

# Management of Treatment-Resistant Depression: Challenges and Strategies

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**Abstract:** Treatment-resistant depression (TRD) is a subset of Major Depressive Disorder which does not respond to traditional and first-line therapeutic options. There are several definitions and staging models of TRD and a consensus for each has not yet been established. However, in common for each model is the inadequate response to at least 2 trials of antidepressant pharmacotherapy. In this review, a comprehensive analysis of existing literature regarding the challenges and management of TRD has been compiled. A PubMed search was performed to assemble meta-analyses, trials and reviews on the topic of TRD. First, we address the confounds in the definitions and staging models of TRD, and subsequently the difficulties inherent in assessing the illness. Pharmacological augmentation strategies including lithium, triiodothyronine and second-generation antipsychotics are reviewed, as is switching of antidepressant class. Somatic therapies, including several modalities of brain stimulation (electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy and deep brain stimulation) are detailed, psychotherapeutic strategies and subsequently novel therapeutics including ketamine, psilocybin, anti-inflammatories and new directions are reviewed in this manuscript. Our review of the evidence suggests that further large-scale work is necessary to understand the appropriate treatment pathways for TRD and to prescribe effective therapeutic options for patients suffering from TRD.

**Keywords:** treatment resistant depression, major depressive disorder, pharmacotherapy, psychotherapy, brain stimulation, novel therapies

## Introduction

Major Depressive Disorder (MDD) and associated mood syndromes are among the most common psychiatric disorders in specialist and general medical practice. These syndromes span life stages and present with varying combinations of symptoms. While depressive symptoms are at times part of normal human behavior, MDD can be debilitating and at its worst, life threatening. MDD can present at any age across the life span, differences in biological vulnerability, age of onset, risk factors, symptomatic presentation and comorbidities are present among people with the same diagnosis. MDD is, therefore, a very heterogeneous disorder, and approximately 30% of people with this illness are resistant to conventional treatments.<sup>96</sup>

Several large-scale clinical trials have examined response rates to traditional therapeutic approaches for depression. In the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study, the cumulative remission rate after 4 trials of antidepressant treatment (within 14 months) was 67%.<sup>125</sup> Even after sequential treatments, 10% to 20% of the MDD patients remained significantly symptomatic for 2 years or longer.<sup>69,70</sup> In general, it is accepted that although antidepressant medications

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can be effective in treating MDD, they fail to achieve remission in approximately 1 out of 3 patients.<sup>73</sup>

Once 2 adequate antidepressant trials have been unsuccessful, the illness is termed treatment-resistant depression (TRD).<sup>125</sup> TRD can also be associated with prolonged, costly periods of inpatient treatment.<sup>140</sup> Several definitions and criteria have been proposed to identify true TRD, but a consensus has not yet been agreed to. As such, TRD presents its own challenges for therapeutic approaches and effective treatments. A meta-review of PubMed literature was performed, recent meta-analyses and original studies were collated. The review was limited to studies. In this paper, we will attempt to provide a cohesive review of the treatment approaches for TRD, as well as the challenges unique to managing this illness.

## Defining Treatment-Resistant Depression

Although many definitions for TRD have been proposed, the general consensus appears to be 2 unsuccessful trials of antidepressant pharmacotherapy (AD). Several “staging” models to classify levels of treatment resistance have been proposed. The initial model proposed by Thase and Rush<sup>138</sup> included treatment resistance levels ranging from one failed AD trial to a lack of response to electroconvulsive therapy (ECT). Further staging models have included the Massachusetts General Hospital Staging method<sup>117</sup> which carefully documents the optimization of medication doses and number of failed medications. The Souery Operational Criteria for TRD provide a slightly different approach to staging TRD as an illness, by defining TRD as any single failure of an adequate (6–8 week) trial of an AD.<sup>133</sup> The Maudsley Staging Method (MSM) assesses treatment resistance in depression in a “multi-dimensional” manner.<sup>34</sup> The majority of investigations into TRD utilize the definition of at least 2 suitable trials of AD without adequate response, although even the term “adequate response” may be fraught with contention, as there is not consensus on what constitutes “adequate.” In fact, even the term TRD may not be the ideal term to define a depressive illness that is not responding to therapeutic interventions. The term “difficult-to-treat depression” has been suggested, with the benefit of not introducing any “therapeutic nihilism” to the psychiatrist–patient relationship.<sup>103</sup> For consistency in this manuscript, we will use the term TRD. There has been considerable debate regarding what constitutes TRD, and whether medications from more than one class must be trialed prior to meeting criteria for this classification, or that the focus

should be regarding homogeneous biological subtypes or endophenotypes.<sup>23</sup> However, the argument may be made that lack of achieving remission may be classified as an inadequate response as residual depressive symptoms can significantly contribute to difficulty functioning. Chronically depressed patients have a lower chance of recovery,<sup>98</sup> and often suffer from TRD.<sup>25,87</sup>

