A Continuing Education Activity

New Treatment Pathways and Patient Management Strategies for Major Depressive Disorder

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TARGET AUDIENCE

This activity has been designed to meet the educational needs of pharmacists practicing in both independent and chain pharmacy settings, involved in the management of patients with major depressive disorder (MDD).

STATEMENT OF NEED/PROGRAM OVERVIEW

MDD is a serious mental illness, characterized by low rates of remission, significant medical comorbidity, and a considerable overall economic toll. To address the educational objectives listed below, this activity will provide instruction on current and emerging treatment recommendations and patient care strategies for pharmacy professionals to use to improve overall clinical, economic, and humanistic outcomes for patients with MDD.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be able to:

- Recommend current and emerging therapeutic approaches to address the treatment gap created by low rates of remission for patients with MDD
- Apply newer recommendations from the updated APA Practice Guidelines to ensure appropriate treatment and overall care for patients with MDD
- Implement evolving patient management techniques to improve outcomes for patients with MDD
- Provide accurate and appropriate counsel as part of the treatment team.

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Susan W. Butterworth, PhD, MS	No financial interest/relationships relating to the topic of this activity
Megan Maroney, PharmD	No financial interest/relationships relating to the topic of this activity
Charles L. Raison, MD	Receives consulting fees from Eli Lilly and Company and Pamlab and receives fees for non-CME/CE services from Pamlab. He also serves on the Steering Committee for NACCME and develops CME content for NACCME and CME Incite. His spouse receives a salary from Insys Therapeutics, Inc.

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REQUIRED COMPUTER HARDWARE/SOFTWARE

Please ensure the computer you plan to use meets the following requirements:

- Operating System: Windows or Macintosh
- Supported Browsers: Microsoft Internet Explorer, Firefox, Google Chrome, Safari and Opera

For questions relating to the certification of this activity contact Postgraduate Institute for Medicine at information@pimed.com.

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New Treatment Pathways and Patient Management Strategies for Major Depressive Disorder

Major depressive disorder (MDD) is among the most common and widespread psychiatric conditions in the United States, currently estimated to affect nearly 22 million individuals aged ≥18 years.[1,2] With a prevalence approaching 1 out of every 10 American adults and being characterized by often debilitating symptoms, the impact of MDD on health outcomes and psychosocial functioning in the US population is extensive.[1] Comorbid MDD is common among patients with chronic medical illness and is accordingly associated with increased morbidity and mortality across a multitude of different disease states.[3] Beyond the synergistic adverse effects of comorbid MDD in chronic illness, the disease independently represents the leading cause of disability in the United States for individuals aged 15 to 44 years.[4] MDD is similarly a leading cause of disability worldwide, accounting for 42.5% of years lived with disability (YLDs) among all mental and substance abuse disorders (Figure 1).[5] Quantifying the burden in disability-adjusted life years (DALYs), for which MDD is also the leading causative factor among mental and substance abuse disorders, it becomes apparent that the disease also impacts lives at a younger age than other prominent medical conditions. The highest proportion of DALYs associated with MDD occur in adolescents and young adults (aged 10–29 years), with an incidence rising abruptly in childhood and peaking in early adulthood. The disability associated with MDD is realized through the ongoing and persistent nature of the disease, which recurs in more than half of individuals who initially experience a single episode and results in role impairment in the same proportion of patients.[6] Antecedent to this multifactoral disease burden are increased health care utilization and corresponding medical expenditures, with direct and indirect costs exceeding $83 billion annually when work-loss and reduced productivity are considered.[7] Less tangible but more significant from a patient care perspective, MDD is recognized as exacting more functional impairment and poorer quality of life (QOL) than other "high-profile" chronic illnesses such as diabetes, heart disease, and arthritis.[8]

