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REVIEW

Treatment-resistant depression: therapeutic trends, challenges, and future directions

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Background: Patients with major depression respond to antidepressant treatment, but 10%–30% of them do not improve or show a partial response coupled with functional impairment, poor quality of life, suicide ideation and attempts, self-injurious behavior, and a high relapse rate. The aim of this paper is to review the therapeutic options for treating resistant major depressive disorder, as well as evaluating further therapeutic options.

Methods: In addition to Google Scholar and Quertle searches, a PubMed search using key words was conducted, and relevant articles published in English peer-reviewed journals (1990–2011) were retrieved. Only those papers that directly addressed treatment options for treatment-resistant depression were retained for extensive review.

Results: Treatment-resistant depression, a complex clinical problem caused by multiple risk factors, is targeted by integrated therapeutic strategies, which include optimization of medications, a combination of antidepressants, switching of antidepressants, and augmentation with non-antidepressants, psychosocial and cultural therapies, and somatic therapies including electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy, deep brain stimulation, transcranial direct current stimulation, and vagus nerve stimulation. As a corollary, more than a third of patients with treatment-resistant depression tend to achieve remission and the rest continue to suffer from residual symptoms. The latter group of patients needs further study to identify the most effective therapeutic modalities. Newer biomarker-based antidepressants and other drugs, together with non-drug strategies, are on the horizon to address further the multiple complex issues of treatment-resistant depression.

Conclusion: Treatment-resistant depression continues to challenge mental health care providers, and further relevant research involving newer drugs is warranted to improve the quality of life of patients with the disorder.

Keywords: treatment-resistant depression, antidepressants, biomarkers, therapeutic options, somatic therapies

Introduction

Major depression is a common debilitating disorder affecting 10%–15% of the population per year. Despite advances in the understanding of the psychopharmacology and biomarkers of major depression and the introduction of several novel classes of antidepressants, only 60%–70% of patients with depression respond to antidepressant therapy. Of those who do not respond, 10%–30% exhibit treatment-resistant symptoms coupled with difficulties in social and occupational function, decline of physical health, suicidal thoughts, and increased health care utilization. Treatment-resistant depression represents a dilemma for health care providers. Major depression with a poor or unsatisfactory response to two adequate (optimal dosage and duration) trials of two

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different classes of antidepressants has been proposed as an operational definition of treatment-resistant depression.[1–4]

It is reported that at any one time 14 million people suffer from depression, and only 50% of them receive some form of treatment. Up to 70% of people who have depression show substantial improvement as measured by commonly used rating scales, such as the Hamilton Rating Scale for Depression (HRSD),[5,6] but they require additional psychosocial interventions for achieving complete remission. It is estimated that 10%–30% of patients with major depression do not respond to typical antidepressant medications,[7] and this group of patients needs trials of a variety of treatment strategies. For this purpose, it is particularly important to determine the adequacy and outcome of prior treatment trials by using the Antidepressant Treatment History Form that helps to exclude "pseudoresistance" cases.[8] Complete remission is achieved in 70%–90% of patients with depression, leaving 10%–30% refractory to treatment, and managed by a variety of therapeutic modalities. Unfortunately, approximately 30% of patients with treatment-resistant depression do not respond to any treatment.[9,10]

According to the findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 50%–66% of patients with depression do not recover fully on an antidepressant medication and one-third of patients do have a remission of their depressive symptoms.[11,12] It is obvious that use of a variety of treatment approaches versus only an antidepressant makes the outcome variable in patients with major depression. Notably, the results of mega STAR*D studies open windows into the effectiveness or ineffectiveness of antidepressant medications among patients seeking treatment in real-world settings, including in primary health care[13,14] and help clinicians to make treatment decisions in patients with treatment-resistant depression. The prevalence of both treatment-resistant depression and non-treatment-resistant depression would impressively be variable across time attributed to methodological issues, definition of treatment-resistant depression, and the therapeutic options used, including neurostimulation therapies.

Treatment-resistant depression defies true definition[9] (Table 1), but mental health experts agree that it should only be diagnosed in patients who have not been helped by two or more antidepressant treatment trials of adequate dose and duration. To add difficulty to the definition of treatment-resistant depression, treatment response and success has different meanings across multiple research settings. By and large, treatment-resistant depression evades universal definition and meaning, and poses a number of diagnostic and therapeutic challenges to mental health experts. The aim of this paper is to review the therapeutic options for treating resistant major depressive disorder, as well as evaluating further therapeutic interventions.

Table 1 Suggested terminology for treatment-resistant depression[9]

Treatment non-response	A response that is poor enough with significant residual symptoms that a change in the treatment plan is called for (eg, failure to evidence at least a 50% reduction in the HRSD score
Treatment response	A response that is good enough that a change in the treatment plan is not usually called for (eg, at least a 50% reduction in HRSD score)
Remission	Attainment of a virtually asymptomatic status (eg, HRSD 7) for at least 2 consecutive weeks
Recovery	Remission for 6 consecutive months
Relative treatment resistance	Non-response to an adequate dose of a potentially effective medication for an adequate length of time
Absolute treatment resistance	Failure to respond to a maximal trial of a single treatment for an extended period of time (eg, imipramine at 300 mg/day for 6 weeks)
Treatment-refractory depression	Treatment non-response (ie, persistence of significant depressive symptoms) despite at least two treatment trials with drugs from different pharmacological classes, each used in an adequate dose for an adequate time period
Adequate dose	An oral dose that is close to the manufacturers' recommended maximal dose. Adequate dose may be smaller for elderly patients
Adequate length of treatment	At least 4 consecutive weeks of treatment, during which the patient has had an adequate dose for at least 3 weeks
Medication intolerance	Inability to achieve or maintain an adequate therapeutic dose of an antidepressant drug due to idiosyncratic reactions or side effects[9]

Abbreviation: HRSD, Hamilton Rating Scale for Depression.

Search methods

In addition to Google Scholar and Quertle websites, literature searches were also conducted using PubMed for the years 1990–2011 and entering the keywords "treatment-resistant depression", "treatment-refractory depression", "partial response depression", and "nonresponsive depression". These words were combined with tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), and atypical antipsychotics, somatic therapies, such as electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy, transcranial direct current stimulation (tDCS), and psychotherapy for a second round of computer searching.

Another round of searching included a combination of keywords, ie, "treatment-resistant depression with augmentation strategies", "combined antidepressants", "switching approaches", "names of individual antidepressant medications", and "nonpharmacological interventions". As a corollary, relevant articles published in English peer-reviewed journals were retrieved. Only those papers including original studies, clinical trials, systematic reviews, and meta-analyses, which directly addressed treatment-resistant depression, were retained for extensive review and inclusion in this study. Some exceptions were made with regard to small case series, and related mainly to somatic therapies.

Therapeutic trials: pros and cons

Well designed clinical trials provide strong evidence-based data for antidepressant therapy for treatment-resistant depression, but there are many difficulties in interpreting their results. There is no absolutely correct dosage for a specific antidepressant, because dosage requirements vary with age, gender, weight, physical health, concomitant medication usage, and tolerance. Confirmation of treatment adequacy by serial plasma drug levels is not the rule in clinical practice, and valid plasma level-response relationships are limited to only a subgroup of TCA and lithium,[9] and are now extended to certain newer antidepressants. In a study that examined the relationship between plasma antidepressant concentration and both clinical response and adverse effects in treatment-resistant depressed adolescents, 334 participants with major depression who had not responded to an SSRI were randomized to one of four treatments, ie, switch to another SSRI (fluoxetine, citalopram, or paroxetine), switch to venlafaxine, switch to SSRI + cognitive behavior therapy, or switch to venlafaxine + cognitive behavior therapy. Adolescents who did not improve by 6 weeks had their dose increased. Plasma concentrations of medication and metabolites were measured at 6 weeks in 244 participants and at 12 weeks in 204 participants.

