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Pharmacologic Approaches to Treatment Resistant Depression: A Re-examination for the Modern Era

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Abstract

Importance of the field—Treatment-resistant depression (TRD) is common and debilitating. Initial treatment is often insufficient to achieve full remission in a given depressive episode, resulting in more frequent episodes, worsened severity, and major disability.

Areas covered in this review—This review surveys literature on the diagnosis and pharmacological management of TRD in light of recent developments. Evidence regarding commonly used treatment options is critically examined and key recommendations are offered. The review ends by considering drugs acting on the melatonin, acetylcholine, and glutamate systems that hold promise as future options for TRD.

What the reader will gain—Recent trends and research findings have impacted how the evidence supporting different approaches to TRD should be evaluated. For example, many earlier TRD studies employed tricyclics (TCAs) as the primary antidepressant, but TCAs have now been superseded by selective serotonin reuptake inhibitors (SSRIs) in routine clinical practice. This deficiency has been addressed by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest effectiveness study of TRD ever conducted. However, design characteristics of the STAR*D study preclude simple comparisons with earlier studies.

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Article Highlights

- **Definition of TRD:** This section describes current ways of defining TRD, focusing on the lack of clear criteria for the condition. It also highlights the importance of careful diagnosis and identification of comorbid illnesses.
- **Pharmacotherapy for TRD:** This section surveys relevant literature on the pharmacotherapy of TRD.
- **Switching:** This subsection examines the strategy of discontinuing an ineffective current drug and starting a different one, highlighting the potential risks and benefits of this approach in light of available data.
- **Augmentation:** This subsection discusses the risk and benefits of adding a new drug to an insufficiently effective primary treatment, reviewing findings with more traditional agents (e.g., T3 and lithium) and with newer options (e.g., atypical antipsychotics).
- **Future Treatments:** This section examines three separate classes of drugs with preliminary evidence of efficacy for TRD, including drugs that act on the melatonin, acetylcholine, and glutamate systems.

Take home message—A shortcoming of most treatment recommendations for TRD is their reliance on older studies that do not reflect the current preeminence of SSRIs in clinical practice. This has distorted the prioritization of pharmacological strategies for TRD. Efforts to correct this distortion with effectiveness research, designed to better reflect current practice trends, require critical consideration of the strengths and limitations of this approach.

Keywords

depression; treatment-resistant; augmentation; atypical antipsychotics

1. Introduction

Major depression, one of the most common psychiatric illnesses worldwide, has a profound public health impact. The World Health Organization (WHO) designated major depression as the most common cause of disease burden in North America, and the fourth leading cause in the world.¹ Despite the widespread availability of effective treatments for depression, many patients do not receive adequate relief from symptoms. Most recently, the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness study showed that approximately half of patients will respond to an initial trial of an antidepressant, with only a third reaching clinical remission with that first trial. Moreover, up to a third of patients may not reach remission despite multiple drug trials.²

These response and remission rates highlight the fact that there is no broad consensus as to what defines treatment-resistant depression (TRD).^{3, 4} In some clinical trials, TRD is defined as a failure of one previous antidepressant regimen during the current treatment episode, while in other studies TRD has been defined as at least four antidepressant failures with or without failure of electroconvulsive therapy (ECT). Given the public health impact of this illness, however, there is no doubt that improving symptoms in depressed patients who fail to fully remit is a major priority for psychiatrists.

A variety of approaches have been delineated in the management of TRD. The first step is generally optimization of the current regimen, which may include dosing changes, extension of treatment for longer periods of time, and use of drug plasma levels, if appropriate. Next steps often include switching within drug classes (e.g., from one selective serotonin reuptake inhibitor (SSRI) to another), switching between classes (e.g., changing to a monoamine oxidase inhibitor (MAOI)), or augmenting with another drug (e.g., lithium, triiodothyronine (T3), or mirtazapine). Recent studies have also demonstrated the utility of using atypical antipsychotics as augmenting agents.

Of the available options, augmentation strategies appear to be more efficacious than within- or between-class switches; at present, some atypical antipsychotics, particularly aripiprazole, have the best evidence bases supporting their use in augmenting treatment with an SSRI. We note here that SSRIs are now the usual standard of care for primary antidepressant treatment, having superseded tricyclic antidepressants (TCAs) in that role over the past 20 years. Although there is extensive data on the use of lithium and T3 augmentation, most of those studies have involved augmentation of TCAs rather than SSRIs.^{5, 6}

While beyond the focus of this review, there are also a number of nonpharmacologic approaches for TRD which merit consideration, including evidence-based psychotherapies,⁷ ECT,⁸ vagus nerve stimulation (VNS),⁹ and transcranial magnetic stimulation (TMS).¹⁰

In this review, we will first discuss issues surrounding the definition of TRD, followed by an examination of the different pharmacotherapy options, including switching classes of

antidepressant drugs and the relative merits of different kinds of augmentation. We will end with a consideration of novel potential pharmacological options for TRD.