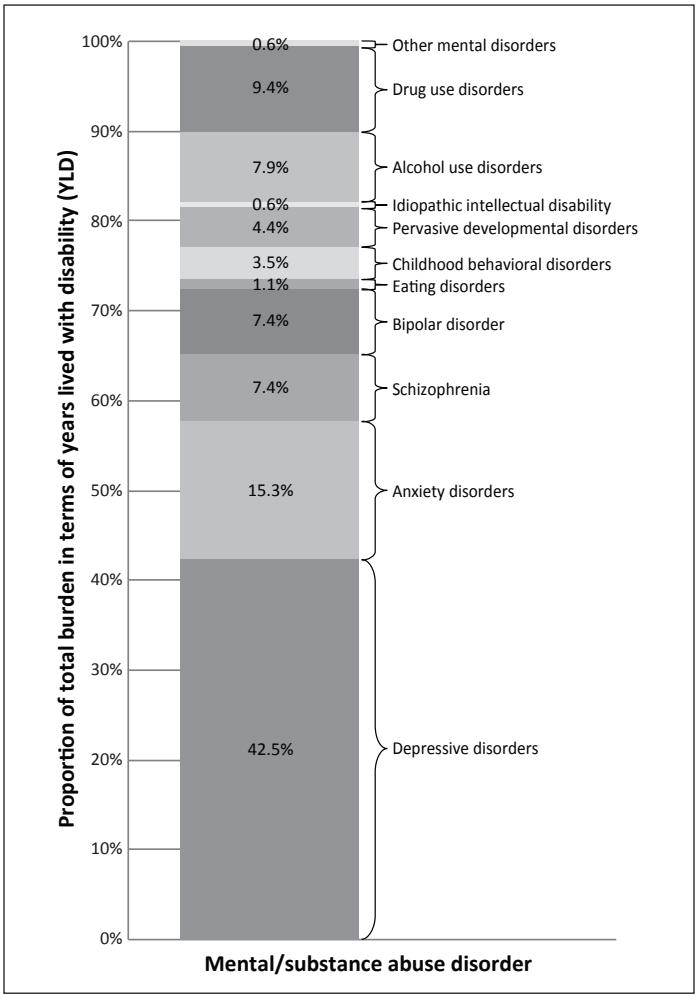

Figure 1. Proportion of years lived with disability (YLDs) explained by mental and substance abuse disorders in 2010.[5]

Although approximately two-thirds of adults with MDD never seek adequate treatment, resulting in potentially devastating consequences, the prognosis associated with the disease is actually favorable upon receiving appropriate therapy.[9,10] Supporting this notion, most patients with MDD respond to acute treatment, and continuation of active treatment offers symptom relief and lowers the risk and severity of relapses.[11] Among current treatment modalities, pharmacotherapy and psychotherapy appear to be the most effective therapeutic options for patients with MDD.[11] Looking specifically at pharmacologic treatment, considering the availability of a myriad of psychotropic agents targeting various neurotransmitter activities, current studies indicate that <50% of patients with MDD have an adequate response to their initial antidepressant therapy, and less than one-third achieve remission.[12] Furthermore, adherence to pharmacotherapy for MDD remains notoriously poor, with only half of patients remaining adherent in the early phases of drug therapy and worsening rates of adherence as treatment progresses.[13] As such, interventions to aid physicians and patients in navigating the complex landscape of MDD pharmacotherapy and improving patient adherence to said therapy are critical for optimal treatment. It is precisely in these two specific capacities where community pharmacists are potentially instrumental for improving outcomes in MDD.

Nowhere in the health care continuum is the ubiquity of MDD more readily apparent than in the community pharmacy setting. Whereas mental health professionals interact with perhaps the greatest proportion of patients with MDD, 11% of *all* Americans aged ≥12 years were estimated to be taking antidepressant medications in 2008.[14] Since then, the antidepressant class has experienced significant growth, particularly in the form of increasing utilization among young

adults aged 19 to 25 years.[15] Community pharmacists fill the vast majority of these prescriptions, which are increasingly written by health care providers in various disciplines.[15] This is exemplified by the fact that antidepressant prescribing outside of psychiatric specialties has risen significantly in recent years. Between 1996 and 2007, the number of visits where individuals were prescribed antidepressants without a documented psychiatric diagnosis increased from 59.5% to 72.7%, and the share of non-psychiatrist providers who prescribed antidepressants without a concurrent psychiatric diagnosis increased from 30% to 55.4%.[16] Resultant of this phenomenon—in concert with the rising prevalence of MDD—the rate of antidepressant use in the United States among all ages increased nearly 400% over the 20 years prior to 2008.[14] These concurrent trends have culminated in antidepressants currently representing the leading therapeutic class in terms of volume, with 264 million prescriptions dispensed to 18.5 million patients 2011.[15]

