Major Depressive Disorder

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LEARNING OBJECTIVES

1. Design initial pharmacotherapy on the basis of patient presentation and current treatment guidelines for major depressive disorder.
2. Assess treatment goals for a patient with major depressive disorder based on rating scales, clinical presentation, and diagnostic specifiers.
3. Develop a pharmacotherapy plan based on inadequate response to antidepressant treatment.
4. Account for differences in pharmacotherapy selection based on special population characteristics.

ABBREVIATIONS IN THIS CHAPTER

CANMAT	Canadian Network for Mood and Anxiety Treatments
CBT	Cognitive behavioral therapy
COVID-19	Coronavirus disease 2019 (pandemic)
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
NICE	National Institute for Health and Care Excellence
PHQ	Patient Health Questionnaire
PHQ-9	Patient Health Questionnaire standard form
RANZCP	Royal Australian and New Zealand College of Psychiatrists
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
T_3	Triiodothyronine
TCA	Tricyclic antidepressant
TRD	Treatment-resistant depression
VAST-D	Veteran Affair's Augmentation and Switching Treatments for Improving Depression Outcomes

Table of other common abbreviations.

INTRODUCTION

Antidepressants are one of the most widely used therapeutic classes of medications in the United States (Martin 2019). One study conducted between 2015–2018 found that 13.2% of U.S. adults used an antidepressant medication in the previous month (Brody 2020). Given the high prevalence of major depression disorder (MDD) in the U.S. population and a widely recognized lack of mental health services to meet the needs of patients with MDD, pharmacists in all practice settings can be expected to be called on to assist in the clinical management of MDD and optimal use of antidepressant medications. This chapter presents an overview of the most current evidence-based treatment guidelines for depression as well as practical strategies for initial and ongoing management of depression.

Epidemiology

Regardless of the method used to estimate the national prevalence of depression, the data support what any clinician can observe—depression is highly prevalent in the United States. The Substance Use and Mental Health Services Administration (SAMHSA) estimates that 7.2% of American adults experienced an episode of major depression in 2018 (SAMHSA 2019). Depression is associated with diminished quality of life and increased disability, and it also accounts for a significant percentage of health care visits (GBD 2017 SDG Collaborators). Around 11% of office visits and ED visits have listed depression as a relevant diagnosis, according to results of the 2018 National Ambulatory Medical Care Survey (Santo 2018). Even more alarming, the suicide rate in the United States has increased after a period of decline. The 1999–2014 data from the National Vital Statistics System show a 24% increase in suicide, from 10.5 to 13.0 per 100,000 population, with faster increases after 2006 (Curtin 2016).

While these national samples underscore the wide prevalence of depression at baseline, the prevalence has also increased with the coronavirus disease 2019 (COVID-19) pandemic. A joint venture between the CDC and the U.S. Census Bureau, the Household Pulse Survey, reported that 41.5% of U.S. adults reported symptoms of anxiety or depression in the previous 7 days in February 2021 (Vahratian 2021). Furthermore, survey respondents noted a lack of access to mental health care, underscoring the need for increasing the number of clinicians available to assist patients with depression.

Pathophysiology

Like many psychiatric illnesses, the manifestation of the disease cannot be wholly explained by one unifying cause. Patients with depression appear to have a genetic predisposition that may be characterized by hereditable changes to brain chemistry. However, developmental and environmental factors also contribute to the disease. Notable risk factors for depression include adverse life events (e.g., childhood abuse, previous trauma, divorce), co-morbid conditions (e.g., anxiety, neuroticism, chronic medical conditions, chronic pain, substance use), and social circumstances (e.g., low educational status, poor social support, disturbed family environment) (Maurer 2018). In addition, women are more likely to experience depression than men.

Classically, the biologic basis for MDD was thought to be dependent on relative deficiencies of the neurotransmitters norepinephrine, dopamine, and serotonin in neural synapses in the brain. With time, however, the understanding has expanded to include the role of receptor sensitivity to these neurotransmitters, leading to a theory of dysregulation of neurotransmitter homeostasis and alteration in neurotrophic support factors, in contrast to simply a deficiency of neurotransmitters (VandenBerg 2020).

Clinical Presentation

Screening is the cornerstone of early recognition and diagnosis of depression and is recommended by the U.S. Preventive Services Task Force (USPSTF) for all adult patients. Although the USPSTF does not endorse a particular screening tool, the Patient Health Questionnaire (PHQ) is often encountered in practice in either the standard (PHQ-9) or short form (PHQ-2) (USPSTF 2016).

DSM-5 Criteria

Any positive screening must be followed up by additional assessment. Further assessment is often performed guided by the mnemonic device *SIGECAPS*, in which each of the letters corresponds to one of the diagnostic criteria for MDD in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) (Table 1). To diagnose MDD, five or more of the symptoms listed in Table 1, not attributable to another medical condition, must be present during a 2-week period, with at least one of the symptoms being depressed mood or loss of interest or pleasure. These symptoms must represent a change from previous mood, cause significant distress or impair function, and occur daily or almost every day in most cases. Weight change and suicidality are exceptions to the criteria of daily or near daily occurrence. These symptoms also must occur in the absence of a history of manic or hypomanic episodes or another mental health condition that better explains the symptoms (American Psychiatric Association [APA] 2013). Of note, occurrence of depressive symptoms within the context of grief or a major loss or trauma may still be considered MDD if the criteria are met.

Differential Diagnosis

A variety of neurologic conditions can manifest with or as depression, including dementia, epilepsy, multiple sclerosis, Alzheimer disease, Parkinson disease, and traumatic brain injury (Maurer 2018). Other mental health conditions that exclude a diagnosis of MDD are listed in Table 2.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Drug knowledge of the major classes of medications for treating depression, including relevant pharmacokinetics and pharmacodynamics, adverse effects, and general recommended dosing of each antidepressant
- General knowledge of the pathophysiology of depression
- Common drug–drug interactions and toxicities associated with antidepressants

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder. Can J Psychiatry 2016;61:540-60.
- Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018;391:1357-66.
- Taylor RW, Marwood L, Oprea E, et al. Pharmacological augmentation in unipolar depression: a guide to the guidelines. Int J Neuropsychopharmacol 2020;23:587-625.

Table 1. *DSM-5* Criteria, Symptoms, and Mnemonic for Diagnosis of MDD

Mnemonic	Symptom	*DSM-5* Criteria	Description	Notes
—	—	1	Depressed mood, empty, hopeless	May also manifest as irritability, particularly in children and adolescents
S	Sleep disorder	4	Insomnia or hypersomnia	Common presenting symptom
I	Interest deficit	2	Anhedonia	Almost always present
G	Guilt	7	Worthlessness, hopelessness, regret, excessive guilt	Must be present to a degree that is excessive or delusional
E	Energy deficit	6	Fatigue or loss of energy	Common presenting symptom
C	Concentration deficit	8	Indecisiveness or difficulty concentrating	In children, may manifest as decreased school performance In older adults, may be mistaken for dementia
A	Appetite disorder	3	Unintended weight loss or weight gain, increased or decreased appetite	Lack of interest in food or cravings (often sweets or carbohydrates)
P	Psychomotor changes	5	Slowed or agitated movements observed by others	Less common symptom, but indicative of high severity of disease
S	Suicidality	9	Recurrent thoughts or plans of death or self-harm	May be passive or active

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MDD = major depressive disorder.

Information from: American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA: APA, 2013.

Table 2. *DSM-5* Criteria to Exclude the Diagnosis of MDD

Condition	Description
Manic or hypomanic episodes	Requires careful evaluation to distinguish bipolar disorder from MDD
Mood disorder caused by another medical condition	Conditions such as multiple sclerosis, hypothyroidism, and stroke should be evaluated if present
Substance-/medication-induced	Example: depression secondary to stimulant withdrawal
Attention-deficit/hyperactivity disorder	Symptoms of irritability, distraction, and difficulty concentrating
Adjustment disorder with depressed mood	Clinically significant distress but does not meet severity or duration criteria for MDD
Sadness	Present as a fundamental part of the human experience but does not meet criteria for MDD

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MDD = major depressive disorder.

Information from: American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM). Arlington, VA: APA, 2013.

Depression Specifiers

In addition to guiding the primary diagnosis of MDD, the *DSM-5* also describes particular presentations of depressive disorders, which can be important for understanding the patient and for treatment selection in some cases. For the depression specifier to apply to a patient, typically several criteria listed should be present for most of the depressive episodes. Further discussion of specifiers is provided later in text in the section on Clinical Guideline Updates in Drug Therapy Management.

Table 3. Select Medications Associated with Depression

Medication	Clinical Pearls
Anticonvulsants	Warning included broadly in FDA labeling, but not causally established
Antihypertensives, such as β-blockers, calcium channel blockers, alpha-2 adrenergic agonists	β-Blockers and α-2 adrenergic agonists likely worsen cardinal symptoms of depression Cardiovascular disease confounds correlation
Hormonal therapies: gonadotropin-releasing hormone antagonists, corticosteroid, clomiphene, hormonal contraceptives	Possible alterations of monoamine oxidase activity from changes in estrogen and progesterone concentrations
Interferon therapies	Boxed warning for interferon alfa Careful monitoring required during therapy Symptoms usually remit quickly on medication discontinuation
Isotretinoin	Linked to depression and other mood disturbances Recommended monitoring in iPledge
Vesicular monoamine transporter 2 inhibitors: deutetrabenazine, tetrabenazine, valbenazine	Boxed warning for (deu)tetrabenazine Observed in the setting of Huntington disease Caused by depletion of synaptic monoamines

Information from: VandenBerg AM. Major depressive disorder. In: DiPiro JT, Yee GC, Posey L, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York, NY: McGraw Hill, 2020.

Drug-Induced Depression

A diagnostic criterion for MDD is that the presenting symptoms are not better explained by a medication. A key point for pharmacists is that numerous medications have been correlated with new-onset or worsening depression. However, causality is difficult to determine for depression. For many reasons, depression may be temporally linked with initiation of medications other than psychiatric agents. An important consideration is that the initiation of medication may be in response to a change in medical status, which may be dramatic or traumatic. Indeed it is well documented that depression is a common comorbidity with other serious medical illness. In addition, many medications have known adverse effects that may worsen a cardinal symptom of depression, such as fatigue or change in appetite. Although the existing data do not clearly define the causality of MDD, clinicians should be attuned to the possibility of medication-induced depression (Table 3).

Recently, several FDA boxed warnings were updated to address these concerns. For example, in 2016 the FDA removed a boxed warning of neuropsychiatric adverse effects from varenicline in response to the EAGLES study, a post-marketing safety study that was required after the warning was initially added in 2009. In the EAGLES study, more than 8000 patients with and without previous psychiatric illness were randomized to varenicline, bupropion sustained release, nicotine patch, or placebo for tobacco cessation and monitored for the rates of neuropsychiatric events. Although neuropsychiatric events with tobacco cessation were higher overall in patients with previous psychiatric illness, there were no differences between the groups in terms of moderate or serious neuropsychiatric adverse events (Anthenelli 2016).

In addition, in 2020 the FDA added a boxed warning to montelukast in response to continued reports of serious adverse effects for mental health in some patients, including depression, suicidality, and other neuropsychiatric adverse events. With the addition of this warning, the FDA also recommended seeking alternative agents for allergic rhinitis before initiating leukotriene receptor antagonists (Law 2018).

Mental Health First Aid

Beyond health care settings, anyone can seek training in Mental Health First Aid (MHFA) through the National Council for Mental Wellbeing (www.thenationalcouncil.org/our-work/mental-health-first-aid/). Analogous to the commonly understood training in physical first aid for laypeople, MHFA seeks to teach people about mental health and substance use issues as well as to equip people to safely respond to mental health crises and prevent harm while connecting the person in crisis to appropriate care. Although this course is not specially designed for health care providers, the skills are relevant for any clinician.