2. Definition of TRD

Major depressive disorder is defined as a period of at least two weeks of either depressed mood or loss of interest or pleasure in nearly all activities; the individual must also report neurovegetative symptoms and/or suicidal ideation.¹¹ However, as noted above, TRD does not have a uniform definition. The lack of clearly defined criteria for TRD often complicates translation of research studies to clinical practice. It is most useful to conceptualize TRD as existing on a spectrum, from failure to respond to one standard antidepressant trial, to failure of multiple antidepressant classes or augmentation strategies, to failure of ECT.^{12, 13}

Accurate characterization is the first step in treating TRD. Recording the failure of prior treatment trials is critical, and can be accomplished by using a standardized instrument, such as the Antidepressant Treatment History Form (ATHF).¹³ This will help separate true treatment failures from failures due to lack of tolerability or other factors. Identification of medical and psychiatric co-morbidities, as well as relevant clinical features, is also essential. For example, hypothyroidism or cancer may present initially as treatment-resistant depressive episodes. Comorbid personality disorders will generally require additional psychotherapeutic intervention, while comorbid anxiety, substance abuse, and melancholic symptoms have been shown to be negative predictors of response to treatment.^{14, 15} A history of early life stress is common in patients with TRD,¹⁶ and this may serve as a marker for significant additional psychiatric comorbidity.¹⁷ Undiagnosed bipolar disorder may present as TRD. The presence of persistent agitated depression, strong family history of bipolar disorder, and hypomanic or manic symptoms may all point toward this condition,¹⁸ and will require a different treatment strategy. Lastly, the presence of psychotic symptoms can result in treatment resistance that will require a specific approach, usually the combination of an antidepressant and an antipsychotic, or ECT.^{19, 20}

Accurately measuring how symptoms change with treatment is another key step in managing TRD. It is generally accepted that treating to full remission decreases the likelihood of relapse.²¹ Identification of residual symptoms, even during remission, is important, as the presence of even a few residual symptoms during remission is predictive of relapse.²² "Response" is defined operationally as a 50% improvement in baseline depressive symptoms, while "remission" is defined as a score below a certain threshold on specified rating scales, such as a score of 7 or less on the Hamilton Rating Scale for Depression (HAM-D)²³ or a score of 10 or less on the Montgomery-Asberg Depression Rating Scale (MADRS),²⁴ or a score of 14 or less on the Inventory of Depressive Symptoms (IDS-SR).²⁵ Another rating scale that has recently gained popularity is the Quick Inventory of Depressive Symptoms (QIDS),²⁶ which was used in the STAR*D trial. Regardless of the scale employed, using a standardized measure to assess patient symptoms can facilitate the more accurate evaluation of treatment outcome.

3. Pharmacotherapy for TRD

There are several approaches to the pharmacotherapy of TRD, starting with optimization of the current treatment. If this fails, more significant changes are undertaken, such as switching within or between classes of medications, or augmenting the primary antidepressant with another drug.

3.1 Optimization

The initial step in addressing TRD is optimization of the current regimen. Optimization involves ensuring that the current medication is being used for sufficient duration, at the ideal

dosage, and with maximal adherence to treatment. A sufficient primary antidepressant trial duration is usually 6–8 weeks,²⁷ although a small proportion of patients require as long as 12 weeks to respond.

Dosage optimization can entail either a dosage decrease, in cases where adverse effects are outweighing any actual therapeutic effects, or a dosage increase, in cases where a therapeutic effect has not yet been achieved. An *adequate* dosage is usually defined as the minimum dose that has been established as clinically effective, but optimization often requires an increase above that, with some authorities advocating at least two thirds of the manufacturer's *maximum* recommended dose.¹³ Evidence supporting dose increases for greater efficacy is primarily anecdotal, even though such increases constitute standard practice. For some antidepressants, dose optimization can also be evaluated by measuring drug concentrations in plasma.²⁸ This approach is most useful when there is an established relationship between plasma drug level and clinical response, as with the TCAs, but far less helpful when that relationship is weak, as with the SSRIs.

Another key issue in optimization is adherence. Poor adherence can be a major problem in treatment optimization, regardless of the disorder being treated, as clinical response will obviously be compromised if drugs are not taken in a reliable fashion. The issue of adherence must be explicitly addressed with the patient with TRD before additional measures beyond optimization are undertaken. Aside from patient self-report, adherence can be assessed to some extent by daily pill diaries (i.e., patient-generated records of all medication ingestions), pill counts (i.e., determining how much medication is left since the last prescription), and electronic monitoring (i.e., medication event monitoring [MEM], in which a microcircuit embedded in the pill bottle cap records each opening and closure). MEM technology is infrequently used outside of research settings, but pill diaries and pill counts are easily incorporated into routine clinical practice. Plasma drug levels can also be used to ascertain drug ingestion, even if there is no correlation with therapeutic effect.