Considering the prevailing incidence of antidepressant prescribing in the community pharmacy setting, coupled with manifest adherence issues with the class, community pharmacists are uniquely and strategically positioned to impact treatment outcomes. Routine, direct contact with patients positions community pharmacists among the most visible health care providers in the care continuum, regardless of the disease state. Community pharmacists fill >85% of all traditional pharmaceutical prescriptions (ie, oral, non-specialty medications) annually in the United States.[15] In addition, nearly all Americans live within 5 miles of a community pharmacy, making community pharmacists readily accessible to patients without scheduled appointments or excessive wait times.[17] Owing partially to this availability and corresponding familiarity, community pharmacists and their advice are well regarded by the public, which can be leveraged to guide therapy and promote medication adherence at the patient level. Maintaining these assertions, pharmacists consistently rank in the top-three professions in terms of integrity in the eyes of the public, unsurpassed by any other type of health care professional.[18] Likewise, pharmacists are rated by the public as the most "trustworthy" source on health and medical information.[18] These cumulative factors present significant potential for advancing care via patient consultation at the community pharmacy level. And because pharmacotherapy plays a predominant role in the treatment of MDD, the conceivable influence and reach of community pharmacists in facilitating therapeutic success is exponentially amplified for this disorder in particular.

Available Pharmacologic Treatment Regimens

In all patient populations with MDD, a combination of medication and psychotherapy generally provides the most rapid and sustained response in terms of symptom resolution and improved patient QOL.[19,20] For practical purposes, pharmacotherapy alone is often a first-line treatment choice due to its feasibility and ease of use in the primary care setting where many patients initially present with depressive symptoms. Initial treatment with antidepressant medications is appropriate for individuals with mild-to-moderate depression, and pharmacotherapy should be a component of the overall treatment strategy for all individuals with severe depression unless electroconvulsive therapy is planned.[11] Due to the adverse event profiles and potential ancillary benefits associated with various agents, prescribing clinicians may weigh a number of patient-specific considerations prior to selecting an antidepressant for the treatment of MDD, including the following:[11]

- Prior antidepressant treatment and response/tolerability, when applicable
- Concomitant medications that may interact with antidepressants, particularly via cytochrome P450 metabolism
- Smoking status
- Presence of chronic pain
- Patient weight (ie, overweight, underweight)
- Presence of insomnia
- Presence of suicidal ideation
- Presence of anxiety-related features

The implications of these considerations are subsequently reviewed in the overview of different antidepressant classes that follows.

First-Generation Antidepressants. Dating back to the 1950s, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have a long record of efficacy in a broad range of affective and anxiety disorders, including MDD. Despite efficacy comparable to newer agents, these first-generation antidepressants are prescribed less frequently in current practice due to their severe adverse event profiles and potential for drug/food interactions.[21] TCAs available for the treatment of MDD include amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine. These agents, which primarily act via serotonin and/or norepinephrine reuptake inhibition, are extensively metabolized by cytochrome P450 and are therefore contraindicated in patients taking potent P450 inhibitors.[11] Potential adverse events associated with TCAs include dry mouth, blurred vision, constipation, urinary retention, tachycardia, confusion, and weight gain. TCAs also possess considerable cardiotoxicity and corresponding lethality in overdose, which is a significant concern in depressed patients with suicidal ideation.[11] Among MAOIs currently available for the treatment of MDD are isocarboxazid, phenelzine, selegiline, and tranylcypromine. These agents act by inhibiting the activity of monoamine oxidase, thus preventing the breakdown of monoamine neurotransmitters (ie, serotonin, norepinephrine, and dopamine) and thereby increasing their availability. This mechanism of action often necessitates a strict diet due to an increased risk of hypertensive crisis when nonselective MAOIs are taken in conjunction with foods and beverages containing potentially high levels of tyramine, such as certain cheeses, pickles, and wines.[11] Similarly, nonselective monoamine oxidase inhibition requires the avoidance of any substance—including prescription, over-the-counter, or illicit drugs/supplements—that increase serotonin, norepinephrine, or dopamine activity.[11] Excesses of these neurotransmitters can result in severe acute consequences, including serotonin syndrome, hypertensive crisis, and psychosis, respectively.[11] As such, it is particularly noteworthy that these agents cannot be used in combination with second-generation selective serotonin reuptake inhibitor (SSRI) antidepressants. Due to these clinical concerns in both groups of agents, TCAs and MAOIs are not typically prescribed unless the patient has experienced a prior failure on one or more of the second-generation classes of agents, which will subsequently be discussed.[11]