Adolescents treated with citalopram whose plasma concentration was equal to or greater than the geometric mean showed a higher response rate compared with those having less than the geometric mean, with parallel but nonsignificant findings for fluoxetine. A dose increase of citalopram or fluoxetine at week 6 was most likely to result in a response when it led to a change in concentration from less than the geometric mean at 6 weeks to the geometric mean or greater at week 12. Plasma levels of paroxetine, venlafaxine, or O-desmethylvenlafaxine were not related to clinical response. Exposure was associated with more cardiovascular and dermatologic side effects in those receiving venlafaxine. It was concluded that the antidepressant concentration may be useful in optimizing treatment for depressed adolescents receiving fluoxetine or citalopram.[15] With respect to psychotherapy, adequacy of treatment may depend on the number of sessions, the expertise of the practitioner, the therapist's adherence to a particular form of therapy, and also interaction within the patient-therapist dyad. The efficacy of ECT trials may be gauged by the total number of treatments, the use of bilateral electrode placement, and verification of seizure occurrence and its timing by electroencephalographic monitoring. Therefore, treatment resistance is linked to a certainty about the adequacy of a specific treatment trial.[16–19]

Researchers have categorized treatment-resistant depression in accordance with antidepressant trials as: stage 0, has not had a single adequate trial of medication; stage 1, failure of an adequate trial of one class of an antidepressant, ie, monotherapy; stage 2, failure of adequate trials of two distinctly different classes, ie, an SSRI and TCA, as two monotherapy trials; stage 3, stage 2 plus failure to respond to one augmentation strategy, ie, lithium or thyroid augmentation of one of the monotherapies; stage 4, stage 3 plus a failure on a second augmentation strategy in terms of monoamine oxidase inhibitors; and stage 5, stage 4 plus failure of an adequate course of ECT.[9] There are other staging methods for treatment-resistant depression, including the Antidepressant Treatment History Form, the Thase and Rush model, the European Staging model, the Massachusetts General Hospital Staging model, and the Maudsley Staging model, with variable predictive validity and reliability.[20] These staging methods help researchers and clinicians to understand the severity and chronicity of treatment-resistant depression and plan trial interventions accordingly.

Patient concerns

Treatment-resistant depression is a difficult condition to treat. Patients with the disorder should interactively share their inner experiences with the treating expert and be able to ask freely any questions related to risk factors underlying treatment-resistant depression, better treatment options, lifestyle changes, costs and insurance coverage, a proper medication schedule, duration of treatment, severity of side effect, suicidal thoughts and attempts, non-suicidal self-injurious behaviors, and intolerance issues. Other related issues to be discussed with patients having treatment-resistant depression are adherence to treatment, impact of medical comorbidities such as heart disease, cancer, thyroid disease, anemia, and eating disorders, interactions

between antidepressants and other medications including herbal supplements, manifestations of impending relapse, and genetic vulnerability. Mental health experts should also address in nontechnical language patients' concerns about somatic therapies, including ECT, VNS, tDCS, rTMS, magnetic seizure therapy, and DBS.[12,19]

Patients with treatment-resistant depression should know about the predictors of good and bad outcomes of treatment. In a UK study that aimed to assess the impact of post-treatment clinical states on longer-term outcome recruited 118 patients with treatment-resistant depression who received specialist inpatient treatment and were followed up for a median of 3 years. Longitudinal outcome, dichotomized into good and poor, was used as the primary outcome and functional measures were used as secondary outcomes. Among the 118 treated patients, 40 (34%) entered clinical remission, 36 (31%) entered partial remission, and 42 (37%) remained in a depressive episode at discharge. At follow-up, 35% had a longitudinally defined poor outcome. According to this study, post-treatment clinical status was the main predictor of both poor and good outcome. Nearly 50% of patients achieved post-discharge recovery, and subsequently had a longer-term outcome comparable with that of patients discharged in remission. Patients who remained in an episode post-treatment were more symptomatically and functionally impaired. In summary, post-treatment clinical states are a useful guide for clinicians in projecting the longer-term outcome for patients with treatment-resistant depression. The persistence of residual or syndromal symptoms predicts a poorer longer-term outcome, whereas treatment to remission is associated with better outcomes.[21]

In another study of young adolescents with SSRI-resistant depression, suicide attempts and nonsuicidal self-injuries were found to have clinical and prognostic significance. This research further called for preventive and therapeutic strategies for treatment-resistant depression and its associated adverse behavioral complications.[22] Patients with treatment-resistant depression also need to be familiar with issues related to weight gain.[23] Like patients with depression and general medical conditions,[24] patients with treatment-resistant depression also have cost concerns associated with variable outcomes and poor adherence to treatment or combined therapies. Patients with depression who respond/remit on antidepressant treatment bear less cost than those who have persistent depression.[25,26] By and large, treatment-resistant depression is associated with extensive use of depression-specific and general medical services, which poses a substantial economic burden, together with work loss costs.[27,28]

In a related context, a randomized, controlled trial evaluated the incremental cost-effectiveness over 24 weeks of combined cognitive behavior therapy plus a switch to a different antidepressant medication versus a medication switch only in adolescents who continued to have depression despite adequate initial treatment with an SSRI. Participants were randomly assigned to switch to a different medication only or to switch to a different medication plus cognitive behavior therapy. Clinical outcomes were depression-free days, depression-improvement days, and quality-adjusted life-years based on depression-free days. It was revealed that combined treatment had a higher net benefit for subgroups of youth without a history of substance abuse, with lower levels of hopelessness, and with comorbid conditions. For youth with SSRI-resistant depression, combined treatment decreases the number of days with depression and was more costly. It was concluded that, depending on a decision-maker's willingness to pay, combined therapy may be cost-effective, particularly for some subgroups.[29]

Risk factors

There is no one reason for treatment-resistant depression. Depression is a heterogeneous disorder, as reflected by treatment heterogeneity and variable nonresponse rates,[30] and the latter could be due to patient age and gender. Elderly patients may be somewhat less treatment-responsive than those at midlife. Conversely, younger women may benefit less from TCA than men or women treated with monoamine oxidase inhibitors.[9] Individuals with fewer interpersonal or economic resources, minority status, lower function and quality of life, and chronic depression may also be less responsive to antidepressant treatment. Furthermore, a higher level of objective stress, poorer social support and family networks, and/or a greater risk of noncompliance also contribute to treatment-resistant depression.[9,31,32] However, for most patients with treatment-resistant depression, it is probably a combination of different risk factors (Table 2) which are as follows: not staying on prescribed antidepressants long enough, ie, for 6–12 weeks when they have their full effect; skipping doses, in terms of poor adherence (blood sample analysis for measuring drug levels is an option for confirming or excluding such a possibility); unpleasant side effects of prescribed psychiatric and non-psychiatric drugs; drug–drug interactions in particular antidepressants and medical treatments; the wrong medicine or the wrong dose for the individual in question; genetic disposition in terms of fast or slow metabolizers of antidepressants; medical comorbid conditions, such as hypothyroidism and anemia, which also

Table 2 Risk factors for treatment-resistant depression

Risk factors	Remarks
Not staying on a medicine long enough	Antidepressants can take as long as 6–8 weeks before they fully take effect
Skipping doses	Take depression medicine exactly as prescribed to know it is working effectively
Unpleasant side effects	Consult doctor for emerging side effects of antidepressants because he/she may offer some help including informing that side effects tend to decrease over time
Drug interactions	Some medicines do not work well with antidepressants and in some cases interactions with dangerous consequences may occur
Wrong medicine or wrong dose	Antidepressant drugs work very differently in different people and finding the right medicine, at the right dose, takes trial and error
Genes	Researchers have found a gene that interferes in the synthesis of tryptophan, a substrate for serotonin synthesis, deficiency of which contributes to treatment resistance
Co-occurring medical conditions	Medical conditions like heart disease, cancer, or thyroid problems, and eating disorders can contribute to depression, and need to be treated simultaneously
Co-occurring psychiatric conditions	Co-occurring Axis I and Axis II diagnosis needs concurrent treatment
Alcohol or drug abuse	Depression may pre- or post-cede substance abuse that need proper treatment as well
Wrong diagnosis	Some people are simply misdiagnosed with treatment-resistant depression and need comprehensive reassessment
Poverty and low education	As environmental effect sizes in affected individuals with treatment-resistant depression may negatively interfere with compliance

contribute to depression by several mechanisms and each needs a separate treatment approach, and ignoring either of them would result in treatment failure and nihilism; and eating disorders, alcohol, and other substance-use disorders, which tend to worsen the depression or might be the main underlying cause of depression.[9,32] Furthermore, breakthrough episodes can also occur among patients partially or fully improved that may contribute to the resistant nature of depression.[33] In addition, misdiagnosis of depression also leads to treatment-resistant depression.[34] Misdiagnosis also includes failure to identify the actual subtype of depression, such as atypical, psychotic, bipolar, or melancholic depression, that has an impact on treatment selection and outcome and may require concurrent pharmacotherapy, such as an antipsychotic or augmentation psychotherapy.[9] Some evidence also indicates a poorer response to TCA in atypical depression, bipolar depression, psychotic depression, and depression associated with significant Axis I, Axis II, or Axis III comorbidity.[31] Further, major depressive disorder that remains unrecognized and untreated may become treatment-resistant depression.[35]