As noted above, the Antidepressant Treatment History Form (ATHF) can be used to evaluate whether previous drug trials were optimized, by allowing clinicians to score treatment adequacy based on the dosage and duration of the medication used.¹³

3.2 Switching

If optimization fails, a more substantive change in the pharmacological regimen is indicated, and one option is switching medications. Switches to an entirely different agent can be either within or between antidepressant classes. Within-class switches (e.g., SSRI to SSRI) are most commonly performed, exploiting the advantage that there is significant cross-tolerability between different drugs within the same class, so that such switches can be performed relatively quickly. Previous reviews have suggested comparable response rates for within- and between-class switches.²⁹

Switching to a different class (e.g., from an SSRI to bupropion or venlafaxine) is another option, and at least one meta-analysis has identified a significant, albeit modest, advantage in switching from SSRIs to non-SSRI treatments.³⁰ This issue was also examined in the second tier of the STAR*D study, in which patients were switched from initial treatment with citalopram to sertraline (i.e., a within-class switch) or to venlafaxine or bupropion (i.e., a between-class switch). Remission rates increased very modestly (3–7%) in switching to any of these treatments, with none significantly more efficacious than another; in the context of the STAR*D study sample and dosing parameters, therefore, switching within- and between-classes had comparable outcomes.

Another between-class switch option involves switching to an older drug, such as a TCA or an MAOI. Both of these classes have limitations, notably anticholinergic and cardiovascular side effects with the TCAs, and dietary and drug interactions with the MAOIs. A benefit of the TCAs, however, is that measurement of plasma drug concentrations may facilitate dosing optimization. Both of these classes were included in the STAR*D study, but the mean dose used for the MAOI tranylcypromine was only 36.9 mg/day, which is on the low end of the usual dosing range.³¹ Concerns about orthostatic hypotension and potential interactions often limit use of the MAOIs. In this regard, the transdermal preparation of selegiline (EMSAM) is usually well tolerated and does not require dietary modification at lower doses (i.e., 6 mg/day), although at higher and generally more therapeutic doses (9–12 mg/day) dietary modification is necessary.³²

3.3 Augmentation

Another major strategy in managing TRD is augmentation, the addition of a different medication, in a different class or acting via a different mechanism of action, to improve the antidepressant effects of an ongoing treatment. This has the advantage of building on previous improvements in mood symptoms, but introduces the increased complexity of polypharmacy to the treatment regimen, which can increase the side effect burden and complicate adherence. Augmentation using an antidepressant with established efficacy can also be referred to as *combination therapy*.

3.3.1 Lithium—Lithium augmentation is one of the oldest and most established of the augmentation strategies. The first reported trial of lithium augmentation by De Montigny et al.³³ described its efficacy in combination with TCAs. The purported mechanism of action was that it had synergistic effects with TCA treatment by enhancing serotonergic neurotransmission.³⁴ In a meta-analysis of the 10 placebo-controlled studies examining lithium augmentation, lithium was substantially more effective than placebo. Lithium doses in these studies ranged from 600–1200 mg/day, with plasma levels of greater than 0.4 mEq/L.³⁵ However, it is important to note that the database for lithium augmentation is older and was developed before most of the modern antidepressant drugs were available; the majority of the relevant studies were conducted when TCAs were the standard of antidepressant care, and the amount of evidence available for lithium as an augmenting agent for SSRIs is considerably less. One small study with citalopram found an advantage of lithium augmentation over placebo, but the controlled phase of this study lasted only 6 days.³⁶ Two studies by Fava et al.^{37, 38} found no clear advantage of lithium augmentation of fluoxetine when compared to an increased dose of fluoxetine or desipramine augmentation.

In the STAR*D study, lithium dosing was generally low; plasma level monitoring was infrequent and also revealed low median levels. These observations raise questions about the adequacy of lithium treatment in the study. The literature supporting lithium as an augmenting agent does indicate that a lower plasma level can be used than for treating mania, but targets are still between 0.5 to 1.0 mEq/L.³⁹ As seen in the STAR*D study, the requirement for regular plasma monitoring represents an additional burden of this treatment.

3.3.2 Thyroid hormone—Thyroid hormone supplementation (usually triiodothyronine [T3], but occasionally thyroxine [T4]) is another older and commonly used augmentation strategy. Its advantage is that it generally tends to be well tolerated and has a favorable side effect profile. The mechanism of action is unclear, but thyroid augmentation may enhance noradrenergic neurotransmission.⁴⁰ Another hypothesis is that thyroid supplementation corrects a bioenergetic deficiency in the brain that is manifested as depression, a theory supported by magnetic resonance spectroscopy showing improvement in brain nucleoside

triphosphate (a marker for adenosine triphosphate [ATP], the main source of cellular energy) levels during open-label T3 augmentation.⁴¹