CLINICAL GUIDELINE UPDATES IN DRUG THERAPY MANAGEMENT

CANMAT 2016 and 2020 RAZCP Treatment Guidelines

Published by the Canadian Network for Mood and Anxiety Treatments (CANMAT) in 2016 as an update to the 2009

document, the evidence-based guideline recommends both nonpharmacologic and pharmacologic treatments for MDD (Kennedy 2016). Principles of this guideline include an individualized assessment and treatment of patients with a data-driven framework for therapy selection.

Evidence-Based Nonpharmacologic Treatment

The evidence supports the efficacy of psychological intervention, particularly cognitive-behavioral therapy (CBT), for treatment of MDD across the spectrum of patient age, sex, race or ethnicity, education level, depression severity, and depression subtype. In addition, CBT has efficacy that is comparable with that of pharmacologic therapy, and CBT in combination with pharmacotherapy is more effective. Efficacy can be seen with a short duration of therapy (about 8 sessions) with persistent efficacy over longer treatment courses. Of note, CBT delivered during the acute phase of depression was more protective than pharmacotherapy alone; however, in severe depression, the onset of improvement is often faster with pharmacotherapy. Therefore, CBT should be regarded as a cornerstone treatment for MDD for both the acute presentation of depression and the maintenance phase, and CBT remains a first-line intervention in conjunction with pharmacotherapy (Kennedy 2016).

Delivery of CBT by telephone and televideo conferencing appears to have equal efficacy to that of face-to-face delivery on-site, which is reassuring, given the current constraints of the COVID-19 pandemic and subsequent reduced access to mental health services. Other psychologic treatments may be used depending on patient preference and response to previous psychological treatment, including interpersonal therapy, behavioral action therapy, problem-solving therapy, mindfulness-based cognitive therapy, and the cognitive-behavioral analysis system of psychotherapy. Neurostimulation treatments, including electroconvulsive therapy and transcranial magnetic therapy, are effective nonpharmacologic options generally reserved after psychotherapy and several medication trials have failed. Electroconvulsive therapy can be used for patients with severe depressive episodes who require emergency treatment and for patients presenting with suicidality. An in-depth discussion of neurostimulation therapy is beyond the scope of the chapter.

Pharmacologic Treatments with Superior Evidence

The CANMAT guidelines reaffirm the role of pharmacotherapy as a first-line treatment for patients with moderate or severe depression. In addition, pharmacotherapy may be considered for mild depression, based on patient preference or a lack of response to nonpharmacologic therapy. Selection of pharmacotherapy for the individual patient relies on several factors that are familiar to clinicians, such as comorbid conditions, previous medication trials, patient preference, medication interactions, cost, and ease of use. The CANMAT guidelines do outline some additional considerations regarding the comparative efficacy of therapy and encourages consideration of comorbid conditions when selecting treatment (Table 4).

Although in general all second-generation antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), bupropion, and mirtazapine, may be considered as first-line pharmacologic treatment for MDD, several network meta-analyses have allowed for some inferred comparisons between these agents that suggest the superiority of escitalopram, mirtazapine, sertraline, and venlafaxine. However, these differences are small, and selection of these agents should not override other compelling patient factors (Cipriani 2018).

The 2020 Royal Australian and New Zealand College of Psychiatrists (RANZCP) clinical practice guidelines recommend a tailored approach to medication management. Escitalopram and vortioxetine can be considered as a first-line treatment if tolerability is prioritized, whereas, if efficacy is prioritized, amitriptyline can be considered based on the larger effect sizes reported in meta-analyses. Mirtazapine, bupropion, and venlafaxine are considered first-line treatments that have well-balanced efficacy and tolerability profiles. Although the CANMAT and RANZCP guidelines differ in their approach, pharmacists should recognize that SSRIs, SNRIs, bupropion, and mirtazapine remain the mainstay first-line treatment options and that treatments can be further tailored based on the factors described previously. Table 5 provides a comparison of the CANMAT and RANZCP guidelines for pharmacologic management of MDD.

Depression Specifiers and Treatments of Choice

A clinician may preferentially use one agent versus another based on the presence of clinical specifiers of depression as outlined in the *DSM-5*. However, no existing treatments are proven superior for depression with melancholic features, atypical depression, or depression with a seasonal pattern. Table 6 summarizes the specifiers for depressive disorders.

GOALS OF THERAPY

Goals of treatment for MDD are to reduce cardinal symptoms, reduce suicidal thoughts and ideation, facilitate safety planning, and assist in functional recovery to level of functioning before the first episode of depression. *Remission*, defined as absence of clinically significant symptoms, is the overall goal of treatment. However, more than half of the patients in acute clinical trials of pharmacotherapy do not experience full remission with their first treatment (Rush 2006). Therefore, therapeutic expectations should be delineated at the start of treatment, and priority should be placed on establishing the best setting for care, which may be hospital, intensive outpatient, or outpatient care, based on the symptom severity, level of functioning, and presence of high-risk specifiers, including catatonia and psychotic symptoms.

Table 4. Considerations for Selection of an Antidepressant

Comorbidity	Preferred Drug	Non-Preferred Drug
Cardiac/risk for QT prolongation	Sertraline	Do not choose a QT-prolonging drug/dose, such as high doses of (es)citalopram, TCAs
Tobacco use	Bupropion sustained release has FDA approval for smoking cessation	No contraindications
Seizure disorder or at risk of seizures	No preferred agents	Bupropion, TCAs
Peripheral neuropathy or pain	Consider duloxetine (FDA approval for both depression and peripheral neuropathy/pain) or high-dose venlafaxine TCAs	No contraindications
History or active eating disorder	No preferred agents	Bupropion, TCAs
Pregnant	Mild to moderate depression: psychotherapy Severe depression: SSRIs, such as citalopram, escitalopram, sertraline	Paroxetine, MAOIs, vortioxetine
Daytime sedation	Activating drugs taken in the morning are preferred, such as fluoxetine, bupropion, vortioxetine, duloxetine	Avoid sedating drugs early in the day, such as paroxetine, mirtazapine, trazodone
Cognitive dysfunction	Consider vortioxetine (high level of evidence). Bupropion, duloxetine, and SSRIs also have evidence	Avoid drugs with anticholinergic effects
Insomnia	Sedating drugs taken at night are preferred, such as mirtazapine	Avoid activating drugs later in the day
Sexual dysfunction	Lower risk with bupropion, mirtazapine, vortioxetine	High risk with SSRIs and SNRIs, such as paroxetine, venlafaxine
Weight gain	Consider SSRI (except paroxetine) or SNRI	Mirtazapine, paroxetine, TCAs
Polypharmacy	Consider drugs with low potential for CYP interaction, such as escitalopram, sertraline, mirtazapine	Strong CYP-interacting drugs, such as fluoxetine, fluvoxamine, paroxetine MAOIs
Suicide risk	Consider drugs with low risk in overdose, such as most SSRIs, mirtazapine	Avoid TCAs, MAOIs Use citalopram cautiously because of risk of QT prolongation in overdose

MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Information from: Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can J Psychiatry 2016;61:540-60; Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2021;55:7-117.

Treatment Goals

Although disease remission is the priority, a response to treatment, or at least a 50% reduction in depressive symptoms after a 4- to 8-week trial of therapy, is the minimal standard clinical goal for the acute treatment phase of depression. Partial response to treatment often indicates a need to further adjust treatment through dose optimization or augmentation strategies. Patients who achieve a response to therapy are encouraged to continue treatment for 4–9 months, with a goal of maintaining therapeutic gains, preventing relapse, and improving the trajectory toward remission. After 6 months of treatment without recurrence, more than 50% of patients will achieve a remission of depression. Risk for depressive relapse is cumulative with additional episodes; therefore, patients with a relapse of depression should continue treatment for a minimum of 1 year and individuals with 3 or more depressive episodes should consider lifelong treatment (Keller 1998).

Table 5. CANMAT and RANZCP Guideline Recommendations for Depression Treatment

Treatment	Canadian Network for Mood and Anxiety Treatments (2016)	Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for Mood Disorders (2020)
First-line	Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors[a] Bupropion Mirtazapine Vortioxetine	Amitriptyline[b] Bupropion Escitalopram Mirtazapine Venlafaxine Vortioxetine
Second-line	Alternative first-line treatment with superior efficacy Tricyclic antidepressants Levomilnacipran Quetiapine extended release Selegiline transdermal Trazodone Vilazodone	Use different first-line treatment
Third-line	Monoamine oxidase inhibitors	Consider alternative antidepressants or electroconvulsive therapy

[a]Includes racemic milnacipran; excludes levomilnacipran.

[b]Higher risk of suicide by overdose.

Information from: Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can J Psychiatry 2016;61:540-60; Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2021;55:7-117.

Although most patients experience a significant improvement during acute treatment (about 60% of patients achieve a response), two-thirds of patients will not achieve full remission of symptoms. Furthermore, about 20% of patients will not achieve full remission after 4 sequential treatments (Rush 2006). Therefore, treatment must be tailored based on the patient's expectations and goals of treatment, pragmatically taking in account both the benefits and limitations that antidepressant therapy can provide. Table 7 presents the therapeutic end points for MDD based on psychometric data from standardized rating scales of depression and suicidality.

Standardized Rating Scales of Depression and Suicidality

A variety of standardized rating scales are used for clinical assessment of depression (see Table 7). Psychometrics can be used as an objective tool at baseline and subsequent follow up to assess the outcomes of pharmacotherapy and track if clinical goals for efficacy are met. The choice of which clinical tool to use is often based on clinician comfort, training, and time constraints.

Early identification and treatment of patients at risk of suicide is essential. Several screening tools for suicide are available for use in conjunction with clinical assessments of depression. Among the screening tools for suicide risk is the Ask Suicide-Screening Questions (ASQ) tool from the National Institute of Mental Health, a 4-question screen that has been validated for patients across a wide range of ages and health care settings. In one study, 97% of patients age 10–21 years at risk of suicide were identified by positive response to any of the four questions (Horowitz 2012).

OPTIMIZING PHARMACOTHERAPY OUTCOMES IN DEPRESSION

Failure to achieve a response or remission with an antidepressant at 4–8 weeks after treatment initiation provides a challenge to clinicians and patients regarding the next best management strategy to pursue. The primary options offered to patients are increasing the antidepressant dose, augmenting the antidepressant with another therapeutic treatment, or switching treatments.

Titrating Antidepressants

Escalating the antidepressant dose is a strategy that many choose as a first step to improve treatment response; however, this approach is controversial. Recent meta-analyses investigating dose-response curves for SSRIs have failed to demonstrate a consistent relationship, with treatment response plateauing in the lower to middle dosing range (Furukawa 2019; Hieronymus 2016). Analyses have not demonstrated response differences with SSRIs over approximate dose equivalents of fluoxetine 50 mg/day (Jakubovski 2016).

Table 6. Specifiers, Criteria, and First-Line Pharmacotherapy for Depressive Disorders

Specifiers	Select Criteria	Notes	First-Line Pharmacotherapy
With anxious features	• Feeling "keyed up" or tense • Feeling often restless • Difficulty concentrating because of worry • Fear that something awful may happen • Feeling of losing control	Prominent feature of both bipolar affective disorder and MDD High anxiety levels are associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse	SSRIs, SNRIs
With mixed features	• Elevated, expansive mood • Inflated self-esteem or grandiosity • More talkative than usual or pressure to keep talking • Flight of ideas or racing thoughts • Increase in energy or activity • Risky behavior • Decreased need for sleep	Mixed features associated with a major depressive episode are a significant risk factor for development of bipolar I or bipolar II disorder	Limited data; lurasidone and ziprasidone have demonstrated positive effects
With melancholic features	• Loss of pleasure in all, or almost all, activities • Lack of response to good things happening • Depression that is regularly worse in the morning • Early morning awakening • Psychomotor changes • Significant anorexia or weight loss • Excessive or inappropriate guilt	Psychomotor changes are almost always present and are observable by others More common in more severe episodes More likely to occur in patients with psychotic features	No superiority data; SNRIs and TCAs have positive data
With atypical features	• Significant weight gain or increase in appetite • Hypersomnia • Leaden paralysis • Long-standing pattern of interpersonal rejection sensitivity	Hypersomnia: sleep > 10 hr/day (or an increase of ≥ 2 hr/day than when not depressed) Leaden paralysis: feeling heavy, leaden, or weighted down, usually in arms or legs	No superiority data overall; MAOIs superior to TCAs
With psychotic features	• Delusions • Hallucinations	Presence of either or both criteria merits specifier	Second-generation antipsychotic in combination with antidepressant
With catatonia	• Catalepsy, negativism • Waxy flexibility, posturing • Stupor, agitation • Mutism, echolalia, echopraxia • Mannerisms, stereotypies, grimacing	Immobility and mutism are common ≥ 3 symptoms required for diagnosis	Benzodiazepines
With peripartum onset	• During pregnancy or • Within 4 wk postpartum	Consider wellbeing of maternal/fetal dyad in therapy selection	No superiority data
With seasonal pattern	• Regular temporal relationship between the major depressive episodes and a particular time of the year which • Remission in other times of the year	In most cases, episodes begin in fall or winter and remit in spring Often characterized by: • Prominent changes in energy • Hypersomnia • Overeating • Weight gain • Craving for carbohydrates	SSRIs and bupropion have been studied, with no superiority data; bupropion has FDA approval

MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Information from: American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA: APA, 2013.; Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can J Psychiatry 2016;61:540-60.