Another symptomatic correlate of treatment resistance is the global severity of depression. A naturalistic study revealed that most patients with a substantial degree of treatment resistance continue to have significant symptoms and functional disability when receiving their usual treatment.[36] Finally, the adverse effects of medication and poor compliance determined by poverty and low education may be additional obstacles to successful treatment of depression.[19,37,38] According to the World Health Organization International Classification of Functioning, Disability and Health, that includes psychiatric disorders,[39] including major depression and treatment-resistant depression, the participation level of patients with depression is an important treatment component that may influence their outcomes and correspondingly might contribute to treatment-resistant depression. Interestingly, based on the perceived relative therapeutic efficacy of available treatment options, depression may also be seen as a secondary compliance risk factor for treatment-resistant depression. In a recent review, risk factors for treatment-resistant depression in adolescents were identified to be the severity of depression, level of hopelessness and suicidal ideation, psychiatric and medical comorbidities, environmental factors such as family conflict, maternal depression, and history of physical and sexual abuse, as well as pharmacokinetics and other biomarkers.[40,41]

In another study, a team of researchers reported that genetic polymorphisms in the transcription factor, cyclic adenosine monophosphate response element binding (CREB1), could be associated with treatment resistance in patients with depression.[42] Also, based on an experimental animal study,[43] researchers reported discovering a mutant gene on chromosome 12 that codes for tryptophan hydroxylase-2. This enzyme helps in the biosynthesis of serotonin, and is produced 80% less than normal by individuals with major or treatment-resistant depression who have this mutant gene, which was also identified in normal individuals (3/219), but much less often than in patients with severe depression (9/87).[44] The implication of this study is that genetic testing, if developed, could identify patients with depression who would or would not respond satisfactorily to one of the antidepressants, eg, a TCA, SSRI, or SNRI.

In summary, depressive illness-related factors, personal characteristics, medication variables, and psychosocial stresses collectively contribute to the development of treatment-resistant depression, and are associated with a considerable disease burden.[45]

Therapeutic options

There are five main strategies (Table 3) used to overcome a partial response or lack of response to antidepressant therapy, ie, optimization, switching, combination, augmentation, and somatic therapies.[46] Because there is no standard treatment approach, mental health experts offer the aforesaid strategies based on re-evaluation of patients with treatment-resistant depression. The patient with depression not responding to antidepressant monotherapy requires a highly individualized treatment plan and, accordingly, some people will respond to a specific treatment, while others do not. Finding the right approach to treat depression can take a lot of effort and time.[29,30] Therefore, the following principles need to be followed to manage patients with treatment-resistant depression: ensure accurate diagnosis, including subtype of depression; assess comorbid psychiatric and medical conditions; evaluate psychosocial stressors, as well as social and family support; ensure adequate dose and duration of treatment; monitor and treat adverse events; educate the patient regarding depression and antidepressants; ensure compliance; and aim for remission. The five approaches are now described briefly.

Table 3 Management strategies for treatment-resistant depression

Therapeutic strategies and options	Remarks
Optimization of antidepressants	Maximize dose for adequate time and check serum levels of prescribed antidepressant if supported by evidence-based data
Switching of antidepressants	Changing from one ineffective antidepressant to similar or different class of antidepressant; SSRI/SNRI to TCA, MAOI, and atypical antipsychotics with antidepressant properties
Combination of antidepressants	Adding another antidepressant from different classes, eg, TCA + MAOI, SSRI + TCA, SSRI + atypical antidepressant, SSRI + buspirone, etc
Augmentation strategies	Adding a second agent that is not an antidepressant but may enhance the antidepressant effect of the drug in question, eg, lithium, thyroid hormones, pindolol, psychostimulants, atypical antipsychotics, sex hormones, anticonvulsants/mood stabilizers, and dopamine agonists
Somatic therapies	ECT, VNS, rTMS, MST, DBS, and TDCS
Integrated approach	Use of antidepressants together with other modes of treatment, which include psychotherapy, risk management strategies, CAM therapies, and life style changes such as exercise and school vacation
Adjunctive approach	Use of a treatment to manage the side effects of antidepressants and also to increase its efficacy
Neurosurgical interventions	Isolated, severe cases of treatment-resistant depression
Continuing research	In genetic, biomarkers, and animal models for drug development

Abbreviations: CAM, complementary and alternative medicine; TDCS, transcranial direct current stimulation; ECT, electroconvulsive therapy; VNS, vagus nerve stimulation; rTMS, repetitive transcranial magnetic stimulation, DBS, deep brain stimulation; MST, magnetic seizure therapy; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

Optimization of antidepressants

The two core features of this strategy are to optimize dosage and duration of antidepressant therapy for patients who have experienced only partial improvement. The advantages of this strategy are to capitalize on the natural history of episodic depression which remits over time and to counteract the tendency of some patients to discontinue the antidepressant prematurely. Furthermore, it helps to distinguish a true enduring antidepressant response from a more transient placebo response. Specifically, placebo responders have a greater likelihood of relapse between weeks 6 and 12 than patients who have responded to active antidepressants.[9,32] An adequate trial of antidepressant therapy has been defined by some clinicians as a minimum of 6 weeks.[7] If the patient exhibits a partial response during this initial period, another 4–6 weeks of treatment should be added. Thus, a total of 10–12 weeks may be required in some cases to elicit a full response to antidepressant therapy.[47] Irrational prescribing of antidepressant medications with regard to dosage and duration is a common cause of treatment failure[9,47] and is common in clinical practice. In a study conducted in a managed care environment, only 11% of patients requiring antidepressant therapy received either an adequate dosage or duration of therapy.[48] This irrational prescribing trend is particularly common in elderly patients,[49] and is especially problematic in low-income and middle-income countries. The older literature suggests that routine prescription of maximal doses of TCA, monoamine oxidase inhibitors, and second-generation antidepressants is associated with a greater likelihood of response than more modest doses in patients with treatment-resistant depression.[9] Notably, administration

of higher doses of first-generation and second-generation antidepressants in patients with treatment-resistant depression requires monitoring of blood levels to track the clinical response and to avoid adverse effects.

Switching strategies

The switching approach mainly involves discontinuing an ineffective antidepressant and starting a new antidepressant from a similar or different class in patients with treatment-resistant depression. Earlier studies found response rates of only 10%–30% for TCA in patients with a past history of lack of response to TCA.[9] A trial course of nortriptyline guided by plasma levels similarly suggested a 30% response in patients with a prior history of TCA failure.[50] Conversely, better response rates of up to 70% have been reported when patients are switched to an alternative class of antidepressant, including the second-generation heterocyclic antidepressants and SSRI/SNRI coupled with a different mechanism of action.[7,30,32,47] Thase and Rush reviewed the relevant literature on old trend switching approaches involving several within and across classes of antidepressants in the population with treatment-resistant depression and similar conclusions were drawn, with the recommendation to conduct larger, controlled, double-blind, crossover studies of SSRI/SNRI-resistant depression using newer antidepressants and TCA.[9] A number of relatively well designed studies,[51–67] which focused on switching strategies from SSRI in major depression, have been conducted to address these issues, and are summarized in Table 4. A summary of the findings of these studies is as follows: response rate 26%–76%; remission rate 28%–87%; a TCA might prove to be a strategy of first choice for patients who do not respond to an SSRI; intolerance to one SSRI does not necessarily mean intolerance to the whole class of SSRI; challenges include collecting controlled data to address the equally important question about the effectiveness of an alternate SSRI when another member of this class is not effective; across-class switch is a good treatment option; in patients unresponsive to SSRI, administration of antidepressants with different mechanisms of action is an effective switching strategy; and switching from an SSRI to a TCA and vice versa in patients who do not respond to a 4-week trial is not associated with an improved response. The last observation runs counter to that predicted by current guidelines.[68]

