of 10-14 are mild major depressive disorder. A treatment plan should include pharmacotherapy or psychotherapy and follow-up. Scores of 15-19 are moderately severe major depressive disorder. This necessitates immediate treatment with pharmacotherapy and/or psychotherapy. Once a patient scores greater than 20 on the PHQ-9, a psychiatric referral is warranted.[3]

Clear guidance regarding actions to be taken based on a patient's PHQ-9 allows for pharmacists in primary care settings to carry out this follow-up, monitoring, and assessment of adherence in perhaps a more frequent manner than primary care physicians may be able and adjust therapy accordingly. Adjustment of therapy may include strategies of optimization, switching, combination or augmentation.

Optimization

The term optimization is used to indicate increasing the antidepressant to maximum tolerated dose for greater control of symptoms in the scenario that remission was not achieved at initial doses. Symptom improvement with antidepressants is not immediate and may take several weeks for clinical response, though earlier onset of symptom relief is a positive indicator of eventual remission.[11] Canadian treatment guidelines suggest increasing the dose for non-improvers at two to four weeks if the medication is well-tolerated.[8] APA guidelines support optimization before switching if side effects are tolerable and a patient exhibits at least a partial response.[5]

The efficacy of this strategy is not well supported, yet this may be a simple way to alter therapy before attempting switching to a different agent or adding a second agent. One meta-analysis found no statistical difference in efficacy between optimization of initial agent compared to switching, although the studies included only evaluated non-responders, not partial responders.[30]

Increasing the dose may expose patients to additional side effects, but that same meta-analysis found no significant difference in dropout rates between optimization and switching.

Switching

Similar to optimization, data regarding the efficacy of switching is not well defined. If a patient fails to respond to initial therapy, switching to another antidepressant may be appropriate, but studies have differed on whether it may be more effective to switch within therapeutic drug class or to a different therapeutic class. The STAR*D trial found no difference in remission rates between patients switched from citalopram to sertraline when compared with patients who switched from citalopram to bupropion or venlafaxine.[31] Conversely, one meta-analysis concluded that switching to bupropion, mirtazapine, or venlafaxine improves remission rates to a greater extent than trial of a second SSRI (RR 1.29, p=0.007) without any difference in discontinuation rates.[32] APA guidelines, along these same lines, suggest that an SNRI may provide benefit even if a patient has not responded to SSRIs.[5]

Canadian guidelines recommend a switching strategy, rather than adding a second agent, if the patient has only tried one agent, if the patient experienced poor side effects with the first agent, if symptoms are less severe, if there was no response with the first agent, or if it is the patient's preference.[8]

When switching agents, multiple factors should be considered. If the initial agent is discontinued too rapidly, the patient may experience discontinuation syndrome. The mnemonic FINISH for flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal, describes patient symptoms after abruptly discontinuing an antidepressant.[8] These symptoms occur within a few days in up to 40% of patients who abruptly stop antidepressant therapy. The

risk of discontinuation syndrome is highest with short half-life agents such as paroxetine and venlafaxine, and lowest with the longer half-life agent fluoxetine.[33] To avoid discontinuation syndrome, a taper over about four weeks is generally recommended when discontinuing therapy.[33]

The risk of discontinuation syndrome should be balanced with the risk of overlapping toxicity. Switching between multiple serotonergic agents increases the risk for serotonin syndrome, especially if starting the second agent before completely stopping the first. Mild symptoms include agitation, tremor and diaphoresis, but may progress to tachycardia, hyperthermia and even organ failure and death.[33] The risk of serotonin syndrome is greatest with MAOIs in combination with other serotonergic agents.

In addition to discontinuation syndrome and serotonin syndrome, the patient's level of symptoms should also be considered in the switching strategy. It may not be appropriate for a patient with a high level of symptoms to be without treatment coverage for several weeks of tapering and washout of the initial agent, whereas for a patient with more mild symptoms it might be more appropriate to have a small gap in treatment in order to avoid overlapping toxicity.

