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Pharmacotherapy for Depression and Anxiety in the Primary Care Setting

Abby Luck Parish, Brenna Gillis, Angelina Anthamatten

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A B S T R A C T

The prevalence of mental health disorders is rising with the coronavirus of 2019 pandemic, and millions of Americans reside in areas with mental health professional shortages. Primary care providers have an opportunity to provide care for commonly occurring mental health disorders. Using a holistic conceptualization of recovery in mental illness, this report provides evidence-based guidance for initiation, titration, and discontinuation of pharmacotherapy for mild to moderate depression and anxiety in the primary care setting. The use of measurement-based care, selection of appropriate class and agent for individual candidates, and patient education are addressed. Best practices for troubleshooting, titration, and referral are discussed.

Introduction

An estimated 51.5 million or 20.6% of adults in America are living with any mental illness.[1] Prevalence of any mental illness is higher among females (24.5%) than males (16.3%) and is higher in younger (29.4% in ages 18–24) than middle-aged (25.0% in ages 26-49) or older adults (14.1% in ages 50 and older).[1] Income inequities are associated with the prevalence of depression, with lower rates of depression being correlated with higher income.[2] The coronavirus disease 2019 (COVID-19) pandemic has compounded rates of mental illness as well as inequities; depression symptoms have been observed to be as much as 3 times as prevalent during the pandemic, with higher rates observed in persons with lower income, less savings, and more stressors.[3]

Of the 51.5 million American adults affected by mental illness, 23 million (44.8%) sought and received some form of mental health services in the past year, but 13.3 million perceived an unmet need for mental health services.[1] Primary care providers have an opportunity to meet the increasing demand for mental health services by providing holistic, evidence-informed care. From 2012 to 2014, there were approximately 30 million visits to physicians for mental health concerns per year, with a third of those being to primary care physicians.[4] The US Preventative Services Task Force (USPSTF) currently advises that adults in primary care settings receive routine screening for depression alongside appropriate diagnosis, treatment, and follow-up, including initiation of pharmacotherapy as needed.[5] The purpose of this review is to outline best practices for pharmacotherapy for the common mental health disorders of depression and anxiety in the primary care setting.

Holistic Care

Given the highly individualized nature of mental illness and recovery, it is important to conceptualize pharmacological treatment for major depressive disorder (MDD) and generalized anxiety disorder (GAD) as existing within a broader context of care, including psychotherapy and other behavioral interventions as indicated. For patients with mild to moderate depression, either antidepressants or psychotherapy may be an appropriate initial treatment modality, depending on patient preference and availability of each form of treatment.[6] Cognitive-behavioral therapy (CBT), in particular, may be just as effective as antidepressants in treating some patients with MDD, particularly those with atypical, melancholic, or anxious subtypes of depression.[6,7] Meta-analyses and systematic reviews support the combination of antidepressant treatment and psychotherapy (particularly CBT) for depression because this combination has been associated with improved acute and sustained response[8] and reduced risk for relapse and recurrence[9] compared with antidepressant treatment alone. Psychotherapy may be even more useful for GAD; a recent meta-analysis observed that psychotherapy had a nearly 2-fold effect on anxiety symptoms as medication.[10] Thus, a referral for psychotherapy is advised for depression or anxiety, by itself or alongside medication. However, affordable psychotherapy may be difficult to access, particularly in the context of the current shortage of mental health professionals; referrals to psychotherapy must therefore be made with consideration to the patient's individual needs and resources. Medication, as an adjunct or alternative to psychotherapy, can be an effective treatment option for MDD or GAD.

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Principles of Pharmacotherapy for MDD

Assessment and Diagnosis

As with any condition, obtaining an accurate diagnosis is a fundamental step in effectively treating MDD. Persons with MDD may initially be identified in the primary care setting through routine depression screening, a practice that the USPSTF endorses with a grade B recommendation,[5] or via self-disclosure of depressive symptoms. After identification of symptoms, establishing a diagnosis of MDD requires a comprehensive symptom history; ruling out medical disorders that can contribute to depressive symptoms, such as thyroid disease; and evaluating for other mental disorders with depressive features, such as bipolar I or II disorder, anxiety disorders, and substance-related disorders.[11,12]

It is particularly crucial to screen patients with depressive symptoms for a history of mania or hypomania. Patients with bipolar disorder tend to experience depressive episodes more frequently than manic or hypomanic episodes, leading to frequent misdiagnosis of bipolar disorder as MDD.[13] Antidepressant monotherapy is an inappropriate treatment regimen for individuals with bipolar disorder because it may increase mood cycling or precipitate a manic or hypomanic episode.[13] Assessing for a family history of bipolar disorder[13] and using a validated screening tool, such as the Mood Disorder Questionnaire,[14] to assess patients for a history of manic or hypomanic episodes can aid clinicians in distinguishing between bipolar disorder and MDD before initiating pharmacotherapy.