The advantages of this strategy are improved adherence, reduced medication costs, and fewer drug interactions,[69] while the disadvantages are that therapeutic gains from original antidepressant are lost, the patient has to wait for the new agent to become effective, and relapse or withdrawal symptoms together with adverse effects may occur during the intervening period. This is particularly true if the half-life of the first agent is quite long, as is the case with fluoxetine (35 days), and another SSRI is started before an adequate washout period has occurred. Other antidepressants that require longer washout periods of up to 14 days are clomipramine, tranylcypromine, moclobemide, bupropion, and phenelzine if switched to another TCA, monoamine oxidase inhibitor, or SSRI. Serotonin syndrome,[70] reflecting toxic serotonin levels in the central nervous system and characterized by hyperalertness, agitation, confusion, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, and, possibly, death, may occasionally develop if the washout period was inadequate when switching from one SSRI antidepressant to another. In summary, the risks of toxicity are greater with higher dosage regimens and an inadequate washout period, although urgent cases may necessitate a shorter switching interval.

Combination of antidepressants

Combination therapy involves the addition of a second antidepressant agent from a different class to the therapeutic regimen of patients with treatment-resistant depression.[30,71] The additional antidepressant is used for 12 weeks or even months in optimum doses.[9] Older antidepressants may be used because they are reported to have good results in treatment-resistant depression coupled with severe, recurrent depression.[72–74] Various types of combination are reported in the literature, but the most common are TCA + SSRI followed by, eg, venlafaxine + TCA, SSRI + SSRI, and SSRI + venlafaxine.[75] Venlafaxine + mirtazapine is frequently used in clinical practice, and this combination produces a good response in patients with difficult-to-treat depression, which is attributed to the synergistic action of this combination. In one study of 32 patients with persistent depressive illness, the mirtazapine + venlafaxine combination was given at some point over a 3-year period between 2002 and 2005. Clinical response rates were 44% at 4 weeks and 50% at 8 weeks. At 6-month review, 56% of the original cohort and 75% of those still receiving treatment had shown a significant response. In total, 44% experienced some adverse effects. Five patients discontinued treatment due to sedation (19%) and weight gain (19%).[76] In another study, the venlafaxine + mirtazapine combination was given to 22 patients with major depression who had failed one trial of antidepressant therapy. The mean duration of treatment was approximately 8 weeks, producing a response

Table 4 Summary of clinical studies of switching from an SSRI in major depression

Reference	Initial treatment	Post-switch treatment	Design	Response rate
Thase et al[51]	Sertraline	Fluoxetine	n = 106, open, non-response, or intolerance	63%
Brown and Harrison[52]	Fluoxetine	Sertraline	n = 91, open, primarily intolerant	76%
Zarate et al[53]	Fluoxetine	Sertraline	n = 31, open, non-response or intolerance	42% at discharge, 26% at follow-up
Joffe et al[54]	Fluoxetine, Sertraline, Paroxetine	Second SSRI	n = 55, open, non-response only	51%
Peselow et al[55]	Paroxetine	Imipramine	n = 15, double-blind, prospective nonresponse	73%
Thase et al[56]	Sertraline	Imipramine	n = 117, double-blind, cross-over prospective non-response	60% in the sertraline group and 44% in the imipramine group
Nierenberg et al[57]	Various	Venlafaxine	n = 84, open, non-response to 3 prior trials	33%
De Montigny et al [58]	Various	Venlafaxine	n = 152, open, nonresponse to at least one prior trial	58% response 28% remission
Kaplan[59]	Fluoxetine, Sertraline, Paroxetine	Venlafaxine	n = 73, open, nonresponse to one prior SSRI	87% full remission
Poirer and Boyer[60]	Various, two thirds SSRIs	Venlafaxine or Paroxetine	n = 172, double-blind, randomized, nonresponse to two prior trials, 1 prospective	Response 52% venlafaxine, 33% paroxetine Remission 42% venlafaxine, 22% paroxetine
McGrath et al[61]	Fluoxetine	Bupropion	n = 18, open, nonresponse to prior prospective fluoxetine trial	28% response
Fava et al[62]	Various SSRI	Mirtazapine	n = 69, open, nonresponse to prior prospective SSRI trial	48% response
Thase et al[63]	Various SSRI	Mirtazapine or Sertraline	n = 243, double-blind, randomized, nonresponse to one prior SSRI, not sertraline	At week 3 and 4 mirtazapine > sertraline, $P < 0.05$ (>50% improvement) and at week 8 mirtazapine and sertraline, P = NS. Remission rate 37% mirtazapine and 29% sertraline
Rapaport et al[64]	SSRI, Citalopram	Risperidone	n = 489, multiple designs, double-blind, placebo-controlled, nonresponse to 1–3 SSRI failures	Median time to relapse was 97 days with risperidone augmentation and 56 with placebo ($P = 0.05$); relapse rates were 56% and 64%, respectively ($P < 0.05$)
Lenox-Smith and Jiang[65]	SSRI	Venlafaxine Citalopram	n = 406, 12-week, double-blind, randomized, parallel-group, multicenter study	Venlafaxine and citalopram with similar efficacy. In severely depressed patients, venlafaxine ER was significantly more effective
Souery et al[66]	Citalopram Despiramine	Despiramine/ citalopram	n = 189, nonresponse, prospective study, 8 weeks	First 4 weeks, no difference between citalopram and despiramine or switch, but in the next 4 week, remitter rates > among non-switched patients, switched patients had more score on HRSD and MADRS, CGI scales
Rosso et al[67]	SSRI	Duloxetine and bupropion	n = 49, a randomized, comparison study, 2 SSRI trial failures	Response rate 60%–70% and remission rate 30%–40%

Abbreviations: ER, extended-release; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; CGI, Clinical Global Impression; NS, not statistically significant; SSRI, selective serotonin reuptake inhibitors.

rate of 81.8% and a remission rate of 27.3%. Only one patient was unable to tolerate the combination, although 50% had significant side effects during treatment.[77]

This approach has certain disadvantages, ie, it does not allow for adequate evaluation of monotherapy, is associated with reduced compliance, has an increased likelihood of adverse effects, is prone to polypharmacy, and has the potential for increased drug interactions. Advantages of the combination approach are that it is coupled with a rapid response, no titration is necessary, initial improvements are maintained, the strategy builds on therapeutic gains, addition of the second compound is generally well tolerated, and the disadvantages of switching strategies are avoided. In addition, the response rate is comparable or superior to drug substitution. In this strategy, there might be a synergistic therapeutic effect, but side effects due to drug–drug interactions also tend to emerge, so careful drug surveillance is needed.[6,69]

