



## REVIEW

### Antidepressant efficacy and side effect burden: an updated guide for clinicians

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#### Abstract

Antidepressant treatment has been evolving and changing since the 1950s following the discovery of the classic antidepressant treatments including tricyclic antidepressants and monoamine oxidase inhibitors. The heterogeneity of the disorder became apparent in the beginning when individuals remained symptomatic despite medication compliance. This spurred further research in order to understand the neurobiology underlying the disorder. Subsequently, newer medications were designed to target specific neurotransmitters and areas of the brain involved in symptom development and maintenance. Our original review article looked at both classic and modern antidepressant medications used in the treatment of major depressive disorder. This manuscript is an update to the original review and serves to provide clinicians with

information about novel antidepressant medications, augmentation strategies with atypical antipsychotics, over-the-counter medications, as well as nonpharmaceutical treatments that should be considered when treating each individual patient who remains symptomatic despite treatment efforts.

**Keywords:** antidepressants, antipsychotics, depression, major depressive disorder, neuromodulator, postpartum depression, therapeutic, treatment-resistant depression.

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## Introduction

As the biological basis for depression continues to be discovered, so do the treatments that can target specific neurotransmitters as well as different areas of the brain. Within the initial review article 'Antidepressant efficacy and side effect burden: a quick guide for clinicians', the heterogeneity of depression was discussed and the importance of recognizing that antidepressant treatments (ADTs) are not 'one-size-fits-all'.<sup>1</sup> ADTs are also heterogeneous and are becoming even more target-specific. This article aims to create an extension of the original review and introduce clinicians to some of the newer pharmacological developments, augmenting atypical antipsychotics, over-the-counter treatments (OTCs), and nonpharmaceutical approaches that can be utilized to tailor individual treatment. This was accomplished by conducting a literature search using the PubMed database to review the latest information available.

## Novel ADTs

### Ketamine and esketamine

Ketamine was developed in the 1960s as a short-acting analog of phencyclidine to be used as an anesthetic drug with less emergent delirium.<sup>2</sup> It has been used as an anesthetic agent either alone or in combination with various procedures. In the early 2000s, the investigation into ketamine's rapid antidepressant effects was spurred as both human and animal models found that neurotransmission via the *N*-methyl-D-aspartate (NMDA) receptor was dysregulated in depression. Drugs that target the NMDA receptor were studied and showed antidepressant properties in both clinical and preclinical studies.<sup>3</sup>

Ketamine works as a noncompetitive NMDA glutamate receptor antagonist. After binding to the NMDA receptor, a cascade of events occurs including rapid increases in presynaptic glutamate release, enhanced regional activity in excitatory networks, and ultimately marked changes in

synaptic plasticity and connectivity. These fast-acting effects of ketamine rapidly oppose the stress-induced prefrontal neural atrophy and synaptic disconnection that is sometimes seen in depression.<sup>4</sup>

Ketamine is not Food and Drug Administration (FDA) approved and is currently administered intravenously, with antidepressant effects often evident within 4 hours of treatment and sustained for 3–7 days with a response rate of approximately 40–60% at 24-hours post-treatment.<sup>4</sup> The rapidity of the effect should be highlighted here while recalling the delayed onset of action to oral antidepressant agents. In addition to reducing depressive symptoms, intravenous ketamine is strongly correlated with decreased suicidal ideation. Even after controlling for improvement in the severity of depressive symptoms, ketamine's effect on suicidal ideation remained significant.<sup>5</sup> The clinical utility of an agent that can reduce symptoms of depression and suicidal ideation during an acute symptomatic period is novel by all means.

Ketamine does have some notable side effects including drowsiness, dizziness, blurred vision, transient increases in pulse and mean blood pressure, lower urinary tract symptoms, as well as significant but reversible dissociative and psychotomimetic effects. Side effects typically occurred within the first 2 hours after infusion and had generally resolved by the fourth hour.<sup>2</sup> In the SUSTAIN 2 safety study, cognitive function remained stable throughout treatment for patients regardless of age.<sup>6</sup> Ketamine had been only available as an infusion form, sparking interest into the exploration of more clinically convenient ways to administer the medication. The metabolites and isomers of ketamine have been studied including the *S*- and *R*-enantiomers. Esketamine is the *S*-enantiomer of ketamine that is approximately 3–4 times more potent than the *R*-enantiomer.<sup>6</sup> Esketamine is FDA approved now for TRD and available as an intranasal spray, potentially requiring lower doses than the intravenous formulation with possibly fewer side effects. Per the manufacturer for the drug, cognitive performance decline was seen at 40 minutes after receiving a dose of the medication but there have been no long-term cognitive deficits at 1 year. It is known that misuse/abuse of ketamine has resulted in long-term cognitive deficits but cognitive effects beyond 1 year are unknown for the prescribed formulations.