Table 7. Therapeutic End Points and Psychometrics for MDD

Therapeutic End Points for MDD

End Point	Definition
Partial Response	25%–49% reduction in symptoms based on psychometrics
Response	50% or greater reduction in symptoms based on psychometrics
Remission	Complete resolution of depressive symptoms; psychometric thresholds vary based on scale

Common Psychometric Tools in MDD

Scale	Administration Time	Description and Use	Scoring
Hamilton Depression Rating Scale (HAM-D)	20–30 min	• Gold-standard clinician scale used in clinical trials to evaluate severity and monitor symptoms and response to therapy • Places higher weight on somatic symptoms • Better scale for severe depression • Excellent reliability and validity for interpretation • Should be administered by trained mental health professional or rater due to large reliance on patient interview techniques	(HAM-D 17) ≥ 23: very severe depression 19–22: severe depression 14–18: moderate depression 8–13: mild depression 0–7: normal/remission
Montgomery–Åsberg Depression Rating Scale	10–15 min, although can be longer	• Common clinician scale in clinical trials to evaluate severity and monitor symptoms and response to therapy • 10-item scale that is adapted from Comprehensive Psychopathological Rating Scale • More priority to symptoms of sadness, suicidal thoughts, and pessimism • Excellent reliability and validity, with greater sensitivity to change over time compared with HAM-D • Can be administered by a trained clinician (both mental health and non-mental health)	35–60: severe depression 20–34: moderate depression 7–19: mild depression 0–6: symptoms absent/ remission
Patient Health Questionnaire-Depression Scale (PHQ-9)	5 min	• Patient-administered screening and scale to assess depressive symptom severity as well as evaluate response to treatment • Sufficient reliability and validity • Use most often in outpatient settings; not common in acute trials to measure treatment response	20–27: severe depression 15–19: moderately severe depression 10–14: moderate depression 5–9: minimal symptoms < 5: symptoms absent/ remission
Beck Depression Inventory (BDI)	5–10 min (based on version)	• Patient administered scale to evaluate depression severity • Should be matched with a clinician rating scale if used to track pharmacotherapy outcomes • Includes subscales focused on cognitive/affective and somatic/performance issues • High degree of reliability and validity	(BDI-21) 30–63: severe depression 17-29: moderate depression 10–16: mild depression 0–9: no depression/remission

Suicide Risk Psychometrics: *Ask Suicide-Screening Questions (ASQ) Tool* [a,b]

1	In the past few weeks, have you wished you were dead?
2	In the past few weeks, have you felt that you or your family would be better off if you were dead?
3	In the past weeks, have you been having thoughts about killing yourself?
4	Have you ever tried to kill yourself? If yes, how? When?
*If the patient answer **YES** to any of the above, ask the following question:*	
5	Are you have thoughts of killing yourself right now? If yes, please describe.

[a]From the National Institute of Mental Health – ASQ Toolkit.

[b]Yes answered to any question is considered a positive screen.

MDD = major depressive disorder.

Information from: College of Psychiatric and Neurologic Pharmacists (CPNP). Psychiatric Pharmacotherapy Review Course. 2020–2021 ed. Lincoln, NE: CPNP, 2020; Sajatovic M, Ramirez LF. Rating Scales in Mental Health. Lexicomp Online [Internet database]. Hudson, OH: Lexi-Comp. Updated periodically; Stein DJ, Kupfer, Schatzberg AF. The American Psychiatric Publishing Textbook of Mood Disorders. Washington DC: Psychiatric Publishing, 2006.

In addition, adverse effects and the rates of discontinuation increase as the SSRI dose is increased, indicating that lower doses may be preferred (Furukawa 2019). Of note, dose-relationship analyses for SSRIs have primarily focused on MDD; thus, these results may not be extrapolated to common comorbid conditions or depressive subtypes, such as obsessive-compulsive disorder or MDD with psychotic features.

Dose relationships among non-SSRI treatments are less established. Venlafaxine has demonstrated a modest dose-relationship increase from 150 mg to 375 mg/day, but discontinuation rates and adverse effects increase as the dose of venlafaxine increases. Conversely, desvenlafaxine demonstrates a flat-dose response between 50–400 mg/day for efficacy, with a clear increase in dose-related adverse effects. Mirtazapine and duloxetine efficacy peaks at 30 mg and 60 mg/day, respectively (Adli 2005; Furukawa 2019).

Tricyclic antidepressants (TCAs) have a dose-response effect and relatively narrow therapeutic windows, so drug concentrations should be monitored if TCAs are used for MDD treatment. Nortriptyline has best efficacy at concentrations between 50 and 150 ng/mL. Imipramine is therapeutic between 180 and 250 ng/mL, with patients more likely to respond at concentrations of 200–250 ng/mL (APA Task Force 1985). Concentration relationships and dose-response curves for other antidepressants are either lacking or inconclusive.

Given the mixed effects of antidepressant dose-response, adjusting antidepressant doses has generated controversy in clinical practice. The minimal effective dose for treating depression should be initially targeted and re-evaluated in 2 weeks. Improvement early in treatment is likely to correspond with a higher likelihood for response and remission. Thus, if a 20%–30% reduction in symptoms is achieved by week 2, continuing at the current dose until weeks 4–6 is practical (Kennedy 2016). If no improvement is seen by 2 weeks but tolerability is acceptable, further dose titrations between weeks 2–4 is likely the most reasonable measure rather than switching medications, given the delay in therapeutic onset. The flat-dose response with SSRIs does not account for individual pharmacokinetic and pharmacogenomic differences between patients. Therefore, if tolerability is not a concern, a dose increase is often the best approach in early treatment, specifically between weeks 2–4.

Clinical guidance on timing for dose adjustments is lacking, but it is often based on shared-decision making with the patient, treatment setting, and pharmacokinetic principles. In the outpatient setting, dose adjustments are made no more often than every 1–2 weeks. Titrations in the inpatient setting can occur more often because of the level of surveillance and monitoring provided to patients. However, clinicians should be mindful of the therapeutic delay in response to treatment and not exceed the appropriate target dose. In any setting, titrating the dose of the antidepressant too quickly can result in increased adverse effects and treatment discontinuation (Malhi 2015).

Failure to achieve a response after 4–6 weeks of treatment at the maximal tolerated dose indicates a need to consider switching treatments, augment the current therapy, reevaluate the diagnosis, or consider the presence of subtypes of depression that are less likely to respond to antidepressant monotherapy. Escalating doses above the recommended approved dose by the FDA is not endorsed in treatment guidelines because of a lack of clinical evidence to recommend higher-than-approved doses for depression solely, unless a comorbid condition (e.g., obsessive-compulsive disorder, body dysmorphic disorder) is present with evidence for dosing above the FDA maximum.

Augmentation

Augmenting antidepressants is a strategy most useful for patients who have had a partial response or response to their initial treatment, but have yet to achieve remission. Augmentation builds on the gains of the current antidepressant by adding additional treatments with differing mechanisms of action to target residual symptoms. Augmentation avoids the potential for losing any benefits already achieved with the current antidepressant treatment, enables patients to be less vulnerable to worsening depression by removing treatment that is providing some benefit, avoids complexities in cross-tapering medications, and may produce a more rapid response and improvement in symptoms. In some circumstances, augmenting medications (i.e., antipsychotics) have demonstrated a higher likelihood of achieving response or remission of symptoms compared with placebo, despite not achieving an initial response with antidepressant monotherapy (Rafeyan 2020; Papakostas 2009).

Treatment guidelines consider augmentation an acceptable strategy after failure to achieve remission with one antidepressant trial. However, the CANMAT guidelines encourage two different trials before adding adjunctive treatments because augmentation may increase adverse effects, drug–drug interactions, adherence difficulties, and costs (Taylor 2020). One of the limiting factors with augmentation is that most clinical trials investigating augmenting agents are short duration (i.e., 4–8 weeks), making it difficult to determine the appropriate length of therapy.

Antipsychotics

Second-generation antipsychotics have the most consistent data as an augmentation strategy for MDD and are recognized by recent treatment guidelines as a first-line augmentation treatment (Taylor 2020). The augmentation agents that have FDA approval are aripiprazole, brexpiprazole, and quetiapine. Risperidone and ziprasidone are considered effective off-label treatments. Olanzapine has FDA approval for treatment-resistant depression (TRD) when used with fluoxetine, but data for augmenting other agents is limited outside

of depression with psychotic features. Cariprazine produced mixed results as an augmenting agent in earlier studies; however, new data showed an improvement in depressive symptoms with the use of 1.5 mg/day, and, at the time of this writing, the manufacturer is currently seeking an FDA indication as an adjunct for MDD (Monaco 2022; Vieta 2019). Lurasidone has positive control data as a monotherapy for mixed and bipolar depression, but it lacks controlled data in unipolar depression (Kennedy 2016).

Although second-generation antipsychotics consistently rank high as first-line adjunctive strategies, they are limited by their adverse effect profile and absence of long-term efficacy and safety data for use in unipolar depression. Atypical antipsychotics can contribute to weight gain, hyperglycemia, hyperlipidemia, and extrapyramidal adverse effects, which necessitate monitoring of cardiometabolic variables (i.e., weight, waist circumference, blood pressure, hemoglobin A1C or fasting glucose, fasting lipid panel) and abnormal involuntary movements at baseline and with continued use. Informed consent and a risk-benefit discussion should be conducted carefully with patients before using an antipsychotic. Because of safety concerns, it is practical to consider less efficacious treatments with more favorable tolerability (e.g., antidepressant combination) or alternative augmenting agents before committing to antipsychotic treatment for many patients. Likelihood to achieve a response and remission varies with each antipsychotic, and indirect comparisons are difficult to establish because of the heterogeneity among studies and differences in receptor activity. Selection should be driven by patient-specific factors, including comorbidities, cost, and patient preference. Table 8 compares common antipsychotic and other augmenting strategies.

Combining Antidepressants

Adding an antidepressant with a different mechanism of action is a common augmentation strategy. However, there is little pharmacologic rationale for combining medications with similar pharmacologic activity, such as combining two SSRIs or combining an SNRI with an SSRI. These combinations have not been well studied and are not endorsed, except when transitioning between therapies. Furthermore, specific classes cannot be combined with other treatments, such as the monoamine oxidase inhibitors (MAOIs), because of toxicities, including serotonin syndrome and hypertensive crisis. Most evidence has investigated the addition of bupropion, mirtazapine, or trazodone to SSRIs or SNRIs.