Validated measurement tools can assist not only in making an MDD diagnosis, but also in establishing baseline symptom severity and monitoring patient outcomes through the course of treatment.[11] Using measurement tools in a systematic manner to monitor patient progress and inform clinical decision-making is known as measurement-based care (MBC).[11] MBC is associated with higher rates of response and remission from depression[15-17] and overall higher levels of treatment effectiveness,[18] compared with pharmacological treatment that is not guided by validated outcome scales.[15,17,18] The Patient Health Questionnaire (PHQ-9) is a validated, widely used, patient-reported symptom scale that evaluates each of the 9 symptom criteria for MDD in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*).[19] The PHQ-9 aids clinicians in distinguishing among mild, moderate, moderately severe, and severe depression, and it includes a question that specifically inquires about suicidal ideation,[19] a symptom some patients might not spontaneously disclose. The PHQ-9 is in the public domain and is available in more than 30 languages.[20]

Goals of Pharmacotherapy for MDD

Routine use of measurement tools aids clinicians in evaluating patients' progress throughout the course of treatment. A *response* to treatment for MDD generally implies "a clinically meaningful degree of symptom reduction,"[21] usually a reduction of at least 50%.[13] Although patients with a response to treatment often experience improved mood and better daily function,[21] residual depressive symptoms are a notable predictor of poorer outcomes—including relapse into another major depressive episode (MDE).[21-23] Thus, in treating patients with MDD, full symptom *remission* should be the goal.[11,13,21] Remission is characterized by an absence, or near absence, of depressive symptoms, and patients in remission typically return to the level of daily functioning they experienced before the MDE.[21] The American College of Neuropsychopharmacology Task Force on Response and Remission in Major Depressive Disorder recommended that remission be ascribed only after patients experience 3 consecutive weeks without depressive symptoms.[21] A patient may be considered to be in *recovery* after a 4-month period of remission from the most recent MDE.[21] Recovery is only broken when there is a recurrence of depressive symptoms substantial enough to meet criteria for a new MDE.[21]

Principles of Antidepressant Titration and Discontinuation

With symptom remission being the goal of depression treatment, clinicians should optimize antidepressant dose and length of treatment to achieve and sustain remission. For patients who do not experience symptom improvement within 2 to 4 weeks of initiating an antidepressant, the dose should be increased, unless tolerability is an issue, in which case, switching to a different agent may be appropriate.[24] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, the largest prospective, randomized, multistep clinical trial of antidepressant treatment for MDD,[25] found average times to remission ranging from 5.4 to 7.4 weeks across all 4 steps of treatment.[26] However, only one-third of patients achieved remission with the first antidepressant tried; another one-third of patients achieved remission after switching to a different antidepressant or adding an adjunctive medication.[26] Implications of the STAR*D data suggest that if at least a response is not achieved after 4 weeks at the maximally tolerated dose of an antidepressant, that particular antidepressant choice should be considered unsuccessful,[27] and switching to a different antidepressant may result in better outcomes.[24] The Figure[28] proposes a stepwise approach for the initial treatment of MDD, including recommendations regarding when to switch antidepressant agents.

Once a patient achieves remission, a clinical practice guideline for the management of adults with major depressive disorder by the Canadian Network for Mood and Anxiety Treatments (CANMAT) recommended continuing treatment for at least 6 to 9 months, as discontinuing antidepressant treatment before 6 months is associated with higher rates of relapse and recurrence of MDD.[24] However, for patients with notable risk factors for recurrence (e.g., MDEs of greater frequency, severity, or chronicity; residual depressive symptoms; comorbid medical or psychiatric conditions), it is recommended to continue treatment for 2 years or longer after achieving remission.[24] When both patient and clinician agree to discontinue an antidepressant, it is advisable to taper the dose gradually over a period of weeks.[24] Abrupt cessation or rapid taper of antidepressants may cause discontinuation symptoms, including sensory disturbances, sleep disturbances, gastrointestinal (GI) upset, dizziness, anxiety, hyperarousal, and dysphoria.[29,30] Discontinuation symptoms are generally mild, but uncomfortable; begin within the first 3 days of discontinuing an antidepressant or starting a taper; and resolve without treatment within 1 to 2 weeks.[30] Antidepressants that are more likely to incite discontinuation symptoms upon cessation are those with short half-lives, such as paroxetine (Paxil) and venlafaxine (Effexor)[29,30]; if a patient has taken an antidepressant with a short half-life for a number of years, it may be advisable to taper over a period of months,[30] instead of weeks. Antidepressants with long half-lives, such as fluoxetine, are less likely to cause a discontinuation syndrome.[29,30]