Both ketamine and esketamine are being used for treatment-resistant depression (TRD). The definition of TRD has no clear consensus; whereas, most clinical trials define TRD as one full failed acute-phase antidepressant medication treatment, others define TRD as up to four failed treatments with or without electroconvulsive therapy (ECT) response.<sup>7,8</sup> In a study esketamine nasal spray worked as a rapid-acting antidepressant for patients with treatment-resistant depression.<sup>9</sup> The FDA recently approved the marketing of esketamine in conjunction with oral antidepressants for the treatment of depression in adults with TRD.<sup>6</sup> Esketamine nasal spray plus antidepressant use has also been found to delay relapse in patients who

achieved stable remission or stable response after 16 weeks of treatment, demonstrating clinically meaningful and statistically significant superiority compared with antidepressant plus placebo.<sup>10</sup> Esketamine received a breakthrough therapy designation in 2016 from the FDA for major depressive disorder (MDD) and imminent risk for suicide.<sup>6</sup> Researchers of a double-blind randomized placebo-controlled study found that ~35% of between-group difference favored esketamine for participants achieving resolution of suicide risk after 24 hours of receiving the first dose. This finding is consistent with the results of the recently published meta-analysis of intravenous ketamine that reported similar findings.<sup>11</sup> Together these studies emphasize the rapid antidepressant effects of both ketamine and its isomer esketamine for TRD providing symptom reduction quickly while oral antidepressant medication takes effect over the longer term (~4–6 weeks). Given that suicidal ideation is fluctuating in intensity, this intervention could provide emergent treatment between onset of suicidal ideation and suicide attempt.

These medications pose many treatment obstacles as well. To reduce the potential for diversion, both drugs are administered under the direct supervision of a healthcare professional. After administration of the intranasal formulation, side effects and vitals must be monitored for 2 hours, and the patient is unable to drive for 24 hours after receiving the treatment. The dosing schedule requires the patient to receive the intranasal spray twice a week for the first 4 weeks, once a week for weeks 5–8, and then once every 2 weeks from week 9 and on. From an outpatient practitioner's standpoint, all of the issues mentioned previously may serve as a hindrance between drug approval/availability and using the medication in clinical practice.

## Brexanolone

Brexanolone is the first FDA-approved medication for the treatment of postpartum depression (PPD). Postpartum/peripartum depression is a specifier under the diagnosis MDD, defined as a new or recurrent major depressive episode with the onset of mood symptoms that occur during pregnancy or the 4 weeks following delivery.<sup>12</sup> In addition to the criteria for MDD, including but not limited to depressed mood, lack of motivation, and suicidal ideation, peripartum depression can also present with or without psychotic features associated with infanticide ideation.<sup>12</sup> Symptoms vary widely, as with all mental health disorders, highlighting the necessity for sound clinical diagnosis and judgement in order to best treat the individual patient. Stabilizing the patient for immediate safety initially may be necessary, before initiating ADT. It is important to consider treatment options given that postpartum depression is estimated to affect 10–20% of women who give birth worldwide and occurs in women in all socioeconomic classes.<sup>13</sup> Not only is the mother impacted by the disorder but the mother–infant relationship can suffer. The degree of maternal sensitivity is associated with the child's emotional regulation and studies show that infants of mothers who struggle with

PPD might have difficulty with emotional regulation in early life as a consequence of disrupted parenting.<sup>13</sup>

Understanding the biological mechanism considered to be associated with PPD or the risk of PPD is paramount in finding a treatment. It has been found that the central nervous system and plasma levels of neuroactive steroid (NAS) rise during pregnancy and then fall rapidly after parturition.<sup>14</sup> When the steroid level drops, MDD symptoms may emerge. Studies have found that transient increases in allopregnanolone are thought to exert antidepressant effects by allosteric modulation of gamma-aminobutyric acid (GABA-A) receptors.<sup>15</sup> Brexanolone (allopregnanolone) is a positive allosteric modulator at GABA-A receptors that appears to have acute anxiolytic and antidepressant effects.<sup>15</sup> Brexanolone is a promising and now approved agent in the treatment of PPD, as it is formulated with a specific mechanism of action directly targeting a speculated underlying cause of the disorder. Brexanolone injection was associated with a higher proportion of patients who achieved remission at 26 *versus* 15% who achieved remission with placebo between 24 hours and 7 days. Brexanolone was found to have a rapid onset of action and durable responses that were sustained for up to 30 days after infusion. Of the patients who had a response at 60 hours, 94% did not relapse at day 30.<sup>13</sup>

