# TRD: A Therapeutic Challenge

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The past 15 years have witnessed considerable advances in the understanding of the prevalence and neurobiology of depression and has seen a remarkable change in the psychopharmacological and psychological treatment of depression. The introduction of the selective serotonin reuptake inhibitors (SSRIs) and the subsequent release of other antidepressants with different mechanisms have provided a wide variety of treatment options. But, the complex etiology of depression continues to challenge the clinical practitioner. It is estimated that 14 million people suffer from depression and only 7.2 million receive some form of treatment. For those who, despite treatment, continue to suffer from treatment-resistant depression (TRD) a modest 30% will achieve remission.[1] TRD is not consistently defined; however, failure to respond to three or more adequate trials is frequently used as a standard. Patients who fail to respond to current therapies, or those who only partially respond and patients who relapse, endure burdens across multiple domains of suffering and function.

## Factors complicating TRD treatment response

Undiagnosed bipolar disorder is a major cause of non-response and presents a number of clinical problems, as well as therapeutic challenges, such as choosing the most effective antidepressant and the worry of mania induction. It is also important to rule-out comorbid medical disorders, such as hypothyroidism, which remains the number one cause of treatment resistance. Depression, as a presenting symptom of multiple medical diseases, will respond to treatment of the underlying causes.

Depression that is comorbid with anxiety disorders presents with:

- more severe symptomatology,
- poorer overall function,
- higher risk of suicide,
- poorer response to treatment,
- poorer prognosis and
- a more chronic, recurrent course.

Personality disorders and substance abuse (including alcohol abuse with or without dependence) are major factors that complicate treatment outcome.

Patients with double depression (major depression superimposed on a dysthymic disorder) have poorer outcomes and tend to relapse faster.

Possible reasons for non-response to pharmacological treatment are listed in Table 1.

**Table 1**

**Reasons for non-response to pharmacologic treatment[2,3]**

- Non-compliance
- Underdosage
- Delayed response
- Poor GI absorption
- Concurrent drug therapy
- Comorbid medical or psychiatric illness
- Incorrect diagnosis
- Psychosocial factors
- True non-response

## TRD treatment strategies

### Pharmacology

SSRIs remain the first-line treatment with better side-effect profiles and tolerability. Aggressive dosing strategies and prolonged courses of treatment are required to treat severe depression. The aim of

treatment is remission when depressive symptoms are absent or extremely limited. If the higher dose and longer duration are unsuccessful and patients are showing only partial response or no response at all, the following pharmacologic strategies may be helpful to treat these patients (Table 2).

### *Optimization*

Optimization is the increase of an antidepressant agent to its maximum tolerated and recommended dose. In the case of partial or non-responders, a dose should be pushed to its highest tolerable levels and the duration of treatment should often be extended to ensure that patients are given adequate time to respond. This principle of adequate dose and duration is often overlooked in the elderly population, who may take longer to respond and in those with comorbid conditions, who may also take longer to respond and require higher dosages.

Table 2

**Augmentation, combination and switching strategies**

Augmentation strategies
- Add lithium
- Add triiodothyromine
- Add buspirone
- Add stimulants (*e.g.*, methylphenidate)
- Add atypical antipsychotics

Combination strategies
- Combine selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)
- Combine SSRIs and bupropion
- Combine SSRIs and mirtazapine
- Combine monoaminooxydase inhibitors (MAOIs) and TCAs

Switching strategies
- Switch SSRI to another SSRI
- Swicth SSRI to serotonin norepinephrine reuptake inhibitor (SNRI)
- Switch SSRI to mirtazapine
- Switch SSRI to bupropion
- Switch SSRI to TCA
- Switch SSRI to MAOI

### *Augmentation*

Augmentation is the addition of a non-antidepressant medication to the original agent, producing pharmacologic synergy to increase the magnitude of the patient's response to the medication. Augmentation strategies are particularly useful for partial responders and when a rapid response is required. There are a variety of agents including:

