Thoughtful prescribing for patients with difficult-to-treat depression

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Major depressive disorder is highly prevalent. Approximately 1 in 20 Canadians are diagnosed with it each year, and it is the second highest cause of disability worldwide.[1] Nonresponse to treatment is common, with response rates between 30% to 60% after initial antidepressant therapy.[2-7] Only around 50% of people remit after 2 sequential treatments, and around 30% experience chronic residual symptoms.[2-7] The term *treatment-resistant depression* is often used to refer to an insufficient response despite an adequate trial of at least 2 antidepressants, although there is no universal consensus on this definition.[3,5,7,8] There is, however, broad agreement on the importance of early treatment optimization, since with each treatment failure the chance of success declines, the likelihood of recurrence increases, and the burden of disease intensifies.[2,4,9,10]

Informed by the available evidence and guidelines,[8,11-17] this article discusses an approach to managing difficult-to-treat depression (DTD) and applies practical recommendations to a patient case. To reflect recent changes to terminology in this field, the term *difficult-to-treat depression* will be used in this article rather than *treatment-resistant depression* and will refer to no response or only partial response (ie, less than 50% reduction in symptom severity) to at least 1 adequate antidepressant trial.[13]

Case presentation

Mia is a nonbinary 23-year-old who uses they-them pronouns (female sex). They present today for a follow-up visit for depression. You diagnosed Mia with moderate to severe depression 6 months ago. They have no other medical conditions. Their family history is relevant for mental health disorders (their mother has anxiety and depression, their father may possibly have bipolar disorder, and their sister has attention deficit hyperactivity disorder and anxiety). Mia participated in 8 sessions of online, group cognitive behavioural therapy and completed an 8-week trial of 20 mg of escitalopram daily, which was minimally helpful. You tried switching Mia to venlafaxine, which they have been taking for the past 6 weeks at a dose of 225 mg daily. Mia is not taking any other medications and is not currently pregnant or sexually active.

Today Mia reports that, while still struggling, they have noted some small improvements. Mia is still experiencing sadness, guilt, and anhedonia most days, but these feelings have been less overwhelming lately. While Mia would previously sleep most of the day, they are now able to get out of bed for a few hours each day to get chores done around the house. They have no trouble sleeping throughout the night. Mia has noted a slight improvement in their irritability, resulting in fewer arguments and confrontations with friends and family than previously. Mia reports an increased appetite and is worried about gaining weight. Mia is still on leave from work and does not feel well enough to go back. They are having trouble "thinking straight," feeling too tired or unmotivated to do most daily activities, and worrying about what their co-workers will think about them.

Thorough reassessment

Before adjusting therapy, it is important to reassess the patient's status and factors that might influence therapy.[8,14] For example, the dose may be subtherapeutic, the duration of therapy might not have been long enough, or the patient may not be taking their antidepressant as prescribed. There may be medical conditions or medications causing or worsening depression. Additionally, it is crucial to assess the patient formally and regularly for any symptoms on the mania spectrum or risk factors for bipolar disorder.[18] The Mood Disorders Questionnaire or Rapid Mood Screener can be used to assist in reassessment; specialists also suggest investigating for agitation, irritability, or distractibility as potential flags for depression with mixed features or bipolar disorder.[19-21] A list of questions to consider is presented in **Table 1**.

Back to the case

You confirm with Mia that they have been taking 225 mg of venlafaxine daily as prescribed for the past 6 weeks. They are not taking any other prescription or over-the-counter medications that could be contributing to their depressive symptoms or interfering with venlafaxine metabolism. You inquire about alcohol and other substances and discover that Mia is drinking 4 to 6 beers a day and is not using any other substances. Findings of laboratory workup from 6 months ago are unremarkable. Mia reports that their family life at home is "not great" but things have been like this for years, with no recent new stressors or adversity. You complete the Mood Disorders Questionnaire, and the score is not positive for bipolar disorder. However, you do note that Mia is experiencing irritability and distractibility, which could potentially be indicative of depression with mixed features. Additionally, their symptoms of hypersomnia and increased appetite are consistent with atypical features of depression.