Brexanolone, despite being well tolerated, does have side effects and some limitations. The most common side effects include: dizziness, sedation, and in rare cases loss of consciousness. At this time, this medication is only available as an intravenous infusion, requiring admission to a hospital for continual monitoring for 60 hours. To prescribe brexanolone, the healthcare facility must be enrolled in a Risk Evaluation and Management Strategy (REMS) program. The REMS is specific to the medication requiring (1) 60 hours infusion with monitoring by a healthcare professional every 2 hours during nonsleep periods, (2) starting treatment early in the day to allow assessment of excessive sedation, (3) pulse oximetry monitoring for hypoxemia, and (4) restriction that the patient cannot be the sole caretaker for the infant because of loss of consciousness risk.<sup>16</sup> During drug administration, mother and child will be separated with regular supervised visits. At this time, it is unknown how the intermittent separation after birth will affect mother and child bonding and attachment. Brexanolone, the first FDA-approved medication for the disorder, provides hope for the future and individuals afflicted by the disorder.

## Augmentation strategies

Medication-based augmentation for MDD can be used to treat both patients in partial remission and those with TRD. The American Psychiatric Association (APA) guidelines state if there is no full response in the acute phase (4–8 weeks) of treatment for MDD it is suggested to either increase the ADT dose, switch medications, or employ augmentation strategies.<sup>17</sup> The definition of augmentation for MDD varies, as some studies

differentiate augmentation (adding an unconventional agent for MDD treatment) from combination strategies (adding an antidepressant approved as ADT monotherapy).<sup>18</sup> However, in the practical clinical setting, augmentation is often considered after two failed monotherapy trials.

Two large-scale studies, in particular, have provided key insights into the possible benefit of augmentation as an alternative or in addition to antidepressant substitution including the National Institute of Mental Health (NIMH)-funded Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial and the Veteran Affairs Augmentation and Switching Treatments for Improving Depression Outcomes (VAST\*D). These studies showed that nonresponders to standard ADT (50–60% of patients) may benefit from augmentation agents including lithium, liothyronine, buspirone, bupropion, and aripiprazole spurring further research into augmentation as a viable option for MDD management.<sup>19–22</sup>

Despite these large-scale study outcomes, the FDA to date has only approved five medications for augmentation of TRD: four second-generation antipsychotics (SGAs), with some considering aripiprazole and brexpiprazole to be third-generation antipsychotics and one NMDA antagonist based on randomized placebo-controlled clinical trials (RPCTs).<sup>18,23</sup>

## Aripiprazole

Aripiprazole was originally developed in the 1980s as a novel atypical antipsychotic for the treatment of schizophrenia.<sup>24</sup> Since the early 2000s, it has also been found to have a wide variety of applications including treatment of acute mania, bipolar maintenance, and irritability in autism.<sup>25</sup> It was the first FDA-approved SGA (2007) for adjunct treatment of MDD.<sup>18,23</sup>

Unlike other SGAs, aripiprazole has the possible mechanism of presynaptic agonism and postsynaptic antagonism at dopamine (D2) receptors in schizophrenia.<sup>18,23</sup> Similar to other SGAs, interactions with serotonin receptors (5-HT1 partial agonism, 5HT2 antagonism) is postulated to augment the treatment of MDD symptoms.<sup>18,23</sup> However, some activity at other serotonin, dopamine, histamine, and  $\alpha$ -adrenergic receptors may lead to sedation, dry mouth, weight gain/metabolic side effects, and hypotension.<sup>25</sup> As with other SGAs, there is a black box warning for increased mortality/morbidity for those including stroke risk in the elderly, those with low blood pressure or cardiovascular disease and diabetic/metabolic syndrome patients.<sup>18,23,26</sup> When prescribing SGAs routine monitoring for fasting lipids, fasting glucose, or HbA1c, waist circumference and vitals are needed.<sup>18,23,26</sup> In particular, extrapyramidal symptoms including akathisia, parkinsonian symptoms, and rarely neuroleptic malignant syndrome (NMS) side effects may develop in some patients, which require further surveillance with abnormal involuntary movement scale (AIMS) scoring.<sup>27</sup> Despite these potential side effects discontinuation was comparable to placebo in several studies.<sup>18</sup> The recommended dose range for MDD augmentation

based on RCTs is suggested to be between 5 and 15 mg/day when taking into account the remission rate and side effect profile.<sup>18,23</sup> As far as interactions are concerned it should be noted that aripiprazole is a substrate of liver enzymes CYP3A4/2D6. When administered with select serotonin reuptake inhibitors (SSRIs) such as paroxetine or fluoxetine SSRIs initial dosage should be cut in half to improve safety and tolerability.<sup>18,23</sup>