1. Lithium augmentation: The efficacy of lithium augmentation is best documented for tricyclic antidepressant (TCA) non-responders, most of whom respond within three weeks of augmentation. However, besides some anecdotal reports, there is no convincing evidence for its efficacy with SSRIs.[4] Responders need to continue their lithium.
2. Triiodothyromine (T3) augmentation: T3 augmentation is equal to lithium augmentation and is better than placebos with tricyclic antidepressants. There are some uncontrolled reports with SSRIs, but few controlled randomized trials. Doses of T3 should be started at 25 mg q.d. and increased to 50 mg q.d.. The best patient response may be seen in anergic depression.
3. Buspirone augmentation: This has been found to be effective in severe and treatment-refractory depression.[5] Doses vary between 10 mg q.d. and 60 mg q.d. An improvement in sexual dysfunction has been reported with buspirone augmentation.
4. Stimulant augmentation: There is anecdotal evidence, but no controlled trials demonstrating that psychostimulants (*e.g.*, methylphenidate, dextroamphetamine, pemoline) are effective in the treatment of medically ill and depressed elderly patients and in combating anergic side-

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effects of SSRIs.[6] Modafinil, a novel psychostimulant, non-dopaminergic drug, in doses of 100 mg q.d. to 200 mg q.d. is reported to improve fatigue and sleepiness.

5. Atypical antipsychotic augmentation: New research involving the augmentation of an SSRI/serotonin norepinephrine reuptake inhibitor (SNRI) with atypical antipsychotics (0.25 mg q.d. to 1 mg q.d. of risperidone, 200 mg q.d. to 400 mg q.d. of quetiapine and 8 mg q.d. to 18 mg q.d. of olanzapine) is effective and generally well tolerated in patients with TRD, though further investigation is needed.[7,8]

### *Combination*

Combination is the addition of an antidepressant to another antidepressant. The reasons to combine are to carry forward a partial response to avoid discontinuation of the initial agent and to treat break through symptoms. The candidates for combination treatment are those with partial response, response without remission and those who are able to tolerate the antidepressant and able to take more than one medication. Even through evidence-based polypharmacy is limited, the current treatment approach is to combine antidepressant agents that have different mechanisms of action.[9,10]

1. SSRIs and TCAs: Open clinical trials suggest that more rapid ß-receptor downregulation and better response result from combining a TCA with an SSRI. An estimated 65% of non-responders to SSRI monotherapy respond to combination SSRI. In TCA therapy, doses of nortriptyline and desipramine should be initiated at 25 mg q.d. and increased to recommended doses of 100 mg q.d. to 150 mg q.d.[11]
2. SSRI and bupropion: Numerous case studies report beneficial use of bupropion when combined with an SSRI. An estimated 70% of partial responders to either bupropion or SSRI monotherapy respond favorably to combination therapy. Bupropion should be initiated at 75 mg q.d. and increased to the recommended dose of 150 mg q.d. to 225 mg q.d.[12]
3. SSRIs and mirtazapine: The combination of mirtazapine (an α–2 antagonist) and SSRI may be an effective and well-tolerated tool in agitated, anxiety-prone treatment-resistant patients who have failed to adequately respond to monotherapy with SSRIs, venlafaxine, or mirtazapine.

*Even through evidence-based polypharmacy is limited, the current treatment approach is to combine antidepressant agents that have different mechanisms of action.*

4. Monoaminooxydase inhibitors (MAOI)/TCA combination treatment: Combining MAOIs and TCAs is another strategy that should be considered for treatment-refractory depressed patients. Concurrent use of MAOIs with SSRIs should be avoided.

### *Switching*

Switching strategies present a whole spectrum of options.[13] Switching within class presents with a slight pharmacological difference and out-of-class presents a differential neurochemical effect to match the depressive subtype comorbidity.

1. Switching one SSRI to another SSRI: Three open trials of historical failures showed 50% to 60% response rates when switching SSRIs.[14] The advantage is that an immediate switch appears to be well tolerated and the disadvantage is possibly less effective than a switch to a non-SSRI.

**Table 3**

**Strategies for dealing with treatment-resistant depression**

| Pharmacology | Psychotherapy |
|---|---|
| • Determine if dosage is adequate and increase if needed | • Build on a therapeutic alliance through empathic understanding of the patient's experience |
| • Add lithium, liothyronine sodium, burspirone, stimulant or atypical antipsychotic if patient only partially responds | • Instill hope, provide reasssurance, support and encouragement |
| • Add TCA, bupropion or mitazapine to SSRIs | • Provide a concise, clear explanation of the illness, the severity and treatment strategies, as well as expected outcome and the importance of compliance |
| • Switch SSRI to SNRI, mirtazapine, bupropion, TCA, MAOI or another SSRI | • Discuss the use of medications and their side-effects |
| • Conisder high-dose tranylcypromine (close monitoring is required) | • Invite family support and provide family education |
| • When all else fails, consider electroconvulsive therapy in severe or psychotic patients | • Suggest cognitive behavioural, interpersonal or dynamic psychotherapy and if indicated, refer to a specialist |
| | • Supplement with written educational materials |