Similar to lithium augmentation, much of the data supporting thyroid augmentation comes from studies with TCAs;⁴⁰ there is also a considerable literature on the use of concurrent thyroid hormone as a means of accelerating response to TCAs in nonrefractory patients.⁴² There have been three placebo-controlled trials of T3 used concurrently with SSRIs to accelerate response and increase response rate, two positive^{43, 44} and one negative.⁴⁵ These studies were not designed to assess augmentation efficacy, since drugs (SSRI and T3/placebo) were initiated simultaneously from the outset of treatment. These studies also mixed non-resistant with varying percentages (8–38%) of TRD patients. There are several open-label studies showing benefits for thyroid augmentation in TRD patients using SSRIs as a primary treatment,^{46–48} and one controlled study showing no difference between augmentation with T3, lithium, and T3 plus lithium in TRD patients.⁴⁹ The STAR*D study compared T3 and lithium augmentation and found no significant difference in remission rates between the two, but did find T3 was better tolerated.⁵⁰

In most published trials, T3 has been used at a dose of approximately 50 mcg/day. Baseline thyroid stimulating hormone (TSH), T3, and free T4 should be measured before starting treatment. However, the lack of controlled data for thyroid augmentation for TRD in patients receiving SSRIs as a primary treatment is an important deficiency in the current literature.

3.3.3 Bupropion and Buspirone—Bupropion is a norepinephrine/dopamine reuptake inhibitor, whereas buspirone is a serotonin (5-HT) 1A receptor partial agonist. Augmentation with one or the other of these agents was compared in the STAR*D trial, in that context following initial nonresponse to citalopram.⁵¹ Selection of these agents enabled evaluation of a drug with a different monoamine reuptake target in combination with ongoing SSRI treatment.

Augmentation with bupropion has enjoyed wide popularity among practicing psychiatrists in recent years, in part because of the drug's good tolerability and favorable side effect profile, including fewer sexual side effects than other antidepressants.⁵² However, bupropion has not been evaluated in a placebo-controlled trial as an augmenting agent. Buspirone, while also well tolerated as monotherapy, has failed to show efficacy in placebo-controlled augmentation studies.^{53, 54}

In the STAR*D study, bupropion and buspirone had comparable efficacy, although bupropion had fewer side effects. Mean daily doses used in STAR*D for bupropion and buspirone augmentation were 267 and 41 mg/day, respectively. The lack of separation between these two treatments could reflect under-dosing of either, but could also reflect a genuine lack of efficacy of both, since the STAR*D design did not include placebo arms. Given its popularity, the lack of placebo-controlled data on bupropion augmentation represents an important deficit in the current literature.

3.3.4 Mirtazapine—The use of mirtazapine as an augmenting agent for TRD is supported by small-scale open-label⁵⁵ and placebo-controlled⁵⁶ trials. In the STAR*D study, mirtazapine was used to augment venlafaxine, with this combination compared to the MAOI tranylcypromine. Efficacy of both the mirtazapine/venlafaxine combination and tranylcypromine monotherapy was low, and these treatments did not differ significantly from each other (although the low dosing of tranylcypromine has been noted above); however, patients reported fewer side effects with the combination treatment.³¹ Given available evidence, mirtazapine may be a reasonable choice as an augmentation agent, but larger controlled trials are needed.

3.3.5 Atypical Antipsychotics—An increasingly common approach to improve antidepressant response for TRD is augmentation with atypical antipsychotics. This strategy has received considerable attention over the last several years, with a large number of published trials now available. While the exact mechanism of augmentation is not known, it is hypothesized that atypical antipsychotics can act as 5-HT_{2A} receptor antagonists, alpha 2 adrenergic antagonists, 5-HT_{1A} agonists, and monoamine reuptake inhibitors.^{57–60} Just as these drugs show considerable variation in their specific mechanisms of action, they have also shown variable efficacy in clinical trials as augmentation agents for TRD.

3.3.5.1 Aripiprazole: There have been three published large (total N = ~ 1000), positive, double-blind, placebo-controlled trials using aripiprazole as an augmentation agent for TRD.^{61–63} Currently this drug has a U.S. Food and Drug Administration (FDA) indication for adjunctive treatment of major depression, the first such indication of its kind. Each of these trials was 14 weeks long, with patients who had failed between 1–3 previous antidepressant trials. The dose of aripiprazole was on average 11–12 mg/day. Aripiprazole was superior to placebo in both response and remission rates, based on the clinician-rated MADRS, in all three trials. However, the first two of these trials^{61, 62} did not find significant improvement in symptoms on patient-rated depression scales (i.e., the QIDS-SR and the Inventory for Depressive Symptoms [IDS-SR]); additionally, in the third trial⁶³ there was no change in overall disability, as measured by the self-reported Sheehan Disability Scale.⁶⁴ These findings raise some concern about the divergence between clinician- and patient-rated outcomes.