## Quetiapine XR

Extended-release (XR) quetiapine fumarate was FDA approved in 2009 for the adjunct treatment of MDD. It is also approved for bipolar depression, schizophrenia, bipolar mania, and bipolar depression. It is postulated that the antidepressant response is due to agonism at 5-HT<sub>1A</sub> and antagonism at the norepinephrine transporter (NET), 5HT<sub>2A</sub> and 5HT<sub>2C</sub> receptors. Moreover, the medication may play a role in neurogenesis and have anti-inflammatory and antioxidant CNS effects.<sup>26,28</sup> Quetiapine is an SGA that has evidence (3 RPCTs) to be effective as a bipolar depression monotherapy.<sup>23</sup> Quetiapine is a low relative risk for extrapyramidal symptoms (EPS) but commonly causes sedation, weight gain, metabolic issues, dizziness, and constipation relative to other SGAs. It is usually best administered in the evening and may have the benefit of improvement of insomnia.<sup>29</sup> Based on at least 10 RCTs, 50–300 mg/day was shown to be effective for MDD augmentation specifically.<sup>23</sup>

## Olanzapine in combination with fluoxetine

Olanzapine in combination with fluoxetine (FDA approved in 2009 for MDD augmentation) was the first medication for the acute management of TRD and has the possible mechanism of antagonism at 5HT<sub>2A</sub>, 5HT<sub>2C</sub> receptors but requires the SSRI fluoxetine for efficacy.<sup>18,23</sup> The medication is also approved for acute depressive episodes in the context of bipolar I disorder.<sup>18,23</sup> The combination pill has at least five RPCTs, with four showing efficacy and rapid reduction in depressive symptoms.<sup>23</sup> Overall, the medication has been demonstrated to be well tolerated but in some cases had severe side effects. Significant increases in body weight and prolactin levels (causing gynecomastia/increased secretions) have been observed. More concerning are elevated cholesterol levels, which were significantly greater in combination than olanzapine alone in comparable doses.<sup>18,30</sup> Considering the medication includes an SSRI, there is also a risk for suicidal ideation in those under the age of 25 years. The long-term tolerability is unclear and may be subject to these side effects, including perhaps one of the greatest risks for metabolic side effects, EPS and tardive dyskinesia relative to other SGA augmentation strategies.<sup>30</sup> Perhaps this medication is most beneficial in severe cases with the need for acute stabilization before switching for another maintenance therapy. The suggested dose range based on RCTs is fluoxetine 25–75 mg/day and olanzapine 5–20 mg/day.<sup>23</sup>

## Brexpiprazole

Brexpiprazole was FDA approved in 2015 for TRD augmentation with the possible mechanism of partial agonism of receptors 5-HT<sub>1A</sub>, D<sub>2</sub>, and antagonism of receptor 5-HT<sub>2A</sub>.<sup>18,23</sup> The medication has also been approved for schizophrenia. Notable is that the medication also is considered by some to be a third-generation antipsychotic (due to partial agonist activity on receptors) but has less D<sub>2</sub> activity than aripiprazole and tenfold the activity at the 5-HT<sub>1A/2A</sub>.<sup>23</sup> Although the medication is similar to aripiprazole, it has lower rates of akathisia, sexual dysfunction, and some improved tolerability. However, due to the recent indication for TRD adjunct use, further study is warranted to better establish treatment outcomes/safety profile.<sup>18,31,32</sup> Further expense and lack of insurance coverage is a possible limitation for some patients.<sup>31,32</sup> The suggested dose range based on RCTs is 1–3 mg/day.<sup>23</sup>

## Inhaled esketamine

This agent was FDA approved in 2019 for MDD augmentation and is the only approved non-SGA. For further details, please refer to the Novel ADTs section.

## Non-FDA-approved agents

Other notable alternative treatment strategies have employed clinical trials for efficacy/outcome evaluation and have been compared to FDA-approved treatments: a recent meta-analysis compared the relative efficacy of mood stabilizers (lithium, lamotrigine, valproic acid), atypical antipsychotics (aripiprazole/quetiapine, olanzapine monotherapy, brexpiprazole, ziprasidone, risperidone), atypical antidepressants (buspirone, trazodone, T<sub>3</sub>), stimulants (dexmecamylamine, methylphenidate), and NMDA receptor targets (D-cycloserine, minocycline, ketamine). The results indicated with respect to effect size that (in descending order of efficacy) trazodone followed by depakote, buspirone, ketamine, and aripiprazole were the only treatments with statistically significant improved outcomes with regard to depressive symptoms. NMDA targeting agents overall as a group had the largest effect size. However, these results were based on a single clinical trial each due to exclusion criteria, except for aripiprazole (four RPCTs).<sup>33</sup> Apart from this meta-analysis, several recent clinical trials for SGAs amisulpride and ziprasidone (least studied) have also been conducted without evidence for overall significant benefit.<sup>23</sup> Perhaps, further investigation into these agents may shed light on their efficacy as future augmenting agents.