## Challenges in Assessing TRD

One of the perils of diagnosing TRD is that of “pseudo-resistance”.<sup>107</sup> Pseudo-resistance may encompass the profile of patients who unfortunately were prescribed suboptimal doses of AD or had early discontinuation of a medication for any number of reasons, including intolerable side effects, patient non-adherence or under-dosing. Further, comorbidities such as anxiety disorders, personality disorders or substance-use disorders may complicate the clinical picture and can have deleterious effects on treatment response.<sup>114,127</sup> When interviewing patients in assessment of TRD, the potential for recall bias when reporting pharmacological trials and response adds a significant layer of difficulty in diagnosing TRD. Prospectively using objective clinical scales such as the Hamilton Depression Rating Scale<sup>48</sup> and the Inventory of Depressive Symptomatology<sup>124</sup> and retrospectively using treatment history forms such as the Antidepressant Treatment History Form (ATHF)<sup>127</sup> can be very helpful in delineating the nature and course of the treatment resistance. Since the ATHF was initially developed, there have been several developments in the treatment of MDD and specifically TRD, some of which will be elaborated upon in the ensuing sections of this paper. As such, the authors of the original ATHF<sup>127</sup> developed an updated and revised version, the short form ATHF (ATHF-SF), as well as an instruction manual and scoring checklist, among other documents.<sup>128</sup> Importantly, the ATHF-SF focuses on the current episode of depression, as opposed to life-time trials of pharmacological treatments, a more streamlined approach to assessing the level of resistance of the current illness episode. Utilizing a standardized approach to understand the level of treatment resistance in the current episode of depression may provide a useful measure of consistency in assessment of TRD.

## Therapeutic Options for TRD

### Traditional Pharmacological Approaches

#### Augmentation

Augmentation or adjunctive therapy includes the addition of a second medication, not usually considered an antidepressant

on its own, to a first-line pharmacotherapeutic option. Below, we have focused on the three main augmentation strategies with strong evidence vs placebo augmentation in detail: lithium, T3 and second-generation antipsychotics.<sup>148</sup>

### Lithium

Lithium is a naturally occurring salt that was first used in psychiatric treatment in the 1960s.<sup>146</sup> The best evidence for augmenting antidepressant pharmacotherapy with lithium comes from studies involving tricyclic antidepressants (TCAs).<sup>24</sup> Less evidence exists for augmentation of current first-line antidepressant pharmacotherapy (from the selective serotonin reuptake inhibitor class). A study by Baumann et al<sup>9</sup> demonstrated benefit to augmenting citalopram with lithium, resulting in a 60% response rate in 24 patients, compared to a 14% response rate in the placebo arm. The STAR\*D trial reported a 16% remission in the group of patients taking citalopram augmented by lithium. However, in this large-scale study, lithium levels were kept quite low, which may have contributed to the low-response rate.<sup>108</sup> Large-scale guidelines, including from the American Psychiatric Association (APA)<sup>3</sup> and the World Federation of Societies of Biological Psychiatry<sup>7</sup> strongly recommend lithium as an effective augmentation strategy in MDD. In fact, a meta-analysis more recently compiled compelling data that lithium is just as effective as the more common second-generation antipsychotics prescribed for augmentation.<sup>104</sup> Despite this evidence, and the anti-suicidal nature of lithium,<sup>22,47</sup> it continues to be under-utilized and under-prescribed.<sup>118</sup>

### T3

Thyroid hormone levels are known to have a significant effect on mood. Triiodothyronine (T3) is usually the form of thyroid hormone prescribed in augmentation of AD pharmacotherapy.<sup>5</sup> This is in contrast to the treatment of hypothyroidism, as T3 is the hormone form which may have CNS activity. As with lithium, the initial T3 studies were performed in augmentation of TCA pharmacotherapy.<sup>5,119</sup> In the meta-analysis referenced here, the augmentation of TCA with T3 had a number needed to treat of 4.3.<sup>5</sup> In the augmentation of SSRIs, open-label studies have shown some promise.<sup>2,63,72</sup> However, in the STAR\*D trial, no statistically significant superiority over augmentation with lithium was discovered,<sup>108</sup> with the T3 augmentation remission rate at 24.7%. Importantly, however, T3 is generally better tolerated than lithium and requires significantly less clinical monitoring.