Table 1. Questions to consider before adjusting therapy for a patient with insufficient response to an antidepressant

CATEGORY	QUESTIONS
Adequate trial	• Has the antidepressant been taken at a usual therapeutic dose for at least 4-8 wk?
Adherence	• Is the patient taking their medication as prescribed?
Interactions	• Is anything interfering with the medication's effectiveness (eg, drug-food interactions, administration method)?
Contributing factors	• Is the patient using any substances (eg, cannabis)? • How much caffeine or alcohol does the patient consume? • Are there any acute psychosocial stressors that could be addressed and resolved? • Does the patient have any concurrent medical conditions for which treatment could be optimized (eg, hypothyroidism, anemia, chronic pain, diabetes)? • Is the patient taking any medications that could be contributing to their depressive symptoms (eg, benzodiazepines, opioids, steroids)?
Clinical status	• Has there been a partial response to treatment? • Does the patient have symptoms indicating the possibility of a bipolar illness? • Does the patient have symptoms that could better be explained by an alternative psychiatric diagnosis (eg, attention deficit hyperactivity disorder, personality disorder, disordered eating, substance or alcohol use disorder)? • What are the primary features of the depressive illness? • What are the most impairing symptoms? • What is the risk of suicide?

According to Mia, the most impairing symptoms are hypersomnia, anhedonia, and inability to concentrate. They also worry about how their illness affects their relationships. Mia endorses some passive suicidal thoughts, but says they have no formalized plans. Mia's mom joins at the end of the appointment and adds that she has noted some improvement in Mia's mood and that Mia has had more positive interactions with family since taking venlafaxine.

Approach to therapy

After reassessment and ensuring a therapeutic dose has been used for a minimum of 4 weeks, there are 3 main options for managing inadequate response to depression treatment: continue the present management for up to 12 weeks, switch medications (even within the same drug class), or add a medication with a different mechanism of action. International guidelines agree there is insufficient evidence to routinely recommend one strategy over another, as success is possible with any option and it is unclear if any one strategy is superior.[2,5,8,13,22,23] Delaying medication change can be controversial. Many studies indicate early improvement (ie, in the first 2 weeks) is a good predictor of full response, and thus some specialists suggest a change should be made if there is no response within 2 to 4 weeks.[8,10,24] However, other studies show that waiting 12 weeks before changing therapy can increase response rates and is appropriate for some patients, especially if they have already tried 2 or more antidepressants and have no acute safety risks.[2,15,22,25-27] The choice between switching or adding medication is largely guided by expert opinion. Consensus-based recommendations are summarized in **Table 2**.[8,15]

Back to the case

You discuss possible next steps with Mia. They decline any formal help to address their high-risk alcohol consumption, but they agree to try to cut back on their own. You advise that a venlafaxine dose increase is unlikely to improve response and may cause side effects. Mia wants to make a medication change today rather than waiting for another 6 weeks, so you suggest either switching to another antidepressant or adding another medication. Mia does not want to give up the slight progress they have had with venlafaxine, nor to go through the process of trying a third antidepressant monotherapy. Together, you agree to add a medication to venlafaxine.

Selecting an adjunctive medication

Since there is limited evidence to guide medication selection in DTD and variation across guidelines,[11-17] one consensus-based approach is to tailor medication choice to specific symptoms and incorporate patient preference when possible. Informed by international guidelines, systematic reviews, and individual trials, medications that have demonstrated efficacy as an adjunct to antidepressants in DTD are summarized below. **Table 3** compares drug-specific benefits and harms that may help guide medication selection.[28-35]

Antipsychotics. Multiple meta-analyses indicate adjunctive atypical antipsychotics are efficacious, and some estimate that 1 in every 7 to 12 patients treated for 4 to 12 weeks will respond or remit.[36-40] However, due to uncertainty about the degree of clinical importance of efficacy outcomes, lack of direct comparison with other options, and a high burden of adverse effects, antipsychotics are not necessarily an automatic choice for adjunctive

Table 2. Considerations to guide treatment strategy after insufficient response to an adequate antidepressant trial

RESPONSE	SWITCH	ADD
No response (no observable change to symptoms)	✓	×
Partial response (symptom improvement between 25% and 49%; patient has not yet reached acceptable levels of functioning or well-being)	✓	✓
Poor tolerability or safety risk	✓	×
Acceptable tolerability	✓	✓
Tried only 1 antidepressant	✓	✓*
Tried 2 or more antidepressants	✓*	✓
Patient prefers a therapeutically reasonable option	✓	✓

Data from Kennedy et al[8] and Cleare et al.[15]
*Uncertainty exists in this situation; may be an inferior strategy.

therapy.[12,17,36,41,42] The risk of discontinuation due to adverse effects is 2 to 6 times greater than placebo in short-term studies, and there are well-established harms with long-term use.[36-40] The evidence for antipsychotics also has limitations, such as short study durations (average of 6 to 8 weeks), high heterogeneity in patient populations and methods, impact on function or quality of life not being adequately assessed, exclusion of participants who demonstrated prior response to placebo, and high rates of competing interests from study authors. Nevertheless, second- or third-generation antipsychotics, especially quetiapine and aripiprazole, remain among first-line options to use adjunctively in patients with DTD as these agents have the most robust evidence among all options.[8,13-15]

