

# State of the art

## *Treatment strategies to improve and sustain remission in major depressive disorder*

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*Major depressive disorder (MDD) is an often chronic, recurrent illness affecting large numbers of the general population. In recent years, the goal of treatment for MDD has moved from mere symptomatic response to that of full remission (ie, minimal/no residual symptoms). The recent Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial showed that even with systematic measurement-based treatment, approximately one third of patients reach full remission after one treatment trial, with only two thirds reaching remission after four treatment trials. Treatment-resistant depression (TRD) is therefore a common problem in the treatment of MDD, with 60% to 70% of all patients meeting the criteria for TRD. Given the huge burden of major depressive illness, the low rate of full recovery remains suboptimal. The following article reports on some current treatment strategies available to improve rates of, and to sustain, remission in MDD.*

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**M**ajor depressive disorder (MDD) is a serious, debilitating illness that affects persons of all ages, races, and socioeconomic backgrounds. The Institute of Medicine (IOM) report, *Priority Areas for National Action: Transforming Health Care Quality*, lists major depression among 20 priority areas for health care quality improvement, identifying the aim “to improve national rates of diagnosis and appropriate treatment of major depression.”<sup>1</sup> MDD occurs in up to one in eight individuals during their lifetime, making it one of the most prevalent of all medical illnesses. According to the *Diagnostic and Statistical Manual-Fourth Edition Text Revision (DSM-IV TR)*,<sup>2</sup> the point prevalence rates for MDD are approximately 2.3% to 3.2% in men and 4.5% to 9.3% in women, with a lifetime risk for developing an episode of 7% to 12% for men and 20% to 25% for women. Depression currently ranks fourth for disability-adjusted life-years worldwide<sup>3</sup> and is projected to jump to second global leading cause of disability by 2020. The recent National Institute of Mental Health-funded Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study showed that remission rates are modest even after two state-of-the-art, diligently delivered treatment steps with the support of depression care specialists.<sup>4,6</sup> Even following four steps, there still remain a large percentage of patients who do not benefit.<sup>7</sup>

### **Treatment-resistant depression**

Treatment-resistant depression (TRD) is a common problem in the treatment of MDD, yet little agreement exists

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about either the definition of TRD or evidence-based options for treatment. According to Rush et al, treatment resistance falls on a continuum.<sup>8</sup> Modest resistance may include an inadequate response to a single antidepressant trial, whereas greater resistance refers to failure of two monotherapy trials or one or more augmentation trials. Various staging schemes have been proposed for TRD, taking into consideration greater or lesser resistance according to the number of adequately delivered trials (in terms of dose, duration, and adherence) given to patients with properly diagnosed disease.<sup>9,10</sup> Souery et al proposed an operational definition for TRD as the failure to respond to two adequate trials of different classes of antidepressants.<sup>11</sup> Similarly, Sackeim et al proposed that clinically significant treatment resistance is present if depression has not benefited from at least two adequate trials of medications from different classes in the current episode.<sup>12</sup> Traditionally, treatment resistance has focused on nonresponse (eg, minimal or no improvement on drug therapy). From the perspective of clinicians and patients, not achieving full remission represents a significant burden and therefore full remission should be the optimal goal.<sup>13</sup> Partial response refers to the situation wherein an individual has responded to antidepressant treatment but still has significant residual symptoms that interfere with work, family, and social activities.