The addition of bupropion to an SSRI has anecdotally been considered a rational strategy for pharmacologic augmentation by converting a single transport inhibitor into a triple reuptake inhibitor. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial assessed response and remission of bupropion sustained release (mean dose 267.5 mg/day) and buspirone (mean dose 40.9 mg/day) added to citalopram for 565 patients who did not achieve remission with citalopram monotherapy. About 30% of patients treated with bupropion achieved a response (31.8%) and remission (29.7%), although neither was statistically better than buspirone augmentation (26.9% response; 30.1% remission). The burden of adverse effects was similar between groups, although fewer patients discontinued treatment with bupropion (12.5%) versus buspirone (20.6%; p<0.001) secondary to adverse effects (Trivedi 2006).

The Veteran Affair's Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) assessed the efficacy of augmenting with aripiprazole, switching to bupropion, or augmenting with bupropion after 1522 patients with MDD failed to respond to antidepressant monotherapy (Mohamed 2017). Remission rates were significantly higher with aripiprazole augmentation (28.9%) compared with switching to bupropion (22.3%; p=0.02). No significant difference was seen between augmenting with bupropion and switching to bupropion for remission. Additionally, no difference in remission was noted between aripiprazole versus bupropion augmentation. However, aripiprazole augmentation produced significantly higher response rates (74.3%) compared with bupropion augmentation (65.6%; p=0.003) and switching to bupropion (62.4%; p<0.001). The number of patients who gained more than 7% of their baseline weight was higher in the aripiprazole arm (9.5%) compared with the bupropion arms (1.9%–2.3%; p<0.001) as well as the number of patients who developed akathisia (14.9% vs. 4.3%–5.3%; p<0.001). In an additional network meta-analysis assessing the efficacy of augmenting agents for MDD, bupropion was not significantly more effective than placebo (OR 1.29; 95% CI 0.78–2.34) (Zhou 2015). More recent meta-analyses have continually failed to show bupropion combinations being superior to monotherapy, although analyses are limited by the low quality of methodologic studies available (Henssler 2022).

Mirtazapine augmentation to SSRIs and SNRIs to improve insomnia associated with depression or response outcomes overall is weakly supported in the literature, with conflicting evidence (Papakostas 2009). In the STAR*D trial, no significant differences occurred in remission rates using the combination of mirtazapine and venlafaxine (13.7%) versus tranylcypromine (6.9%) after three subsequent failed treatment trials (McGrath 2006). Conflicting evidence exists between recently published controlled-trials and meta-analyses. A large placebo-controlled trial (239 patients) evaluating mirtazapine augmentation (30 mg/day) versus placebo in primary care patients who experienced treatment failure with SSRIs or SNRIs at an adequate dose did not show a significant improvement in either response or remission (Kessler 2018). Although large clinical trials have not produced robust findings, a recent meta-analysis evaluating the efficacy of combination treatments found that alpha-2 autoreceptor antagonists (e.g., mirtazapine) are an effective combination strategy and superior to monotherapy (Henssler 2022).

Table 8. Comparison of Common Augmentation Treatments for MDD

Generic Name	Mechanism of Action	Oral Dosage for Augmentation (mg/day)	Common Adverse Effects and Safety Profile	Likelihood of Response[a] vs. Placebo OR (95% CI)[b]	Clinical Pearls
First-Line Strategies					
Aripiprazole	• Serotonin$_{2A}$ antagonist • D_2 partial agonist • Serotonin$_{1A}$ partial agonist	*Initial* 2–5 mg/day *Target* 5-10 mg/day Maximum 15 mg/day	*Adverse effects* • Agitation • Akathisia • Headache • Insomnia • Nausea • Restlessness • Tremor • Weight gain *Safety profile* • Less sedating than most other SGAs • Fewer metabolic adverse effects[c] than most other SGAs • Less effect on prolonging QTc interval than most antipsychotics • Activating, may increase insomnia and anxiety	1.85 (1.27–2.72)[d]	• FDA approval as adjunctive treatment • Dose adjustments required with CYP 2D6 and CYP 3A4 inhibitors and inducers • Typically a fast onset of response (1–2 wk) • Only SGA with positive randomized-controlled trial data in older adult patients • NNT based on meta-analysis of clinical trials for response: 7
Quetiapine extended-release	• Serotonin$_{2A}$/D_2 antagonist • Significant blockade at M_1, alpha$_1$, and H_1 receptors	*Initial* 50 mg/day *Target* 150–300 mg/day	*Adverse effects* • Constipation • Dizziness • Dry mouth • Fatigue • Hypotension • Metabolic changes • Weight gain *Safety profile* • More sedating than most other SGAs • Intermediate impact on metabolic adverse effects[c] • Lower risk of extrapyramidal adverse effects relative to other antipsychotics	1.92 (1.39–3.13)[d]	• FDA approval as adjunctive treatment • Positive data for treating depression confounded with sleep difficulties • NNT based on meta-analysis of clinical trials for response: 10

Table 8. Comparison of Common Augmentation Treatments for MDD (*continued*)

Generic Name	Mechanism of Action	Oral Dosage for Augmentation (mg/day)	Common Adverse Effects and Safety Profile	Likelihood of Response[a] vs. Placebo OR (95% CI)[b]	Clinical Pearls
Risperidone	• Serotonin$_{2A}$/D$_2$ antagonist • Significant blockade at alpha$_1$ receptors	*Initial* 0.5–1 mg/day *Target* 1–3 mg/day	*Adverse effects* • Akathisia • Dizziness • Dry mouth • Elevations in prolactin • Increased appetite • Parkinsonism • Tremor • Weight gain *Safety profile* • Intermediate sedation and impact on metabolic adverse effects[c] • Higher risk of extrapyramidal adverse effects and hyperprolactinemia vs. other SGAs	1.49 (0.94–2.51); NS	• Not FDA approved • Typically a fast onset of response (1–2 wk) • Subject to CYP 2D6 interactions • NNT based on meta-analysis of clinical trials for response: 8
Second-Line Strategies					
Brexpiprazole	• Serotonin$_{2A}$ antagonist • D$_2$ partial agonist • Serotonin$_{1A}$ partial agonist	*Initial* 0.5–1 mg/day *Target* 2 mg/day Maximum 3 mg/day	*Adverse effects* • Akathisia • Headache • Weight gain *Safety profile* • Less sedating than most other SGAs • Fewer metabolic adverse effects[c] than most other SGAs	NR	• FDA approval as adjunctive treatment • Not available generically • Dose adjustments required with CYP 2D6 and CYP 3A4 inhibitors and inducers • Typically a fast onset of response (1–2 wk) • NNT based on pooled-analysis of clinical trials for response: 12
Bupropion sustained release	Weak NE/DA reuptake inhibitor	*Initial* 100–150 mg/day *Target* 300–400 mg/day in 2 divided doses	*Adverse effects* • Anxiety • Decreased seizure threshold • Dry mouth • Insomnia • Tremor • Weight loss	1.29 (0.78–2.34); NS	Cautious use with CYP 2D6 substrates

(*continued*)

Table 8. Comparison of Common Augmentation Treatments for MDD (*continued*)

Generic Name	Mechanism of Action	Oral Dosage for Augmentation (mg/day)	Common Adverse Effects and Safety Profile	Likelihood of Response[a] vs. Placebo OR (95% CI)[b]	Clinical Pearls
			Safety profile • Contraindicated in seizure disorders and eating disorders • Activating, may increase insomnia and anxiety • Low risk of sexual adverse effects and may improve sexual adverse effects as adjunctive treatment		
Lithium	• Inhibition of inositol monophosphatase • Decrease in second messenger systems, including cAMP • Inhibition of glycogen synthase kinase-3β	*Initial* 300 mg/day *Target* 600–1200 mg/day (guided by therapeutic lithium concentration; 0.6–1.0 mEq/L)	*Adverse effects* • Acne • GI distress • Hypothyroidism • Leukocytosis • Nonspecific T-wave flattening • Polydipsia • Polyuria • Sedation • Tremor • Weight gain *Safety profile* • Avoid in patients with underlying renal disease	1.56 (1.05–2.55)[d]	• Dosage and serum concentrations varied in studies, most targeted 0.6–1.0 mEq/L; most patients received > 600 mg/day of lithium, but higher therapeutic concentrations (>1.0 mEq/L) are discouraged for MDD augmentation because of poor tolerability and lack of demonstrated benefit • Because of narrow therapeutic index, requires close monitoring of serum concentrations and avoidance of drugs placing patients at risk of lithium toxicity (thiazide diuretics, NSAIDs) • Treatment response may be early when added to TCAs (48–72 hr) • Requires baseline and periodic monitoring of therapeutic drug concentrations, renal function, parathyroid and thyroid function, renal function, serum electrolytes, CBC with differential, weight, and ECG in patients age > 40 yr or with a history of conduction abnormalities • NNT based on meta-analysis of clinical trials for response: 5

Table 8. Comparison of Common Augmentation Treatments for MDD (*continued*)

Generic Name	Mechanism of Action	Oral Dosage for Augmentation (mg/day)	Common Adverse Effects and Safety Profile	Likelihood of Response[a] vs. Placebo OR (95% CI)[b]	Clinical Pearls
Mirtazapine	• Alpha$_2$ receptor antagonist • Noradrenergic/specific serotonergic modulator	*Initial* 15 mg/day *Target* 15–45 mg/day *Maximum* Up to 60 mg endorsed by CANMAT guideline	*Adverse effects* • Dry mouth • Sedation • Weight gain *Safety profile* • Less risk of GI distress because of serotonin-3 antagonism; may mitigate GI symptoms with SSRIs/SNRIs • May cause next-day sedation because of long plasma half-life	NR	• Less risk of sexual dysfunction relative to SSRIs/SNRIs • Less risk of pharmacokinetic drug–drug interactions; secondary multiple elimination pathways; no significant CYP inhibition • May be beneficial in targeting residual anorexia and sleep disorders associated with depression • Large trial in primary care failed to show an advantage of mirtazapine for augmentation; however, efficacy demonstrated in recent meta-analysis
Modafinil	• DA reuptake inhibitor • Enhances activity in brain wake-centers	*Initial* 100–200 mg/day *Target* 100–400 mg/day	*Adverse effects* • Dizziness • Headache • Nausea • Insomnia • Rash *Safety profile* • Activating properties	NR	• Less misuse potential vs. other stimulants; use caution or avoid in patients with substance use disorders • Beneficial for patients with residual symptoms of apathy, fatigue, and sleepiness
Olanzapine	• Serotonin$_{2A}$/D$_2$ antagonist • Significant blockade at M$_1$ and H$_1$ receptors	*Initial* 5 mg/day *Target* 5–20 mg/day	*Adverse effects* • Akathisia • Constipation • Dizziness • Dry mouth • Fatigue • Increased appetite • Metabolic changes • Weight gain *Safety profile* • More sedating than most other SGAs • More metabolic adverse effects[c] than most other SGAs	1.40 (0.96–2.24); NS	• FDA approval for treatment-resistant depression in conjunction with fluoxetine • Often produces a fast onset of response (1–2 wk) • Positive data for treating depression with psychotic features • Subject to CYP 1A2 inhibitors (fluvoxamine, ciprofloxacin) and CYP 1A2 inducers (carbamazepine, cigarette smoking) • NNT based on meta-analysis of clinical trials for response: 19

(*continued*)

Table 8. Comparison of Common Augmentation Treatments for MDD (*continued*)