Second-Generation Antidepressants. Emerging in the 1980s, second-generation antidepressants generally demonstrate greater selectivity for specific neurotransmitters and are thereby typically associated with more favorable adverse event profiles. Most prominently, the SSRI class represents the largest and most extensively studied share of second-generation antidepressants. Other classes of second-generation antidepressants include the serotonin-norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants (Table 1).[11] This latter group of agents is categorized as such because their mechanisms of action are different from the other two classes, but also from one another, in targeting various unique combinations of the neurotransmitters serotonin,

Table 1. Second-generation antidepressants.[11]

Antidepressant	Therapeutic Dose Range (mg/day)[a]	Perceived Advantages	Perceived Disadvantages
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Citalopram	20-40 mg	• Fewer significant cytochrome P450 interactions	
Escitalopram	10-20 mg	• More potent than racemic citalopram • Lowest dose typically effective • Fewer significant cytochrome P450 interactions	• Higher cost than racemic citalopram • Potential step-therapy requirements for coverage
Fluoxetine	20-80 mg	• Fewer discontinuation symptoms • Long half-life; ideal in poor adherence or missed doses	• May be excessively stimulating • Potential for more cytochrome P450 interactions • Slower to reach steady state; may require more time to elicit desired effect
Paroxetine	20-60 mg (max 40 mg in elderly)		• Shorter half-life; greater potential for discontinuation symptoms • Potentially sedating • Contraindicated in pregnancy • More anticholinergic effects • Potential for more significant cytochrome P450 interactions
Sertraline	50-200 mg	• Safety shown in post-MI • Fewer cytochrome P450 interactions	• Potential for more gastrointestinal adverse events
Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)			
Venlafaxine	75-375 mg, dosing twice or three times daily	• Fewer cytochrome P450 interactions • Preferred for women taking tamoxifen • No blood pressure monitoring necessary at lower doses	• Blood pressure monitoring necessary at higher doses • Requires slow taper to reduce likelihood of discontinuation symptoms • Greater potential for cardiotoxicity and lethality in overdose than SSRIs
Desvenlafaxine	50-400 mg, doses >50 mg may not provide additional benefit	• Same as venlafaxine	• Same as venlafaxine
Duloxetine	60-120 mg, dosing divided twice daily	• Potential analgesic effect in patients with chronic pain, including neuropathy in patients with diabetes	• Blood pressure monitoring necessary at baseline and periodically • No generic alternative available • Potential step-therapy requirements for coverage • Potential for more cytochrome P450 interactions
Atypical Antidepressants			
Buproprion	300-450 mg, start 150 mg in the morning and increase to twice daily after 7 days.	• Typically increases energy levels • Little to no sexual side effects • Minimal weight gain	• Potentially overstimulating • May lower seizure threshold at higher doses • Avoid in patients with history of seizures, significant CNS lesions, or recent head trauma • Typically twice-daily dosing with 8 hours between doses • Potential for insomnia if the second daily dose is taken within 8 hours of bedtime • May cause electrolyte abnormalities in patients with severe eating disorders • Potential for rash, including a risk of desquamation
Mirtazapine	15-45 mg, dose at bedtime (7.5 mg for those in need of sedative hypnotic)	• Few drug interactions • Little to no sexual side effects	• Sedation at low doses • May initially stimulate appetite, resulting in weight gain
Trazodone	150-600 mg	• Anxiolytic properties • Optional once-a-day dosing	• Sedation
Nefazodone	300-600 mg		• Concerns related to hepatotoxicity • Twice-daily dosing

norepinephrine, and dopamine.