## Remission as the goal of treatment

The chronic nature of MDD contributes to difficulty in achieving the goal of remission—ie, full return to pre-morbid functioning between episodes. Residual symptoms of depression (including low mood, early insomnia, weight loss, and hopelessness) are often accompanied by significant occupational and psychosocial dysfunction, as well as being associated with early relapse and increased recurrence rates.<sup>14,15</sup> There is considerable evidence that even with treatment, residual symptoms often persist, leading to psychosocial dysfunction,<sup>16-18</sup> and the longer a patient remains symptomatic, the lower the chances of a complete recovery.<sup>17</sup>

## Treatment strategies to achieve remission

### Pharmacological treatments

#### *Initial treatment - monotherapy versus combination therapy*

Evidence to date suggests that the longer it takes to get to remission (ie, the more treatment trials required), the greater the risk of treatment resistance. Consensus opinion therefore suggests that aggressive initial treatment is the most appropriate strategy. Medications recommended for initial treatment of a major depressive episode (MDE) include selective serotonin reuptake inhibitors (SSRIs—fluoxetine, paroxetine, sertraline, citalopram, and escitalopram), serotonergic noradrenergic reuptake inhibitors (SNRIs—venlafaxine and duloxetine), bupropion, and mirtazapine. All these antidepressants are considered similar in regard to efficacy (Level A data—evidence derived from randomized, controlled clinical trials), with treatment selection based upon individual patient characteristics (comorbidities, concomitant medication, treatment history) and patient preference. In a soon to be published update on the Texas Medication Algorithm Project (TMAP) for MDD, the expert panel convened recommends that a trial of at least 6 weeks' duration on the maximum tolerated antidepressant dose be carried out before moving to the next treatment trial (algorithm stage). During the course of treatment with an individual antidepressant, the panel recommends that clinicians monitor patients based on certain time points in the clinical trial known as critical decision points (CDP) in the algorithm. CDPs use symptom-based rating scales to measure changes in depressive symptoms (eg, the Quick Inventory of Depressive Symptomatology—QIDS<sup>19,21</sup>), side effects (eg, Frequency and Intensity of Side Effect Rating Scale—FIBSER<sup>22</sup>), and tolerability, to help the clinician and patient make decisions regarding the algorithm at specified time points. This revised set of algorithm recommendations reflects the most current available research evidence for treatment of MDD in combination with the consensus of leading experts in this area.

#### *Combination treatments*

The low remission rates with any initial monotherapy and the modest additional remission achieved with a subsequent switch or augmentation medication step suggest the potential need for using medication combinations at the outset of treatment of MDD. Currently, combinations of antidepressants are used in practice at the second or subsequent steps when relapse occurs in the longer term, or, in some cases, even acutely as a first step when speed of effect is a clinical priority. Such combinations could

potentially offer higher remission rates, lower attrition, or provide greater longer-term benefit if used as initial treatments as compared with monotherapy. Our own group is currently coordinating a large, NIMH-funded, multisite study comparing two combination therapies with monotherapy when used as initial treatments in the current MDE in patients with chronic and recurrent major depression.

The paradigm of using combination treatments is analogous to treatment for other severe general medical conditions (eg, cancer, congestive heart failure, malignant hypertension, HIV, etc). That is, more vigorous initial treatment efforts are implemented initially, rather than using an extended trial-and-error, multistep approach to isolate the single best medication or combination. Furthermore, the likely higher remission rate with combinations may also reduce attrition during short-term and longer-term treatments for MDD. Finally, antidepressant medication combinations may have pharmacological additive effects or create a broader spectrum of action in short-term treatment.

### *Sequential treatment strategies*

Over time, many different strategies have been developed in an effort to overcome the problem of partial or nonresponse to treatment. These include augmentation strategies, switching agents, combining antidepressants (two medications or medication and psychotherapy), and dual-action agents.

In terms of sequential treatment approaches, as yet there are no randomized studies suggesting which specific treatment sequence is best, and further studies are clearly needed to evaluate the comparative efficacy and tolerability of different approaches. Adaptive strategies to date rely primarily on consensus-based, clinical decision-making, rather than on innovative study designs that address the identification of the best sequence for individual or groups of patients. Traditional approaches have considered each step in the sequence as a new trial, but we know that each treatment step builds on the previous treatment, and that resistance to one step increases the chances of resistance to subsequent steps. In addition, despite patient and provider education, suboptimal medication dosing and duration of exposure remain the norm.<sup>23-26</sup> These difficulties herald the need for a paradigm shift in how clinical decision-making is incorporated into clinical practice and research study designs.