Antidepressant Selection and Troubleshooting

Within the larger classes of antidepressants (i.e., selective serotonin reuptake inhibitor [SSRIs], serotonin norepinephrine reuptake inhibitors [SNRIs]), differences among individual agents are relatively minimal,[24] and all medications within these 2 classes share the primary mechanism of serotonin reuptake inhibition.[13] However, it is common to see individual patients tolerate or respond differently to one antidepressant compared with another within the same class.[13] Individual variations in medication

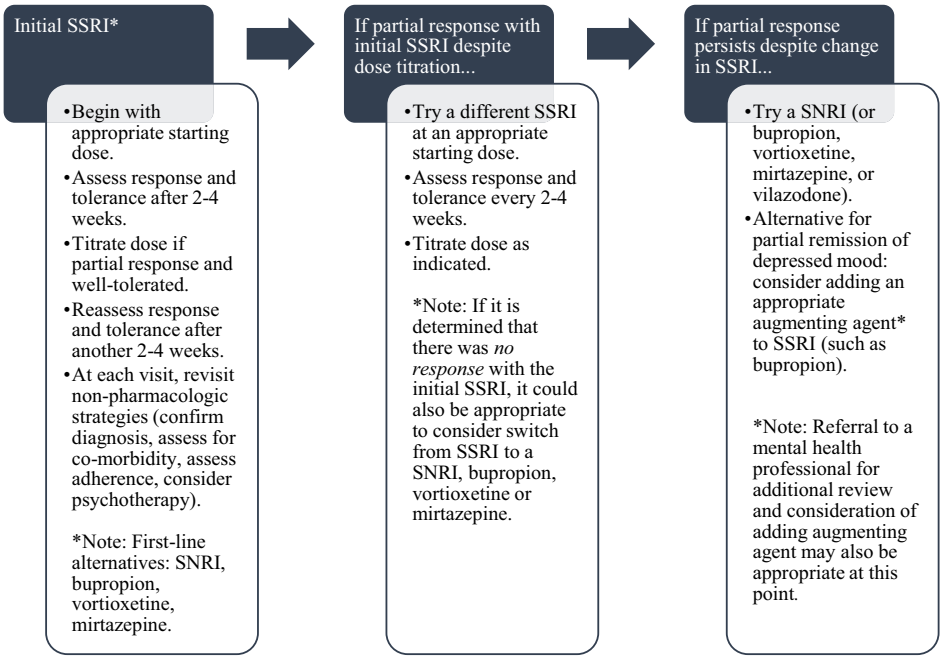

Figure. An example of a stepwise approach to initial treatment of unipolar depression.[13,24,28]
SNRI = serotonin norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitor.

response could potentially be influenced by secondary pharmacologic characteristics that are dissimilar among the various antidepressants[13]; genetic variants affecting the pharmacokinetics and pharmacodynamics of antidepressants may also influence the variability seen in patients' responses.[31] At the present time, there are no evidence-based methods for perfectly matching an individual patient with the antidepressant that will be most effective and tolerable for that individual.