Lithium. According to meta-analyses, around 1 in every 3 to 9 patients with DTD treated with adjunctive lithium for 3 to 6 weeks may respond.[39,43,44] While response rates appear comparable to other adjunctive options, many trials were of short duration, had small sample sizes, and studied lithium as an adjunct to tricyclic antidepressants (TCAs).[2,39,40,43,44] Lithium was reported to decrease all-cause mortality (number needed to treat of about 36) and reduce deaths by suicide (number needed to treat of about 28) over an average of 81 weeks compared with TCAs, phenelzine, and placebo (pooled data); however, there is low confidence in these data due to heterogeneity and reliance on post hoc analyses.[45,46] Discontinuation rates due to adverse effects range from 4% to 23% across trials, and 20% to 30% of patients have gradual renal decline over many years (eg, ≥20 years), but end-stage renal disease is uncommon (0.5%).[44,47-49] Serum lithium level monitoring is recommended to maintain a target of 0.5 to 0.8 mmol/L (primarily to prevent toxicity rather than to target a specific therapeutic range). Canadian guidelines recommend adjunctive lithium as a second-line treatment, Australian–New Zealand and British guidelines recommend lithium as a first-line treatment, and it is listed by other groups as a reasonable option.[8,12-15]

Bupropion. Although commonly used in practice, adjunctive bupropion has mixed evidence in patients with DTD. Bupropion efficacy is supported by a few randomized controlled trials and the large, naturalistic STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study.[2,50-52] Bupropion had comparable efficacy to adjunctive aripiprazole in a randomized controlled trial in a United States veteran population.[53] Conversely, in a large study of patients with chronic recurrent depression, adjunctive bupropion was not different than selective serotonin reuptake inhibitor (SSRI) monotherapy, one unpublished industry-sponsored trial also had negative results, and some meta-analyses suggest its efficacy is not different than placebo.[39,40,54,55] Bupropion is often well tolerated. Canadian guidelines list adjunctive bupropion as a second-line treatment in patients with DTD, and some other groups also list it as an option.[8,12,15,17]

Mirtazapine. Adjunctive mirtazapine for patients with DTD lacks evidence from controlled trials. Efficacy is supported by a very small randomized controlled trial (N=26) in American patients and a large, open-label randomized controlled trial (N=1646) in Japanese patients.[56,57] Conversely, there is compelling evidence from a randomized controlled trial (N=480) carried out in the United Kingdom that adding mirtazapine to an SSRI or selective norepinephrine reuptake inhibitor (SNRI) does not result in better outcomes compared with continuing current SSRI or SNRI therapy.[58] A Cochrane review also found no difference in depressive symptom severity compared with placebo when mirtazapine was added to SSRIs or SNRIs.[59] Furthermore, the controlled trial conducted in Japan showed that while adding mirtazapine to an SSRI or SNRI was superior to placebo, it was not different than switching to mirtazapine monotherapy. Additionally, some studies indicate switching to a TCA has equal or superior efficacy compared with adding mirtazapine.[2,57,60,61] Even so, adjunctive mirtazapine may provide benefit for some patients and trialling this option can usually be done without much risk, as pooled

dropout rates (due to adverse effects or any cause) were not statistically different than for placebo.[41] Canadian, British, and American guidelines list adjunctive mirtazapine as a second-line treatment and other guidelines also list it as an option.[8,12,14]

Other. Other adjunctive medication options for patients with DTD are less supported by the evidence and guideline recommendations vary. Olanzapine and risperidone have been studied and have conflicting results and a low degree of certainty on positive outcomes.[36-40,59,62]

Table 3. Factors that may help guide adjunctive medication selection for patients with DTD