One switching option is a direct switch. With this strategy, the first agent is stopped and the second agent is started on the next day. Scenarios where this may be appropriate include: duration of therapy with first agent was less than six weeks so less likely to have discontinuation syndrome, severe side effects with the first agent, switching to a similar mechanism (e.g. SSRI to SNRI or switching within same class) where the second agent may minimize withdrawal effects of the first agent. This is not appropriate for switching from fluoxetine to another SSRI or SNRI however, because of the long half-life of fluoxetine. A gap of four to seven days is needed in that scenario.[33]

On the other end of the switching spectrum is a washout strategy. The first agent is stopped, the patient goes without treatment while that agent is completely eliminated, then the second agent is initiated. The APA guidelines provide scenarios and timelines for this approach. If switching from a long half-life drug like fluoxetine to an MAOI, a five-to-six-week washout period is needed. If switching from a shorter half-life agent or an MAOI to an MAOI, a two-week washout period is required.[5] The duration of washout is determined by the half-life of the first drug, with five half-lives providing sufficient clearance to initiate the second agent.[33] The benefit of this strategy is safety, but the switch is slow and leaves the patient without treatment for a period of time. If considering switching to an MAOI, practitioners should ensure the patient does not have significant medication interactions and will be able to adhere to dietary restrictions.

In-between a direct switch and a washout is the option of tapering to a switch or cross-tapering. In these scenarios, the first agent is tapered down in dose, then the second agent is started at full dose, or as the first agent decreases, the second agent is increased simultaneously. The benefit of this strategy is no gap in treatment coverage, but overlapping toxicities are a risk. Tapering to a direct switch is an option if switching from SSRI to SSRI or from duloxetine to SSRI or venlafaxine.[33] Cross-tapering between SSRIs and TCAs should be done with caution since some SSRIs will inhibit metabolism of certain TCAs. Cross-tapering clomipramine with SSRIs, venlafaxine or duloxetine is an absolute contraindication due to significant risk of serotonin syndrome.[33] Fluvoxamine inhibits the metabolism of amitriptyline, clomipramine, and imipramine and paroxetine and fluoxetine inhibit the metabolism of clomipramine and nortriptyline.[9] When cross-tapering from TCA to SSRI, taper TCA to 50% of initial dose before starting SSRI at normal starting dose.[33]

Combination

Combination therapy refers to adding a second antidepressant while augmentation refers to adding a second agent not typically considered an antidepressant. APA guidelines suggest adding a non-MAOI antidepressant from a different pharmacological class as the initial agent.[5] Canadian guidelines for treating depression suggest adding a second agent if the patient has failed two or more antidepressants, the initial agent was well tolerated with partial response, there is a specific symptom to target, the patient has more severe symptoms, or based on patient preference.[8]

Evidence supporting the efficacy of combination therapy is not well-defined and several studies have shown no added benefit over monotherapy. Add-on mirtazapine was not significantly more effective than placebo for patients on SSRI or SNRI monotherapy in one recent trial ($p=0.266$).[34] The CO-MED trial concluded neither bupropion plus escitalopram nor venlafaxine plus mirtazapine was more effective at inducing remission or response than escitalopram monotherapy among patients with recurrent or chronic depression, though venlafaxine plus mirtazapine was associated with more side effects.[35] Remission rates among these groups ranged from 41.8%-46.6% and response rate ranged from 57.4% to 59.4%.

Conversely, some studies have shown added benefit with the addition of bupropion or mirtazapine. Addition of bupropion to SSRI or venlafaxine improved outcomes and decreased sexual dysfunction in one study.[36] The addition of bupropion resulted in significant improvement in 78% of patients who were partial or non-responders. Similarly, another study found combination citalopram and bupropion to provide significantly more remission in patients who had failed at least one monotherapy than did switching to another monotherapy (remission 28% vs 7%, $p<0.05$).[37] Adding mirtazapine to optimized monotherapy (most commonly an SSRI) showed significant short-term remission benefits compared to monotherapy alone (45.5% vs 13.3%, $p=0.068$).[38]

While a TCA or MAOI may also be an option for combination therapy, APA guidelines suggest reserving these agents for treatment-resistant depression that has not remitted with other combination agents.[5] Antidepressant agents suggested as adjunct options within the Canadian depression guidelines include bupropion, mirtazapine, and TCAs, although augmentation agents are more favored.[8] Adding a second antidepressant may be associated with additional side effects without significant efficacy benefit. Combination strategies should aim to combine agents of differing mechanisms to avoid overlapping toxicities or serotonin syndrome.