Augmentation strategies

Augmentation therapy involves adding a second agent (but one that is not routinely regarded as an antidepressant) to the therapeutic regimen when there is only a partial response to the primary antidepressant agent.[38] The reported strength of recommendation for augmentation or switching is best supporting evidence.[78] Various augmenting agents, including lithium, atypical antipsychotics, thyroid hormone, pindolol, buspirone, dopamine agonists, sex steroids, glucocorticoid-specific agents, herbal products, and newer anticonvulsants, have been used in patients with treatment-resistant depression.[19] Augmentation options, mechanisms, and dosing strategies for the various agents are summarized in Tables 5–7. The key points are as follows: downregulation of central beta-adrenergic receptors, which explains the 4–6-week delay in obtaining clinical improvement; lithium enhances not only serotonin neurotransmission but also impacts other neurotransmitter systems and neuromodulators, with a response rate of 30%–65% in patients with treatment-resistant depression who have failed several classes of antidepressants and coupled with equal augmentation efficacy at serum blood levels of 0.4 and 0.8 mEq/L; response may take just 2 days or up to 3–6 weeks, which is considerably shorter than the delay expected with switching, which involves taper of the first drug, washout, and delay in onset of the second drug; antagonism of $5HT_{2A}$ receptors, common among atypical antipsychotics, is also seen with mirtazapine and nefazodone and is coupled with enhanced release of frontal dopamine and norepinephrine, which is thought to be a key action of antidepressant agents; fluoxetine–olanzapine reported 40% improvement among patients with treatment-resistant depression as compared with 30% and 25% improvement with fluoxetine and olanzapine alone, respectively; olanzapine, aripiprazole, quetiapine, and ziprasidone had mixed results in a population with treatment-resistant depression; T3 25–50 μg/day for 2–3 weeks is more effective than T4 for augmenting TCA, monoamine oxidase inhibitors, SSRI, and lithium in patients with treatment-resistant depression; monitoring thyroid function before T3 administration for a baseline reading as well as after administration is important; pindolol, a $5\text{-}HT_{1A}$ postsynaptic antagonist, accelerates the onset of action of antidepressants by preventing negative feedback to the presynaptic $5\text{-}HT_{1A}$ receptor but is currently not recommended for this purpose; unlike open-label studies, buspirone is ineffective in randomized controlled trials; stimulants had no positive results in randomized controlled trials involving patients with treatment-resistant depression; after adjusting for the selection bias inherent in the STAR*D comparison of augmentation versus switching, clinically meaningful differences in the adverse event profiles between these strategies were not observed; risperidone (remission rate [RR] 26.7%), valproate (RR 48.7%), buspirone (RR 32.6%), trazodone (RR 42.6%), and thyroid hormone (RR 37.5%) added to paroxetine 20 mg/day was effective and well tolerated in 225 Chinese patients with stage II treatment-resistant depression; an add-on multicenter trial of 183 patients with treatment-resistant depression failed to detect a statistically significant difference between lamotrigine and placebo given for 10 weeks, but post hoc analysis suggested that future studies of the efficacy of lamotrigine should focus on specific subgroups with depression; a double-blind, placebo-controlled study found that topiramate augmentation potentiates the efficacy of SSRI (fluoxetine, citalopram, sertraline) in the treatment of resistant depression; and further large, comparative, double-blind, randomized clinical trials of augmentation agents in patients with treatment-resistant depression are needed.[9,30,79–99]

The level of evidence for common augmentation agents is as follows: lithium and T3 (best evidence); atypical antipsychotic drugs (some evidence); stimulants, inositol, estrogen, omega-3 fatty acids, and dopamine agonists (little evidence); herbal supplements, lamotrigine (no evidence); and tetraiodothyronine and pindolol (not effective).[46]

Comorbidity

Patients with treatment-resistant depression need to be assessed for comorbid medical and other psychiatric conditions. This is mandatory because 75.5% and 46.9%

Table 5 Augmentation options for treatment-resistant depression

Medication	Available data	Remarks
Traditional agents		
Mirtazapine[77]	Positive RCTs,[77] STAR*D	Limited data
Bupropion[100]	Multiple open-label trials, RCTs, STAR*D	Rapidly effective and more data are needed
Buspirone[96]	Negative RCTs, STAR*D	Ineffective in RCTs
T3	Limited RCTs with SSRI,[78,96] positive when combined with TCA[91,93]	Comparable with lithium in STAR*D but fewer side effects
Lithium	Limited RCTs with SSRI,[78,80] positive when combined with TCA[93]	Comparable to T3 in STAR*D but more side effects
Lamotrigine[97]	Negative RCTs	Small numbers, mixed populations
Valproate[96]	Pilot RCT, effective and well tolerated	Data are limited and larger sample size RCTs are needed
Topiramate[98]	Positive RCT[98]	RCTs with larger sample needed
Pindolol[94]	Negative RCTs[94]	Positive data for antidepressant effect acceleration, not recommended for augmentation
Stimulants[81]	Negative RCTs [81]	May have a role for adjunctive treatment of apathy. Accelerates the antidepressant effect
Sex hormones	Mixed data, most for testosterone	Significant long-term side effects
Atypical antipsychotics		
Aripiprazole[89]	3 positive RCTs,[89] FDA indication	Negative self-report outcomes
Olanzapine/fluoxetine[23]	One positive RCT,[23] multiple equivocal RCTs,[85] FDA indication	Weight gain, metabolic syndrome
Quetiapine[99]	One negative RCT, two positive unpublished RCTs with extended-release formulation	Weight gain, metabolic syndrome, helpful adjunctive agent for some patients with TRD but placebo-controlled trials are needed
Risperidone[96]	Two positive RCTs, one negative	Trials with short treatment lead-in (4–5 weeks on previous antidepressant treatment)
Ziprasidone[85]	Mixed open-label data only[85]	
All antipsychotics	Response (odds ratio = 1.69) and remission (odds ratio = 2.00) versus placebo from RCTs	Discontinuation rates for adverse events higher versus placebo (odds ratio = 3.91)

Note: Information sourced from a number of papers.[11,13–14,23,31,77–98,100]
Abbreviations: RCTs, randomized controlled trials; FDA, Food and Drug Administration; SSRI, selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; TRD, treatment-resistant depression.

of patients with unipolar and bipolar treatment-resistant depression (n = 49) were reported to have at least one other Axis I and two additional Axis I diagnoses, respectively, which included anxiety disorder and substance abuse. Axis I comorbidity appears to be differentially associated with treatment resistance in unipolar and bipolar depression.[101] It is also true with treatment-resistant depression, which is probably associated with a variety of physical diseases at an etiological level, including painful syndromes.[102] In addition, both physical and psychiatric comorbid conditions contribute to treatment resistance in patients with depression. Patients with comorbidities who showed a partial response to TCA, monoamine oxidase inhibitors, SSRI, and SNRI may derive benefit from the use of stimulants, ie, methylphenidate 10 mg three times daily, dextroamphetamine 5 mg three times daily, or modafinil 100–200 mg once daily. These medications are reported to accelerate the effects of antidepressant therapy, but have a potential for abuse and randomized controlled trials failed to produce any treatment benefits.[76,81] However, these medications may have a role in the adjunctive treatment of apathy.[30,81] Nefazodone, another compound used concurrently with prescribed medications in patients with treatment-resistant depression (n = 20) and high psychiatric comorbidity (post-traumatic stress disorder, substance use disorder, and personality disorder) produced good results, with 50% of patients (n = 11) showing substantial improvement, and a smaller proportion having a more modest clinical response.[84] Duloxetine and venlafaxine have also been used in several studies with fairly good results.[103] The basic principles of treating treatment-resistant depression with comorbidities remain the same and all options need to be used sequentially.[104]

Electroconvulsive therapy

ECT is a recognized mode of treatment for a variety of mental disorders, including treatment-resistant depression.[105,106] ECT is still the most consistently effective in patients with treatment-resistant depression, with a response rate

Table 6 Mechanism of action of agents used as augmentation for treatment-resistant depression

Augmentation agent	Mechanism of action
Lithium	Potentiate serotonergic neurotransmission, modulates phosphatidyl-inositol pathway
Triiodothyronine	Potentiate norepinephrine neurotransmission, corrects subclinical hypothyroidism that causes depression-like symptoms
Atypical antipsychotics	Improve frontal serotonin, norepinephrine, and dopamine functions, and other neurotransmitters such as glutamate
Psychostimulants	Improve norepinephrine and dopamine neurotransmission
Inositol	Precursor of diacylglycerol and inositol triphosphate
Estrogen	Affects gamma aminobutyric acid, serotonergic, noradrenergic and cholinergic neurotransmission
Omega-3 fatty acids	Normalize communication in nerve cells; lower tumor necrosis factor-α; lower interleukin-B; lower prostaglandins E 2, 3, 4; and increase brain-derived neurotrophic factor
Dopamine agonists	Increase dopamine tone
Herbal supplements	May impact monoaminergic neurotransmission
Lamotrigine	Blocks 5-hydroxytriptamine 3 receptors, potentiates dopamine
Tetraiodothyronine	Potentiates norepinephrine neurotransmission
Pindolol	Increases serotonergic tone

of 50%–70%.[30] Furthermore, ECT remains the treatment of first choice for the most severe, incapacitating forms of treatment-resistant depression, though the strength of the recommendation of ECT is level C.[78] Surprisingly, relapse rates are significantly higher in patients with treatment-resistant depression after a successful course of therapy.[107] Research is needed to establish the efficacy of alternative methods to prevent relapse following successful ECT, including maintenance ECT and combination pharmacotherapy strategies. Patients who fail to respond to ECT as proposed in Stage 5 treatment-resistant depression represent some of the most challenging cases. Predictors of nonresponse to ECT need to be in place. In a large patient population with treatment-resistant depression, ECT was an effective treatment for approximately two thirds of cases. A lack of response to ECT was associated with bipolar subtype, presence of manic symptoms during depression, slightly less severe depressive symptomatology, and protracted duration of the depressive episode.[108] In a recent study of adolescents with treatment-resistant depression, continuation ECT and maintenance ECT were useful and safe treatment strategies for selected adolescents with severe treatment-resistant depression, and symptom remission was achieved without cognitive impairment.[109]

