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Dr. Jennifer Swainson is a psychiatrist at the Misericordia Community Hospital in Edmonton with expertise in treating difficult mood disorders and their comorbid conditions. Dr. Swainson is certified by the American Board of Obesity Medicine and has interest in the reciprocal relationships between mood disorders, sleep, and obesity and their subsequent treatment considerations when they co-occur. Dr. Swainson has served on several advisory committees to the College of Physicians and Surgeons of Alberta (CPSA) in regard to CPSA tracking of high risk medications, and considerations for safe prescribing of ketamine for depression. Dr. Swainson is a co-author of the Canadian Network in Mood and Anxiety Treatments (CANMAT) 2023 Depression Treatment Guidelines and was lead author of the 2021 CANMAT Task Force Update on Ketamine for Depression. She is involved in clinical research and has authored numerous other publications focused on ketamine and esketamine for depression and has been an advocate for safe and accessible use of ketamine for mood disorders. Dr. Swainson is an active teacher of students and residents, and is a frequent speaker for family physicians on topics of mood and insomnia.



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DEPRESSION UPDATE: A BRIEFING ON THE CANADIAN MOOD AND ANXIETY DISORDER TREATMENT (CANMAT) 2023 DEPRESSION GUIDELINES AND ADVICE FOR THEIR APPLICATION IN PRIMARY CARE

Introduction

The Canadian Mood And Anxiety Disorder Treatment (CANMAT) guidelines for depression, last published in 2016, have now been updated with literature through to 2023, and have been recently published in 2024 (Lam et al, Canadian J Psych, In press 2024). This 92-page document thoroughly addresses aspects of depression management, using evidence based on the literature, and supplemented by an expert consensus of the 57 co-authors. While thorough, this document remains cumbersome for a busy primary care clinician to sort through and apply to everyday practice. Here, we present a summary of evidence for the treatment of depression, along with practical advice for clinical decision making in primary care.

Screening and Diagnosis

The CANMAT 2023 recommends screening patients with risk factors for depression with a validated self-rated instrument such as the Patient Health Questionnaire-2 (PHQ-2), and if positive, the PHQ-9. Risk factors cited in the CANMAT guidelines include a history of childhood adverse events, family history of mood disorders, chronic

and non-psychiatric medical illnesses (including obesity as per Obesity Canada recommendations), psychiatric comorbidities, substance use disorders, insomnia and night shift work, female sex (especially during puberty, pregnancy, postpartum, perimenopause), recent stressful life events, job strain/income inequality, bereavement, peer victimization/bullying/cyberbullying, gender dysphoria, and a sedentary lifestyle/significant screen time.

(The PHQ-2 and PHQ-9 may be found here: <https://www.albertahealthservices.ca/frm-19825.pdf>)

A PHQ-9 score greater than 10 with both sensitivity and specificity rates of 88% is positive for major depression.¹ In addition to the total score, the frequency of symptoms must be considered. Major depressive disorder is suggested if 5 or more of the items are reported as occurring at least "more than half the days", but this must be followed up with a clinical interview to assess individual symptoms, as well as psychiatric and medical differential diagnoses that could be contributing to the symptoms.

Clinicians should consider screening patients with depression for bipolar disorder, because bipolar depression would require treatment with a mood stabilizer.² Antidepressant monotherapy in a patient with bipolar disorder is unlikely to be efficacious and may cause harm by eliciting mania or hypomania. The Rapid Mood Screener (RMS) is a 6-item self-rated scale with an 88% sensitivity and an 80% specificity for bipolar I disorder.³ Factors from a person's history that may point toward bipolarity include a family history of bipolar disorder, earlier age of first depressive episode (i.e. teens), atypical depressive features (e.g. hypersomnia, increased appetite), depression during pregnancy/postpartum, premenstrually related mood symptoms, pathological guilt, leaden paralysis, and psychotic depression.⁴

ADVICE: Screen at risk patients first with the PHQ-2:

- In the past two weeks, have you been bothered by having little interest or pleasure in doing things?
- In the past two weeks have you felt down, depressed, or hopeless?

If one answer is YES, proceed to the PHQ-9

If the PHQ-9 is positive, follow up with a clinical assessment

Treatment

Prompt treatment of depression is paramount as a longer duration of depression is associated with a greater resistance to treatment and a reduced likelihood of remission. Psychoeducation for patients to emphasize that returning for their follow up appointments is essential to ensure that their treatment can be optimized. Patients should receive psychoeducation about the fact that early treatment is most likely to have the best outcome.