In summary, limited data are available regarding the efficacy of augmentation strategies for MDD on a long-term basis. Standardization of TRD criteria (as detailed in the Novel ADTs section) and an emphasis on longitudinal studies would allow for improved treatment decisions/outcomes. Owing to a limited number of FDA-approved treatments, further study of other potential viable medications is needed. Currently, when



prescribing SGA augmentation, providers must consider the need for additional lab monitoring and be aware of interactions due to risk for potential complications, particularly in select patient populations including the elderly, those with dementia, metabolic disorders, and patients with cardiovascular disease. Furthermore, studies show that side effects of SGAs contribute to dropout and possible nonadherence.<sup>23,24</sup> On the other hand, NMDA antagonists carry the risk of elevated blood pressure, respiratory depression, and possible habit formation, as previously mentioned. Despite these concerns, there is increasing evidence that TRD augmentation strategies are effective. The risks must be weighed against potential benefits of reduced relapse, earlier treatment response in the acute phase, enhanced symptom reduction, increased remission rate, and potential improvement in quality of life for patients.

## ‘Over-the-Counter’ ADTs

A wide variety of over-the-counter supplements are used to treat depression symptoms. This category includes but is not limited to S-adenosyl methionine (SAME), L-methylfolate, St. John’s Wort (SJW), and omega-3 fatty acids. Although they generally lack FDA approval, there is growing evidence to support their use in select patients.

### S-Adenosyl Methionine

SAMe is a naturally occurring amino acid metabolite that functions as an enzyme substrate in the synthesis (homocysteine cycle) of monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine. SAMe concentrations are deficient in a wide variety of neurological and psychiatric disease states, such as in Alzheimer’s dementia, Parkinson’s disease, and MDD.<sup>34</sup> Studies suggest that both oral and parenteral treatments with SAMe cross the blood–brain barrier. More than 50 clinical trials, including open-label trials, RCTs, and controlled trials, have evaluated it in the treatment of depressive disorders. A meta-analysis in 2002 that included 28 studies on the efficacy of SAMe in the treatment of MDD concluded that compared with placebo, treatment with SAMe was associated with an improvement of 6 points on the Hamilton Rating Scale of Depression. This equates to a partial response to treatment and is felt to be clinically significant. There was also no clinically significant difference in outcomes when treatment with SAMe was compared to conventional pharmacological treatments.<sup>35</sup>

### L-Methylfolate

Similar to SAMe, L-methylfolate is involved in the chemical reaction cascade (biopterin cycle) that synthesizes monoamines. It is the brain’s bioactive form of folate, also known as B9, and is the form that can cross the blood–brain barrier.<sup>36</sup> It has been established that low levels are associated with a wide variety of neuropsychiatric disorders, including MDD, schizophrenia, and dementia. People with low levels

often show an inadequate response to antidepressants.<sup>37</sup> Studies suggest that adding L-methylfolate to SSRI and SNRI treatment can increase the effectiveness of treatment and is a viable augmentation strategy.<sup>38</sup> There is notable data that suggests that supplementation with L-methylfolate is especially effective in patients with a BMI equal to or greater than 30.<sup>39</sup> It is FDA approved as a medicinal food and requires a prescription in the United States.

### St. John’ Wort

SJW, also known as *Hypericum Perforatum L.*, has been used for centuries to treat a wide variety of diseases, including depression, sleep disorders, and hemorrhoids. It contains multiple active ingredients and these ingredients seem to contribute to the treatment of depression to varying degrees. There are multiple proposed mechanisms and the extent to which the different mechanisms contribute to its therapeutic effects is unclear.<sup>40</sup> A systematic review in 2016 provided promising results: SJW monotherapy for the treatment of mild-to-moderate depression was superior to placebo and its therapeutic effect did not differ significantly from conventional ADT. Adverse event rates were comparable to placebo and less common when compared to treatment with conventional ADT. There was, however, significant heterogeneity between the studies included, and there was a lack of data on severe depression. Only one study that focused on severe depression was included.<sup>41</sup>

### Omega-3 polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acids (Omega-3 PUFAs) have been shown in some studies to be effective and in others to provide little to no benefit in the treatment of MDD.<sup>42</sup> Their antidepressant effect may be due to anti-inflammatory action. The two main types of omega-3 PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). According to one recent meta-analysis, the most effective ratio of EPA to DHA was >60% and the ideal dose of EPA was between 720 and 1000 mg/day. This meta-analysis included studies that looked at the use of omega-3 PUFAs as both monotherapy and augmentation therapy and found that omega-3 PUFAs were beneficial in the treatment of MDD.<sup>43</sup>