MEDICATION	UNIQUE BENEFITS OR ROLE IN THERAPY	ADVERSE EFFECTS AND RISKS
Aripiprazole 2-15 mg/d Recommended*: 2.5-5 mg/d	• Mixed features (eg, co-occurring manic symptoms, irritability, agitation)[28] • Atypical features (eg, hypersomnia, hyperphagia, mood reactivity)[29] • Psychotic features • Possibly useful if comorbid substance use disorders or fatigue, or for older adults[30]	• Sedation or insomnia • Extrapyramidal symptoms, especially akathisia • New impulse control disorders (eg, pathological gambling, compulsive eating, uncontrollable sexual urges) • Metabolic adverse effects
Brexpiprazole 1-3 mg/d Recommended*: 2 mg/d	• Mixed or atypical features as above (less evidence than for aripiprazole) • Psychotic features • Possibly useful if comorbid substance use disorders or fatigue	• As for aripiprazole, with possibly less akathisia (dose related) • New impulse control disorders
Quetiapine 50-300 mg/d Recommended*: 150 mg/d	• Mixed features (eg, co-occurring manic symptoms, irritability, agitation)[28] • Psychotic features • Comorbid anxiety or insomnia	• High rates of metabolic adverse effects and weight gain • Sedation, dizziness, hypotension, anticholinergic effects, sexual dysfunction, and possible euphoria • Extrapyramidal symptoms
Lithium Serum level: 0.5-0.8 mmol/L (response seen at as low as 0.4 mmol/L)	• Mixed features (eg, co-occurring manic symptoms, irritability, agitation, impulsivity)[28] • Possible benefit if suicidality a concern,[30] or for older adults[31,32]	• Gastrointestinal side effects, polyuria, polydipsia, tremor, sedation, weight gain, sexual dysfunction, cognitive side effects, arrhythmias • Chronic use has risk of renal and thyroid injury • Fatal in overdose • Many drug-food-hydration interactions • Concerns of possible teratogenicity in women of reproductive age
Bupropion 150-300 mg/d	• Prominent features: fatigue, amotivation, hypersomnia • Comorbid or subclinical ADHD • Less sexual dysfunction compared with other drug options; may help counteract SSRI-induced sexual dysfunction[33,34] • Weight neutral • Possible benefit in older adults with normal appetite and sleep patterns	• Stimulating, reduced appetite, tachycardia, hypertension, tremor, sweating • Seizure risk (dose dependent) • Caution: heavy alcohol use, disordered eating, unstable cardiovascular disease, anxiety, insomnia
Mirtazapine 15-45 mg at bedtime	• Comorbid anxiety, comorbid insomnia, and low appetite • May help counteract gastrointestinal side effects from other drugs	• Sedation, hypotension, weight gain, dry mouth, and edema
Lamotrigine 100-200 mg twice daily Slow titration	• Mixed features (eg, co-occurring manic symptoms, irritability, agitation, mood lability)[28] • Weight neutral, typically well tolerated	• Transient gastrointestinal side effects and minor dermatologic side effects • Rare: Stevens-Johnson syndrome (<0.1%)[35] and toxic epidermal necrolysis, hepatotoxicity
Liothyronine (triiodothyronine) 25-62.5 µg/d	• Subclinical hypothyroidism • Possibly more efficacious in biological females	• Tachycardia, tremors, anxiety, and diarrhea
Modafinil 100-400 mg/d	• Prominent features: fatigue, hypersomnia, amotivation • Comorbid or subclinical ADHD	• Stimulating, reduced appetite, tachycardia, hypertension, tremor, headache, anxiety, agitation, insomnia • Rare: psychiatric symptoms, dermatologic side effects • Teratogenicity reported

ADHD—attention deficit hyperactivity disorder, DTD—difficult-to-treat depression, SSRI—selective serotonin reuptake inhibitor.
*Recommended dose when used as adjunctive therapy. This is based on optimal balance of efficacy and adverse effects as demonstrated in clinical trials.

Brexpiprazole and cariprazine have less data and inconsistent results in controlled trials.[39,40,63] The use of adjunctive lamotrigine is mainly supported by expert opinion rather than evidence, but it is usually well tolerated and may provide benefit for patients with labile or irritable mood symptoms.[14,64] Liothyronine (triiodothyronine) might be efficacious as an adjunct, especially in those with subclinical hypothyroidism, and there is evidence to support its use; however, it is not commonly prescribed.[2,12,49,65,66] Stimulating medications such as modafinil and lisdexamfetamine may be helpful for depression symptoms of fatigue and poor concentration, although the evidence base is small and imprecise, and cardiovascular adverse effects and potential risk of misuse may be of concern in some patients.[67,68] Buspirone efficacy data come from open-label studies and the STAR*D trial, whereas blinded controlled studies do not demonstrate superiority to placebo.[2,69,70] Ketamine given intranasally or intravenously has demonstrated immediate and considerable reductions in depressive symptoms and may be a preferred option in some patients with severe refractory depression; however, long-term efficacy and safety are still largely unknown and access is a substantial barrier.[12,71-74] While it is not drug therapy, neurostimulation such as repetitive transcranial magnetic stimulation or electroconvulsive therapy can be effective options to consider for patients after trialling 2 to 3 medications.[75,76]