The CANMAT clinical guideline for the management of adults with MDD asserted that "selecting an antidepressant involves an individualized needs assessment for each patient."[24] The following considerations may be useful in guiding a needs assessment and selecting an initial antidepressant:

- If a patient has taken a specific antidepressant in the past with good efficacy and tolerability, it may be appropriate to prescribe that medication again for the current MDE.
- Response to SSRIs has been found to be similar among first-degree family members as a result of shared genetic and/or environmental factors.[31] If a patient reports a family history of positive response to a specific antidepressant, it may be useful to try that antidepressant first.
- When selecting an initial antidepressant, it can be helpful to try and match a medication's side effect profile to the patient's symptoms. For instance, a clinician might select a more sedating antidepressant for patients with notable insomnia. The Table presents unique characteristics of individual antidepressants and potential benefits and considerations of select antidepressants.
- SSRIs, SNRIs, bupropion (Wellbutrin), mirtazapine (Remeron), and vortioxetine (Trintellix) are considered to be first-line medication options for MDD.[24]
- For medications that have instant-release and extended-release formulations (eg, bupropion [Wellbutrin, Wellbutrin SR, Wellbutrin XL), venlafaxine [Effexor, Effexor XR], paroxetine [Paxil, Paxil CR]), patient adherence may be higher with the extended-release formulation. However, medication efficacy and tolerability do not differ between the formulations.[24]
- Some antidepressants are more costly than others. It is important to consider patients' financial means, prescription coverage, and the availability of coupons and copay assistance when selecting a medication to prescribe.
- When treating a person of childbearing potential, it is important to ascertain whether the patient is sexually active and their current method of contraception, if using. If the patient desires a pregnancy in the near future or is not using a reliable method of contraception, it is advisable to select an antidepressant with a favorable safety profile during pregnancy—and to avoid antidepressants with potentially higher risks (eg, paroxetine [Paxil, Paxil CR], venlafaxine [Effexor, Effexor XR]), if possible.[32,33]

Even with careful medication selection, side effects and tolerability issues may still occur. Common side effects of antidepressants include GI effects (i.e., nausea, diarrhea, constipation), insomnia, agitation, headache, dizziness, xerostomia, and sexual dysfunction.[28] The following strategies may be useful in addressing tolerability concerns:

- If side effects are not excessive and the patient is agreeable, consider waiting for several weeks because most side effects are short-term and resolve with time.[28]
- Decrease the dose or consider a slower titration if side effects are persistent or excessive.[28]
- Consider switching to a different antidepressant if side effects remain excessive after decreasing the dose or if the patient considers the side effects to be unacceptable.[28]
- For patients who experience mild activation or insomnia after starting an antidepressant, consider dosing in the morning; for those who experience sedation, dose at bedtime.[28]
- Serotonin syndrome is a term that refers to a spectrum of clinical findings, from mild to life-threatening, which can occur in the presence of excess serotonergic agonism.[34] It is characterized by a combination of mental status changes, autonomic hyperactivity, and/or neuromuscular abnormalities.[34] Prescribers must avoid co-administration of an SSRI or SNRI with an

Table
Clinical Considerations for Individual Drugs Used in the Treatment of Depression and Generalized Anxiety Disorder in Adults[28]