### Second-Generation Antipsychotics

In contrast to lithium and T3, second-generation antipsychotics (SGAs) have been investigated as adjunctive therapies in combination specifically with current first-line treatment strategies (i.e. SSRIs and SNRIs). As SGAs are relatively recently developed medications, it has been in the interest of pharma companies to investigate whether these medications can be helpful to treat affective illnesses and therefore be approved to encompass a further class of disorders. This has resulted in several large-scale placebo-controlled RCTs. SGAs are known to have some effect on serotonin receptors and therefore may be effective in combination with SSRI/SNRIs in treating TRD. Specifically, quetiapine,<sup>8,31</sup> aripiprazole,<sup>12,13,88</sup> olanzapine<sup>132</sup> and risperidone<sup>68,86</sup> have good evidence in the augmentation of ADs for TRD. Quetiapine at a dose of 300mg per day demonstrated up to 48% response and 24.5% remission in combination with SSRIs and has since been approved for adjunctive treatment of MDD by the FDA.<sup>8,31</sup> Olanzapine was examined specifically in combination with fluoxetine, with the combination demonstrating 60% response in a sample of 28 patients with TRD.<sup>132</sup>

### Optimizing, Combining and Switching Classes of Antidepressant Pharmacotherapy

Both the CANMAT and NICE guidelines for treating MDD have recommendations for how to best optimize pharmacotherapy when a patient presents with partial or no symptom response to an initial antidepressant trial. For brevity, we direct readers to these two documents.

The majority of patients seeking pharmacotherapy for MDD are initially started on selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors as first-line treatments for MDD. Older classes of antidepressant pharmacotherapy are reserved for trials of medication once SSRI/SNRI options have been exhausted. Importantly, there is little concrete evidence that switching to medication from the same antidepressant class is an effective strategy for MDD.<sup>112</sup> However, several studies have reported that changing classes of medication after non-response to the initial class of antidepressant pharmacotherapy significantly increases response rates. Thase et al<sup>139</sup> and Peselow et al<sup>116</sup> each examined switching from SSRI/SNRI medications to tricyclic antidepressants (TCAs), specifically imipramine, and reported response rates of 44–73% in total. Monoamine Oxidase Inhibitors (MAOIs) include medications such as tranylcypromine, phenelzine and moclobemide. These are inhibitors of MAO-A and B enzymes and are very effective

antidepressants. The majority of studies examining efficacy of switching to an MAOI were conducted by switch from a TCA,<sup>95,137</sup> and demonstrated response rates of up to 60%. One step of STAR\*D compared tranylcypromine to a combination of mirtazapine and venlafaxine in a group of patients who had not responded to three medication trials. Unfortunately, no significant difference was found in response between the two groups, with only 6.9% remission in the tranylcypromine group, which also suffered from poorer tolerance of the MAOI.<sup>94</sup>

## Psychotherapy

Psychotherapeutic approaches may be undertaken in combination with somatic or pharmacological treatments, or on their own once several other interventions have been attempted. There appears to be a significant comorbidity of personality disorders with MDD, which then leads to diminishing returns with respect to first line pharmacological treatments.<sup>105,106,134</sup> As such, psychotherapy may be employed to address a comorbid diagnosis. A recent Cochrane review examined 6 studies of psychological interventions for TRD,<sup>59</sup> including dialectical behavioural therapy, cognitive behavioural therapy, interpersonal therapy and intensive short-term dynamic psychotherapy. In combination with usual care, psychotherapy overall contributed to an improvement in depressive symptoms, especially when the psychotherapy employed was cognitive behavioural analysis system of psychotherapy (CBASP), cognitive behavioural therapy, interpersonal therapy or mindfulness-based cognitive therapy.<sup>141</sup> Interestingly, cognitive behavioural therapy appeared to have good effects in the “medium” and “long term” ranges (12 and 46 months, respectively) after the acute treatment phase in terms of lower depression scores.

## Brain Stimulation

There are multiple modalities of somatic or brain stimulation therapies which have been investigated and applied in the treatment of TRD and are not first line but are turned to once several trials of pharmacotherapy and/or psychosocial therapies have been ineffective.

## Electroconvulsive Therapy

ECT is the established best therapeutic option for TRD, but its neurophysiological mechanism of action is yet to be elucidated.<sup>66,126</sup> ECT is delivered as a series of high frequency electrical pulses to either the non-dominant right hemisphere and vertex (i.e., unilateral ECT) or bitemporally

(bilateral ECT). In ECT, repetitive electrical stimulation over the cortex results in an entrainment of pyramidal cell firing with the subsequent generalization of cortical activity and production of a generalized, tonic-clonic seizure, which typically self-terminates within 30–60 s.