Augmentation

Augmentation is a second two-agent option that may be considered if a patient has failed previous therapy, is getting a partial response with a well-tolerated agent, or has more severe symptoms.[8] Augmentation refers to adding a non-antidepressant as the second agent to augment the activity of the first. APA guidelines specifically suggest lithium, thyroid hormone, or a second-generation antipsychotic.[5] Canadian guidelines recommend aripiprazole, quetiapine, and risperidone as first-line adjunct options, and brexpiprazole, lithium, olanzapine, thyroid hormone, and modafinil as second-line adjuncts.[8]

A network meta-analysis compared aripiprazole, bupropion, buspirone, lamotrigine, lithium, methylphenidate, olanzapine, pindolol, quetiapine, risperidone, and thyroid hormone as adjunct agents for treatment-resistant depression and found only quetiapine (OR=1.92, 95% CI 1.39-3.13) aripiprazole (OR=1.85, 95% CI 1.27-2.27), thyroid hormone (OR=1.84, 95% CI 1.06-3.56), and lithium (OR=1.56, 95% CI 1.05-2.55) were more effective at inducing clinical response than monotherapy plus placebo.[39]

Antipsychotics are the most well-supported augmenting agents but their antidepressant benefit is not necessarily a class effect.[40] The FDA has only approved quetiapine XR, aripiprazole, brexpiprazole and olanzapine (in combination with fluoxetine) for this indication. Additionally, depression and anxiety benefit in antipsychotics is seen at lower doses than that needed to treat psychosis. Higher doses may actually induce more depression symptoms by blocking dopamine. Doses for depression are as follows: quetiapine 15-300mg, aripiprazole 2-15mg, olanzapine 2.5-10mg, brexpiprazole 0.5-2mg.[40]

Lithium is another augmenting option, with proven efficacy in patents who have not responded to previous medication trials. In the STAR*D trial, among patients who had not achieved remission with initial citalopram and second-step switch or augmentation, 15.9% achieved remission with lithium augmentation compared to antidepressant alone, with no difference in discontinuation rates.[41] An added benefit, lithium has also been shown to reduce suicidal behavior. One trial that compared adjunct quetiapine and adjunct lithium found comparable remission and discontinuation rates among patients who had failed at least one antidepressant.[42]

Thyroid hormone, specifically T3, was also found to be an effective augmentation strategy in the STAR*D trial. In patients who had failed initial therapy and failed a switch or augmentation strategy, 24.7% remitted with T3 augmentation.[41]

The VAST-D trial was designed to compare switching, combination and augmentation strategies. Among patients who had failed at least one antidepressant, patients either switched to bupropion, added bupropion to current regimen, or added aripiprazole to current regimen for twelve weeks. Augmentation with aripiprazole was comparable to combination bupropion but more efficacious than switching to bupropion (OR of remission 1.42, 95% CI 1.06-1.89) and had the lowest dropout rates of the three groups.[43] Supporting this finding, a more recent study found

aripiprazole augmentation more effective than bupropion combination in patients who had failed an SSRI (remission rates 55.4% vs 32.0%, p=0.031).[44]

Conclusion

Current strategy for the treatment of major depressive disorder often takes the form of trial and error, leading to suboptimal outcomes for many patients and lower rates of remission. APA guidance regarding medication profiles and treatment strategies is often generalized and somewhat outdated. Medications are frequently addressed as classes, providing little guidance for agent-specific considerations. This review sought to unpack recommendations and evidence published more recently than the APA guidelines in 2010.

While this review does not explore the impact of comorbidities on depression treatment strategy, evidence exists for specific patient populations and should be considered for individualized treatment. Pregnant patients and adolescents may have unique considerations, as well as patients with cardiovascular disease, concomitant psychiatric diseases, and the elderly.

Since depression is so prevalent among conditions treated in a primary care setting, ambulatory care pharmacists are in a unique position to offer the ability for closer follow-up and monitoring as well as medication recommendations and adjustments in the event of partial response or non-response. Treatment of depression can be approached much like other chronic disease states. The PHQ-9 questionnaire may be used to trend symptom improvement. Patient counseling and shared decision making can help improve adherence.

Practitioners should consciously avoid stagnancy in treatment in the event of a partial response and aim for complete remission to decrease likelihood of a second major depressive episode in

the future. Careful evaluation of medication and patient-specific factors has the potential to significantly improve treatment success. Differences among antidepressants in side effect profile and potential drug interactions may indicate which agent is most ideal in a particular patient. For the substantial number of patients who do not remit with initial monotherapy, multiple strategies exist to improve symptom burden.