Generic Name	Mechanism of Action	Oral Dosage for Augmentation (mg/day)	Common Adverse Effects and Safety Profile	Likelihood of Response[a] vs. Placebo OR (95% CI)[b]	Clinical Pearls
Omega-3 fatty acids	• Role in depression is unknown • May exert anti-inflammatory action	*Initial* • Varies • 1–2 g/day (EPA + DHA) *Target* • Varies • 1–4 g/day (EPA + DHA)	*Adverse effects* • GI distress • Diarrhea • Fishy aftertaste • Halitosis • Heartburn *Safety profile* • Anticoagulant effect at high doses; monitor bleeding risk if used in conjunction with anticoagulants and platelet inhibitors	NR	• Optimal dose and EPA/DHA ratio yet to be established; most evidence is for products with > 60% EPA composition • Quality assurance of commercially available products may be lacking because of lack of regulatory oversight
S-adenosyl-l-methionine	Involved in the transmethylation and activation of monoamines	*Initial* 400 mg/day *Target* 800–1600 mg/day	*Adverse effects* • Anxiety • Dry mouth • GI distress • Insomnia • Restlessness *Safety profile* • May increase homocysteine concentrations	NR	• Oxidizes rapidly when exposed to air; high risk for disintegration and loss of potency; do not shake tablets; store in original container in a cool, dry place • Quality assurance of commercially available products may be lacking because of lack of regulatory oversight
Triiodothyronine	Triiodothyronine hormone	*Initial* 25 mcg/day *Target* 25–50 mcg/day	*Adverse effects* • Anxiety • Headache • Hypertension • Palpitations • Sweating • Tremor • Weight loss *Safety profile* Contraindicated in hyperthyroidism, uncontrolled hypertension, cardiac arrhythmias	1.84 (1.06–3.56)[d]	• Best available data are for augmenting TCAs • Thyroid function tests (TSH, free thyroxine, free triiodothyronine) should be obtained at baseline, at 3 mo, and every 6–12 mo • Assess BMD every 2 years in postmenopausal women for osteoporosis risk • NNT based on meta-analysis of clinical trials for response: 4.3

Table 8. Comparison of Common Augmentation Treatments for MDD (*continued*)

Generic Name	Mechanism of Action	Oral Dosage for Augmentation (mg/day)	Common Adverse Effects and Safety Profile	Likelihood of Response[a] vs. Placebo OR (95% CI)[b]	Clinical Pearls
Third-Line Strategies					
Lisdexamfetamine	• Prodrug of dextroamphetamines • DA/NE reuptake inhibitor • Increases presynaptic release of DA/NE	*Initial* 30 mg/day *Target* 30–70 mg/day	*Adverse effects* • Appetite suppression • GI distress • Headache • Hypertension • Insomnia • Irritability • Tachycardia *Safety profile* • Activating properties • Misuse potential • Serious CV events may occur with misuse	NR	• Avoid in patients with active substance use disorders • Meta-analysis and clinical trials have not shown statistical benefit as augmenting agent
L-methylfolate	Cofactor in synthesis of monoamines	*Initial* 7.5–15 mg/day *Target* 15 mg/day	*Adverse effects* are minimal *Safety profile* • Well-tolerated; low risk with use	NR	• Designated as a medical food and requires a prescription • Conflicting evidence for better outcomes in patients with MTHFR gene polymorphisms • Not covered by many commercial and state insurance plans
Methylphenidate	DA/NE reuptake inhibitor	*Initial* 5–10 mg/day in divided doses *Target* 10–60 mg/day in divided doses	*Adverse effects* • Appetite suppression • GI distress • Headache • Hypertension • Insomnia • Irritability • Tachycardia *Safety profile* • Activating properties • Misuse potential • Serious CV events may occur with misuse	1.37 (0.74–2.99); NS	• Avoid in active substance use disorders • Lack of quality evidence for support in younger adult patients • May benefit older adults with depression complicated by apathy or fatigue

(*continued*)

Table 8. Comparison of Common Augmentation Treatments for MDD (*continued*)

Generic Name	Mechanism of Action	Oral Dosage for Augmentation (mg/day)	Common Adverse Effects and Safety Profile	Likelihood of Response[a] vs. Placebo OR (95% CI)[b]	Clinical Pearls
Trazodone	• Serotonin$_{2A}$ antagonist/ serotonin reuptake inhibitor • Significant binding to H_1 and alpha$_1$ receptors	*Initial* • Varies • 25–50 mg at bedtime *Target* • Varies • 50–300 mg at bedtime	*Adverse effects* • Dizziness • Dry mouth • Fatigue • Sedation *Safety profile* • Rare risk of priapism (1 in 8000–10000)	NR	• May be useful in targeting residual symptoms of insomnia • Data are lacking for improving depression outcomes
Ziprasidone	Serotonin$_{2A}$/D_2 antagonist	*Initial* 40 mg/day in divided doses *Target* 80–160 mg/day in divided doses	*Adverse effects* • Akathisia • Dizziness • Dry mouth • Nausea • Sedation • Weight gain *Safety profile* • Activating at lower doses • Higher degree of prolonging QTc interval than most antipsychotics • Fewer metabolic adverse effects[c] than most other SGAs	NR	• Requires administration with ≥ 500 calories for adequate absorption
Limited Evidence for Use in MDD					
Buspirone	Serotonin$_{1A}$ partial agonist	*Initial* 7.5 mg twice daily *Target* 15–60 mg/day in 2 to 3 divided doses	*Adverse effects* • Dizziness • Nausea • Headache *Safety profile* • Subject to CYP 3A4 kinetic interactions, including grapefruit juice, because of high-first pass metabolism • Risk for additive adverse serotonergic effects	1.25 (0.82–2.12); NS	• Effective treatment for generalized anxiety disorder • Requires multiple daily dosing because of short half-life • Low risk of sexual adverse effects; may mitigate sexual adverse effects associated with SSRIs/SNRIs

Table 8. Comparison of Common Augmentation Treatments for MDD (*continued*)

Generic Name	Mechanism of Action	Oral Dosage for Augmentation (mg/day)	Common Adverse Effects and Safety Profile	Likelihood of Response[a] vs. Placebo OR (95% CI)[b]	Clinical Pearls
Lamotrigine	Inhibition of voltage-dependent Na+ channels	*Initial* 25 mg/day *Target* 200 mg/day	*Adverse effects* • Ataxia • Diplopia • Dizziness • Headache • Uncomplicated rash *Safety profile* • Associated with very rare, but serious life-threatening reactions[e] and serious cardiac and conduction abnormalities • Increased risk of rash progressing to Stevens-Johnson syndrome/toxic epidermal necrolysis if titrated too quickly or combined with inhibitors of UGT (valproate)	1.12 (0.57–2.59); NS	• Recognized as effective treatment for bipolar depression in treatment guidelines • Not as effective as an augmenting agent for unipolar depression

[a]*Likelihood of response* is defined as 50% reduction in symptoms.

[b]Based on the results of Zhou X, Ravindran AV, Qin B, et al. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. J Clin Psychiatry 2015;76:e487-98.

[c]Metabolic adverse effects include weight gain, hyperglycemia, and dyslipidemia.

[d]Statistically significant.

[e]These very rare, but serious life-threatening reactions include aseptic meningitis, multiorgan hypersensitivity reactions, and hemophagocytic lymphohistiocytosis.

BMD = bone mineral density; CANMAT = Canadian Network for Mood and Anxiety Treatments; CV = cardiovascular; DA = dopamine; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; H = histamine; M = muscarinic; MTHFR = methylene tetrahydrofolate reductase gene; MDD = major depressive disorder; NE = norepinephrine; NR = not reported; NS = not statistically significant; SGA = second-generation antipsychotic; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TSH = thyroid-stimulating hormone; UGT = UDP-glucuronosyl transferse.

Information from: Catalano G, Robeel RA, Cheney GA, et al. Antidepressant augmentation: a review of the literature and a review of the pharmacoeconomic considerations. J Clin Psychopharmacol 2020;40:396-400; Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can J Psychiatry 2016;61:540-60; Rafeyan R, Papakostas GI, Jackson WC, et al. Inadequate response to treatment in major depressive disorder: augmentation and adjunctive strategies. J Clin Psychiatry 2020;81:OT19037BR3; Ravindran AV, Balneaves LG, Faulkner G, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 5. Complementary and alternative medicine treatments. Can J Psychiatry 2016;61:576-8; Stahl S, Grady MM, Munter N. Stahl's Essential Psychopharmacology: Prescriber's Guide. 2018. Cambridge University Press. New York, NY, 6th ed. Zhou X, Ravindran AV, Qin B, et al. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. J Clin Psychiatry 2015;76:e487-98.

Trazodone is often used for targeting sleep deficits and depressive symptoms in conjunction with other antidepressants, despite a paucity of evidence to support this use. Most studies investigating trazodone in combination with other antidepressants have lasted only a few days or 1 week and focused primarily on sleep outcomes. Small studies have shown improvements in sleep outcomes with using low-dose trazodone (50 mg/day) at bedtime in conjunction with activating antidepressants (i.e., SSRIs, bupropion). However, it remains unclear if trazodone impacts overall depressive symptoms outside sleep metrics, and additive serotonergic effects are possible with concomitant use with SSRIs/SNRIs (Fagiolini 2012). Overall, the evidence for using antidepressant augmentation with bupropion, mirtazapine, and trazodone is only weakly supported in the literature.

Buspirone

Heightening serotonin neurotransmission through the addition of serotonin$_{1A}$ partial agonists such as buspirone was a strategy incorporated in the STAR*D trial. Although an improvement in response was seen, there was no difference compared with bupropion augmentation (Trivedi 2006). Studies investigating buspirone augmentation compared with placebo for patients who experienced a failure of response to SSRI monotherapy did not show statistical improvement in depression outcomes (Appelberg 2001; Landén 1998). Not surprisingly, buspirone did not demonstrate a significant improvement versus placebo in a network meta-analysis comparing augmenting agents, and the CANMAT guidelines do not currently endorse this drug (Kennedy 2016; Zhou 2015).

Psychostimulants

The use of psychostimulants as an augmentation strategy is endorsed by various treatment guidelines, with modafinil generally recognized as a second-line adjunctive treatment. A pooled analysis of studies investigating modafinil augmentation showed a statistically significant reduction in depressive symptoms on the Hamilton Depression Rating Scale compared with placebo ($p<0.01$), with notable improvements in targeting difficulties with fatigue or excessive sedation. Conversely, armodafinil has not been investigated for unipolar depression (Rafeyan 2020; Fava 2007).

Although endorsed by the CANMAT as a third-line treatment, methylphenidate has failed to show a statistical advantage over placebo in four clinical trials and did not show a statistical advantage of eliciting a response to treatment compared with placebo in a large, network meta-analysis (Rafeyan 2020; Zhou 2015). Methylphenidate plus citalopram did provide benefit in older adult patients relative to citalopram monotherapy or placebo; however, the combination was started initially and not added after a failure of treatment response (Lavretsky 2015).

A proof-of-concept study initially showed benefit of adding lisdexamfetamine in escitalopram nonresponders, but larger studies and a subsequent meta-analysis failed to show a significant improvement with lisdexamfetamine used as an augmenting agent for MDD (Giacobbe 2018; Richards 2017; Trivedi 2013).

Hormone Supplementation

Hormone therapies have been evaluated as an adjunctive treatment for patients with MDD. Testosterone augmentation has not shown benefit in patients with TRD without the presence of clinical hypogonadism. Testosterone replacement therapy does have a role in treating depressive symptoms secondary to clinical hypogonadism. Small studies have shown some antidepressant activity of estrogen replacement therapy in perimenopausal women, primarily those experiencing menopause symptoms, such as vasomotor symptoms and vaginal dryness. No augmentation benefit with estrogen replacement therapy has been established in postmenopausal women (Dwyer 2020).

Thyroid supplementation, specifically triiodothyronine (T_3), is the most studied and evidence-based hormone augmenter in MDD. A meta-analysis of 292 patients from 8 studies using T_3 augmentation in patients who experienced failure to achieve remission with TCA treatment demonstrated that those treated with T_3 were more likely to respond to therapy (57%) compared with placebo (24%) and were twice as likely to achieve a response (RR 2.09; 95% CI, 1.31–3.32; $p=0.002$) (Aronson 1996). Randomized controlled data for use of T_3 augmentation in patients treated with SSRIs/SNRIs is mixed, with one trial showing a significant benefit compared with placebo when added to sertraline and another trial showing no difference from placebo when added to paroxetine (Cooper-Kazaz 2007; Appelhof 2004). In addition, the STAR*D trial showed no difference in remission rates with T_3 (24.7%) and lithium (15.9%; $p=0.425$) when added after two sequential failed trials, although T_3 was better tolerated (Nierenberg 2006). Findings from a network meta-analysis showed statistically significant improvement with T_3 augmentation, with remission being 3-fold greater with T_3 compared with placebo (Dywer 2020; Zhou 2015). The use of other thyroid supplements has not been thoroughly evaluated in controlled trials, and these are not recommended for use in MDD.