As mentioned previously, SSRIs represent the most extensively studied group of second-generation antidepressants, with several options available within the class: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. In addition to a lengthy history of safe and effective use, SSRIs are advantageous due to their ease of dosing, low toxicity in overdose, and generally low cost in light of the availability of unbranded versions. Furthermore, the adverse event profile of SSRIs is generally considered more tolerable than that of some other agents; this promotes improved medication adherence, particularly coupled with the ease of dosing in the class.[11] Common adverse events include gastrointestinal upset, sexual dysfunction, and changes in energy level (ie, fatigue and restlessness). SSRIs are also believed to be relatively unproblematic in patients with cardiovascular disease, in that these agents do not appear to affect blood pressure, heart rate, cardiac conduction, or cardiac rhythm. The only exception is citalopram, which has been associated with dose-dependent QT prolongation.[11] In accordance with these advantages associated with the class, SSRIs are considered appropriate for the first-line treatment of MDD in virtually all patient types—including children, adolescents, and the elderly—by the American Psychiatric Association (APA), assuming certain characteristics specific to the patient do not suggest that he or she may be better served by an agent from a different class.[11]

SNRIs, including venlafaxine, desvenlafaxine, and duloxetine, may also be used in the first-line treatment of MDD, particularly in patients with significant fatigue or pain syndromes associated with their depressive episodes.[11] Alternately, these agents play an important role in the second-line treatment of patients who have not responded to first-line SSRI therapy. The adverse event profile of the SNRIs is generally tolerable and similar to that of the SSRIs; however, SNRIs are uniquely associated with specific noradrenergic side effects, such as hypertension.[11]

Community pharmacists, with their regular ongoing interactions at the patient level, can be pivotal...for monitoring adverse events, assessing patient desires, and guiding the course of therapy...

The atypical antidepressants generally each have unique characteristics that correspond to their various mechanisms of action, allowing clinicians to carefully tailor therapy within this class to the individual needs and/or preferences of the patient. For example, bupropion—a norepinephrine-dopamine reuptake inhibitor—may be prescribed for patients who experience fatigue related to depression and/or in those trying to quit smoking.[11] Bupropion is also devoid of the sexual side effects and weight gain associated with the SSRI class and may be prescribed in combination with an SSRI to counteract the latter agent's sexual side effects.[11] However, bupropion may cause or exacerbate anxiety in certain patients and should thus be avoided in patients with co-occurring anxiety in MDD.[11] Conversely, mirtazapine may be particularly beneficial in resolving concurrent MDD and anxiety symptoms.[11] This noradrenergic and specific serotonergic antidepressant is associated with drowsiness, and as such may be useful for patients with MDD who also suffer from insomnia. Notable adverse events associated with mirtazapine include increased appetite, weight gain, and increased blood lipid levels.[11] Similar to mirtazapine, trazodone and nefazodone have sedative properties that may prove beneficial in patients with MDD and related insomnia.[11] These serotonin antagonist and reuptake inhibitors are likewise anxiolytics and can thus have a beneficial effect for patients with co-occurring anxiety in MDD.[11] Trazodone and nefazodone feature similar adverse event profiles, but prescribing of nefazodone has been somewhat limited by rare incidences of hepatotoxicity associated with the agent.[11]

To compare the effectiveness of all of these seemingly divergent classes of second-generation antidepressants, the Agency for Healthcare Research and Quality (AHRQ) conducted a literature search and corresponding series of meta-analyses using data from studies involving the following agents in the treatment of depressive disorders:[21]

- Bupropion
- Citalopram
- Desvenlafaxine
- Duloxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Mirtazapine
- Nefazodone
- Paroxetine
- Sertraline
- Trazodone
- Venlafaxine

AHRQ reported that no substantial differences in efficacy could be detected among second-generation antidepressants for the treatment of acute-phase MDD.[21] Even the statistically significant differences in response rates between some drugs were deemed minimal and not likely to be clinically relevant.[20] Furthermore, no differences in efficacy were apparent in patients with accompanying symptoms, such as pain or insomnia, or in subgroups based on age, sex, ethnicity, or comorbidities, although evidence within these subpopulations was limited.[21] AHRQ concluded that the pertinent differences between these agents instead exist in the incidence of specific adverse events and the onset of action.[21]

The results of this analysis and the prevailing recommendations from the APA underscore the importance of clinician consideration and intervention in the pharmacologic treatment of MDD. Considering comparable efficacy among second-generation antidepressants, prescribers should select therapeutic agents based primarily on adverse events, cost, and unique patient needs and/or preferences. Community pharmacists, with their regular and ongoing interactions at the patient level, can be pivotal in this process for monitoring adverse events, assessing patient desires, and guiding the course of therapy when applicable.