In the treatment of TRD, ECT is applied 2–3 times per week and acute courses can range between 6–18 total sessions. A report from the Consortium for Research in ECT (CORE)<sup>57</sup> revealed that over half of the subjects showed an improvement within the first week. Other studies have reported that over 50% of patients who have failed to respond to one or more adequate antidepressant medication trials respond to ECT.<sup>120</sup> Meta-analyses have shown that ECT is superior to sham ECT, placebo or antidepressant medications.<sup>45,111</sup>

Unfortunately, ECT has suffered from extensive stigma in the public eye, likely due to the invasive nature of the treatment and largely due to subsequent negative and abusive portrayals in the media<sup>91</sup> including in *One Flew Over the Cuckoo's Nest*, where ECT was portrayed as a punishment, delivered to an individual who did not have a psychotic or affective illness as a form of behavioural control. Along with restriction to access due to availability and risk of memory side effects, this stigma has resulted in ECT being administered to an exceptionally small proportion of individuals with MDD. In fact, a recent investigation of American health insurance databases identified that only 0.25% of almost 1 million patients with a mood disorder received ECT.<sup>142</sup> This gross underutilization of ECT persists, despite significant progress in reducing the cognitive side effect profile and alterations in the method of ECT, including seizure threshold titration, inclusion of highly tolerable anaesthetic agents and improvements in peri-procedural care. In 2001, however, the American Psychiatric Association published guidelines<sup>4</sup> advising that ECT should be used more frequently than just in “last resort” scenarios in severe medication-resistant patients or where the psychiatric condition is “life-threatening.”

ECT remains the most effective option to treat TRD, especially in situations where a patient's life may be at risk.<sup>149,45</sup> ECT was initially thought to be the most effective in what was previously termed “melancholic depression”, but evidence has demonstrated that a depressive episode with catatonic or psychotic symptoms has a greater likelihood of responding to a course of ECT.<sup>113</sup>

There are several different forms of ECT which have different response rates and side effect profiles in TRD. Bitemporal Standard pulse ECT is the most commonly



used form,<sup>76</sup> with a response rate of up to 75%. While the response rate for Right Unilateral Ultrabrief ECT is slightly lower, it remains highly effective. A report by the CORE Group<sup>57</sup> found that 65% of patients who underwent bilateral ECT 3 times per week achieved remission by the tenth treatment. In the entire sample, 75% of patients achieved remission by the end of the course, reinforcing the impressive efficacy rate of ECT.

## Repetitive Transcranial Magnetic Stimulation

rTMS is a relatively recently developed form of brain stimulation targeting TRD, among other psychiatric diagnoses. Focused pulses of an electromagnetic coil are repetitively discharged over the scalp to stimulate cortical neurons and alter neural excitability without a seizure. Stimulation is applied non-invasively, on the scalp and usually targeted over the DLPFC using a handheld magnetic coil. rTMS has been approved as a treatment for TRD by Health Canada (2002), the US FDA (2008), and equivalent agencies in the European Union, Australia and Israel. The efficacy of rTMS has been established in several dozen randomized controlled trials of thousands of patients over the past 20 years and affirmed in several large meta-analyses.

rTMS was initially tested in healthy volunteers, who demonstrated moderate mood improvements<sup>44,115</sup> after application over the left DLPFC. Interestingly, in the initial studies applying treatment to patients with MDD, rTMS was applied over the vertex, not the DLPFC. In two patients with MDD, Hoflich et al only found small improvements to mood, although this was likely due to very low frequency of stimulation (0.3Hz) over the vertex and comparatively few number of stimuli.<sup>50</sup> Using focal, high-frequency TMS, George and colleagues found strikingly beneficial effects of rTMS to the left prefrontal cortex in four of six patients with TRD;<sup>43</sup> in one of these patients, the beneficial effects of rTMS were associated with normalisation of prefrontal hypometabolism, as shown by positron emission tomography.