Lithium

Lithium is endorsed in the guidelines as either a first- or second-line adjunctive treatment. In a meta-analysis of 10 randomized, placebo-controlled trials, patients augmented with lithium achieved higher response rates (41.2%) versus placebo (14.4%) and were significantly more likely to respond to treatment (OR 3.11; 95% CI 1.80–5.37) (Crossley 2007). Use of lithium is often constrained by its adverse effect burden, narrow therapeutic index, potential for drug–drug interactions, and extensive oversight and monitoring.

Complementary and Alternative Medications

Several complementary alternative medications have been studied as adjunctive treatments for MDD. Common therapies

include St. John's wort and non-herbal supplements, such as omega-3 fatty acids, *S*-adenosyl-l-methionine (SAMe), and l-methylfolate. St. John's wort is recognized as a second-line adjunctive treatment in the CANMAT guidelines, but limited evidence is available regarding its use as an add-on treatment. St John's wort can block the serotonin transporter and induce expression of CYP 3A4, making it a risky augmenting agent to combine with most antidepressants.

Omega-3-fatty acids, including eicosapentaenoic acid and docosahexaenoic acid, have shown improvement in depression outcomes in several meta-analyses when added to antidepressants and tends to be well-tolerated, although the effect is small (Ravindran 2016).

Based on a Cochrane Review, SAMe is an effective add-on strategy in patients treated with SSRIs, but the quality of evidence is low and requires further investigation (Galizia 2016). A prescription food, L-methylfolate, has demonstrated improvement in response rates when added to SSRIs (32.3%) compared with placebo (14.6%; p=0.04) when dosed at 15 mg/day, but effects are not seen at lower doses (Papakostas 2012). There is a lack of evidence to recommend other common complementary and alternative medications used as adjunctive treatments in depression, including cannabidiol, probiotics, folate, inositol, tryptophan, and *Rhodiola rosea* (Malhi 2021; Liu 2019; Ravindran 2016).

Switching Antidepressants

Switching antidepressants is recommended for patients who experience intolerable adverse effects or if unacceptable safety risks arise with treatment. If dose reductions do not alleviate dose-related adverse effects (e.g., sexual dysfunction, GI effects), a switch to an alternative antidepressant should be considered or nonpharmacologic measures should be trialed.

Switching is also common if the patient has not experienced a response to treatment once the medication dose has been maximized. Compared with augmentation strategies, switching antidepressants can improve adherence, minimize tolerability issues with combination agents, reduce the risk of drug–drug interactions, and reduce polypharmacy and prescribing cascades. Depending on the agents used, monotherapy generally reduces overall costs of treatment (Procyshyn 2021; Kennedy 2016). Switching treatments poses the risk of losing therapeutic gains that may have occurred with a treatment, particularly if a partial or full response was obtained with the initial treatment.

Data are conflicting regarding the decision to switch antidepressants. Observational studies and randomized controlled trials have shown a benefit from switching antidepressant treatment in nonresponders. However, the decision of which treatment to select after a treatment failure is controversial. The STAR*D trial showed no significant difference in efficacy outcomes after the failure of citalopram and switching to sertraline, venlafaxine, or bupropion, yet in other trials a modest benefit in switching to a different class of medication is shown (Papakostas 2008; Rush 2006).

In addition, new data are questioning the value of switching relative to continuing treatment after nonresponse. A meta-analysis compared the efficacy of switching versus continuing antidepressant treatment in nonresponders. No study showed a statistical advantage for switching over continuing the failed treatment; however, one study did show a significant improvement in continuing the failed treatment longer compared with switching (p=0.001) (Bschor 2018). Given that comparative data are lacking for the efficacy outcomes of different switching strategies, switching antidepressants should be a shared-decision making process with the patient, taking into account adverse effect potential, drug–drug interactions, and cost of therapy.

Switching antidepressants can be carried out in different manners, most often through direct switches, cross-tapering, or fully discontinuing treatment (i.e., conducting a wash-out) and starting the new treatment afterwards. A complete wash-out is required if an overlap of two antidepressants is contraindicated because of severe drug–drug interactions, such as with MAOIs. Complete washouts are recommended for patients who had significant adverse effects soon after initiating an antidepressant to prevent any overlap of adverse effects.

Clinicians should be mindful that patients may be vulnerable to worsening symptoms of depression caused by the loss of efficacy of current therapy and the subsequent delay in onset of the new antidepressant. If symptoms of depression are moderate to severe, it may not be feasible to withdraw the antidepressant before starting a new treatment, especially if some symptomatic improvement was achieved previously.

In addition, abrupt discontinuation or rapid withdrawal of medications that inhibit the serotonin transporter can result in flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances (e.g., vertigo, electrical shock sensations or "brain zaps"), and hyperarousal symptoms (e.g., anxiety, agitation). Shorter half-life medications (i.e., fluvoxamine, paroxetine, venlafaxine, vilazodone) tend to pose higher risks when quickly withdrawn, whereas longer half-life medications (i.e., fluoxetine, vortioxetine) pose minimal risk. Although TCAs have long half-lives, patients can experience cholinergic rebound with acute withdrawal.

Cross-tapering is a strategy to mitigate risks of worsening depression and discontinuation symptoms. This strategy involves reducing the current antidepressant dose gradually toward discontinuation, while initiating and titrating the new antidepressant to a therapeutic dose. Cross-tapering of antidepressants can generally be performed quickly and typically should not last more than 1–2 weeks because prolongation can result in undue adverse effects and potentially result in unneeded polypharmacy, with patients inadvertently remaining on both treatments. Exceptions can be made if a cross-taper was unsuccessful and must be extended because of presence of discontinuation adverse effects or intolerable adverse effects with the new antidepressant (Hirsch 2022).

Patient Care Scenario

M.L., a 42-year-old man, presents to his outpatient care team for follow-up management of his depression. The patient is being reevaluated today for his second depressive episode in the clinic for the past 12 weeks. At his initial visit, a PHQ-9 rating scale was performed and his score was 25, with no evidence of suicidality present. M.L. was restarted on fluoxetine 20 mg/day, with which he previously experienced remission, and he was scheduled for follow-up in 3 weeks. At 3-weeks follow-up, he had experienced minimal improvement, and the fluoxetine dose was further titrated to 40 mg/day. At 7-week follow-up, M.L. said he felt better but was still not functioning well. A PHQ-9 was performed, and his score was 14. Fluoxetine was increased to 60 mg/day at the patient's request. Today, at 12-week follow-up, M.L. reports still struggling with depression, but thinks that the fluoxetine is "doing something." He describes some experiences of reduced libido, but thinks it secondary to his depression. A PHQ-9 is performed, and his score is 11. What is the next best step in managing M.L.'s depression?

ANSWER

Evaluating the PHQ-9 scores it is indicative that M.L. had achieved a partial response to fluoxetine 40 mg/day at 7 weeks and a full response without remission (i.e., 50% reduction in symptoms based on psychometrics) with a further dose increase to 60 mg/day at his 12-week follow-up. His current PHQ-9 score is indicative of moderate level of depression, requiring further intervention. Discussions with the patient could include optimizing the dose of his fluoxetine, augmenting fluoxetine with additional treatments, or considering a switch to a different antidepressant. Although the maximal dose for treating depression with fluoxetine is 80 mg/day, SSRIs tend to display a flat-dose response. In addition, based on new analyses, doses greater than 40–50 mg equivalents of fluoxetine have failed to show a significant improvement over low- to mid-range doses of SSRIs. In addition further increases could pose a higher risk of treatment-emergent adverse effects (e.g., worsening libido). It is unlikely that escalating the dose of fluoxetine to 80 mg/day will provide additional benefit, and it is likely that the treatment effects have plateaued. Although the strategy of switching to a different medication may be offered to this patient, there is a risk that he could lose the therapeutic gains achieved with antidepressant treatment. The higher treatment dose of fluoxetine may be a barrier to switching because many switches involving fluoxetine require a small washout based on its long-half life.

Exploring augmentation strategies with M.L. is the optimal choice because he has gained benefit with SSRI treatment but has yet to achieve remission. Various augmentation strategies can be discussed with him. As an adjunct to pharmacotherapy, evidence-based psychotherapy such as CBT and interpersonal therapy should be discussed, if not currently being used. Therapeutic options with high-quality evidence either from treatment guidelines or large meta-analyses include second-generation antipsychotics (e.g., quetiapine, aripiprazole), lithium, esketamine, and T_3 augmentation, all of which may presented as potential options to address M.L.'s residual depressive symptoms. Because of the limited guidance for selecting one first-line option over another, the priority of treatment is based on comorbidities, concomitant medications, cost, and patient acceptance of the adverse effect risks associated with treatment. The applicable risks and benefits of each therapy should be discussed with the patient, including the monitoring variables with all treatments. The addition of aripiprazole, brexpiprazole, or risperidone would require the use of a lower dose because of the strong CYP 2D6 inhibition by fluoxetine. Lithium augmentation to a SSRI can increase serotonergic adverse effects, and close monitoring is needed for the signs and symptoms of serotonin syndrome. In general, T_3 augmentation tends to be well tolerated; however, the evidence for its augmenting potential is less established when adding on to SSRI treatment. Esketamine is an effective add-on to SSRI treatment. However, M.L. does not qualify because he has not experienced a failure of two different trials of therapy or does not present with acute suicidality.

1. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can J Psychiatry 2016;61:540-60.
2. Taylor RW, Marwood L, Oprea E, et al. Pharmacological augmentation in unipolar depression: a guide to the guidelines. Int J Neuropsychopharmacol 2020;23:587-625.
3. Zhou X, Ravindran AV, Qin B, et al. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. J Clin Psychiatry 2015;76:e487-98.

It is important to be cautious when cross-titrating TCAs with other CYP-inhibiting antidepressants because TCAs are CYP 2D6 substrates and are subject to plasma concentration increases when CYP 2D6 inhibitors are added and thus can result in TCA toxicity. Before initiation of any CYP 2D6-inhibiting antidepressant, TCAs should be tapered to a low dose, and a short washout should be considered when converting from fluoxetine.

Directly switching antidepressants is a common strategy when converting between drugs in the same class. Stopping the current treatment and starting the new treatment at the starting dose or equivalent dose are both sensible approaches. Direct switches are recommended for patients who have difficulty following instructions for the cross-taper or when the treatments are mechanistically similar. Cross-tapers are a more appropriate approach if the dose of the

Box 1. Resources for Switching Antidepressants

- College of Family Physicians of Canada. PsychedUp. SwitchRx:Online Medication Switching Tool.
- British Columbia Guidelines. Switching Antidepressants. 2013
- Keks N, Hope J, Keogh S. Switching and stopping antidepressants. Aust Prescr 2016;39:76-83.

current antidepressant is high because it may be difficult to tolerate a direct switch at an equivalent dose (Hirsch 2022). Resources for the strategies of switching antidepressant are listed in Box 1.

SPECIAL POPULATIONS

Whereas the framework for diagnosis and treatment of MDD is preserved across various patient groups, additional factors must be considered for special populations.

TRD and Suicidality

Esketamine/Ketamine

In early 2019, intranasal esketamine received FDA approval for TRD. In 2020, the FDA updated the indication to include patients with suicidal ideation or behavior. Racemic ketamine and the derivative esketamine are antagonists of N-methyl-D-aspartate receptors and appear to modulate glutamate and γ-aminobutyric acid systems to limit pathologic hyperactivity in the subgenual anterior cingulate cortex, a mechanism shared with conventional antidepressant medications. Reductions in suicidal ideation may occur rapidly after a single dose of ketamine, within 1–2 days, and may persist for up to 6 weeks with recurring treatment. Treatment is typically used adjunctively to other established treatments; however, monotherapy can be used. Dosing information is summarized in Table 9.