Emerging Pharmacologic Treatment Regimens. Several recently approved antidepressants designating new molecular entities were not included in the aforementioned AHRQ analysis and warrant further attention as they come into routine clinical practice. Vilazodone, which received approval in January 2011, is the first SSRI available that is also a partial agonist of serotonergic (5-HT_{1A}) receptors, although its mechanism of action is not fully understood.[22] In two randomized, double-blind trials in adults with MDD, vilazodone 40 mg once daily (titrated over 2 weeks) was shown to be significantly superior to placebo at improving depressive symptoms, as measured by response rates according to the Montgomery-Asberg Depression Rating Scale (MADRS) (44% vs 30%, P=0.002).[23] Among 2177 patients diagnosed with MDD enrolled in safety studies, the most common adverse events were diarrhea, nausea, vomiting, and insomnia. In all, 7.1% of patients who received vilazodone discontinued treatment because of an adverse

reaction compared with 3.2% of control patients. The drug was not associated with change in body weight at 8 weeks, and there were no reported drug-related abnormalities in hepatic or cardiac parameters or vital signs. There were no clinically significant differences for either gender in Arizona Sexual Experience Scale (ASEX) scores at the end of treatment, with reported adverse effects on sexual function including decreased libido (4% with vilazodone vs <1% with placebo), abnormal orgasm (3% vs 0%), delayed ejaculation (2% vs 0%), and erectile dysfunction (2% vs 1%).[22]

In July 2013, the FDA approved the fourth and latest SNRI indicated for MDD. Levomilnacipran is an active enantiomer of the racemic drug milnacipran and therefore has similar effects and pharmacology. The agent, which is available as a once-daily sustained-release formulation, is the most noradrenergically active of the available SNRIs on the basis of in vitro studies.[24] Specifically, levomilnacipran was found to have two-fold greater potency for norepinephrine relative to serotonin reuptake inhibition and 17 and 27 times higher selectivity for norepinephrine reuptake inhibition compared with venlafaxine and duloxetine, respectively.[24] The efficacy of extended-release levomilnacipran has been established against placebo in doses ranging from 40 mg/day to 120 mg/day.[25,26] No controlled studies have been conducted of levomilnacipran against an active comparator to date. The most common adverse events reported with levomilnacipran in clinical trials included nausea, constipation, and excessive perspiration. In addition, approximately 1% to 3% of enrollees reported a significant increase in blood pressure and ≤6% reported a significant elevation in heart rate.[25,26] According to the prescribing information for levomilnacipran, caution should be used in patients with pre-existing hypertension, cardiovascular or cerebrovascular disorders.[27]

Licensed for the treatment of MDD in September 2013, vortioxetine is a multimodal antidepressant primarily acting via inhibition of serotonin reuptake. It is also an agonist at 5-HT_{1A} receptors, a partial agonist at 5-HT_{1B} receptors, and an antagonist at 5-HT_3, 5-HT_{1D}, and 5-HT_7 receptors, although the contribution of these latter activities to vortioxetine's antidepressant effect is not fully understood.[28] The approval of this first-in-class agent was based on five short-term (6-8 week) trials of vortioxetine against placebo, including one trial examining efficacy in elderly adults.[29-33] The results of these clinical trials demonstrated a statistically significant reduction in overall symptoms of depression in patients treated with vortioxetine compared with placebo, as measured by either the Hamilton Depression Scale (HAMD-24) or MADRS. In these studies, the most consistent results were derived from a dose range of 15 to 20 mg/day. A long-term (24-64 week) maintenance study demonstrated a significantly longer time to relapse among patients treated with vortioxetine compared with placebo, defined as a MADRS score ≥22 or as judged by the investigator.[34,35] Furthermore, two studies in which lower doses of 2.5 to 5 mg/day were administered to patients showed no significant difference in efficacy between the vortioxetine and placebo.[36,37] Principal adverse events reported in clinical trials included nausea, diarrhea, dry mouth, constipation, vomiting, dizziness, and sexual dysfunction.