### Conventional High Frequency Left DLPFC rTMS

The first large clinical trials for rTMS in MDD were published in 2007<sup>110</sup> and subsequently in 2010.<sup>42</sup> This second study produced a 14.1% remission rate in the blinded study and approximately 30% remission rate in the follow-up open-label trial. Importantly, the retention rate was 88% overall in the randomized controlled trial

(RCT) and minor adverse effects were no different in the active vs sham arms of the trial. The remission rate was likely low as patients had fewer stimulus trains and fewer days of treatment. In 2014, Berlim et al reported response rates of 29.3% in 1371 TRD patients,<sup>149</sup> almost double the 16.8% response rates seen with antidepressant medications beyond the third sequential trial.<sup>125</sup> A systematic review and meta-analysis published in the Journal of Clinical Psychiatry relatively recently, reported that rTMS was 5 times more likely to help TRD patients achieve remission than placebo (“sham”) TMS.<sup>40</sup> Moreover, rTMS has an adverse effect discontinuation rate of only 4.5% in stark contrast to the 25.1% discontinuation rate for antidepressant medication.<sup>21,64</sup>

### Deep rTMS

A second approach with rTMS is to apply the stimulus with rTMS coils of different designs, which allow pulses to target areas deeper into the cortex.<sup>29</sup> These coil designs may include double-cone coils,<sup>81</sup> Hesel-coils (H-coils)<sup>123</sup> and halo coils.<sup>130</sup> Early research into these alternate coil designs and configurations determined that by increasing the strength and depth of the stimulus in the cortex, there was a reciprocal relationship with focality of the stimulus.<sup>28</sup> That is, the potential of the coil to target structures further from the cortical surface is accompanied by a broader area of stimulus. Deep TMS devices were approved by the FDA beginning in 2013 (the H1-coil) in the treatment of depression, based largely on a study by Levkovitz et al.<sup>77</sup> In this study of 212 patients with MDD, the remission rate with deep TMS was 32.6%, compared to 14.6% with sham rTMS. Deep TMS has been shown to be relatively well tolerated, especially in late-life populations.<sup>65</sup> Thus, deep TMS is emerging as a further therapeutic rTMS option in TRD.

### Theta-Burst Stimulation

Theta-burst stimulation (TBS) is a recently developed form of rTMS that appears to more closely target and induce cortical plasticity than conventional rTMS by approximating the endogenous theta frequency emitted by the brain.<sup>136</sup> Bursts of 3 stimuli are delivered at a frequency of 50Hz, 5 times per second. TBS can be delivered in either an intermittent (2 s of stimuli then 8 s off for a 10-s train) or continuous pattern. Intermittent TBS (iTBS) is delivered in this 10-s train manner for 190 s (just over 3 mins), consisting of a total of 600 pulses. Several small trials initially indicated that iTBS had the potential to be effective

in TRD.<sup>19,53,78</sup> These studies prompted a large-scale non-inferiority RCT directly comparing iTBS with conventional 10Hz rTMS.<sup>14</sup> In this trial, 414 patients were randomized to either 10Hz rTMS or iTBS and the efficacy of iTBS was found to be noninferior to conventional rTMS. Importantly, tolerability was high in both arms and pain/discomfort scores were similar in each treatment arm. This trial, the largest brain stimulation trial to date, prompted the FDA to approve iTBS as a novel treatment for TRD.

### Accelerated rTMS Protocols

As daily rTMS is quite well tolerated but requires several days to weeks of treatment to induce symptom response, newer protocols of multiple treatment sessions per day have been proposed, especially in TRD patients who require urgent response, such as those with acute and severe suicidal ideation. Accelerated treatment schedules have been proposed for both conventional rTMS and TBS treatment paradigms.

Neurophysiological evidence supporting these proposals demonstrates higher levels of neuroplasticity and cortical excitability with multiple rTMS sessions in one day.<sup>85</sup> The question of a dose–response relationship has also been posed.<sup>41</sup> Several open-label trials of differing accelerated rTMS schedules have been conducted and all found improved remission and response rates, when compared to once daily rTMS<sup>6,51,93</sup> including response rates of up to 56%.<sup>93</sup> More recently, Fitzgerald et al<sup>36</sup> directly compared accelerated rTMS to standard rTMS in a randomized control trial of 115 patients and found no discernible difference in either response or remission rates between the two groups. In this study, patients in the accelerated treatment arm received 3 treatments per day over 3 days in the first week, 3 treatments per day over 2 days in the second week and a single day of 3 treatments in the final, third week, which was compared to daily treatment (5 days per week) for 4 weeks in the standard rTMS arm. There were, however, higher rates of treatment discomfort in the accelerated arm, and this contributed to slightly higher rates of treatment discontinuation in this arm. Most recently, Williams et al<sup>143</sup> examined the effects of multiple iTBS treatments per day in a small sample of patients who did not previously respond to a full course of rTMS and an acute course of ECT. Specifically, patients received 10 sessions of iTBS each day for 5 days, a total of 90,000 pulses. Interestingly, the treatment was well tolerated and 4 out of the 6 patients achieved remission at the final session. This intensive study makes an excellent case for

ultra-accelerated rTMS in severely treatment refractory patients who would greatly benefit from rapid response to treatment.