Other somatic therapies

These reversible but more invasive therapies were developed to avoid the adverse effects and complications of ECT and at the same time to be more effective in treatment-resistant depression. rTMS and VNS are approved by the US Food and Drug Administration for the treatment of intractable seizure disorders and treatment-resistant depression. However, with regard to treatment-resistant depression, other neuromodulation therapies, including DBS, magnetic seizure therapy, and tDCS, are in the experimental stages.[30,88,110–112] Notably, the Food and Drug Administration has approved DBS for compassionate use in severe obsessive-compulsive disorder.

Studies of somatic therapies seem to be producing promising results. In an open-label study, 21 patients who failed two antidepressant trials were given rTMS therapy (high-frequency, 10 Hz, intensity of 110%) for 4 weeks, keeping the dose of pre-existing antidepressants unchanged. Nineteen patients completed the study and were assessed. In intention-to-treat analysis, the mean HRSD-17 scores were reduced from 30.80 ± 5.00 to 19.00 ± 6.37. Only four patients reported headache, but there was no discontinuation due to adverse effects. The study indicated the potential utility of rTMS as an augmenting agent in treatment-resistant depression. Both high frequency left-sided and low frequency right-sided unilateral rTMS are efficacious in treatment-resistant depression. Similar benefits have been suggested for sequential bilateral rTMS (low frequency right-sided then high frequency left-sided).[113] In another study, subjects aged 18–85 years were recruited from a tertiary care university hospital. Seventy-four subjects with treatment-resistant depression and a 17-item HRSD score greater than 21 were randomized to receive unilateral, bilateral, or sham rTMS. The rates of remission were compared between the three treatment groups. The remission rates differed significantly between the groups using a modified intention-to-treat analysis that excluded subjects who did not respond to ECT during the current episode. The remission rate was significantly higher in the bilateral group than in the sham group. The remission rate in the unilateral group did not differ in either group.[114] These studies, including a meta-analysis, call for larger controlled studies to compare the efficacy of sequential bilateral rTMS and high frequency

Table 7 Dosing strategies for augmentation agents for treatment-resistant depression

Augmentation agents	Recommended dosing strategies	Side effects
Lithium	Initially 150 mg twice daily to be increased in accordance with blood level (0.4–0.8 mEq/L) and clinical response	Tremors, weight gain, polydipsia, polyurea
Triiodothyronine	25–50 μg/day for 3 weeks	Irritability, sweating, palpitation, and anxiety
Olanzapine	2.5–5 mg/day	Sedation and weight gain
Ziprasidone	20–40 mg/day	Sedation and weight gain
Risperidone	0.5–1 mg/day	Sedation and weight gain
Methylphenidate	5–30 mg/day	Insomnia, irritability, GI symptoms, abuse and blood pressure/heart rate variability
Dextroamphetamine	10–20 mg/day	Insomnia, irritability, GI symptoms, abuse and blood pressure/heart rate variability
Modafinil	200 mg/day	Headache, dizziness, nausea and dry mouth
Primapexole	0.25–2.5 mg/day	Nausea and agitation
Inositol	500–1000 mg/day	Not available
Estrogen	0.1–0.2 mg patch	Risk for breast and uterine cancer, weight gain, and edema
Omega-3 fatty acids	6 g EPA and 2 g DHA	Unpleasant fishy burp
Lamotrigine	12.5–25 mg/day initially; increase by 12.5–25 mg/week up to 100–220 mg/day	Nausea, headache, blurry vision, rash and sleepiness

Notes: Pindolol, T4, and herbal supplements are not recommended.

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GI, gastrointestinal.

left-sided rTMS in depression and treatment-resistant depression.[114,115]

In another study, 22 patients with major depression were randomly assigned to a crossover protocol comparing tDCS and placebo stimulation add-on to a stable antidepressant medication. The parameters of active tDCS were: 1 mA or 2 mA for 20 minutes daily, with the anode over the left dorsolateral prefrontal cortex and the cathode over the contralateral supraorbital region. Active and placebo tDCS was applied for 2 weeks using indistinguishable direct current stimulators. Patients, raters, and operators were blinded to the treatment conditions. The results showed that there was no significant difference in depression scores after 2 weeks of real tDCS compared with 2 weeks of sham tDCS. However, subjective mood ratings showed an increase in positive emotions after real tDCS compared with sham tDCS. Anodal tDCS, applied for 2 weeks, was not superior to placebo in patients with treatment-resistant depression. A modified and improved tDCS protocol should be investigated in controlled pilot trials to develop effective tDCS for treatment-resistant depression.[116]

In an interesting single treatment-resistant depression patient analysis, VNS produced good results and achieved a cost saving over modified ECT.[117] Both ECT and VNS could be combined in managing severe cases of treatment-resistant depression. VNS has some disadvantages, including hoarseness of voice caused by the stimulator delivering the electrical pulse, and rarely infection due to surgical implantation of a small device into the left chest wall.[117] In an open-label study of resistant major depressive episode, the predictors of response to VNS were a history of resistant depression, mild to moderate resistant depression, non-severe resistant depression, and no history of use of ECT.[118] The long-term effects and tolerability of VNS need to be determined to ascertain its suitability for use in treatment-resistant depression.

A multicenter pilot study of 21 patients with treatment-resistant depression who received DBS found that patients treated with subcallosal cingulate gyrus DBS had an RESP50 of 57% at one month, 48% at 6 months, and 29% at 12 months. However, the response rate after 12 months of DBS increased to 62% when response is defined by 50% reduction in baseline HRSD-17 score (RESP50). Reductions in depressive symptoms were associated with amelioration of disease severity in patients who responded to surgery. Overall, findings from this study corroborated the results of previous reports showing that outcome of subcallosal cingulate gyrus DBS may be replicated across centers.[119] Ward and Irazoqui have provided greater detail on target structures, motivation, response rates, and the proposed mechanism of action of somatic therapies used in treatment-resistant depression.[4] Data from a follow-up study suggested that in the long term (up to 6 years), DBS remains a safe and effective treatment for treatment-resistant depression.[120] Finally, psychosurgery, such as subcaudate tractotomy, limbic leucotomy, anterior capsulotomy, and anterior cingulotomy remain the last line of somatic treatment for patients with severe treatment-resistant depression.[30]

Complementary and alternative medicine

The therapeutic role of ethyl eicosapentaenoic acid, an essential fatty acid, as an augmentation agent for traditional antidepressants in treatment-resistant depression has been reported.[30] Puri et al showed that eicosapentaenoic acid improved some symptoms, including suicidal ideation and social phobia, in a single patient with severe treatment-resistant depression. This compound also induced neurobiological changes, such as a 30% increase in the volumetric niacin response, a 53% increase in the relative concentration of cerebral phosphomonoesters, a 79% increase in the ratio of cerebral phosphomonoesters to phosphodiesters, and a reduction in the lateral ventricular volume of the brain.[121] The therapeutic value of L-methylfolate, a medicinal food, is emphasized in patients of Hispanic origin with treatment-resistant depression.[122] The efficacy of other complementary and alternative medicines in patients with treatment-resistant depression needs to be studied because these therapies have minimal adverse effects and their contribution to the management of various diseases is expanding rapidly. Conversely, in modern medicine, of about 65% of patients who discontinue antidepressants, 45% of them do so because of unpleasant side effects.[123] Regarding lifestyle changes, researchers reported positive effects of moderate physical exercise on quality of life in patients with treatment-resistant depression.[124]