## Nonpharmaceutical treatment

### Electroconvulsive therapy

ECT is the oldest neurostimulation therapy for TRD and has been in use for over 75 years for the treatment of conditions ranging from severe depression (either unipolar or in the context of bipolar disorders), mania, psychosis, and catatonia. However, its most common use in the United States is for the treatment of severe and recurrent MDD when trials of pharmacological treatment alone have been unsuccessful.<sup>44,45</sup> Although there is agreement among providers on the urgency

of delivering ECT for severe and acute depressive symptoms, such as suicidal ideation, severe weight loss, malnutrition or dehydration from appetite loss, depression with psychosis, or worsening medical condition as a result of depressive symptoms, there is still disagreement on when to refer patients for ECT for less urgent indications.<sup>44</sup>

Significant controversy and stigmatization are surrounding the use of ECT. The history of overly extensive use and delivery without the procedural modifications that are now standard (such as anesthesia, oxygenation, and muscle relaxants, which were introduced in the 1950s), played a significant part in the stigmatization of this otherwise effective treatment. The earlier applications of ECT certainly violated biomedical ethical principles when delivered without patient consent and could result in significant injury when delivered without the aforementioned procedural modification. Misrepresentation in the media and lack of understanding of an exact mechanism of action only compounded the stigma.<sup>46</sup>

Today, ECT is delivered under general intravenous anesthesia with muscle paralysis. It delivers a mild electrical current to specific areas of the brain via electrodes placed on the scalp to induce a generalized seizure.<sup>45</sup> Early research by Chronholm and Ottosson showed that the seizure itself, rather than the electrical stimulation, was crucial to the therapeutic effect.<sup>47</sup> However, there are a number of theories regarding the mechanism of action, including monoamine neurotransmitter, neuroendocrine, anticonvulsant, and neurotropic theories. The monoamine theory postulates that effect comes from enhanced dopaminergic, serotonergic, and adrenergic neurotransmission, in addition to GABA and glutamate alterations post-ECT. The neuroendocrine theory suggests that the therapeutic effect of ECT is secondary to the release of hypothalamic and pituitary hormones, including prolactin, TSH, adrenocorticotropic hormone, and endorphins. The anticonvulsant theory centers on the seizure as the therapeutic mechanism. Finally, the neurotrophic theory suggests that the therapeutic effect comes from inducing neurogenesis and increased neurotrophic signaling in the brain.<sup>44</sup>

ECT is initiated with an acute phase, which involves treatment three times a week for 2–4 weeks, followed by treatment once per week for several weeks; the total number of treatments is usually 6–12 and generally less than 20.<sup>45,48,49</sup> Overall, remission rates range from 50 to 80%. Virtually all patients who remit with the acute course should be prescribed continuation and maintenance treatment, either with antidepressants or other psychotropics. Upon completing a series of successful ECT and continued on optimized pharmacotherapy, relapse rates are ultimately around 65%; however, another valid option for some patients is to continue with ECT as a maintenance treatment, often referred to as maintenance ECT (m-ECT). By continuing with ECT past the acute phase, in addition to pharmacotherapy, the relapse rate drops to 37%.<sup>45,49,50</sup> It should be noted that the continuation of ECT past the acute phase consists of two separate phases: continuation ECT

(c-ECT) and maintenance ECT (m-ECT). c-ECT refers to the treatment over the 6 months following acute ECT intended to prevent the treated episode from worsening after achieving a partial remission. m-ECT refers to treatment following that 6 month period, aimed at preventing a reoccurrence, which may be considered for prolonged periods, including indefinitely if clinically necessary.<sup>50–52</sup> Although the two are not interchangeable terms, for this paper, ECT treatment continuing past the acute phase will be referred to as c/m-ECT, unless referred to separately for purposes of discussing specific research studies.

Although the use of c/m-ECT for maintenance treatment of depression has been documented since 1938, up until the past few decades there had been an overall lack of literature on the use of c/m-ECT.<sup>52</sup> The Consortium for Research on ECT (CORE) study was one of the first RTCs to compare the use of c-ECT to a continuation pharmacotherapy (c-PHARM) of lithium and nortriptyline) in patients who responded to acute ECT and found that although relapse rates at 6 months did not differ statistically between two arms (37.1% for c-ECT and 31.6% for c-PHARM), they also did not find differences in memory outcomes between the unrelapsed recipients of c-ECT and c-PHARM alone at the 6-month mark. The fact that no memory outcome differences were found nor any differences in tolerability between c-PHARM and c-ECT shows that concern for memory side effects (which will be discussed later) should not be a primary factor in choosing c/m-ECT over c-PHARM after acute ECT.<sup>52</sup> These results beg the question of whether combined pharmacological and ECT maintenance treatment would provide additional benefit. This was studied in the Prolonging Remission in Depressed Elderly (PRIDE) study, evaluating pharmacotherapy of venlafaxine and lithium *versus* c-ECT plus venlafaxine and lithium. The study found a statistically significant difference between the two groups. The Hamilton Depression Rating Scale scores were lower in the c-ECT plus pharmacology group than in the continuous pharmacotherapy arm. Additionally, they found no difference in Mini-Mental State Exam scores between the two arms. C/m-ECT is not the standard first choice for maintenance treatment after an episode of MDD that remitted with acute ECT. However, it should be considered in elderly patients who have responded to acute ECT in the past, had prior relapse on adequate pharmacotherapy, are unable to tolerate medications, and/or express a specific preference for ECT.<sup>53</sup>