Back to the case

You review the above options with Mia to decide which adjunctive medication might be best suited. You rule out bupropion because of Mia's alcohol use and mirtazapine because it will likely contribute to their symptoms of hypersomnia and increased appetite. You consider quetiapine and aripiprazole next. You review Mia's cardiovascular and metabolic risk factors and deem Mia low risk. Compared with quetiapine, aripiprazole may have a more favourable effect on Mia's hypersomnia, impaired concentration, and increased appetite. Quetiapine may be an equally reasonable option for the mixed features of depression, but it comes with an added risk of sedation and weight gain. Lithium may help improve Mia's irritability and suicidality; however, Mia prefers the side effect profile of the atypical antipsychotics. You defer consideration of the other adjunctive medications, as they have less robust evidence. You inquire about medication affordability and find out that Mia is currently covered under their mom's plan. Together with Mia, you choose to prescribe 2 mg of aripiprazole daily as an adjunct to 225 mg of venlafaxine daily.

Practical tips for prescribing and monitoring adjunctive antipsychotics

For people with DTD, adjunctive antipsychotics are typically prescribed at the lowest dose and slowly titrated to effect. Higher doses within the labelled range (**Table 3**)[28-35] do not consistently demonstrate superior efficacy but do increase the risk of most adverse effects.[77] Consider using measurement-based care to support clinical assessment (eg, Patient Health Questionnaire–9, Beck Depression Inventory, Quick Inventory of Depressive Symptomatology, the Clinical Global Impressions scale).[8,16,78] To monitor for efficacy in DTD, it is helpful to set goals that focus on specific symptoms, global function, and patient-important outcomes, rather than targeting complete remission of core depression symptoms.[79,80] Monitoring is required for metabolic, cardiovascular, and neurologic adverse effects (**Table 4**),[81-84] as well as for general tolerability (eg, sedation, anticholinergic effects,

Table 4. Suggested monitoring parameters for patients prescribed second- and third-generation antipsychotics: *A dash indicates the test is not necessary.*

PARAMETER	BASELINE	AT 1 MO	AT 3 MO	AT 6 MO	ANNUALLY
Weight (BMI)	✓	✓	✓	✓	✓
Waist circumference	✓	—	✓	✓	✓
Blood glucose or HbA_{1c}	✓	—	✓	—	✓
Lipid levels	✓	—	✓	—	✓If risk factors
Vital signs	✓	✓	✓	✓	✓
ECG	✓		✓If risk factors	—	✓If risk factors
Acute EPS, including akathisia	—		Every visit until dose is stabilized		
Tardive EPS	—	—	—	✓	✓Or every 3-6 mo if high risk
Prolactin level	✓	—	—	If clinically indicated or high risk	
Complete blood count	✓	—	—	✓	✓

BMI—body mass index, ECG—electrocardiogram, EPS—extrapyramidal symptoms, HbA_{1c}—hemoglobin A_{1c}.
Data from Galletly et al,[81] Zaidi et al,[82] Marder and Cannon,[83] and Bool et al.[84]

sexual dysfunction). Regularly revisit conversations with patients to see if they are willing and able to add psychotherapy to their overall treatment approach, and explore what other nonpharmacologic support or interventions may be beneficial.[85,86]

Case resolution

You discuss specific goals, focusing on function and outcomes that are important to Mia (being able to get out of bed without substantial struggle by 11:00 AM, getting into fewer arguments with their mom and sister, being able to concentrate on and find pleasure in daily activities). You document relevant baseline findings. You advise Mia to self-monitor for any troublesome side effects, such as akathisia, worsening sedation or agitation, weight gain, or changes in impulsivity. You provide Mia with information about various nonpharmacologic strategies and encourage them to continue with psychotherapy. You plan to follow up with Mia in 2 weeks.

Conclusion

Depression can be difficult to adequately treat, and there is limited evidence to guide pharmacologic therapy. After a thorough reassessment and ensuring contributing factors are addressed, treatment approaches and medication selection should be individualized based on available evidence, clinical factors, and patient preference. Offer nonpharmacologic strategies that best suit each patient and encourage psychotherapy. When considering adjunctive medication, clinicians are encouraged to interpret the literature cautiously, prescribe antipsychotics selectively, and discontinue medications not providing benefit or when harm outweighs benefit. Regular monitoring for symptoms, adverse effects, suicide risk, and patient's level of functioning is essential.

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