Drug	Class	Notes
Citalopram (Celexa)	SSRI	Potential benefits • May have particular benefits for those who are excessively activated by other SSRIs Considerations • May start 20 mg daily and increase to 40 mg if needed • Doses beyond 40 mg have been associated with QTc prolongation (consider risk factors); lower dosing recommended for those over 60 years of age • Has unique mild antihistamine properties that may contribute to sedation and fatigue in some; consider taking at night if patient experiences daytime sedation
Escitalopram (Lexapro)	SSRI	Potential benefits • Known as S-citalopram, may have faster onset and better efficacy with reduced side effects compared with R,S-citalopram (citalopram) • For those who will use an antidepressant during pregnancy, a large study[32] determined that escitalopram had the lowest proportion of elevated adjusted odds ratios (none) for associations between maternal antidepressant use and birth defects; consider benefits and risks and individualize decisions[33] using shared decision-making[5] • FDA-approved for the treatment of GAD Consideration • May start 10 mg daily and increase to 20 mg as needed
Fluoxetine (Prozac, Prozac weekly)	SSRI	Potential benefits: • May be more activating, increasing energy for some; consider administration early in the day • May have particular benefits for those with hypersomnia, fatigue, low energy • Possible weight loss • Has a longer half-life, which has various clinical implications, including being less likely to be associated with discontinuation effects[24] Consideration • May start 20 mg daily and increase after a few weeks by 20 mg increments as needed; typical maximum is 80 mg
Paroxetine (Paxil, Paxil CR)	SSRI	Potential benefits • Also has indication for vasomotor symptoms of menopause • Mild anticholinergic actions may offer potential advantages for those with insomnia or anxiety • FDA-approved for the treatment of GAD Considerations • May start 20 mg daily (25 mg CR) and increase by 10-mg increments (12.5-mg increments for CR) as needed; typical maximum is 50 mg (62.5 mg CR) • Mild anticholinergic actions can cause constipation, dry mouth, sedation • Weight gain is not unusual, occurring in a significant minority • Withdrawal effects can be more common or severe than with some SSRIs; if discontinuing, gradually taper over many months; consultation with a mental health expert may be helpful for taper • The American College of Obstetricians and Gynecologists recommended avoiding use in pregnant women and women planning pregnancy when possible[33]
Sertraline (Zoloft)	SSRI	Potential benefits • May have particular benefits for those with hypersomnia, fatigue, low energy, increased appetite • May be activating, increasing energy for some; consider administration early in the day Considerations: • May start 50 mg daily and increase by 25- to 50-mg increments as needed; typical maximum is 200 mg • May have more adverse GI effects (such as diarrhea) than other SSRIs; may not be optimal for those with irritable bowel syndrome
Venlafaxine (Effexor, Effexor XR)	SNRI	Potential benefits • May have particular benefits for those who do not respond or remit on treatment with SSRIs • Lower dose may be more serotonergic for some, with more dual serotonin and norepinephrine effects at higher doses (consider titrating dose before concluding lack of response) • FDA-approved for the treatment of GAD Considerations • May start 37.5 mg (extended-release) daily and increase by 75-mg increments as needed up to 225 mg • Withdrawal effects can be more common or severe than with some other antidepressants; if discontinuing, taper the dose over many months to prevent withdrawal symptoms; consultation with a mental health expert may also be helpful when considering strategies for taper • May increase BP, so may not be optimal for those who have hypertension or cardiac disease • There are some concerns with use during pregnancy; a large study[32] determined that venlafaxine had meaningfully elevated associations with many specific birth defects (consider benefits and risks and individualize decisions[33])
Desvenlafaxine (Pristiq)	SNRI	Potential benefits • Primary metabolite of venlafaxine in an extended-release formulation with once daily dosing and similar efficacy • Less impact on BP is expected Consideration • May start 50 mg daily; increase to 100 mg if needed
Duloxetine (Cymbalta)	SNRI	Potential benefits • Well-documented efficacy for the painful physical symptoms of depression • May offer particular benefits for those with neuropathic pain in diabetes, chronic musculoskeletal pain, or fibromyalgia • FDA-approved for the treatment of GAD Considerations • May start 30–40 mg daily and increase to 60 mg as needed; typical maximum is 120 mg (studies have not demonstrated increased efficacy at doses beyond 60 mg per day) • May increase BP or urinary retention

Table (*continued*)

Drug	Class	Notes
Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL)	NDRI	Potential benefits • May have particular benefits for those o who have a partial or suboptimal response to SSRI therapy despite appropriate trial o with unacceptable and persistent sexual dysfunction o with emotional flattening, cognitive slowing, or apathy o seeking additional support for smoking cessation • May be cautiously added as an adjunct to SSRIs to treat partial responders or mitigate SSRI-induced sexual dysfunction • Possible weight loss • May be more activating, increasing energy for some; consider administration early in the day Considerations • May start 150 mg (extended-release) daily and increase to 300 mg as needed; typical maximum is 450 mg • May increase BP • May not be optimal for those with comorbid anxiety or insomnia • Seizure risk increased for those with predisposing factors • Avoid for those with bulimia and anorexia, either currently or in the past
Mirtazapine (Remeron)	Serotonin norepinephrine receptor antagonist	Potential benefits • Multifunctional drug with 5 principal mechanisms of action[13]; affects serotonin, norepinephrine, alpha 2, and histamine receptors • May have particular benefits for those with insomnia, agitation, decreased appetite, persistent GI effects, or sexual dysfunction Considerations • May start 15 mg daily and increase by 15-mg increments as needed; typical maximum is 45 mg • Sedation is common and may be pronounced • May cause significant weight gain, which may be desirable for some patients such as older adults with weight loss and/or difficulty with sleep
Vortioxetine (Trintellix)	Multimodal antidepressant	Potential benefits: • May have particular benefits for those who do not respond to other antidepressants with other mechanisms of action • Demonstrated beneficial cognitive effects, such as processing speed, executive and cognitive control[24] • May have less sexual dysfunction Considerations • May start 10 mg daily and increase to 20 mg as needed • May cause adverse GI effects (such as nausea and constipation, which may be marked) • No generic option currently
Vilazodone (Viibryd)	Multimodal antidepressant; serotonin partial agonist reuptake inhibitor (SPARI)	Potential benefits • May have particular benefits for those with comorbid depression and anxiety • May have less sexual dysfunction Considerations • May start 10 mg daily and increase to 20 mg if needed; typical maximum is 40 mg • Must be taken with food to ensure adequate absorption[24] • Titrate as directed to avoid adverse GI effects[24]
Trazodone	Serotonin receptor antagonist and reuptake inhibitor	Considerations • May start 150 mg daily in divided doses for depression; increase in 50-mg increments as needed; typical daily outpatient maximum is 400 mg • Expected to be less efficacious for depression and less tolerable at doses required for depression • Sedation is common, even at lower doses, and can be pronounced; often not tolerated as a monotherapy for moderate to severe depression but may be a helpful for insomnia (a common but off-label use)
Buspirone (Buspar)	Non-benzodiazepine anxiolytic	Considerations • May start 7.5–15 mg twice daily and increase in 5-mg increments as needed; typical daily maximum is 60 mg, divided in 2 or 3 times daily dosing • Not controlled • Not expected to cause sexual dysfunction or weight gain • Sedation is not unusual, occurring in a significant minority • FDA approved for the treatment of GAD
Hydroxyzine (Atarax, Vistaril)	First-generation antihistamine	Considerations: • May take 50–100 mg every 4–6 hours up to 4 times daily, or less frequently on an as-needed basis • Quick onset (15–20 minutes) • May be used for short-term symptoms of anxiety or during transition to a maintenance therapy, then discontinued or used as needed • Sedation is common and can be pronounced, but is usually transient as tolerance develops