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Appendix

Table #1 Comparative Efficacy and Tolerability

Class	Medication	Efficacy (OR)	Acceptability (OR)
SSRIs	Citalopram	1.52	0.94
	Escitalopram	1.68	0.9
	Fluoxetine	1.52	0.88
	Fluvoxamine	1.69	1.1
	Paroxetine	1.75	0.95
	Sertraline	1.67	0.96
SNRIs	Desvenlafaxine	1.49	1.08
	Duloxetine	1.85	1.09
	Milnacipran	1.74	0.95
	Levomilnacipran	1.59	1.19
	Venlafaxine	1.78	1.04
Novel Antidepressants	Bupropion	1.58	0.96
	Mirtazapine	1.89	0.99
	Nefazodone	1.67	0.93
	Trazodone	1.51	1.15
	Vilazodone	1.6	1.14
	Vortioxetine	1.66	1.01
TCAs	Amitriptyline	2.13	0.95
	Clomipramine	1.49	1.3

*Efficacy: response rate (50% reduction of symptoms).
Odds ratio of all agents were statistically more effective than placebo

*Acceptability: dropout rate compared to placebo.
Fluoxetine was more tolerable and clomipramine was less tolerable than placebo. Remaining agents were not statistically different than placebo.

Commonly Reported Side Effects

Table #2

Class	Drug	Common Side Effects
SSRIs	Citalopram	nausea, dry mouth, sweating
	Escitalopram	nausea, male sexual dysfunction
	Fluoxetine	nausea, dry mouth, somnolence, nervousness, anxiety, insomnia, tremor, anorexia
	Fluvoxamine	**nausea,** constipation, dry mouth, headaches, dizziness, somnolence, agitation, insomnia, sweating, tremor, anorexia
	Paroxetine	nausea, constipation, diarrhea, dry mouth, headaches, dizziness, somnolence, insomnia, sweating, asthenia, male sexual dysfunction
	Sertraline	nausea, diarrhea, dry mouth, headaches, dizziness, somnolence, insomnia, fatigue, tremor, male sexual dysfxn
SNRIs	Desvenlafaxine	nausea, dry mouth, dizziness, sweating
	Duloxetine	nausea, constipation, dry mouth, insomnia, male sexual dysfxn
	Milnacipran	nausea, headaches
	Levomilnacipran	nausea, dry mouth, headaches, male sexual dysfxn
	Venlafaxine	IR formulation: **nausea,** constipation, dry mouth, headaches, dizziness, somnolence, nervousness, insomnia, sweating, asthenia, anorexia, male sexual dysfunction XR formulation: less constipation, asthenia, anorexia
Novel Antidepressants	Bupropion	SR formulation: nausea, dry mouth, headaches XL formulation: **headaches,** anxiety
	Mirtazapine	constipation, dry mouth, **somnolence,** increased appetite, weight gain.
	Vilazodone	nausea, diarrhea, headaches
	Vortioxetine	nausea

*in bold if reported >30%

Table #3 Typical Dosing

Class	Drug	Usual Daily Dose Range	Daily Frequency
SSRIs	Citalopram	20-40mg	Once daily
	Escitalopram	10-20mg	Once daily
	Fluoxetine	10-80mg	Once or twice daily
	Fluvoxamine	50-300mg	Once or twice daily
	Paroxetine IR CR	20-60mg 12.5-75mg	Once daily Once daily
	Sertraline	50-200mg	Once daily
SNRIs	Desvenlafaxine	50mg	Once daily
	Duloxetine	40-60mg	Once or twice daily
	Levomilnacipran	40-120mg	Once daily
	Venlafaxine IR XR	75-375mg 75-225mg	Two or three times daily Once daily
Novel Antidepressants	Bupropion IR SR XL	200-450mg 150-400mg 150-450mg	Three times daily Twice daily Once daily
	Mirtazapine	15-45mg	Once daily
	Trazodone	150-400mg	Three times daily
	Nefazodone	200-600mg	Twice daily
	Vilazodone	40mg	Once daily
	Vortioxetine	10-20mg	Once daily

Table #4: CYP Substrates and Inhibitors

Enzyme	Substrate	Inhibitor
1A2	duloxetine (major)	fluvoxamine (strong)
2B6	bupropion (major)	
2C19	citalopram (major) escitalopram (major)	fluoxetine (moderate) fluvoxamine (moderate)
2D6	paroxetine (major) duloxetine (major) vortioxetine (major)	fluoxetine (strong) paroxetine (strong) duloxetine (moderate) bupropion (strong)
3A4	citalopram (major) escitalopram (major) levomilnacipran (major) mirtazapine (major) trazodone (major) vilazodone (major)	nefazodone (strong)