2. Switching SSRI to SNRI: The rational is that a dual action is better than single action with potential synergistic effects. In open label trials, 30% to 69% of varying degrees of resistance responded to a switch to venlafaxine.[15] The possible advantage is that SNRIs are superior to SSRIs in severe/melancholic depressions and the disadvantage is that BP is elevated at higher doses.
3. Switching to mirtazapine: Mirtazapine is an adrenergic antagonist that enhances the transmission of norepinephrine and serotonin. Switching can be immediate and the maximum recommended dose is 45 mg q.d. to 80 mg q.d. Fourty seven per cent of patients responded to an open label trial after non-response to SSRIs.[16] Disadvantages are sedation and weight gain.
4. Switching to bupropion: Bupropion is a norepinephrine and a dopamine reuptake inhibitor. Switching can be immediate, but SSRI-induced discontinuation reactions may occur when switching. In a double blind study among 30 TCA non-responders, bupropion was superior in reducing depressive symptoms.[17] An advantage is a reduced incidence of weight gain and sexual dysfunction than compared to SSRIs.
5. Switching to TCAs: The advantage of a TCA switch is the superiority of some TCAs compared to SSRIs in severe/melancholic depression. The disadvantages are sedation, anticholinergic side-effects, weight gain and lethality in overdose.
6. Switching to MAOIs: This is particularly useful in atypical unipolar depression and anergic bipolar depression. Of note is the use of high dose tranylcypromine (90 mg q.d. to 170 mg q.d.) in severe refractory patients to multiple antidepressant agents, combination treatments and electroconvulsive therapy (ECT) with a 50% remission rate.[18] The disadvantages are dietary restrictions, risk of hypertensive crises and serotonin syndromes as well as wash outs before starting and after ending treatment.

When the above treatments fail, consider the following:

- ECT: ECT is indicated in severe, psychotic or acutely suicidal depression. It is also useful in patients who cannot tolerate antidepressants.
- Vagus nerve stimulation (VNS): VNS was recently approved by the US Food and Drug Administration for TRD. The treatment involves the surgical implantation of a small device into the left chest that delivers continual electrical

pulses to the right vagus nerve. Early studies have shown that the response rates tend to increase over time to about 15% of the highly treatment resistant subjects treated.

Other device-based treatments (*i.e.*, transcranial magnetic stimulation and deep brain stimulation) are under investigation.

### *Psychotherapy*

Establishing a therapeutic relationship is essential in the management of patients who suffer from severe depression. The patient must feel supported and the physician must provide an empathic understanding of the patient's experience and convey a message of hope and optimism. Involving the family in the therapeutic alliance is often beneficial. Relatives can receive support and gain emotional strength that they can pass on to the patient.

#### *Depression-focused psychotherapies*

Of the more specific types of psychotherapy, depression-focused psychotherapies include:

- cognitive therapy,
- behaviour therapies (behavioural activation and problem-solving),
- interpersonal psychotherapy and
- cognitive behavioural analysis systems of psychotherapy.

Their commonalities, effective in moderately-severe depression are to be:

- time-limited,
- focused (present tense),
- structured,
- pragmatic,
- personally relevant and
- hope-instilling.

Comorbid pharmacology, or psychotherapy treatment, is emphasized in the American Psychiatric Association's practice guidelines and is particularly suggested for severe recurrent depression, chronic and double depression, complicated and comorbid disorders and TRDs.

Additive, time-limited dynamic psychotherapy (DP) has been shown to be beneficial for this high-risk population (Table 3).

## *Conclusion*

As the vast majority of patients with depression fail to achieve and sustain remission, strategies for treating resistant depressions remain a fundamental interest for all mental health clinicians. It is important to ensure that the diagnosis is confirmed, that dosing and duration of treatment are adequate and that patients are compliant with medication(s).

Treatment-resistant patients remain a therapeutic challenge and require a treatment approach that is comprehensive and, at times, innovative. This article reviewed different treatment strategies that have proven beneficial in the hopes of reducing the pain and suffering of these patients and, ultimately, conquering depression. Dx

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