Lifestyle Modification and Complementary and Alternative Medicines

Lifestyle and complementary and alternative medicines (CAM) treatments do not reach the level of evidence of pharmacotherapy; however, the CANMAT 2023 guidelines note that they could be used as monotherapy for mild depression (with a PHQ-9 score of 5–9) if this is the patient's preference. These treatments can be considered as adjunctive measures for moderate to severe depression (with a PHQ-9 of >9).

Lifestyle interventions, which include light therapy, healthy diet (Mediterranean style diet, or a "healthy" diet avoiding processed foods and added sugars), exercise, smoking cessation, and sleep hygiene, have all demonstrated a potential benefit in managing depression. Of these, light therapy and exercise have the strongest evidence. Supplements with some evidence for treating depression include Omega 3's⁵ (CANMAT 2023) and

Vitamin D.⁵ CAM treatments with supporting evidence for treating depression include acupuncture, L-methyl folate, St. John's Wort (but not with antidepressants due to serotonin syndrome risk), S-adenosylmethionine, dehydroepiandrosterone, saffron, lavender, and roseroot.

ADVICE: *Mild depression with little functional impairment may be treated with lifestyle interventions/CAM and/or psychotherapy but ensure that the patient follows up with you to assess the efficacy of this treatment approach. Consider pharmacotherapy if the patient is not improving.*

Psychotherapy

Psychotherapy is often used in combination with pharmacotherapy for moderate-to-severe depression, but it may be effective on its own for mild depression. The strongest evidence is for Cognitive Behavioural Therapy (CBT), Interpersonal Therapy, or Behavioural Therapy occurring at least once, but preferably twice a week, and the CANMAT 2023 guideline note that there is little evidence for therapy occurring less than weekly in the acute phase of treatment. Barriers to accessing timely therapy are a reality, and despite having little evidence of support, potentially helpful guided digital health interventions, such as online CBT are listed in the guidelines as treatment options.

New additions to the guidelines include several second line psychotherapy options; mindfulness based cognitive therapy, short term psychodynamic therapy, and transdiagnostic psychological treatment of emotional disorders. A new listing as a third line of therapy is "Meta Cognitive therapy." While evidence does not support commonly practised eclectic uses of multiple forms of therapy (CANMAT 2023), non-standardized therapies are difficult, if not impossible, to study. From a practical standpoint, the optimal therapy may be what your patient can access, and the patient-therapist rapport has previously been noted to be the most predictive of positive outcomes.⁶

ADVICE: *In acute depression, frequent psychotherapy, provided once or twice a week, offers the most benefit. Establishing a positive patient rapport with the therapist is important.*

Pharmacotherapy

Within the CANMAT document, multiple pharmacotherapy options are included, and potential side effects are described. Here, treatment choices will be presented through a lens of balancing efficacy with side effects. In particular, the long-term risk of weight gain and metabolic effects are considered owing to the frequency of related comorbid conditions in primary care.

Antidepressant	Class	Typical Dose Range	Notes to Consider
Bupropion (most often used in XL form)	NDRI	150–300 mg	• Favourable side effect profile
Vilazodone	Multimodal	10–40 mg	• Favourable side effect profile
Vortioxetine	Multimodal	10–20 mg	• Favourable side effect profile
Desvenlafaxine	SNRI	50–100 mg	• Favourable side effect profile
Duloxetine	SNRI	60–120 mg	• Consider use if comorbid neuropathic pain, fibromyalgia
Levomilnacipran	SNRI	40–120 mg	
Venlafaxine-XR	SNRI	75–225 mg	• Significant discontinuation syndrome
Citalopram	SSRI	20–40 mg	• CANMAT flags QTc as a potential issue
Escitalopram	SSRI	10–20 mg	
Fluoxetine	SSRI	20–60 mg	
Fluvoxamine	SSRI	100–300 mg	
Paroxetine	SSRI	20–50 mg	• Associated with significant weight gain • Significant discontinuation syndrome
Sertraline	SSRI	50–200 mg	
Mirtazapine	NaSSA	30–60 mg	• Consider use if weight gain is desired (low body mass index)

Table 1. Potential first line anti-depressants and dosage ranges; *courtesy of Jennifer Swainson, MD.*

Abbreviation: QTc: Corrected QT interval

Choice of Initial Antidepressant

The CANMAT guideline list 17 first line antidepressants, 14 of which are available in Canada. The new first line additions since the 2016 guideline are levomilnacipran, a serotonin-norepinephrine reuptake inhibitor (SNRI), and vilazodone (multimodal). Another new addition (second line) is a combination of dextromethorphan and bupropion, approved in the United States but unavailable in Canada.