BP = blood pressure; GI = gastrointestinal; FDA = US Food and Drug Administration; SNRI = serotonin norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitor.

MAOI due to the prevalence of severe serotonin syndrome associated with this combination.[34] To further minimize risk of serotonin syndrome, prescribers should be mindful of a patient's overall proserotonergic burden and minimize the concomitant use of agents with serotonergic agonism (including antidepressants, valproate, opioid analgesics [particularly tramadol], antiemetics, triptans, linezolid, ritonavir, dextromethorphan, methylenedioxymethamphetamine [MDMA or "ecstasy"], St. John's wort, and ginseng).[34]

Patient Education

Pertinent education points include the medication's indication (ie, MDD, anxiety), including any off-label use; common side effects, their expected duration, and how to minimize or manage discomfort; potential adverse effects, including when and how to contact the clinician or seek emergency care; known drug–drug interactions; and, for persons of childbearing potential, the known safety data and potential risks associated with taking the

antidepressant during pregnancy. The following education points are specific to antidepressants and may also be useful to address at the time of the initial prescription:

- The beneficial effects of antidepressants are not immediate. To promote realistic expectations, it is helpful to inform patients that they may not begin to experience improvement until they have taken the antidepressant consistently for several weeks.
- Abrupt discontinuation of antidepressants may cause uncomfortable discontinuation symptoms, particularly if the medication has been taken for longer than 6 to 8 weeks.[30] Patients should be advised not to discontinue their antidepressant abruptly and to consult with their clinician if they desire to taper or stop their medication for any reason.
- On all antidepressant medications, there is a Black Box Warning regarding an increased risk for suicidal thinking and behavior in children, adolescents, and young adults under age 25, compared with placebo.[35] Patients under age 25 must be educated about this risk and advised to contact their clinician or seek emergency care if suicidality develops.
- While healthy research participants have not been observed to exhibit significantly greater motor impairment with the combination of alcohol and antidepressants than with alcohol alone, the manufacturers of antidepressants still suggest avoiding alcohol during therapy.[36] (Note: bupropion [Wellbutrin, Wellbutrin SR, Wellbutrin XL] increases seizure risk.[28] It may be safer to recommend that patients taking bupropion abstain from alcohol, particularly those taking higher doses.)