Limitations of ketamine and esketamine use revolve largely around tolerability and safety monitoring (Table 10). Patients receiving ketamine or esketamine should be in a clinical setting with experience in diagnosis and treatment of mood disorders and the ability to measure cardiovascular and respiratory function for 2 hours after administration. In addition, all requirements of the Risk Evaluation and Mitigation Strategies program must be adhered to.

An additional limitation is that studies have not consistently demonstrated efficacy of ketamine in patients older than 65 years. Several small studies showing no difference compared with placebo in this population (McIntyre 2021). Pooled-analysis of esketamine resulted in an NNT of 8 and 7 for response and remission, respectively (Citrome 2020).

Other Treatments

In a high-quality systematic review and meta-analysis of lithium compared with placebo or active control, lithium was more effective than placebo in reducing completed suicide (OR 0.13; 95% CI, 0.03–0.66) and deaths from any cause (OR 0.38; 95% CI, 0.15–0.95). However, the differences between lithium and active controls were not significant (Cipriani 2013). Electroconvulsive therapy is a highly effective modality for treatment of MDD, particularly for MDD with psychotic

Table 9. Dosing of Ketamine and Esketamine for TRD

Medication[a]	Initial Dose	Maximum Dose	Route	Timing	Duration	Notes
Ketamine	0.5 mg/kg	No additional efficacy >1.0 mg/kg	IV over 40 min	Twice weekly[b]	• 4–6 treatments initially • Long-term use not established	• Dose based on IBW for overweight or obesity • No FDA approval
Esketamine	56 mg	84 mg	Intranasal	• Twice weekly for 4 wk, followed by once weekly for 4 wk • May continue weekly or change to every 2 wk	• Efficacy and safety established for up to 1 year	• FDA approval for treatment-resistant depression • Dose escalation based on patient/provider preference

[a]Data from package inserts.

[b]Timing of administration is variable.

IBW = ideal body weight; TRD = treatment-resistant depression.

Information from: Manufacturer's package inserts; Lexicomp Online [Internet database]. Hudson, OH: Lexi-Comp. Updated periodically.

Table 10. Ketamine/Esketamine Adverse Event Monitoring in MDD

Adverse Effect[a]	Description	Frequency of Use	Monitoring Variables	Notes
Dissociation	Dissociation, perceptual disturbances, abnormal sensations, derealization, and depersonalization	About 75% of patients receiving IV ketamine	CADSS; however, this tool is not validated and likely underestimates occurrence and thus should not be relied on	Usually attenuates with subsequent treatments
Psychotomimetic	Induction of psychosis	Primarily occurs with comorbid primary psychotic disorders	—	—
Neurologic	Dizziness, drowsiness, light-headedness	—	Instruct patient to not drive a car until after a night of sleep	—
Hemodynamic	Increased heart rate and BP	*Ketamine* 10%–50% of patients 20%–30% of patients have BP > 180/100 mm Hg or HR > 110 beats/minute *Esketamine* 2.1% of patients require intervention	BP ECG	—
Genitourinary	Nocturia, painful hematuria, dysuria, urinary urgency, and incontinence	*Ketamine (recreational)* 20%–40% of patients *Esketamine* Not observed	Urinalysis	Dose and duration dependent Usually resolves on discontinuation
Abuse liability	Schedule III substance	No evidence of increased risk of substance use disorders with supervised clinical use	Toxicology screening if a concern	—

[a]Data from package inserts.

BP = blood pressure; CADSS = Clinician Administered Dissociative States Scale; HR = heart rate; IV = intravenous.

Information from: Manufacturer's package inserts; Lexicomp Online [Internet database]. Hudson, OH: Lexi-Comp. Updated periodically.

features and TRD. Although the evidence is largely retrospective, available data suggest a reduction in suicidality with electroconvulsive therapy treatment. Olanzapine/fluoxetine has FDA approval for TRD with an NNT of 8 and 13 for response and remission, respectively (Citrome 2020). The use of this combination is often limited by cardiometabolic adverse effects. The challenges with these treatments may be complex, and augmentation strategies are often chosen as the therapeutic modalities for TRD (see Table 8).

Pediatrics/Adolescents

Like all other patient populations, treatment of depression in children and adolescents may be pharmacologic and/or nonpharmacologic. A stepped treatment approach is outlined in the 2019 National Institute for Health and Care Excellence (NICE) guideline depression in children and young people (Table 11).

NICE Guidelines for Children and Adolescents

If pharmacotherapy is used, the patient should be closely monitored for hostility and suicidal ideation or behavior. Although emergent suicidality is uncommon in this population, all antidepressants carry a boxed warning for suicidality for this age group. This risk is highest at treatment initiation, and patients and caregivers should be counseled to seek help immediately if these changes are observed. Fluoxetine should be started at 10 mg/day, which may be increased to 20 mg/day if needed after at least 1 week.

Of note, only fluoxetine is supported by the NICE guidelines. However, escitalopram may be a reasonable alternative

Table 11. Stepped Therapy in NICE Guidelines for MDD

At Risk	Nonpharmacologic	Pharmacologic
Mild depression	• Watchful waiting (follow up in 2 wk) • Cognitive behavioral therapy • Interpersonal psychotherapy • Nondirective supportive therapy	Not indicated
Moderate or severe	*Age 5–11 yr* • Family-based interpersonal psychotherapy • Family therapy • Cognitive behavioral therapy *Age 12–18 yr* • Individual cognitive behavioral therapy	Fluoxetine
Nonresponsive depression	Intensive psychological therapy	Fluoxetine Sertraline Citalopram Antipsychotic augmentation

NICE = National Institute for Health and Care Excellence.

Information from: National Institute for Health and Care Excellence (NICE). Depression in children and young people: identification and management. NICE guideline [NG134]. London, UK: NICE, 2019.

in cases of lack of response or poor tolerability of fluoxetine. The dosing is to start escitalopram at 5 mg/day and titrate by 5 mg to a maximum of 20 mg/day. If withdrawal symptoms are noticed, total daily dose should be split into twice daily dosing (Utah Academy of Pediatric and Adolescent Psychiatry 2016).

Older Adults

Depression is common among older adults, and use of antidepressants is high in this population. In a study evaluating prevalence of use of antidepressants, the use increased with age and was highest among women age 60 and older (24.3%) (Brody 2020). In general, the standard treatment principles can be applied to this population. Comparable to pharmacotherapy, CBT maintains efficacy. Among patients with cognitive deficits, problem-solving therapy, which is a specific form of CBT, may be preferred, and longer durations of therapy (6 months) may be required for significant treatment effect.

Antidepressants are effective in older adults, although response rates are somewhat lower compared with the general population. It is recommended to initiate treatment at 50% of the usual starting dose and titrate to therapeutic effect (Table 12). Another difference to be mindful of in this older population is that response may be significantly delayed, at around 12 weeks versus 4–6 weeks in younger adults. Augmentation strategies may be used for inadequate response; however, it is generally preferred to increase the dose or switch to an alternative therapy as an initial strategy to minimize medication burden (Marvanova 2021).

Postpartum Depression

Between 3% and 6% of women will experience the onset of a major depressive episode during pregnancy or in the weeks or months after delivery, with about 50% of postpartum major depressive episodes actually beginning before delivery. Women with peripartum major depressive episodes often have severe anxiety and even panic attacks. Rarely, peripartum-onset mood episodes can present either with psychotic features (*DSM-5*). Screening should be performed using the PHQ or with the Edinburg Postnatal Depression Scale (EPDS) during the comprehensive postpartum visit. Standard pharmacologic and nonpharmacologic treatments may be used, though in 2019, the FDA approved brexanolone for the treatment of postpartum depression.

Brexanolone

Brexanolone is a modulator of γ-aminobutyric-acid type A receptors. Phase 3 trials showed a statistically significant reduction in Hamilton Depression Rating Scale score at 60 hours after brexanolone infusion compared with placebo. However, a difference of −5.5 (95% CI, −8.8 to −2.2) and −2.5 (95% CI, −4.5 to −0.5) is a modest treatment effect (Zheng 2019). Furthermore, the dosing, administration, and monitoring requirements for brexanolone are a significant barrier. It is an intravenous infusion given over 60 hours in a monitored setting in case of excessive sedation or loss of consciousness. Because of these potential complications, it is also subject to a restricted distribution network and a Risk Evaluation and Mitigation Strategies program.

Table 12. Preferred Treatments for MDD in Older Adults

Medication[a]	Standard dose	Typical dose in older adults	Renal or hepatic impairment	Clinical Pearls
Citalopram	*Initial* 20 mg *Target* 20–40 mg	10–20 mg	Hepatic impairment; maximum dose 20 mg/day	Assess for prolonged QTc SIADH
Escitalopram	*Initial* 10 mg *Target* 10–20 mg	5–10 mg	Hepatic impairment; maximum dose 10 mg/day	Assess for prolonged QTc SIADH
Fluoxetine	*Initial* 20 mg *Target* 20–80 mg	Standard dose, although tolerability is improved at lower doses for older adults; consider lower starting doses	Hepatic impairment; reduce dose by 50%	Assess for drug interactions (CYP 2D6) SIADH
Sertraline	*Initial* 50 mg *Target* 50–200 mg		Hepatic impairment; reduce dose by half	SIADH
Duloxetine	*Initial* 30–60 mg *Target* 60 mg		Hepatic impairment—avoid	Avoid in BPH Assess for drug interactions (CYP 2D6) SIADH
Venlafaxine extended-release	*Initial* 37.5–75 mg *Target* 75–225 mg		If CrCl < 30 mL/min, do not exceed 112.5 mg/day	Avoid in BPH SIADH
Mirtazapine	*Initial* 15 mg *Target* 15–45 mg		Moderate or severe renal or hepatic impairment; use with caution	
Bupropion	*Initial* 150–200 mg *Target* 150–300 mg, varies based on formulation		Severe hepatic impairment; maximum dose 150 mg every 48 hr	Assess for drug interactions (CYP 2D6)

[a]Data from package inserts.

BPH = benign prostatic hypertrophy; CrCl = creatinine clearance; MDD = major depressive disorder; SIADH = syndrome of inappropriate diuretic hormone secretion.

Information from: Manufacturers' package inserts; Lexicomp Online [Internet database]. Hudson, OH: Lexi- Comp. Updated periodically; Procyshyn RM, Bezchlibnyk-Butler KZ, Jeffries JJ, eds. Clinical Handbook of Psychotropic Drugs. Boston, MA: Hogrefe, 2021.