As was noted earlier, the significant side effects (outside the risks associated with anesthesia) include cognitive impairment, typically temporary anterograde amnesia and/or retrograde amnesia and confusion, which for some patients could continue for days.<sup>49</sup> Although the anterograde amnesia usually resolves shortly after the last treatment, some degree of retrograde amnesia (especially recent memories) may last for a longer period, typically resolving by 6 months.<sup>48</sup> However, it should be noted that there are two widely used electrode placements, symmetric bitemporal and right unilateral electrode placement. By using unilateral placement, there is a decrease in risk of cognitive side effects.<sup>45</sup>

Additional side effects include risks of severe bradycardia and asystole (particularly in patients with pre-existing cardiac disease), status epilepticus, and aspiration pneumonia (in patients who did not follow pre-ECT instructions to not eat or drink 8 hours before treatment); if arrhythmia does occur, they are usually transient and can be managed with antiarrhythmic medication if there is no spontaneous resolution.<sup>48,54</sup> The transient rise in heart rate and blood pressure typical of the treatment may also increase cardiac workload and intracranial pressure; the risks associated with these increases can be managed by optimizing hypertension treatment before ECT or using antihypertensives during ECT if necessary.<sup>48</sup>

For c/m-ECT, although the risks and benefits of each treatment are the same, the fact that c/m-ECT is delivered on an outpatient basis means another set of factors must be considered. Patients must be compliant, reliable enough to follow preprocedure instructions, and have social supports to drive them home and monitor them (especially if they have a history of post-ictal confusion). Additionally, some patients may need more than a day off of work to recuperate from general anesthesia or prolonged confusion, which may not be an option for some if their job does not allow such flexibility.<sup>52</sup>

Although there are significant side effect concerns, ethical issues relating to its past use, stigma, and risks of general anesthesia, ECT is one of the most effective treatments for depression in psychiatry, with remission rates that are significantly higher than our more commonly used pharmacotherapies.

## Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive, nonpharmaceutical therapy used for the treatment of MDD, which uses external magnets to deliver magnetic pulses to the dorsolateral prefrontal cortex and induces electrical potentials that depolarize neurons in targeted regions of the brain. Transcranial magnetic stimulation (TMS) was originally developed to assist in mapping cortical function and determine the integrity of corticospinal pathways by stimulating the motor cortex and observing peripheral muscle activity and evoked potentials. These depolarizations are believed to directly affect neuronal circuitry that has been implicated in a variety of psychiatric disorders. The first TMS device was approved in 2008 for treatment of MDD assuming that the patient has failed one ADT, and a number of others have been cleared since then.<sup>45,55–57</sup>

The full, acute treatment is delivered 30 minutes daily over a course of 4–6 weeks.<sup>55</sup> Before delivering treatment, the provider must choose the intensity of the magnetic field to be delivered by determining the patient's cortical excitability or motor threshold (the minimum amount of single-pulse energy to the motor cortex required to induce motor neuron firing and muscle contraction of contralateral thumb) as well

as the optimal site for a motor response, which will assist in finding the prefrontal cortex regions for treatment. Identifying the motor threshold (MT) and the optimal site also helps to minimize side effects and prevent the spread of action potentials to the motor cortex, thereby decreasing the risk of generalized seizure.<sup>55</sup>

A number of studies have demonstrated the positive effects of rTMS in comparison to sham-control trials, one of which found 29.3% response to treatment and 18.6% remission.<sup>58,59</sup> Once clinical response and/or remission has been achieved, it is estimated that the benefits of an acute course of rTMS could last 3–12 months as studied in Mantovani and colleagues and Dunner and colleagues, respectively; however, continued antidepressant management often is needed to further maintain the benefits of treatment.<sup>60,61</sup> Potential management strategies could include using available evidence-based antidepressant strategies such as TMS taper, post-TMS pharmacotherapy, psychotherapy, exercise, or a combination of the above. More research is needed to determine the length of effect and maintenance strategies.<sup>55</sup>