In the advent of these next-generation antidepressants, pharmacists and other clinicians should remain vigilant as new data emerges. Those agents employing novel mechanisms of action and/or complimentary mechanisms in particular present significant promise for the treatment of a burgeoning and increasingly diverse population of patients with MDD. These agents initially provide valuable alternatives to current second-line treatment options in the event of a first-line failure, and—assuming comparable efficacy in future head-to-head trials—potential first-line treatment options in the future. Ultimately, as available data and clinical experience grows, so will the roles of these recently approved antidepressants. In terms of guiding therapy and facilitating improved outcomes, the same treatment selection principles apply to these recently introduced agents as are used with earlier second-generation antidepressants; that is, safety and efficacy remain the paramount criteria, followed by patient-specific characteristics, preference, and cost. Regardless of where they eventually fit into pharmacologic treatment algorithms, the expanded array of treatment options realized through these newer antidepressants bolster the health care provider's ability to tailor therapy to the unique characteristics of individual patients.

Integrating MDD Practice Guidelines in the Pharmacy Setting

In order to effectively counsel patients with MDD at the pharmacy counter and ultimately facilitate improved treatment outcomes, community pharmacists should have an understanding of the guidelines by which physicians ideally prescribe antidepressant medications. Whether pharmacotherapy or another therapeutic modality is initially selected for a particular patient, the treatment of MDD is divided into three phases: acute, continuation, and maintenance (Figure 2).[11,38,39] This 3-phase model of depression treatment represents a thorough and continuous course of pharmacotherapy to provide sustainable outcomes, thereby mimicking the treatment paradigms of many other chronic conditions.[11,38] Treatment in the acute phase should be aimed at inducing remission of the major depressive episode and achieving a full return to the patient's baseline level of functioning with no residual symptoms.[11] Pharmacologic treatment, either alone or in combination with psychotherapy, begins with the selection of an appropriate antidepressant medication. As discussed previously, considering comparable efficacy across virtually all FDA-approved agents, that initial selection should be based on the following:[11]

1. Anticipated side effects and the safety or tolerability of these side effects for the individual patient

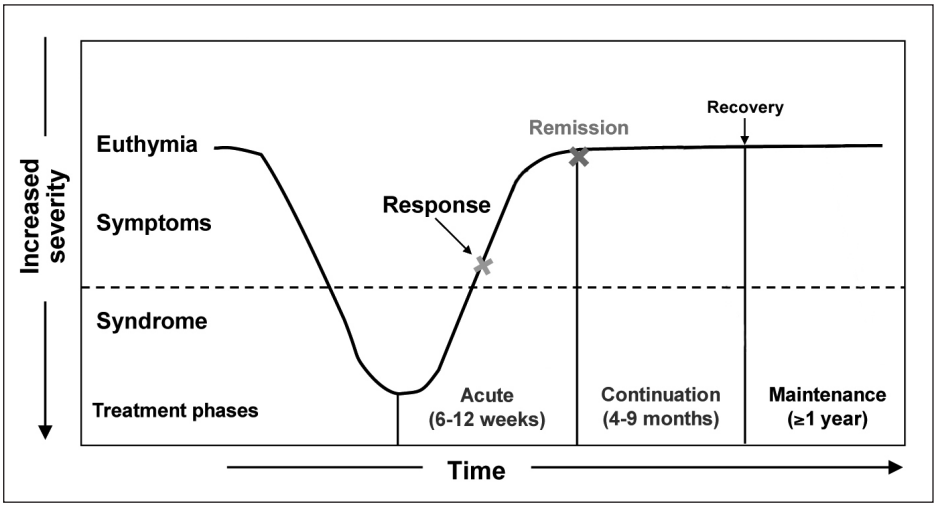

Figure 2. Phases of treatment for MDD.[11,38,39]

2. Pharmacological properties of the medication such as potential for drug interactions and considerations in those with renal or hepatic impairment
3. Medication response in prior episodes
4. Other factors (patient preference, cost, ancillary effects of various agents, etc)