In the initial registration trials, aripiprazole was dosed slightly lower when used in conjunction with fluoxetine because of concerns about pharmacokinetic interactions, but a subsequent study showed no changes in aripiprazole concentrations when used with venlafaxine, fluoxetine, escitalopram or sertraline.⁶⁵ Another recent analysis found that the presence of anxious or atypical features did not appear to affect the response or remission rates found with aripiprazole,⁶⁶ which may be clinically important given clear evidence from the STAR*D study showing worse outcomes for these subgroups.⁶⁶ In light of these considerations, aripiprazole is a reasonable choice for augmentation for TRD, with the continued caveat regarding discrepant results between clinician- and patient-rated outcomes.

3.3.5.2 Olanzapine: Olanzapine augmentation has been evaluated for TRD in two positive^{67, 68} and three negative controlled trials,^{68–70} in all cases using the olanzapine/fluoxetine combination (OFC). In two of the negative trials, OFC was no more effective than fluoxetine or olanzapine monotherapy;^{68, 69} in the third, it was no more effective than fluoxetine or venlafaxine, although superior to olanzapine monotherapy.⁷⁰ As expected from previous clinical trials in other disorders, there was significant weight gain during treatment with olanzapine; in some analyses weight gain was greater with OFC than with olanzapine monotherapy.⁷¹ Based on the available data, however, olanzapine (in combination with fluoxetine) has received FDA approval for the acute treatment of TRD. The clinical implications of these findings will need to be further clarified, as there are no data directly comparing olanzapine to other augmenting agents with more benign side effect profiles.⁷²

3.3.5.3 Quetiapine: Quetiapine augmentation has been evaluated for TRD in two large (total N = ~800), positive, placebo-controlled phase III registration trials^{73, 74} (using the extended-release [XR] formulation), and in one negative trial (using the immediate-release formulation).⁷⁵ All three studies employed doses of about 300 mg/day. These findings have been presented but not yet published in peer-reviewed journals, so careful assessment of the safety and efficacy outcomes in these data will be needed to clarify their implications for the use of quetiapine augmentation in clinical practice.

3.3.5.4 Risperidone: Findings with risperidone augmentation have been generally positive in controlled studies. Two trials with a 4–5 week lead-in phase for antidepressant treatment have shown superiority over placebo,^{76, 77} although the brevity of the lead-in phase confounds the interpretation of these results. However, a third double-blind trial showed no difference from placebo in MADRS-rated depressive symptoms, even though suicidality ratings were significantly better with active drug.⁷⁸ Another study showed no significant difference from placebo in time to depressive relapse or relapse rate during long-term risperidone augmentation.⁷⁹ Given the mixed data available, risperidone may be considered as an augmentation option, but perhaps not as first-line in the atypical antipsychotic class.

3.3.5.5 Ziprasidone: Ziprasidone has potent monoamine reuptake inhibiting properties, which would suggest its utility for depression.⁸⁰ However, data supporting its use as an augmentation agent are very limited, with one positive open-label^{81, 82} and one negative open-label trial.⁶³ Based on the available data, ziprasidone does not appear to have a role as an augmentation option at this time.

3.3.5.6 Paliperidone, Iloperidone, Asenapine: There are no data yet available on the augmentation efficacy of these most-recently FDA-approved antipsychotics, including paliperidone, the 9-hydroxy metabolite of risperidone, iloperidone or asenapine.

3.3.5.7 Meta-Analyses of Atypical Antipsychotic Augmentation: Two meta-analyses on the use of atypical antipsychotics for augmentation in TRD have recently been published. The first, by Papakostas et al.,⁸³ showed a pooled response rate of 57% for patients given atypical antipsychotics, compared to 35% for placebo. This earlier meta-analysis included significant amounts of open-label data in addition to data from controlled studies. To address the issue of possible bias due to the inclusion of open-label data, Nelson and Papakostas⁸⁴ repeated the initial analysis with only controlled trials. They found that adjunctive antipsychotics were significantly more effective than placebo for response (odds ratio = 1.69) and remission (odds ratio = 2.00). Mean odds ratios did not differ between atypical agents and were generally not affected by trial duration or definition of treatment resistance. In this meta-analysis, patients receiving atypical augmentation were more like to discontinue due to side effects than were those given placebo (odds ratio = 3.91).