### *Switching, augmentation, and combination strategies*

There is increasing evidence that augmentation and switching are effective strategies after failure of an adequate antidepressant treatment trial. In general, augmentation is the preferred clinical choice when the patient is showing at least a partial response to the primary antidepressant and the primary medication is well tolerated. In contrast, switching is preferred when the patient has shown no response to the initial antidepressant. In determining the choice of the switching agent, clinical consensus suggests a trial with an antidepressant from a different class than the first medication. However, there is now evidence that switching from one SSRI to another SSRI may be a reasonable strategy.<sup>4</sup> Furthermore, switching from a medication to a depression-focused psychotherapy, or vice versa, appears to produce comparable outcomes.<sup>27</sup> In terms of augmentation, many agents have been investigated with variable evidence of efficacy, including lithium,<sup>28-31</sup> triiodothyronine (T3),<sup>32,33</sup> buspirone,<sup>6,34</sup> atypical antipsychotics,<sup>35,36</sup> lamotrigine,<sup>37,38</sup> dopaminergic agonists,<sup>39,40</sup> pindolol,<sup>41,42</sup> and psychostimulants,<sup>43,44</sup> as well as antidepressants with a different neurochemical profile to the primary agent. Despite the widespread use of these strategies, further supporting evidence from placebo-controlled trials is still lacking.<sup>45</sup> Other novel targets are also being investigated including melatonergic receptor agonists, N-methyl D-aspartate (NMDA), glucocorticoid, omega-3 fatty acids, novel monoamine oxidase inhibitors, substance P, triple reuptake inhibitors,<sup>46</sup> nicotinic acetylcholine receptor antagonists, and endocannabinoid receptor antagonists.

### **Nonpharmacological treatments**

Other, nonpharmacological, treatments have also been evaluated in terms of their potential as treatment options in patients not responding to antidepressants.

#### *Somatic treatments*

There has been growing interest in the potential application of vagus nerve stimulation (VNS) in the nonpharmacological treatment of TRD.<sup>47-53</sup> In July 2005, the US Food and Drug Administration approved VNS with an indication for the adjunctive long-term treatment of chronic or recurrent depression for adults refractory to antidepressant drugs (with the recommendation that

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patients have failed at least four traditional therapies before using VNS).

Similarly, repetitive transcranial magnetic stimulation (rTMS) has been studied as an adjunctive treatment for drug-resistant MDD.<sup>54-56</sup> However, results so far have been conflicting, a fact that may be related to variability in stimulation parameters and small sample sizes, as well as heterogeneity of concomitant drug treatments. Larger trials are ongoing. Other novel neurostimulation treatments with preliminary evidence of efficacy for TRD include deep brain stimulation<sup>57,58</sup> and magnetic seizure therapy.<sup>59,60</sup>

There remains controversy within the field in terms of the efficacy and safety of electroconvulsive therapy (ECT) as a treatment modality. Following a meta-analysis, a group of researchers in the United Kingdom recently found that ECT is an effective short-term treatment for depression, with some evidence suggesting that ECT is more effective than pharmacotherapy.<sup>61</sup> However, in a recent study, another group looked at ECT versus pharmacotherapy as a treatment for relapse prevention, finding that both treatments had limited efficacy with more than half of patients experiencing relapse or dropping out of the study.<sup>62</sup>

## *Psychotherapy*

Cognitive, interpersonal, and behavioral psychotherapy have all been shown to be effective in the treatment of depression, with results comparable to those found with antidepressant medications in randomized controlled trials.<sup>63-65</sup> Specifically, cognitive behavioral therapy (CBT) appears to reduce residual symptoms in depression and ultimately reduces the risk of relapse.<sup>66-69</sup> It has also been suggested that combined treatment with antidepressant medication and psychotherapy may be more effective than either strategy alone.<sup>70,71</sup> However, others caution that the advantage of combined treatment may be limited to treatment of patients with more complex depressive disorders, including characteristics such as comorbidity, chronicity, treatment resistance, episodicity, and severity.<sup>72</sup>