A recent meta-analysis of antidepressants found vortioxetine (multimodal antidepressant) to be the most efficacious and acceptable antidepressant, followed by escitalopram.⁷ Amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were reported to have slightly better efficacy but these overall differences were not felt to clearly distinguish these first line

agents from the others (CANMAT 2024). Amitriptyline is considered as a second line treatment owing to its side effect profile.

Given the number of first line treatment options, the initial choice of antidepressant should be made in collaboration with the patient and with consideration of the side effect profile. Weight gain, sedation, and sexual side effects are frequently reported as long-term side effects that may lead to medication non-adherence and a lower quality of life, and in the case of weight gain, medical morbidity. Based on available data, and the CANMAT author consensus, only 4 of the 14 first line agents are described as having a favourable side effect profile in all 3 of those areas (**Table 1**). These include bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI), desvenlafaxine (SNRI),

vilazodone (multimodal antidepressant), and vortioxetine (multimodal antidepressant). The selective serotonin reuptake inhibitors SSRIS and duloxetine are generally associated with significant sexual side effects; thus, they may not be the optimal first choice of treatment. Mirtazapine and paroxetine are associated with the most significant weight gain, and mirtazapine is also associated with significant sedation. While any first line agent may be appropriate, and other factors such as cost, patient preference, comorbidities, and the potential for drug interactions must be considered, a simple and practical practice algorithm includes choosing one of the four antidepressants with the more favourable side effect profile (**Table 1**).

ADVICE: Consider efficacy and tolerability when selecting an antidepressant. CANMAT identifies four first line antidepressants as having a more favorable side effect profile when considering long term risks of weight gain, sedation, and sexual side effects. There are antidepressants with better long-term side effect profiles than the commonly used SSRIs.

Follow up of the First Antidepressant Trial

Follow up should occur 2–4 weeks after antidepressant initiation. At this time, both efficacy and tolerability should be assessed. If there is little response by 4 weeks after dose optimization, response or remission at 8–12 weeks is unlikely, and the patient should be assessed for factors contributing to the non-response including medication adherence, adequacy of dose and duration, comorbid psychiatric or medical factors, and ensuring a correct diagnosis.

After determining that the diagnosis of unipolar depression is correct, the decision for the next step should be made in collaboration with the patient. A dose increase may be considered if the initial treatment is well-tolerated. If the initial antidepressant has poor tolerability, there has been a lack of response, or if the patient prefers, the antidepressant may be switched. While the CANMAT reports that there is little data to support a preference for switching to a different class of antidepressant, it is a common practice to attempt an agent with a different mechanism, again considering the side effect profile.

If an optimized dose of an antidepressant elicits a partial response and is well tolerated, the next step would be to add an adjunctive medication. Repeated antidepressant switches are unlikely to be of benefit.

TIP: If you switch antidepressants, do it only once before moving on to the addition of an evidence based adjunctive treatment.

Adjunctive Treatments

The only 2 first line adjunctive agents are third generation atypical antipsychotics—aripiprazole and brexpiprazole (**Table 2**). A new addition to the guidelines is another third-generation atypical agent, cariprazine, which, though indicated as an adjunct therapy for depression in the United States, is considered off label in Canada for this use, and is considered a second line treatment in the CANMAT 2023. These third-generation antipsychotics are considered distinct from second generation antipsychotics owing to their mechanism of dopamine partial agonism, and the fact that they are less likely than several other atypical antipsychotics to be associated with weight gain, but they may be more likely to cause extrapyramidal side effects such as akathisia. Adjunctive therapies with the best evidence should typically be used first. To mitigate the weight gain risk of atypical antipsychotic adjuncts, the addition of metformin or glucagon-like peptide-1 (GLP-1) agonists may be considered.⁸

Other second line add-on strategies include antidepressants such as bupropion or mirtazapine, lithium, triiodothyronine, or modafinil. Risperidone and quetiapine have been newly relegated to the second line in the 2023 guidelines owing to concerns with metabolic effects, and failed trials for risperidone. Olanzapine remains a second line treatment owing to its significant metabolic effects.

ADVICE: When using atypical antipsychotics as an adjunctive treatment, use aripiprazole, brexpiprazole, or cariprazine before risperidone, quetiapine or olanzapine owing to better evidence for efficacy and/or a better metabolic profile.