Psychotherapy

In general, psychotherapy alone is effective in mild to moderate depression, and when combined with antidepressants, is associated with better results in severe depression than either therapy alone. Traditionally, the strength of recommendation for psychotherapy is B level, and it has been considered useful in the management of treatment-resistant depression, primarily as an adjunct to help patients maintain morale and optimism.[78] Currently, various studies have also justified the use of psychotherapy, especially cognitive behavior therapy, when using switching and augmentation approaches in patients with treatment-resistant depression.[9,30,100] In a comparative study that recruited patients with treatment-resistant depression who responded unsatisfactorily to citalopram and were assigned randomly to either augmentation of citalopram with cognitive therapy or sustained-release bupropion or buspirone or switch to cognitive therapy or another antidepressant, sertraline, sustained-release bupropion, or extended-release venlafaxine, Thase et al[100] found that pharmacologic augmentation was more rapidly effective than augmentation of citalopram using cognitive behavioral therapy, whereas switching to cognitive behavioral therapy was better tolerated than switching to a different antidepressant. Few randomized controlled trials[125,126] have investigated interventions for treatment-resistant depression in young people, and results from these show modest benefit from antidepressants, with no additional benefit of cognitive behavioral therapy over medication. Overall, there is a lack of evidence about effective interventions to treat young people who have failed to respond to evidence-based interventions for depression. Research in this area is urgently required.[125,126] In a related development, research suggests that children and adolescents with school difficulties are less likely to respond to fluoxetine compared with those with no school difficulties. Depressed adolescents in the Treatment of Resistant Depression in Adolescents study, who had not responded to a previous adequate trial of an SSRI, were randomly assigned to one of the following: another SSRI, venlafaxine, another SSRI + cognitive behavioral therapy, or venlafaxine + cognitive behavioral therapy. Participants were classified into four groups, depending on whether their enrollment in the study and end of treatment was during school or summer vacation. There was a significant interaction between school difficulties and timing of treatment, with the lowest rates of response being among adolescents having school difficulties and ending their treatment during the active school year. School problems are relevant to treatment response in depressed adolescents and should be incorporated into the treatment plan. These findings also suggest that the time of year might need to be taken into consideration for analysis of clinical trials in school-aged youth.[127] In a systematic review,[128] researchers examined the utility of psychotherapy in the management of treatment-resistant depression, and found it to be useful. However, the evidence was sparse and the results were mixed. Given that quality trials are lacking, rigorous clinical trials are recommended to guide practice, including in primary care.[128]

A team of researchers examined the long-term outcome of participants in the Treatment of SSRI-Resistant Depression in Adolescents, in which 334 adolescents with major depressive disorder initially resistant to SSRI treatment were randomly treated for 12 weeks with another SSRI, venlafaxine, another SSRI + cognitive behavioral therapy, or venlafaxine + cognitive behavioral therapy. Responders then continued with the same treatment through week 24, while non-responders were given open treatment. By 72 weeks, an estimated 61.1% of the randomized adolescents had reached remission. Randomly assigned treatment, ie, that given for the first 12 weeks,

did not influence the remission rate or time to remission, but the group assigned to SSRI had a more rapid decline in self-reported depressive symptoms and suicidal ideation than those assigned to venlafaxine. Participants with more severe depression, greater dysfunction, and alcohol or drug use at baseline were less likely to remit. The depressive symptom trajectory of the remitters diverged from that of non-remitters during the first 6 weeks of treatment. Of the 130 participants in remission at week 24, 25.4% relapsed in the subsequent year. While most adolescents achieved remission, more than one third did not, and one quarter of the patients who remitted experienced a relapse. The investigators suggested more effective interventions are needed for patients who do not show robust improvement early on in treatment.[129]

Future treatment options

New drugs approved for the management of depression are on the market (Table 8). These medications include desvenlafaxine (an SNRI), escitalopram (an SSRI), and a reformulation of trazodone (Oleptro™). A number of drugs, including riluzole, that act on glutamate receptors and have antidepressant activity have also been developed and are approved for managing major depression.[81,130] Studies have explored the role of ketamine, an NMDA antagonist, in treating treatment-resistant depression and acute suicidal ideation.

Table 8 Future treatment options for treatment-resistant depression

Medication/intervention	Comments
Melatonin drugs (agomelatine)	Preliminary data only, no inclusion of TRD population in registration trials, not yet studied as an augmenting agent
Acetylcholine drugs (scopolamine, mecamylamine, varenicline)	Intravenous infusions used for scopolamine, studied as augmenting agents rather than primary treatment, small numbers in published results, large trials underway
Glutamate drugs (ketamine, NR2 antagonists, riluzole)	Short-term symptomatic relief, only intravenous infusions used, further trials underway
Neurostimulation	VNS approved for TRD but long-term treatment needed, TMS showed less efficacy in more treatment-resistant patients but use of TMS in TRD under investigation, DBS trials underway

Abbreviations: NR2, NMDA receptor subunit; TRD, treatment-resistant depression; VNS, vagus nerve stimulation; DBS, deep brain stimulation; TMS, transcranial magnetic stimulation.

Ketamine appears to have a rapid antidepressant effect, within hours or a day, although these effects only last for 7–10 days. Patients need to be admitted to hospital to receive ketamine intravenously from an anesthesiologist, while their vital signs are closely monitored. Ketamine is a drug of abuse and induces trance-like or hallucinatory states. Like other anesthetics, ketamine also produces mild to moderate cognitive side effects. Ketamine treatment may be akin to ECT and studying ketamine may reveal mechanisms underlying depression and help to identify drugs that can be prescribed as antidepressants to a wider patient population.[131] In a comparative study of 17 patients with treatment-resistant depression non-responsive to ECT and 23 patients with treatment-resistant depression who had not previously received ECT were given a single open-label infusion of ketamine 0.5 mg/kg and evaluated using the Montgomery-Åsberg Depression Rating Scale at baseline (60 minutes before the infusion), as well as at 40, 80, 120, and 230 minutes after infusion. Depressive symptoms were significantly improved in the ECT-resistant group at 230 minutes, with a moderate effect size. At 230 minutes, the group not exposed to ECT showed significant improvement with a large effect size. Ketamine appears to improve depressive symptoms in patients with major depression who had previously not responded to ECT. These preliminary results warrant further investigation in a larger sample size to determine the effectiveness of ketamine in patients with depression not responsive to other treatments.[132] In one study, 10 participants with treatment-resistant depression were given riluzole, another NMDA antagonist, along with their regular antidepressant. After 6–12 weeks, they experienced an almost 10-point drop on the HRSD.[130]

Triple reuptake inhibitors that block the reuptake of serotonin, norepinephrine, and dopamine, are the newest drugs in the stable of monoamine antidepressants.[133] Currently, there are no randomized controlled trials on these agents and research is preliminary. It is believed that triple reuptake inhibitors devoid of an effect on sexual function could be used as second-line treatment when patients with depression do not respond to an SSRI.[134,135] Non-conventional antidepressants, such as tianeptine, are also used for treatment-resistant depression with some benefits.[133] Another new drug, agomelatine, the first melatonergic antidepressant containing a 5-HT_{2C} receptor antagonist and a melatonin-1 agonist, is approved in Europe to treat major depression. It has a unique mechanism of action by targeting the melatonin system in the brain,[81] and randomized controlled trials in the treatment-resistant depression population are needed. In another

development, loss of brain-derived neurotrophic factor was found in major depression. Brain-derived neurotrophic factor is a member of the nerve growth factor family, which helps with the survival and growth of neurons. However, stress seems to decrease levels of brain-derived neurotrophic factor. Increasing brain-derived neurotrophic factor may be a new strategy for developing new antidepressants. Furthermore, compounds that influence the endocannabinoid system involved in depression, and neuropeptide systems, such as galanin and melanin-concentrating hormone, may be used in the treatment of treatment-resistant depression.[133] Several neuropeptides and their receptors have also been identified as potential targets for pharmacologic intervention by corticotropin-releasing factor and substance P.[136] Some investigators have suggested use of Sertoli cell therapy in patients with treatment-resistant depression.[137] Acetylcholine drugs, such as scopolamine, mecamylamine, and varenicline, have been used in small studies involving patients with treatment-resistant depression, with positive results.[81,138,139]