Potential adverse effects with atypical antipsychotics are an important consideration. These agents carry significant risks of weight gain and metabolic syndrome, although the degree of risk differs by drug. All of these drugs carry black box labeling warnings for increased mortality in elderly patients with dementia-related psychosis.⁸⁵ Atypical antipsychotics may also result in neuromotor side effects, including extrapyramidal symptoms, tardive dyskinesia, and neuroleptic malignant syndrome. Long-term safety and efficacy data with atypical antipsychotic augmentation are very limited, and there have not yet been comparisons between atypical antipsychotic augmentation and more traditional augmentation regimens.^{86, 87} However, it is equally important to recognize that placebo-controlled trials of lithium augmentation comprise a total of only 269 patients (with another 469 in comparator-controlled studies), compared to the approximately 3,500 included in trials of atypical antipsychotic augmentation.^{5, 84} Older studies with lithium and T3 also suffer from other methodological limitations, including inadequate criteria for treatment resistance and response, variability in duration and dosing, and idiosyncratic designs.⁵

3.3.6 Stimulants and Related Compounds—Controlled data for stimulant augmentation for TRD have generally been negative. The older amphetamine-like stimulants have always been attractive candidates as augmenting agents because of their documented euphorogenic effects, mediated primarily by their ability to enhance dopamine neurotransmission. However, a recent study examining the use of extended-release methylphenidate in patients with TRD

found no separation between drug and placebo in response or remission rates.⁸⁸ Another trial with extended release methylphenidate replicated these findings, although improvement was seen in fatigue and apathy.⁸⁹ A major concern with amphetamine-like stimulants is the risk of abuse and diversion, particularly in patients with comorbid substance abuse.⁹⁰

Atomoxetine, a norepinephrine reuptake inhibitor used clinically for similar indications as are stimulants (e.g., attention deficit hyperactivity disorder [ADHD]), did not separate from placebo in patients with a partial response to sertraline treatment in a large-scale placebo-controlled trial.⁹¹ Modafinil, a newer stimulant which has been proposed to have a mechanism of action independent of its effects on dopamine, has been investigated as an augmenting agent in two large, placebo-controlled trials. Initial improvement in depressive symptoms seen with modafinil was not sustained, although apathy and fatigue remained significantly improved from baseline.^{92,93} A subsequent retrospective pooled analysis suggested that modafinil augmentation may improve depression in TRD patients with significant sleepiness and fatigue.⁹²

3.3.7 Pindolol—Pindolol is a nonselective beta-adrenergic receptor antagonist that is approved for use in the management of hypertension. Its action as an antagonist at the neuronal 5-HT_{1A} autoreceptor led to studies of its antidepressant effects. Initial open-label trials suggested efficacy as an augmentation agent for TRD and as an adjunct for accelerating response to primary antidepressants in unselected depressed patients.⁹⁴ However, most placebo-controlled augmentation studies in TRD have been negative,^{95, 96,97} with only one small positive study.⁹⁸ Placebo-controlled studies of pindolol's ability to accelerate the onset of primary antidepressants have been more variable, and there is still a lack of consensus in the field.^{99,100} At this point, pindolol does not appear to have a role in the treatment of TRD.

3.3.8 Lamotrigine—Lamotrigine is approved by the FDA for maintenance treatment in bipolar disorder, and appears to have particular efficacy in treating bipolar depression.¹⁰¹ Several retrospective studies^{102, 103} have suggested lamotrigine as an augmenting agent for TRD, putatively reflecting its mechanism of action as an inhibitor of presynaptic glutamate release. However, there are at least two small, placebo-controlled trials that found no difference in TRD response rates to lamotrigine augmentation,¹⁰⁴ although in the second study therapeutic doses of lamotrigine were maintained for less than 3 weeks due to the titration schedule.¹⁰⁵ These data do not support a role for lamotrigine in the management of TRD.

3.3.9 Sex hormones—While several open-label studies examining testosterone for men have been promising, controlled studies have been mixed; one small placebo-controlled augmentation study was positive in men with low or low-normal testosterone levels,¹⁰⁶ and two other small controlled augmentation trials were negative.^{107, 108}

Estrogen augmentation for women with TRD has also been examined, with similarly mixed results. An initial open-label study of estrogen augmentation was positive,¹⁰⁹ and one small placebo-controlled study in perimenopausal women who had partially responded to SSRI treatment found benefit from the addition of estrogen.¹¹⁰ However, another augmentation study found improvement with testosterone, but not progesterone or estrogen plus progesterone.¹¹¹

At this point, it is still unclear if hormone augmentation with androgenic or estrogenic compounds is effective for TRD, although there may be more utility for this approach in selected patient populations with low hormone levels. The potential for significant long-term adverse health consequences with these agents warrants caution in their use.

4. Future treatments

4.1 Melatonin Receptor Agonists

Melatonin may be effective in the treatment of seasonal affective disorder,¹¹² and agomelatine, a 5-HT_{2C} receptor antagonist and melatonin-1 agonist, has shown promise in several trials for antidepressant effects.^{113–116} In the available clinical trials, patients with TRD have largely been excluded, so there is little data on the efficacy of these compounds for TRD at this time.