As there are several forms of rTMS and numerous approaches attempting to maximize response, it can be challenging to keep track of the best rTMS approach for patients with TRD. Brunoni et al<sup>15</sup> examined data regarding the bulk of the existing rTMS therapies available with respect to efficacy and tolerability with the goal of establishing a treatment hierarchy. This novel analysis of 81 rTMS studies examined 8 different rTMS approaches and compared them with sham rTMS. All rTMS interventions were well tolerated, in a similar manner to sham. High frequency, low frequency, bilateral rTMS and TBS were all found to be superior to sham stimulation in terms of response. The analysis suffered from small sample sizes of several investigatory trials and called for new, large-scale, high quality randomized controlled trials to further categorize rTMS paradigms by efficacy. The evidence, therefore, reinforces that rTMS is an effective and well-tolerated therapeutic option for TRD, but more evidence is needed to create a clear hierarchy of rTMS approaches.

### Magnetic Seizure Therapy

In magnetic seizure therapy (MST), a powerful repetitively discharged magnet induces focal synchronous activity in the targeted cortical region which then spreads, resulting in a generalized seizure in a similar procedure to ECT.<sup>56</sup> It is focally discharged over the prefrontal cortex and evidence shows significantly fewer cognitive side effects with MST. As the magnetic field passes freely through the scalp and skull to discharge cortical neurons, there is no shunting of energy toward subcortical structures,<sup>80</sup> thus sparing the memory centres of the brain. As with ECT, several treatments are necessary to result in significant mood symptom improvement. Few clinical trials have yet to be reported regarding the efficacy of MST when compared to other therapeutic options for TRD, but those published consistently demonstrate a clear antidepressant effect with fewer cognitive or memory side effects. A study by Kayser et al<sup>67</sup> reported a 69% response rate in 26 patients with TRD, comparable to ECT response rates. Comparably, an earlier pilot study of 13 patients<sup>37</sup> reported a response rate of 38% and remission rate of 15%. It should be noted that these studies utilized lower powered MST devices and newer devices have been developed with higher power capacity, comparable to high-dose ECT. The majority of these early studies of MST applied stimulation to the vertex of the

skull. A recent paper by Daskalakis et al<sup>27</sup> reported an open-label trial applying MST to the prefrontal cortex, with 3 different study arms – each arm applied a different MST frequency, ranging from 25–100Hz. This larger scale trial analysed outcomes for 86 patients with moderately resistant TRD, as assessed by the ATHF. The high-frequency MST resulted in the highest remission rates in patients who underwent at least 8 treatments (33.3%), although this jumped significantly in patients who completed the full MST treatment protocol (to 60%). Cognitive scores remained unaffected, aside from autobiographical memory scores, which would be expected to decrease over time.<sup>92</sup> The results of this open-label trial<sup>27</sup> appear promising and comparable to ECT, opening the door for further careful direct comparison with ECT and possibly a new favourable brain stimulation option for TRD.

## Deep Brain Stimulation

In DBS, a permanent neurosurgical implant is placed in the brain, with a specific target to activate or silence. The implant is connected to a pulse generator in the chest wall that is externally controlled to repetitively stimulate the target area.<sup>83</sup> Several regions have been investigated as targets in TRD, namely the nucleus accumbens, ventral capsule and striatum, and the subgenual cingulate cortex (SCC). In small studies, each area has demonstrated promise, and the single high dose study targeting the SCC reported a 92% response rate at 2 years post-implantation in a TRD sample.<sup>52</sup> Earlier studies of DBS applied to the SCC report variable response rates over several months that appear to improve over time, ranging from 29% to 75%.<sup>74,82,90</sup>

## Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is proposed to modulate brain activity via stimulation of the tenth cranial nerve, the vagus nerve. It is believed that the stimulation of this cranial nerve alters various networks of the brain in order to treat psychiatric disease. All VNS systems have required surgical implantation until recently, with the development of transcutaneous systems, which are not yet FDA approved for TRD.<sup>20,54</sup> The implanted VNS system consists a pulse generator, inserted underneath the skin of the chest. This is then connected to an electrode attached to the left vagus nerve in the neck; together this system delivers pulsed electrical signals to the vagus nerve. A separate device programs the pulse generator stimulation parameters and the implanted device can be temporarily deactivated by holding a magnet over the pulse generator. The FDA approved VNS as an adjunctive

long-term therapy for TRD, specifically in patients who have not responded to 4 or more different medications.<sup>17</sup> Interestingly, there appears to be a bimodal distribution with respect to the timing of response. A portion of VNS patients respond “acutely,” whereas for others, the main effects appear to emerge after approximately 3 months of treatment.<sup>17</sup>