Pregnancy and Lactation

About 20% of pregnant patients have coexisting MDD, and treatment should be individualized for patients with MDD who are pregnant. Nonpharmacologic therapies remain effective, and most pharmacologic agents may be considered for this population. Whereas some agents may be preferred in pregnancy (sertraline) and some not preferred (paroxetine), in general, pharmacologic treatment should be used if necessary for maternal mental health at an individualized and minimized, but effective, dose. In addition, if a medication has

Table 13. Antidepressants in Pregnancy and Lactation

Medication Class	Pregnancy	Lactation
SSRIs, SNRIs, vilazodone, vortioxetine	• SSRIs are one of the most well-studied pharmacologic classes in pregnancy • Major teratogenic risk with SSRI treatment is similar to non-exposed pregnant women • Teratogenic risk of individual SSRIs remains unclear from case-control studies, but paroxetine exposure during first trimester is associated with septal and atrial heart defect • Poor neonatal adaption syndrome (25%–30%) with SSRI and SNRI use in pregnancy ◦ Possibly related to withdrawal or toxicity ◦ Symptoms: autonomic instability, respiratory distress, difficulties feeding, and sleep disturbances leading to prolonged hospitalization ◦ Typically self-limiting with supportive care • Persistent neonatal pulmonary hypertension (0.1%–0.3%) associated with SSRI use after gestational age 20 wk • SSRI exposure in utero associated with increased risk of autism spectrum disorder, but is confounded by maternal psychiatric conditions • Vortioxetine may pose risk in excess of SSRIs and should be reserved in perinatal populations until more data are available • SNRIs and vilazodone are less studied in pregnancy, but potential risks associated with use are similar to SSRIs	• SSRIs and SNRIs are excreted in breastmilk • Infant exposure through lactation tends to be low or negligible • Sertraline or paroxetine at lowest effective dose is preferred because infant exposure is lower compared with other SSRIs • Fluoxetine and citalopram have higher infant serum concentrations relative to other SSRIs • Other SSRIs (fluoxetine citalopram) may be considered if evidence of a previous positive treatment response • Venlafaxine and desvenlafaxine have higher infant serum concentrations relative to other antidepressants; compatibility is uncertain and benefits and risks should be weighed with use • Available data for lactation are limited for duloxetine, levomilnacipran, vilazodone, and vortioxetine
TCAs	• No clear association of TCA exposure in pregnancy and congenital abnormalities • Neonatal withdrawal is a complication, characterized by jitteriness, irritability, and anticholinergic effects at birth; symptoms are self-limited with supportive care	• TCAs are excreted in breastmilk • Infant exposure through lactation tends to be low • Imipramine and nortriptyline may be recommended first-line agents if effective for past episodes and no contraindications exist • Doxepin should be avoided because of higher relative infant dose and increased sedation
MAOIs	• Evidence of major teratogenicity with use • Because of dietary restrictions, drug-interactions, and positive evidence of teratogenicity, avoid MAOIs in pregnancy	Not recommended
Bupropion	• Similar teratogenic risk for pregnant women treated with bupropion and controls • Congenital heart defects in some studies during pregnancy, but data are inconclusive	Compatibility is uncertain; benefits and risks must be weighed with use
Mirtazapine and trazodone	Limited human data suggest low risk for congenital malformations	Compatibility is uncertain; benefits and risks must be weighed with use

MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Adapted with permission from Grady S. Depression. In: College of Psychiatric and Neurologic Pharmacists (CPNP), ed. CPNP Psychiatric Pharmacotherapy Review Course, 2021–2022 ed. Lincoln, NE: College of Psychiatric and Neurologic Pharmacists, 2021.

been effective for treating MDD in an individual patient, that medication generally may be continued.

Antidepressant use during pregnancy has potential fetal risks, but causality is difficult to establish. Uncontrolled depression confers higher risks of pregnancy-related complications, making it difficult to determine whether antidepressant medication is the teratogen or whether observed complications are the result of incompletely treated depression. In summary, antidepressant use has been associated with a small risk of congenital malformations and neurodevelopmental effects. However, compared with controls, there does not appear to be demonstrable harm from the medication, and the risks of discontinuing or withholding medication will often outweigh the risks of using the medication (Ornoy 2017).

Almost all antidepressant medications are compatible with breastfeeding and should be continued without hesitation if appropriate for the lactating patient. Potential exceptions are lithium and venlafaxine. Although not contraindicated in breastfeeding, these treatment decisions should be individualized. Among SSRIs, fluoxetine would not be a preferred agent because of its long half-life and increased milk transfer, but it may be considered acceptable if other options are not tolerated or effective (Table 13).

CONCLUSION

In the context of the COVID-19 pandemic and wide shortage of mental health providers, clinical pharmacists will continue to be heavily relied on to treat patients with MDD. Although treatment approaches have not dramatically changed in the past 5 years, new research provides better guidance on augmentation approaches. Moreover, new therapeutic options, such as esketamine and brexanolone, offer much needed novel treatment strategies to the arsenal for treating depression. Pharmacists will continue to play a vital role in optimizing and tailoring pharmacotherapy for patients who fail to achieve remission on monotherapy or require specialized treatments for resistant forms of depression.

Practice Points

Many challenges face clinical pharmacists in their efforts to optimize pharmacotherapy for patients with MDD, especially for patients who do not experience remission with their first trial of therapy. New data and treatments have emerged to assist clinicians in tailoring antidepressant therapy for specific patient populations.

- **The CANMAT and RAZCP guidelines endorse the use of SSRIs, SNRIs, bupropion, mirtazapine, and vortioxetine as first-line treatment options for MDD.**
- **Dose optimization, augmentation, and switching remain the primary strategies for addressing inadequate treatment response.**
- **Pharmacologic augmentation strategies for MDD with moderate- to high-quality evidence include aripiprazole, brexpiprazole, quetiapine, risperidone, lithium, and T_3 supplementation.**
- **Although common in practice, combining antidepressants with differing mechanisms of action is only weakly supported in the literature.**
- **Esketamine represents an intranasal treatment designed to treat depressive symptoms in patients with MDD with acute suicidal ideation and TRD.**
- **Brexanolone offers a specific and needed treatment option for postpartum depression; however, clinical pharmacists should recognize the barriers and the monitoring required for treatment.**

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

K.M., a 49-year-old man, presents to his primary-care provider, asking for his testosterone level to be tested. He reports extreme fatigue despite sleeping around 10 hours per night and a 4.5-kg (10-lb) weight gain over the last 3 months. Upon further questioning, K.M. reveals stressors with taking care of his parents and in his marriage. He feels down most days of the week over the last several months and has noticed his temper is more short than normal. K.M.'s testosterone level returns on the lower end of the normal range. A PHQ-9 is 13.

1. Which one of the following best evaluates K.M.'s presentation?

   A. Moderate depression with melancholic features
   B. Moderate depression with atypical features
   C. Severe depression with no additional specifier
   D. Moderately severe depression with melancholic features

2. Which one of the following is best to recommend as initial pharmacotherapy for K.M.?

   A. Paroxetine 20 mg orally daily
   B. Amitriptyline 50 mg orally daily
   C. Selegiline 6 mg transdermal patch daily
   D. Fluoxetine 20 mg orally daily

3. One week ago, a 67-year-old man began treatment for a first episode of depression with vortioxetine 10 mg daily. He is still significantly depressed and is complaining of nausea, diarrhea, and insomnia. The patient's medical history includes benign prostate hyperplasia and a distant history of seizure disorder. His outpatient provider would like to switch treatments. On the basis of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) Clinical Practice Guidelines, which one of the following is the best to recommend as an alternative treatment for this patient?

   A. Bupropion
   B. Venlafaxine
   C. Mirtazapine
   D. Amitriptyline

Questions 4 and 5 pertain to the following case.

S.L. is a 28-year-old man enrolled in a clinical study evaluating clinician decision-making for treating initial episodes of depression. A score of 42 on the Montgomery-Åsberg Depression Rating Scale (MADRS) scale was documented on S.L.'s first evaluation, and 8 weeks ago he was started on sertraline 50 mg every morning. Four weeks ago, the dose of sertraline was escalated to 100 mg/day. Today, at his appointment, a MADRS is obtained, scoring a total of 36. S.L. reports no adverse effects with sertraline.

4. On the basis of his current MADRS score, which one of the following best evaluates S.L.'s treatment response to sertraline?

   A. Non-response
   B. Partial response
   C. Full response
   D. Remission

5. Which one of the following is best to recommend next for management of S.L.'s depression?

   A. Continue sertraline 100 mg/day.
   B. Stop sertraline and start escitalopram 10 mg/day.
   C. Augment sertraline 100 mg/day with trazodone 50 mg at bedtime.
   D. Taper and discontinue the sertraline over 2 weeks then start duloxetine 30 mg/day.

Questions 6–8 pertain to the following case.

J.R., a 31-year-old woman with no significant medical history, presents to her primary care provider for management of her second episode of depression. Twelve weeks ago, J.R. started 10 mg of escitalopram and further titrated to 20 mg after 6 weeks of treatment. Her Hamilton Depression Rating Scale score has dropped from 28 to 12 since starting escitalopram.

6. Which one of the following is best to recommend for J.R.?

   A. Increase escitalopram to 30 mg/day.
   B. Augment with buspirone 15 mg/day.
   C. Augment with risperidone 0.5 mg at bedtime.
   D. Augment with olanzapine 5 mg at bedtime.

7. J.R. would prefer to use a more holistic and natural approach in targeting her residual depressive symptoms. Which one of the following is best to recommend as an adjunctive treatment for J.R.?

   A. Estrogen
   B. Cannabidiol
   C. L-Methylfolate
   D. St. John's wort

8. J.R. switches from escitalopram to sertraline 100 mg/day and begins adjunctive psychotherapy. Her depression remits after 8 weeks of treatment. Which one of the following is best to recommend regarding how long J.R. should continue sertraline 100 mg/day?

   A. 3 months
   B. 6 months
   C. 1 year
   D. Indefinite

9. A consultant pharmacist would like to carry out a pilot project for monitoring treatment outcomes of antidepressant therapy for patients with major depression and concomitant general medical comorbidities in a long-term skilled nursing facility. Which one of the following clinician rating scales would be best to use for this project?

    A. Beck Depression Inventory
    B. Hamilton Depression Rating Scale
    C. Patient Health Questionnaire short form (PHQ-2)
    D. MADRS

Questions 10–12 pertain to the following case.

L.J. is a 52-year-old female military veteran with a medical history that includes active opioid use disorder and stage 2 chronic kidney disease. She is admitted to inpatient psychiatry for management of severe melancholic depression. L.J. has currently been treated with fluoxetine 60 mg/day and has received this dose for 1 year with little improvement. Her care team is considering an augmentation strategy.

10. Based on the results of the VAST-D trial and patient specific characteristics, which one of the following is the best to recommend for L.J.?

    A. Increase the fluoxetine dosage to 80 mg/day.
    B. Augment fluoxetine with bupropion 150 mg sustained release.
    C. Augment fluoxetine with mirtazapine 15 mg/day.
    D. Augment fluoxetine with aripiprazole 2.5 mg/day.

11. After consultation with L.J., the care team would like to convert her to imipramine. Which one of the following is the best strategy to recommend for L.J.?

    A. Stop fluoxetine and start imipramine at its starting dose.
    B. Directly switch fluoxetine to an equivalent dose of imipramine.
    C. Stop fluoxetine and wait 4–7 days before starting low-dose imipramine.
    D. Reduce the fluoxetine dose to 40 mg/day and gradually initiate imipramine at its starting dose.

12. L.J. is successfully transitioned to imipramine and titrated to blood concentration of 200 ng/mL; however, she still is unable to discharge due to significant depressive symptoms. The care team would like to add an adjunctive treatment. Which one of the following is the best adjunctive treatment to recommend for L.J.?

    A. Lithium
    B. Ziprasidone
    C. Lisdexamfetamine
    D. Triiodothyronine

13. A 53-year-old man with treatment-resistant depression (currently on sertraline 150 mg and aripiprazole 5 mg by mouth daily) continues to experience suicidality. He is being evaluated for esketamine treatment. The patient has no history of psychosis, substance use disorder, or cardiovascular disease other than well-controlled hypertension. Which one of the following best evaluates the use of esketamine for this patient?

    A. He may require pharmacotherapy to manage elevations in blood pressure and heart rate during treatment.
    B. Ketamine would be preferred because it is likely more effective for reductions in suicidal behavior than esketamine.
    C. Esketamine has been shown to be safe and effective as indefinite therapy.
    D. The risk of abuse makes this therapy non-preferred for this patient.

14. An 87-year-old man was started on sertraline 25 mg orally daily for MDD. After 1 week it was increased to 50 mg, and 2 weeks later was increased to 100 mg daily. PHQ-9 at 2 month follow up had lowered from 17 to 11. The patient reports no adverse effects from the medication. The patient's caregiver is concerned that the medication is not working. Which one of the following is best to recommend for this patient?

    A. Make no changes to the current regimen.
    B. Add bupropion extended release 150 mg orally daily.
    C. Add aripiprazole 2.5 mg orally daily.
    D. Change to escitalopram 20 mg orally daily.

15. A 33-year-old woman is diagnosed with postpartum depression 6 weeks after delivering a healthy, full-term baby who is currently exclusively breast fed. She has a history of MDD and took fluoxetine as a young adult with good effect. However, she has not taken any medication for the last few years and her MDD has been controlled with CBT. The patient feels she would benefit from starting a medication for depression again but worries a lot about potential risks of antidepressant exposure on her newborn. Which one of the following is best to recommend for this patient?

    A. Brexanolone
    B. Fluoxetine
    C. Sertraline
    D. Bupropion