4.2 Acetylcholine Receptor Drugs

Drugs that affect the acetylcholine receptor (AChR) system have demonstrated promise as a possible approach to TRD, using both nicotinic (nAChR)- and muscarinic (mAChR)- selective compounds. Initial placebo-controlled studies of monotherapy with intravenous scopolamine, a muscarinic antagonist, were positive in a TRD population, generating considerable excitement in the field.¹¹⁷ More recently, attention has been directed towards the nAChR. In one small controlled trial, mecamylamine, an nAChR antagonist, yielded greater response rates than placebo during augmentation of citalopram.¹¹⁸ Another unpublished controlled trial of mecamylamine augmentation found improvement in rates of response, but not remission,¹¹⁹ and a study of S-mecamylamine is underway.¹²⁰ A small, open-label study in smokers with TRD found antidepressant effects of augmentation with varenicline, an nAChR partial agonist.¹²¹ While data are still preliminary, drugs that affect the acetylcholine system may be future options for TRD.

4.3 N-methyl-D-aspartate (NMDA) Receptor Drugs

Recent studies of N-methyl-D-aspartate (NMDA) receptor antagonists for TRD reflect an acknowledgement of the limitations of the monoamine hypothesis of depression and emerging interest in the role of glutamate function in psychiatric illness. Controlled results with memantine, an NMDA-receptor antagonist, were disappointing.¹²² Ketamine, an NMDA-receptor antagonist used clinically as an anaesthetic, was subsequently evaluated, and a placebo-controlled trial of intravenous ketamine showed significant antidepressant effects that were sustained for up to one week after the initial dissociation period resolved.¹²³ Since this initial finding, several ongoing clinical trials investigating ketamine for TRD have been undertaken.¹²⁴ There has been one positive placebo-controlled trial of intravenous CP-101,606, an NR2 subunit-selective NMDA antagonist, in which rapid antidepressant effects without dissociation persisted at least a week after initial infusion in augmentation of ongoing paroxetine treatment.¹²⁵ Riluzole, a putative glutamate release inhibitor that is approved for the treatment of amyotrophic lateral sclerosis, showed evidence of efficacy in a small open-label augmentation trial,¹²⁶ although a small controlled trial for relapse prevention after acute ketamine administration was negative.¹²⁷

5. Conclusions

Currently available treatments have limited efficacy for TRD, a state of affairs that is complicated by a lack of consensus on the definition of TRD itself. However, although there is no clear “magic bullet” to address TRD, there are a wide variety of pharmacological options available with established, even if modest, efficacy. Several novel therapeutic options, targeting neurotransmitter systems outside of the standard monoamine hypothesis, are currently being investigated as promising alternatives.

6. Expert Opinions

6.1 Limitations of the TRD Criteria

A persisting problem in evaluating the clinical implications of research findings on TRD is the lack of uniform diagnostic criteria. While there are staging methods available,^{128, 129} none has achieved widespread use. A recent review suggested that the most frequently used definition of TRD in published studies is failure to achieve remission after two adequate antidepressant trials within the current major depressive episode.¹³⁰ This might be a reasonable criterion given the current state of knowledge, although its utility depends critically on how the adequacy of a trial is defined. The field will need to directly address this issue so that patients can be more accurately and reliably identified and staged prior to treatment.

6.2 Limitations of Available Efficacy Data

There are important weaknesses in the data on pharmacological options for TRD. For example, although lithium augmentation is usually recommended as a first-line strategy, there is very little placebo-controlled data examining the efficacy of lithium as an augmentation agent for SSRI treatment; most of the supporting evidence for this approach involves the use of TCAs as the primary antidepressants. Findings with lithium augmentation of SSRIs in the STAR*D study were not encouraging, but as noted above, there are significant limitations to that study, which was in any case not placebo-controlled or blinded. In the absence of directly relevant data, positive or negative, evaluation of the role of lithium augmentation as an option for TRD is problematic in the current treatment environment, in which most depressed patients are receiving primary pharmacotherapy with SSRIs.

Another, and probably more significant, weakness is the limited comparative data. While the STAR*D study did compare different approaches at different “tiers” of treatment, the lack of placebo controls, blinding, or true randomization limit conclusions that can be drawn regarding efficacy. Moreover, the STAR*D study was designed before the massive increase in data on atypical antipsychotic augmentation; these agents were not included in the study, and there are currently no data comparing older augmentation regimens with these newer options. This is a critical deficiency in the database, as the atypical antipsychotics have medically significant side effect profiles and are more expensive than older agents, so their proper place in the treatment hierarchy is a matter of real consequence.

6.3 Treatment recommendations

6.3.1 Diagnosis and severity—The first step in addressing TRD is correctly establishing the diagnosis. Ascertaining whether bipolar disorder or psychotic depression is present is essential. Comorbid anxiety disorders may indicate a poorer prognosis, and such patients may need adjunctive anxiolytics or other treatments. Identifying other Axis I (including substance use) and Axis II disorders is also critically important, as these conditions may require different treatment approaches. Obviously, the possible contributions of medical comorbidities on Axis III to the clinical presentation must be evaluated.