## **Strategies to sustain remission**

### **Disease self-management**

There is evidence that patient-focused interventions rather than purely disease-focused interventions have a

more sustainable impact on outcomes. Disease self management is predicated on promoting patient self-management and physician adherence to guidelines.<sup>73</sup> Despite the fact that disease management has demonstrated its potential for improving quality of care for an index disease,<sup>74,75</sup> few programs coordinate care among providers or to manage health conditions unrelated to the index disease. A growing body of evidence suggests that more comprehensive, multifaceted innovations that simultaneously address health care provider practice, patient education, and patient self-management tend to have more compelling results.<sup>76-78</sup> There is also a great need for programs working within, rather than outside of, primary care,<sup>79</sup> where the majority of patients with depression are actually seen.

Research suggests that applying a chronic care model to depression care may result in better quality of care and clinical outcomes.<sup>79</sup> Self-care and medical care are both enhanced by effective collaboration among chronically ill patients and health care providers. Self-care refers to engaging in activities that promote health, adhering to recommended treatment, self-monitoring of physical and emotional status, and monitoring effects of the illness on emotions and relationships.<sup>79</sup> Collaborative management is care provided to strengthen and support self-care in chronic illness, while assuring that effective medical, preventive, and health maintenance interventions occur. Essential components of collaborative management include: (i) identification of patient-defined problems; (ii) targeting, goal-setting, and planning; (iii) creation of a continuum of self-management training and support services; and (iv) active and sustained follow-up.<sup>79</sup>

### **Measurement-based care**

Even in guideline-driven practice, clinical treatment of depression is often associated with wide variations among practitioners. Clinicians often change from one antidepressant to another too quickly or, conversely, conduct an unnecessarily prolonged treatment trial with an obviously unsuccessful medication or psychotherapy.<sup>5,80</sup> Practitioners also differ in how they assess the outcomes of treatment (symptoms, function, side-effect frequency and burden), with global judgments often used instead of specific symptom assessments, even though the former are less accurate.<sup>81</sup> These differences lead to wide variability in treatment implementation and likely also result in wide variations in outcomes in typical practice.

Other chronic medical conditions, such as diabetes mellitus, utilize laboratory as well as symptom and function measures in research settings that are readily usable in clinical practice. To our knowledge, however, no system to provide specific feedback or prompts related to symptoms, side effects, and recommended tactics (ie, when and by how much to change the dose) during treatment has been successfully used in a large clinical trial for patients with psychiatric disorders. It is now clear that measurement-based care (MBC) is an essential component to any adaptive decision support system, allowing the physician to individualize decisions about care for the patient based on their progress and their ability to tolerate the medication.<sup>5,82,83</sup> The medication algorithms developed by our group allow for sequential, adaptive MBC treatment approaches including switching or augmenting antidepressant treatment in the case of patients who do not fully remit following an adequate trial (at an adequate dose and duration) of an antidepressant.<sup>5,84,85</sup> Both the TMAP and STAR\*D trials occurred in real-world clinical settings and emphasized the importance of an MBC approach—wherein the physician routinely assessed depression symptom severity, adherence to treatment, and side effects at each visit, and used this information when following the medication treatment protocol.<sup>5</sup>

### Well-being therapy

This is one of several psychotherapeutic strategies emerging from a growing interest in positive psychology. Well-being therapy is based on Ryff's multidimensional model of psychological well-being,<sup>86</sup> covering six dimensions: autonomy, personal growth, environmental mastery, purpose in life, positive relations, and self-acceptance. Well-being therapy as described by Fava and Ruini is a short-term, psychotherapeutic strategy that extends over eight sessions and emphasizes self-observation with the use of

a structured diary, as well as the interaction between the therapist and patient.<sup>87</sup> Well-being therapy is structured, directive, and problem-oriented, with the goal of the therapist being to lead the patient from an impaired level to an optimal level of psychological well-being.