Pharmacogenetics

Pharmacotherapy for MDD has historically involved quite a bit of trial and error with significant individual variation in symptom response, some of which has been hypothesized as being related to individual genomic differences. Research on the impact of genetics on antidepressant pharmacodynamics (or therapeutic effects) has not yet yielded clinically useful observations. However, genetic differences affecting pharmacokinetics (or the movement and metabolism of drugs) have been associated with drug response phenotypes.[37,38] Specifically, genes determining the degree of enzymatic activity at CYP2D6 and CYP2C19 can affect the speed and extent to which a person metabolizes several commonly prescribed antidepressants, with more enzymatic activity and thus faster metabolism being associated with less available active medication or antidepressant and thus less symptom response.[37,38] Genetic profiles for individual patients can be obtained to assist in guiding antidepressant selection. Studies comparing genetic-report-guided prescribing with traditional prescribing have often used lower quality, heterogenous methods with smaller samples, contributing to challenges in data aggregation across studies.[37,38] Meta-analysis of available data suggests that genetic report-guided prescribing may have a very small positive effect on rate of symptom response, and data are currently insufficient to advise routine use of genetic reports in any setting.[37,38]

Principles of Pharmacotherapy for Anxiety

Assessment and Diagnosis

Anxiety is considered to be a normal reaction to stressors, but in excess, it can impede function.[39] Anxiety is fairly common, with as many as 11.7% of adults in the United States reporting regular worry, nervousness, or anxiety.[40] Anxiety and depression are commonly comorbid with one another, with 45.7% of persons with lifetime depression having 1 or more anxiety disorders.[41] Generalized anxiety disorder (GAD) is the most common anxiety disorder and is characterized by "persistent and excessive worry that interferes with daily activities."[39] Similar to MDD, use of a validated tool for screening and measurement-based care is advised. The GAD-7 is a brief screening tool, and like the PHQ-9 for assessing MDD, it is based on the symptom criteria from the *DSM-5* for GAD.[42]

Goals of Pharmacotherapy for GAD

Similar to MDD, the goal of pharmacotherapy for GAD is sustained reduction of symptom burden. Anxiety is more likely than depression to emerge earlier in life and to be chronic or sustained (as opposed to episodic).[43] Remission or sustained recovery may be less likely for anxiety than for depression, with one longitudinal study describing remission rates for GAD at 1, 2, and 5 years as 15%, 25%, and 38%, respectively.[44,45] Similarly, in the first phase of the STAR*D study, depressed patients who had comorbid anxiety were significantly less likely to achieve remission and more likely to experience side effects or adverse events of therapy than persons with nonanxious depression.[46] Patients with GAD in primary care settings may be more likely to achieve symptom reduction due to their relatively milder symptom burden at baseline compared with patients in mental health specialty settings.[47] Although remission or sustained recovery is the ideal goal of pharmacotherapy for GAD, it may be difficult for some people to attain; thus, reduction in symptom burden and improvement in function are also reasonable goals of therapy.

Pharmacotherapy Options and Strategies for GAD

Several antidepressants, including SSRIs, SNRIs, vilazodone (Viibryd), and mirtazapine (Remeron) are effective for reducing symptoms of anxiety and are considered first-line therapy for long-term management.[48] It should be noted that not all antidepressant medications are FDA-approved for treating anxiety disorders. Escitalopram (Lexapro), paroxetine (Paxil, Paxil CR), duloxetine (Cymbalta), and venlafaxine (Effexor, Effexor XR) are approved by the U.S. FDA for treatment of GAD.[48] Citalopram (Celexa), desvenlafaxine (Pristiq), vilazodone (Viibryd), and mirtazapine (Remeron) are serotonergic antidepressants that do not have a specific indication for any anxiety disorder; however, data is available to support their effectiveness for treating anxiety if off-label use is considered.[49,50] A general approach for prescribing a drug off-label includes identifying evidence and support for use, checking for any warnings, discussing the options and rationale with the patient, and documenting evidence, rationale, and patient consent.[51]

Outcomes between antidepressant classes for anxiety are fairly equivocal, so an SSRI may be preferred as initial therapy due to anticipated overall tolerability.[50] Agent selection should be guided by consideration of what has worked for the person or their first-degree relative in the past, matching medication selection with patient illness characteristics, and selecting an agent with a side effect profile that is favorable for a given patient. A desirable effect of antidepressants for persons with depression is activation, or increased energy. However, persons with anxiety may experience the activating effects of antidepressants as restlessness or even increased anxiety or panic. Some antidepressants are associated with more activation than others, and those with the strongest association, bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL), fluoxetine (Prozac), and venlafaxine (Effexor, Effexor XR), may be dosed cautiously for persons with a history of anxiety or panic.[28]

Titration should be undertaken to effect, with persons with GAD sometimes ultimately requiring higher doses of antidepressants than persons with MDD.[52] Clinicians should bear in mind that onset of symptom improvement with antidepressants may be delayed in GAD, compared with MDD, with some patients achieving response after 12–24 weeks[53] and remission after 6 months.[13] Additionally, due to the often chronic and sustained course of GAD, compared with episodic MDD, pharmacotherapy may be continuous. Relapse prevention studies have shown significant benefit for patients maintaining medication treatment, as opposed to switching to placebo, for timeframes up to 18 months.[53] However, discontinuation of pharmacotherapy for GAD can be attempted, with care being taken to monitor for and promptly address any re-emergence of symptoms.