In summary, preliminary data for the aforementioned newer antidepressant therapies support the view that larger, randomized, controlled studies are needed in future. A stepwise treatment algorithm for patients with treatment-resistant depression need to be used for better decision-making, better responses, and a higher remission rate in the population with treatment-resistant depression.[11,140]

Discussion

This paper is a narrative review of the literature on treatment-resistant depression. In addition to Google Scholar and Quertle database searches, multiple rounds of computer searching of PubMed using key words and a combined strategy might have led to some relevant articles, especially in young and elderly populations, having been missed, and possibly biasing our results. However, the astronomical database on treatment-resistant depression published regularly and globally is difficult to synthesize. Furthermore, selection and review of all articles by a lone author is an uphill task and selection bias might have entered into this qualitative review. Despite these caveats, this review reports important findings and developments in the therapeutic paradigms for treatment-resistant depression over two decades. The prevalence of treatment-resistant depression is 10%–30%,[7] but some researchers have suggested that it could be more than 30%,[11,12,69] according to definitions of treatment-resistant depression and other methodological issues. With advances in the treatment of resistant depression, it is not surprising that its prevalence would temporally decrease or change.

It seems that depression should only be considered drug-resistant after at least 6 weeks of two trials of antidepressant therapy.[9,51] Some researchers suggested extending this period for up to 10–12 weeks in patients who respond partially to trials of antidepressant therapy.[15,47] Nonetheless, at least 30% of patients continue to manifest residual symptoms with poor quality of life and impairment in overall functioning.[51] In addition to requiring several recommended therapeutic options, this core group of patients with treatment-resistant depression warrants a comprehensive search for factors responsible for the persistence of depression, which include but are not limited to the patient's characteristics and environment, including stresses, a comorbid psychiatric or somatic disorder, and drug abuse or addiction.[19,40–42,44,45] Arguably, the suggested therapeutic strategies for treatment-resistant depression have variable outcomes in terms of response and remission rate, as well as disadvantages due to multiple factors, including the adverse effect profile of antidepressants.

It is reported that optimization of a first-line antidepressant in adequate doses and for an extended period of up to 12 weeks is based on weak evidence.[19,69,81] Similarly, trials comparing continuation of the first-line antidepressant versus switching to another antidepressant from a different class have reported conflicting results.[9,19] A switching strategy may benefit a small proportion of patients, but the elimination half-life of the discontinued drug, such as fluoxetine, and washout period must be taken into account to limit the risk of interactions during the transition period.[9,19,69,81] A combination approach also has some disadvantages because it increases the risk of adverse effects, possibly without a substantial clinical benefit.[19] Evidently, a second course of antidepressant monotherapy tends to treat up to 50% of those who have failed with the initial treatment effectively, when the second drug has a profile distinct from the initial medication. It means that 25% of patients with treatment-resistant depression respond to optimization and combined strategies, and another 50% tend to respond to switching options. The remaining 25% of patients with treatment-resistant depression are candidates for augmentation strategies.[81]

The strength of evidence supporting a trial of augmentation or a switch to a new agent is very similar, with remission rates of 25%–50% in both cases.[141] A review of comparative trials suggested that adjunctive use of lithium and thyroid hormone have an established antidepressant effect in patients with treatment-resistant depression, but there is no firm evidence that adding lithium to non-TCA treatment increases the chances of remission.[78,91,93,96,141]

According to other researchers, thyroid hormone, a benzodiazepine, buspirone, and pindolol as augmenting agents have limited proven antidepressant effects.[19,78,94,96] Furthermore, Connolly and Thase[141] as well as others [46,78,96] have reported that of these two options, ie, lithium versus thyroid hormone, T3 augmentation seems to offer the best benefit/risk ratio for augmentation of modern antidepressants. However, lithium is known to have a narrow therapeutic window and needs blood level monitoring to avoid the toxicity and fatalities associated with high lithium levels.[77,78,80] With regard to newer generations of antidepressants, after failure of a first-line SSRI, neither a switch within a class nor a switch to a different class of antidepressant is unequivocally supported by the data, although switching from an SSRI to venlafaxine or mirtazapine may potentially offer greater benefits.[75–77,141] In an open-label study, mirtazapine was effective in 38% of patients with depression resistant to standard antidepressants.[142] It is noted that switching from a newer antidepressant to a TCA after a poor response to the former is not supported by strong evidence.[142] Augmentation with an antiepileptic or a psychostimulant is not supported unequivocally but they are reported to be more harmful than beneficial because of adverse effects, including the addiction potential of stimulants.[46,81,96–98] Conversely, the use of psychostimulants with conventional antidepressants is recommended in patients with treatment-resistant depression because significant improvement was demonstrated, in particular with respect to energy, mood, and psychomotor activity. It was concluded that their rapid onset of action (2–3 hours) after administration may help cover the therapeutic latency period of conventional antidepressants and probably potentiates their effect.[143] According to some studies, augmentation with atypical antipsychotics has had mixed results,[23,85,96] but quetiapine and aripiprazole were relatively supported by the evidence.[89,99] It is noted that Symbyax®, a combination of olanzapine and fluoxetine, is approved for the acute management of treatment-resistant depression.

ECT has a place in the management of patients failing multiple optimized monotherapies, switching options, combined approaches, and augmented treatment strategies[30,105,106,108] but carries a risk of reversible memory disorders.[19] Surprisingly, patients with treatment-resistant depression who responded to ECT were found to have a high relapse rate,[107] which could be prevented by maintenance ECT. Some studies reported no cognitive impairment with ECT in adolescents with treatment-resistant depression.[109] In this regard, replication research is required to support or refute such results. The role of other somatic interventions, including VNS, rTMS, DBS, and tDCS, in patients with treatment-resistant depression is expanding with greater efficacy, but have some side effects and need further research, especially large controlled randomized studies targeting particular areas in the brain implicated in major depression and treatment-resistant depression.[4,112–120] The efficacy of psychotherapy in patients with treatment-resistant depression is fairly good, and 50% of patients tend to get benefits from psychotherapies, especially cognitive behavioral therapy and mindfulness-based cognitive behavioral therapy.[19,100,144] Additional cognitive behavioral therapy in the young population with treatment-resistant depression has limited or no value and needs further research.[126] Regular exercise and use of some complementary and alternative medicines impact positively on treatment-resistant depression and need further research using herbal supplements.[124]

Conclusion

In summary, 70% of patients with major depression respond to initial antidepressant therapy, leaving 30% of patients who are refractory to treatment and therefore need special treatment-resistant depression management strategies. Twenty-five percent of patients with treatment-resistant depression tend to respond to optimization and combined treatment paradigms and another 50% of patients are reported to respond to switching therapeutic options. Augmentation strategies target the remaining 25% of patients suffering from treatment-resistant depression, with inconsistent outcomes. Overall, although there is no strict compartmentalization of treatment response and remission rate in the population with treatment-resistant depression, about one third of patients with the disorder continue to be resistant to available therapeutic options, and hence pose a major therapeutic challenge to mental health experts.

Recommendations

Based on this narrative review, that has some caveats, the following recommendations are made:

- Each individual with treatment-resistant depression is a unique case and needs detailed evaluation to identify the prior antidepressant response and also to make a correct diagnosis.
- Assessment of risk factors for treatment-resistant depression is equally important to guide mental health professionals in tailoring an appropriate management plan for patients with treatment-resistant depression.
- There are a wide variety of options for the treatment of major depression and treatment-resistant depression,

therefore every therapeutic paradigm needs to be utilized when helping patients with treatment-resistant depression.

- In light of the demonstrated importance of truly adequate treatment to the long-term outcomes of patients with treatment-resistant depression, further randomized clinical trials involving newer drugs and psychotherapies and somatic therapies are needed in the future.

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Disclosure

The author reports no conflicts of interest in this work.

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