To date, well-being therapy has been used in several clinical studies, both as a treatment for the residual phase of affective disorders,<sup>69</sup> and also in terms of prevention of recurrent depression.<sup>66</sup> In one study looking at prevention of relapse in recurrent MDD, well-being therapy was a specific part of a cognitive behavioral package that also included cognitive behavioral treatment of residual symptoms and lifestyle modification. Of 40 patients with recurrent MDD who had been successfully treated with antidepressants, after tapering and discontinuing medication, half were randomly assigned to the CBT package and half to clinical management. Results showed a significantly lower relapse rate at a 2-year follow-up compared with controls (25% vs 80%), with the CBT package highly significant in delaying recurrence ( $P=0.003$ ). It should be noted that well-being therapy in this study was only part of a package, and so it is not possible to say what contribution it made to this finding.

### Conclusions

Given the burden of major depressive disorder and the fact that only about one third of patients respond to initial antidepressant treatment, further research is needed to improve these suboptimal outcomes.

The goal for treatment of major depression has shifted over time from mere response to full remission, particularly given the negative psychosocial and personal implications of untreated residual symptoms.

In addition, given the recurrent nature of MDD, once remission has been achieved, the challenge is to sustain it. □

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## **Estrategias terapéuticas para mejorar el trastorno depresivo mayor y mantener la remisión.**

*El trastorno depresivo mayor (TDM) con frecuencia es una enfermedad crónica y recurrente que afecta a un gran número de personas en la población general. En años recientes, el objetivo del tratamiento del TDM ha cambiado desde la mera respuesta sintomática a la remisión total (por ej. síntomas mínimos/ no residuales).*

*El reciente estudio STAR\*D (Sequenced Treatment Alternatives to Relieve Depression) demostró que incluso con un tratamiento basado en la medición sistemática, aproximadamente un tercio de los pacientes alcanza la remisión completa después de un ensayo terapéutico, y sólo dos tercios alcanzan la remisión después de cuatro ensayos terapéuticos. La depresión resistente al tratamiento (DRT) es por lo tanto un problema común en el tratamiento del TDM, y el 60% a 70% de todos los pacientes reúne los criterios para DRT. Considerando la enorme carga de la enfermedad depresiva mayor, el bajo porcentaje de recuperación completa persiste subóptimo. El siguiente artículo revisa algunas estrategias terapéuticas actuales disponibles para mejorar los porcentajes tanto de remisión como del mantenimiento de ésta en el TDM.*

## **Stratégies thérapeutiques pour améliorer et maintenir la rémission dans les troubles dépressifs majeurs**

*Les troubles dépressifs majeurs (TDM) constituent une maladie souvent chronique et récurrente qui touche un grand nombre de sujets dans la population générale. Ces dernières années, l'objectif du traitement des TDM est passé d'une simple réponse symptomatique à une rémission totale (c'est-à-dire, symptômes résiduels absents ou minimaux). L'étude récente STAR\*D (Sequence Treatment Alternatives to Relieve Depression) a montré que même avec un traitement systématique basé sur des mesures, à peu près 1/3 des patients sont en rémission totale après un essai thérapeutique contre 2/3 après 4 essais. La dépression résistante au traitement (DRT) est donc un problème fréquent, avec 60 à 70 % de l'ensemble des patients en présentant les critères. Compte tenu du handicap énorme que représentent les TDM, le faible taux de guérison totale reste sous-optimal. L'article qui suit expose certaines stratégies thérapeutiques actuelles capables d'améliorer et de maintenir les taux de rémission dans les TDM.*

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