In summary, there are several modalities of brain stimulation which have proven effective in TRD. A large meta-analysis of non-surgical brain stimulation in TRD reported on studies of different electrode placements in ECT, several types of rTMS and transcranial direct current stimulation (tDCS).<sup>100</sup> Over 6000 patients underwent one of these brain stimulation treatments, despite many trials being of small sample size. As expected, evidence lent itself to ECT, high frequency left and low-frequency right rTMS, with less evidence for the more recently developed forms of brain stimulation. As with the majority of studies in brain stimulation, the bulk of evidence supporting the efficacy of these treatments was assessed by depression scores at the end of the acute course of treatment, with few strategies reported to describe continuation treatment or prevention of relapse. Overall, ECT has the best evidence in the literature to enter a maintenance or continuation phase of therapy, with 84% of individuals who have remitted with ECT relapsing within 6 months if no further treatment (ECT or pharmacotherapy) ensued.<sup>129</sup> In the PRIDE Study,<sup>71</sup> patients were randomized to a pharmacotherapeutic arm or a combination of continuation ECT with pharmacotherapy, with relapse rates of 20.3% and 13.1%, respectively at the 6-month mark. There is some emerging evidence for a maintenance course of rTMS after effective acute treatment, although this has largely been limited to open-label studies.<sup>10,35,109</sup> Large scale, clear data on how best to prevent relapse with rTMS is urgently needed in the field.

## Novel Therapeutics

### Ketamine

Ketamine is a widely investigated N-methyl-D-aspartate (NMDA) antagonist as a potential therapeutic option for TRD and is considered a rapid acting antidepressant (RAADs). More recent evidence purports that ketamine’s antidepressant effects are at least in part due to action on  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors downstream from the initial NMDAR effects.<sup>147</sup> Although initially investigated as a psychomimetic substance,<sup>75</sup> the antidepressant effect of ketamine was

quickly recognized after a low dose intravenous infusion.<sup>11</sup> Interestingly, the antidepressant effects were not thought to be due to intoxication but were noted around 3 hrs after the IV infusion had been discontinued and appeared to continue over several days. This rapid response was reinforced by several randomized blinded and open-label studies and included a significant reduction in suicidal ideation in TRD patients.<sup>1,58,89,99</sup> On average, the effects of ketamine appear to come on rapidly and last approximately 5–7 days<sup>145</sup> with a preferential treatment effect in individuals with comorbid anxiety or an “anxious depression”.<sup>60,61</sup> More recently, an intranasal form of esketamine (a ketamine enantiomer) has been developed, which has shown good effect with continued treatment in combination with an oral antidepressant<sup>26</sup> and has now been approved by the FDA for restricted use in TRD.

## Psilocybin

Psilocybin is the psychedelic compound isolated from hallucinogenic mushrooms. It is metabolized by the body into psilocin, which is a partial serotonin receptor agonist. The majority of research into this compound has been limited to small, open label or pilot trials of patients with TRD. In a group of 12 patients with TRD, a feasibility study of high-dose psilocybin demonstrated response rates of 58% up to 3 months after 2 doses of psilocybin, an initial low dose to assess safety and a subsequent high dose (25mg) one week later, despite the psychedelic effects lasting approximately 6 hrs.<sup>16</sup> In this study the substance was relatively well tolerated, although transient anxiety was frequently experienced, as was mild tachycardia.

## Anti-Inflammatories

Inflammation is increasingly thought to play a role in TRD, as elevated C-reactive protein and cytokines appear to be elevated in patients with MDD and specifically TRD.<sup>18,55,135</sup> Cyclooxygenase-2 inhibitors (COX-2 inhibitors) were initially the focus of anti-inflammatory research in TRD and were investigated as augmentation options for traditional antidepressant pharmacotherapy.<sup>32,101</sup> COX-2 inhibitors are known to block prostaglandin production, which appears to be elevated in blood samples of some patients with TRD.<sup>79</sup> More recently, a tumour necrosis factor (TNF) antagonist, infliximab, has been investigated specifically in TRD patients with elevated plasma CRP levels, compared to TRD patients without elevated peripheral inflammatory markers.<sup>121</sup> The depressive symptoms of patients with elevated CRP levels preferentially