Novel Adjunctive Approaches

Intravenous ketamine and intranasal esketamine are newly recognized in the 2023 guidelines as effective adjunctive treatments that are listed in the second line due to limitations with patient access. Both treatments must be administered and observed in a health care setting and are generally not conducive to most primary care practices. Additionally, the public mental health system offers limited opportunities for these treatments. Non-intravenous forms of ketamine are now considered a third line adjunct, however, data are limited for optimal dosing or frequency, thus careful consideration must be given before prescribing this form of treatment.⁹ CANMAT has previously advised that non-intravenous ketamine should be used only by or in conjunction with specialist support.^{9,10} Additionally, prescribing guidelines and monitoring requirements from provincial colleges may vary.

While there is much mainstream media and online discussions about psilocybin and “microdosing”, psilocybin remains an investigational treatment and is not recommended to treat depression.¹¹ Cannabis is also not recommended owing to a lack of efficacy, and it has been

Line of Treatment	Adjunctive Agent	Target Dose ¹	Ease/Appropriateness of Use in Primary Care
First Line	Aripiprazole	2–10 mg	YES
	Brexpiprazole*	0.5–2 mg	YES
Second Line	Bupropion	150–450 mg	YES
	Intranasal esketamine*	56–84 mg intranasally	NO, needs to be administered and monitored
	Intravenous (IV) racemic ketamine*	0.5–1.0 mg/kg IV	NO, needs to be administered and monitored
	Olanzapine	2.5–10 mg	NOT routinely–weight gain
	Quetiapine-XR*	150–300 mg	NOT routinely–weight gain
	Risperidone*	1–3 mg	NOT routinely–Weight gain
	Lithium	600–1200 mg (therapeutic serum level: 0.5–0.8 mmol/L)	YES, but check TSH, CR, and note target Li level
	Cariprazine*	1.5–3 mg	YES
	Mirtazapine / Mianserin	30–60 mg/30–90 mg	YES—but note fatigue/weight gain
	Modafinil	100–400 mg	YES–cost may be an issue
	Triiodothyronine	25–50 mcg	YES
Third Line	Other antidepressants, including tricyclic antidepressants	Varies with the medication	YES, if comfortable prescribing
	Stimulants	Varies with the medication	YES—see CADDRA stimulant dose tables
	Lamotrigine*	100–300 mg	YES—start at 25 mg and increase weekly due to Stevens Johnsons risk
	Non-IV racemic ketamine*	Varies with the medication	NO
	Pramipexole*	1–2 mg twice daily	YES
	Ziprasidone	20–80 mg twice daily	YES, but rarely used in psychiatry due to limited clinical efficacy
Investigational	Psychedelic-assisted psychotherapy*	Moderate to high doses accompanied by psychotherapy	NO
Not Recommended	Cannabis* (insufficient evidence for efficacy; risk of harm)	NOT applicable	NOT applicable

Table 2. Adjunctive Treatment Options for Depression; *courtesy of Jennifer Swainson, MD.*

*Table adapted for primary care from the CANMAT 2023 depression guideline.

¹ Dose ranges are taken from product monographs; in clinical care, doses below and above the range may be used.

Abbreviations: CADDRA: Canadian ADHD Resource Alliance; CANMAT: Canadian Mood And Anxiety Disorder Treatment Guidelines; CR: creatinine; IV: intravenous; Li: lithium; TSH: thyroid stimulating hormone