Once the diagnosis of TRD is accurately made, standardized rating scales may be useful in assessing symptom severity; such scales can be administered at regular intervals to continually measure symptom response (or lack thereof) to sequential treatment interventions. If possible, drug changes should be executed one at a time, to minimize the confounding effects of multiple simultaneous changes and thereby increase the likelihood that the causal basis of any clinical improvement is understood. Augmentation, rather than switching, may be more efficacious, although it carries the additional complications of polypharmacy and associated issues of medication adherence.

6.3.2. Treatment—Of the pharmacologic treatments available, the most rigorous data available is for augmentation with atypical antipsychotics, particularly aripiprazole. However, the preponderance of evidence in favor of atypical antipsychotics is due to a lack of data using older augmentation agents with SSRIs, rather than failed trials with those agents. Given the potential serious side effects and complications of the atypical antipsychotics, augmentation with these agents should not be undertaken lightly. Selection of a specific atypical antipsychotic should be guided by a consideration of available data on efficacy and adverse effects for that drug.

Given the lack of data on lithium augmentation with SSRIs, and the relatively high burden of potential acute and chronic side effects with that drug, lithium augmentation should be reserved until some other treatment options have failed. Again, this recommendation assumes the use of an SSRI as the primary antidepressant; lithium augmentation of TCA treatment is an appropriate early-line choice. T3 is also an appropriate choice for augmentation of TCAs, whereas its role in augmenting SSRIs for TRD is less clear. While beyond the scope of this review, most patients with TRD should be engaged in an evidence-based psychotherapy. There is preliminary evidence supporting the efficacy of mirtazapine augmentation for TRD. Until there is more evidence, buspirone, bupropion, and sex hormones have an unclear role in the treatment of TRD. There does not seem to be an evidence-based role for pindolol, stimulants and related compounds, or lamotrigine in TRD.

7. Future directions

Clearly, current pharmacological options for TRD are not sufficient. There are several exciting areas in pharmacotherapy development that hold promise for the future, including drugs that act on the glutamate, acetylcholine, and melatonin systems. Given increasing recognition of the role of inflammation in depression, one can also hope that agents affecting these processes may prove to have utility for TRD.¹³¹ The role of newer neuromodulation approaches, such as TMS, VNS, and DBS, either as monotherapies or as augmentation strategies, is still evolving. Both TMS and VNS have received FDA approval for TRD. However, given the associated costs, and in some cases, risks, of these approaches, comparative efficacy trials with older agents will be important. Ultimately, better understanding of the basic pathophysiology of TRD will be needed to develop better-targeted and more effective treatments.

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Table 1**Augmentation Options for Treatment-Resistant Depression (TRD)**

Medication	Available data	Comments
<u>Traditional Agents</u>		
Mirtazapine	Positive RCTs, STAR*D	Limited data
Bupropion	Multiple open label-trials, STAR*D	No RCTs
Buspirone	Negative RCTs, STAR*D	Ineffective in RCTs
T3	Limited RCTs with SSRIs, positive when combined with TCAs	Comparable to lithium in STAR*D but fewer side effects
Lithium	Limited RCTs with SSRIs, positive when combined with TCAs	Comparable to T3 in STAR*D but more side effects
Lamotrigine	Negative RCTs	Small Ns, mixed populations
Pindolol	Negative RCTs	Positive data for acceleration
Stimulants	Negative RCTs	May have a role for adjunctive treatment of apathy
Sex Hormones	Mixed data, most for testosterone	Significant long-term side effects
<u>Atypical Antipsychotics</u>		
Aripiprazole	3 positive RCTs, FDA indication	Negative self-report outcomes
Olanzapine/OFC	One positive RCT, multiple equivocal RCTs, FDA indication	Weight gain, metabolic syndrome
Quetiapine	One negative RCT, two positive unpublished RCTs with XR formulation	Weight gain, metabolic syndrome
Risperidone	Two positive RCTs, one negative	Trials with short treatment lead-in (4–5 weeks on previous AD treatment)
Ziprasidone	Mixed open-label data only	
All Antipsychotics	Response (odds ratio = 1.69) and remission (odds ratio = 2.00) vs. PBO from RCTs	Discontinuation rates for adverse events higher vs. PBO (odds ratio = 3.91)

Key: STAR*D, Sequenced Treatment Alternatives to Relieve Depression; RCT, randomized controlled trial; PBO, placebo; AD, antidepressant; OFC: olanzapine/fluoxetine combination

Table 2**Future Options for Treatment-Resistant Depression (TRD)**

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, mecamlamine, varenicline)	IV infusions used for scopolamine, studied as augmenting agents rather than primary treatment, small Ns in published results, larger trials underway
Glutamate Drugs (ketamine, NR2 antagonists, riluzole)	Short-term symptomatic relief, only IV infusions used, further trials underway
Neurostimulation (VNS, TMS, DBS)	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

Key: NR2: NMDA receptor subunit; VNS: vagus nerve stimulation; TMS: transcranial magnetic stimulation; DBS: deep brain stimulation