responded to infusions of infliximab and their CRP levels dropped post-treatment in a corresponding manner, whereas patients without elevated inflammatory markers did not seem to fall into the responder category. The neurosteroid brexanolone, an intravenous formulation of allopregnanolone which acts by enhancing GABAergic inhibition, was FDA approved this year for the treatment of post-partum depression.<sup>144</sup> By allosterically enhancing GABA<sub>A</sub> receptor function, the antidepressant activity of allopregnanolone is attributed to an increase in GABAergic inhibition.<sup>97,102</sup> Taken together, these results suggest that anti-inflammatory therapy may have a novel role in treating TRD patients, but largely only in those who demonstrate markers of inflammation.

## Novel Therapeutic Compounds and Rapid Acting Antidepressants

As further investigations into MDD and specifically TRD result in the clarification of the disorder's pathophysiology, the development of novel therapeutic compounds has begun to emerge. These include, but are not limited to, modulators of other central neurotransmitters, such as opioid modulators, cholinergic modulators and  $\gamma$ -aminobutyric acid (GABA) modulators. Of particular interest as medications are RAADs, of which ketamine is the most widely accepted. Novel compounds are now being developed or existing compounds re-examined in this light. In recent years, attention has turned to the endogenous opioid system as one of interest in TRD, particularly when comorbid with anxiety symptoms, as happens relatively frequently, with a negative impact on treatment response.<sup>62</sup> Novel compounds targeting the delta opioid receptor have shown promise in small initial drug development trials.<sup>122</sup> Existing medications such as buprenorphine have been combined with other compounds to better target the mu and kappa opioid receptors in the hopes of achieving an antidepressant response. These novel combination compounds were deemed tolerable and did not result in opioid withdrawal or tolerance and induced a moderate antidepressant effect,<sup>33</sup> showing most promise as an adjunctive therapy. Evidence of hypercholinergic states in MDD<sup>39</sup> has also guided research towards the development and examination of anticholinergic compounds, such as the repurposing of scopolamine, an antimuscarinic medication. In a sample of patients with MDD, an initial intravenous infusion of scopolamine resulted in significantly reduced depression and anxiety symptoms within a few days, when compared to placebo.<sup>30</sup> The



GABA system has been of particular interest in the field of TRD research as it has downstream effects on the serotonergic and noradrenergic systems<sup>84</sup> and there is evidence of reduced GABA levels in patients with MDD.<sup>49,131</sup> A recently developed positive allosteric GABA<sub>A</sub> receptor modulator, SAGE-217, was investigated in a multi-site trial of 89 patients with MDD for its potentially acute antidepressant effects.<sup>46</sup> On the 15<sup>th</sup> day of medication administration, of the 45 patients in the active drug arm, 79% met response criteria (>50% reduction in Hamilton Rating Scale for Depression scores), whereas 41% met response criteria in the placebo arm. These novel therapeutics all show promise in effectively treating TRD and warrant further investigation and comparison to existing efficacious TRD therapies.

## Conclusions

There are several challenges which accompany the treatment of TRD, not the least of which is the relatively large proportion of patients with MDD who may be classified as having TRD. While several approaches, both traditional and novel, have been developed as described above, further work is necessary to understand the TRD as an illness to adequately treat TRD and notably, to ensure sustained response or continued remission. Several guidelines outlining the treatment of MDD may help to direct practitioners in a logical, step-wise approach (CANMAT, APA, NICE), however, specific guidelines for TRD have not been widely accepted to our knowledge and is certainly out of the scope of a review such as this. A logical approach would likely include beginning with the least invasive and intensive interventions which have the most evidence for efficacy in TRD. Particular promise may be emerging with the newer acute treatments that have recently been approved by the FDA to specifically treat TRD (iTBS and intranasal esketamine). However, large multi-centre trials are still necessary to examine the overarching patterns of TRD illness and treatment response as a whole. Moreover, despite several guidelines touching on recommendations for maintaining response or remission from MDD with effective treatment, aside from continuation strategies with ECT, there is little known about maintaining remission from TRD. In a recent editorial in JAMA Psychiatry, Dr. M. Freeman addresses this specific topic, with recommendations to individualize maintenance interventions.<sup>38</sup> That is, the importance of continuing with the treatment that helped the patient reach remission from the most

recent depressive episode. With further understanding of the pathophysiology of TRD, patterns of response and how these differ from MDD, we, as treating physicians, may be able to save patients the time, frustration and hopelessness that accompanies numerous failed treatment trials.

## Disclosure

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