Another agent which is available for use in GAD is buspirone (BuSpar), a nonsedating, non–dependence-forming, long-acting agent that reduces anxiety by 5-HT 1A partial agonism and enhancement of dopamine and norepinephrine activity.[13] In most cases, clinical effects can be observed 1–2 weeks after initiation, and similar to SSRIs and SNRIs, buspirone can then be titrated to effect.[13] Because its mechanism of action is novel, it can be used as an add-on for persons with a partial response to SSRIs or SNRIs, or it can be used as monotherapy for persons who do not tolerate SSRIs or SNRIs due to side effects (including sexual side effects) or weight gain.[13,48]

Noncontrolled options for short-acting relief of anxiety are limited. Hydroxyzine (Atarax, Vistaril) is a first-generation antihistamine that can be used for relief of acute anxiety symptoms.[28] With an onset of 15–20 minutes, it can be dosed as needed and taken after acute anxiety begins or on a schedule and taken routinely to reduce anticipated anxiety.[28] Routine use should be limited to a few weeks, and if symptoms persist, long-term therapy options such as an SSRI should be considered.[28]

Use of Benzodiazepines

In September 2020, the FDA issued a safety communication requiring an update to the Boxed Warning for benzodiazepines to address "serious risks of abuse, addiction, physical dependence, and withdrawal reactions."[54] The updated guidance suggests that prescribers carefully weigh anticipated benefits versus risks of benzodiazepines, including assessing risk of abuse, misuse, and addiction; limit to lowest dose and shortest duration of therapy necessary; and conduct careful monitoring for abuse, misuse, and addiction throughout therapy.[54] In a recent meta-analysis of therapies for anxiety, pooled data for benzodiazepines indicated a modest positive effect on symptoms of anxiety with a similar effect size to SSRIs, SNRIs, and buspirone, but the tolerability of benzodiazepines was quite a bit worse than SSRIs, SNRIs, and buspirone.[55] Ideal use of benzodiazepines should be short-term, judicious in dose, with careful attention to education about and screening for dependence or misuse throughout follow-up.[54,56]

Referral to Specialty Care

The USPSTF recommendation for depression screening in primary care notes that primary care providers should be prepared to treat and follow-up on treatment response, including using referrals to mental health specialists for medication management and counseling services as needed.[5] The US Health Resources and Service Administration currently classifies 129 million Americans as residing in a mental health professional shortage area.[57] Primary care providers can help alleviate mental health specialty shortages by practicing to the full extent of their training, providing pharmacologic and nonpharmacologic care to persons with mild to moderate symptoms, and reserving referrals for appropriate cases.[58] Patients with severe symptoms, comorbidities (including history of hypomania or mania), or atypical or incomplete response to treatment may benefit from consultation with a mental health specialist.

Conclusion

In the current shortage of mental health professionals, primary care providers are in a front-line position to offer evidence-based pharmacotherapy to patients with common mental health disorders, thereby reducing inequities and increasing the public's access to potentially life-changing treatment. This review offers clinicians a succinct, evidence-informed overview of treatment principles and pharmacologic options for mental health diagnoses commonly encountered in primary care, MDD and GAD. Key messages from this review include that the goal of treatment for mental health disorders should be sustained remission of symptoms, when possible, and that pharmacotherapy is best offered within a broader context of holistic care—including psychotherapy and other behavioral interventions, as needed. Primary care providers are encouraged to practice to the full extent of their training by taking a prominent role in meeting the unmet treatment needs of individuals with common mental health disorders.

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Abby Luck Parish, DNP, AGPCNP-BC, GNP-BC; Brenna Gillis, DNP, PMHNP-BC; and Angelina Anthamatten, DNP, FNP-BC are faculty at Vanderbilt University School of Nursing, Nashville, TN. Dr. Parish can be contacted at abby.parish@vanderbilt.edu.

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