The most common side effects are head, scalp, and possibly facial discomfort, facial twitching from excitation of superficial nerve branches, and headaches. Less common side effects include mania or hypomania, scalp burns, vasovagal response, and tonic-clonic seizures (estimated at 1 in 30,000 chance). Both scalp burns and risk of seizures are attributed to higher settings, such as too much stimuli, increased frequency, too high of intensity, and without enough time between trains.<sup>55,57</sup> Contraindications to the administration of rTMS include the presence of ferromagnetic or magnet sensitive objects in the patient's head or neck, as magnetic pulses may cause objects to heat and/or move; this also includes ferromagnetic ink in tattoos, piercings, and any medical or surgically implanted devices.<sup>55</sup>

When comparing rTMS to ECT, ECT is more effective; however, it appears that rTMS response rates are poor in patients who have already failed ECT.<sup>45,57</sup> However, weighing the potential cognitive side effects and risks of general anesthesia of ECT to the side effects of rTMS demonstrates why rTMS may be considered before trials of ECT.

## Vagal nerve stimulation

Vagal nerve stimulation (VNS) was initially developed and approved for treatment-resistant epilepsy in 1997.<sup>45</sup> In 2000, Elger and colleagues studied and demonstrated mood improvements in patients receiving VNS treatment for epilepsy.<sup>62</sup> Later, in the period from 2001 to 2005, it received its approvals for TRD in Canada and Europe, followed by the United States for treatment of TRD in patients 18 years and older who had not responded to four or more antidepressant treatments.<sup>45</sup>

Treatment is delivered by a pacemaker (pulse generator) surgically implanted under the skin of the left chest, which

connects to an electrode placed on the left vagus nerve that is afferent in nature. The procedure to insert the device is a same-day surgery, which can be performed with local or general anesthesia; the device is then activated by a wand connected to a hand-held computer that sets parameters of current, frequency, pulse width, and duty cycle (duration that stimulation is on or off).<sup>63</sup>

The mechanism of action occurs through the stimulation of the vagus nerve, which connects to the monoaminergic CNS cycle. Subsequent projections either directly or indirectly communicate with a number of areas of the brain implicated in symptoms of depression. This results in stimulation of these regions and modulates concentrations of neurotransmitters implicated in depression, such as serotonin, norepinephrine, GABA, and glutamate, thereby changing the activity of these key regions in ways not dissimilar to proposed mechanisms of antidepressant pharmacotherapy.<sup>45,63</sup>

Although we know that VNS has been found to affect many of the same areas of the brain, neurotransmitters, and signal transduction mechanisms that we see in conventional ADT, the time to clinical response is significantly longer at anywhere from 3 to 12 months, whereas antidepressants may take up to 2–12 weeks.<sup>63</sup> This is a considerable amount of time for the clinical effect, in comparison to many other, more rapidly acting treatments previously mentioned for TRD. However, despite the long wait, adjunctive VNS has been shown to have superior long-term effect compared to conventional psychopharmacology treatment, with a 5-year cumulative response rate of 67.6% compared to 40.9% for treatment as usual, and remission rate of 43.4% compared to 25.7% for treatment as usual.<sup>64</sup> VNS is one of the most durable TRD approaches in regard to sustaining response. It is worth noting that studies comparing VNS and ECT showed

improved outcomes in VNS for those who are responders and nonresponders to ECT.<sup>45</sup> This indicates that VNS is a strong choice once other nonpharmaceutical treatments have failed to provide sufficient response.

Given that the treatment is surgical, there are risks to be considered. Complications include temporary salivation, coughing, paralysis of vocal cords, lower facial weakness, and more rarely bradycardia and asystole. The risks of surgical complications and risks associated with the use of general anesthesia should also be considered. The most common side effect is voice alteration and hoarseness (70%) upon device activation, which is generally temporary. However, it should be noted that despite the invasive nature of implanting the device, continuation of VNS, could be considered less invasive in maintenance, as general anesthesia is only required once for the procedure *versus* the numerous times for delivery of a full acute course of ECT.<sup>45</sup> In summary, VNS is an effective treatment for a patient who has failed both a number of pharmacotherapies and other nonpharmaceutical treatments.

## Conclusion

In most uncomplicated cases of MDD, a selective serotonin reuptake inhibitor (SSRI) is often first-line treatment, with initial therapy selection usually based on side effect profile.<sup>1</sup> If the patient does not sustain remission, another trial of antidepressant may be utilized. However, with TRD, treatment becomes complicated. At this time, all possible treatment alternatives in this paper may be considered. This paper is intended to provide the reader with additional information regarding the vast array of options available to treat each individual TRD patient and provide remission for those in need.

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