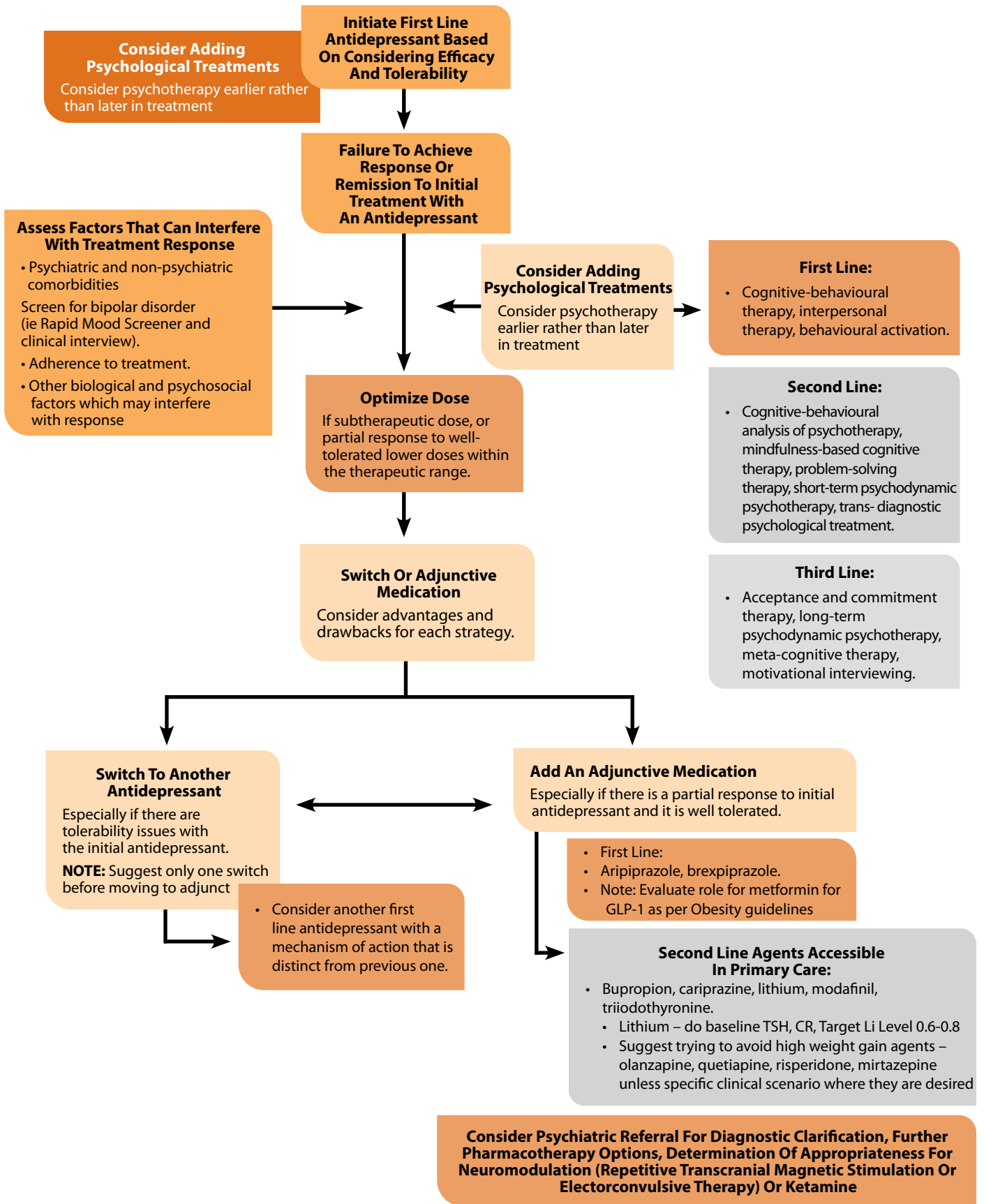


Figure 1. Algorithm for initial antidepressant treatment; adapted from CANMAT paper.

found to worsen the course of both depression and bipolar disorder.¹²

ADVICE: *Non-medical/self treatment with ketamine or psilocybin should be actively discouraged.*

Remission

Once a patient reaches remission after a first episode, the antidepressant should be continued for 6 to 12 months. If there is a history of multiple episodes or risk factors for recurrence, the antidepressant should be continued for 2 years or more. Risk factors include residual depressive symptoms, more severe depressive episodes, previous depressive episodes, comorbid medical or psychiatric illness, limited supports, life stressors, and a history of childhood maltreatment.

ADVICE: *If the patient required an adjunctive treatment to reach remission, the depression was more difficult to treat and would be at risk of recurrence.*

When to Seek Psychiatric Consultation

Trials of 2 antidepressants plus at least one adjunctive treatment should be tried before seeking psychiatric consultation. If the patient has not responded to this sequence of treatments, they can be considered to have treatment resistant, or difficult-to-treat depression, and may benefit from more complex pharmacotherapy, or interventions such as intravenous ketamine, or neuromodulation such as electroconvulsive therapy or repetitive transcranial magnetic stimulation. Psychiatric consultation may also help elucidate comorbidities or other factors contributing to a patient's non-response to treatment.

Conclusion

In a busy primary care practice, identifying depression with patient-rated screening tools can be of benefit. Depression treatment can include a combination of lifestyle modification, psychotherapy, and pharmacotherapy. Pharmacotherapy treatment options are many and can be simplified by considering the side effect profile and selecting agents that are least likely to carry long term side effect risks.

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Financial Disclosures

None declared.

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