For many patients, an SSRI, SNRI, mirtazapine, or bupropion is optimal for initial treatment, with other treatments reserved for those in whom these drugs do not elicit an adequate response.[11] Frequently, an SSRI is the first-line antidepressant of choice for patients who are pharmacologic treatment-naïve, assuming the absence of underlying patient-specific factors that indicate a different type of agent should be selected. Regardless of which particular antidepressant is used for initial pharmacotherapy, the APA recommends that treatment response be assessed after a patient has received the drug for an adequate amount of time—generally 4 to 6 weeks—before making any adjustments.[11] If the patient shows minimal response (ie, symptom improvement <50%) after the initial 4 to 6 weeks of therapy, the patient should be reevaluated and assessed for adequate dosing, therapeutic adherence, and adverse events, with adjustments made as needed.[11] If the patient shows no response after the initial 4 to 6 weeks of therapy, or still displays only a minimal response 4 to 6 weeks after the initial assessment in the acute phase, two pharmacologic strategies may be considered, assuming the patient is already at the optimal dose of their current antidepressant: switching antidepressant medications or augmentation with an additional depression-focused pharmacotherapy, be it either another antidepressant or a nonantidepressant psychotropic medication (Figure 3).[11,39,40] Considering that less than half of patients have an adequate response to their initial antidepressant therapy, there is a reasonable chance that one of these strategies will have to be employed in the treatment of any given patient with MDD.[11]

In selecting a different antidepressant for a therapeutic switch, prescribers may choose either a different antidepressant from the same class of agents or a non-MAOI agent from a different class.[11] While these two different approaches represent somewhat of a dichotomy among prescribing clinicians, findings from the landmark STAR*D trial demonstrate that both strategies demonstrate comparable efficacy in achieving remission.[12] That said, after two subsequent failures within the same class of antidepressants, the APA does recommend considering switching to an agent from a different class.[11] In this regard, the recently approved antidepressants discussed previously provide a valuable therapeutic option, most notably for the treatment of nonresponders.

As an alternative to switching therapies, augmentation consists of adding another psychoactive agent to the original antidepressant in a combination regimen. Augmentation represents one of the most comprehensively studied treatment strategies for nonresponse or partial response to antidepressant (often SSRI) therapy, specifically augmentation with low-dose atypical antipsychotics or anxiolytic agents.[11,40] Augmentation with other antidepressants such as mirtazapine or bupropion is also supported by considerable efficacy data.[11,40] The risk of drug interactions and poor adherence inherent to multi-pill regimens should be taken into account when considering combination/augmentation strategies.[40] The rationale behind both switching and augmentation is similar in that targeting different neurotransmitters may eventually elicit an improved response to therapy. Although lacking in clinical experience, recently approved multimodal antidepressants with new neurotransmitter targets or novel combinations of targets may potentially provide a similar or even amplified effect in monotherapy or combination therapy, respectively. However, data in this area are lacking until further studies are conducted in a broader range of patient types.

While the APA advocates these strategies for pharmacotherapy in the acute phase of MDD treatment, the available literature provides some alternative considerations that should be taken into account. The duration of treatment intervals between assessments for response that the APA recommends (ie, 4-6 weeks, assess, 4-6 weeks, assess) are generally in keeping with the preponderance of available data.[11,21] In the aforementioned AHRQ analysis, a review of the literature showed that more than a third of patients with MDD do not respond to therapy with second-generation antidepressants for 6 to 12 weeks. However, multiple meta-analyses confirm that antidepressants demonstrate the greatest improvement in depressive symptoms and maximal separation from placebo within the first two weeks of treatment.[41] The implications of these findings in supporting early assessment and switching after only 2 weeks of therapy and nonresponse were confirmed by a randomized study that assessed an in-class SSRI switch among nonresponders to sertraline.[42] In the study, nonresponders who were switched to paroxetine after 2 weeks demonstrated a 75% response rate (ie, ≥50% improvement in the MADRS) at week 8 compared with 19% among initial nonresponders who were continued on sertraline out to week 8 (P=0.002).[42] According to another meta-analysis, this early response also appears

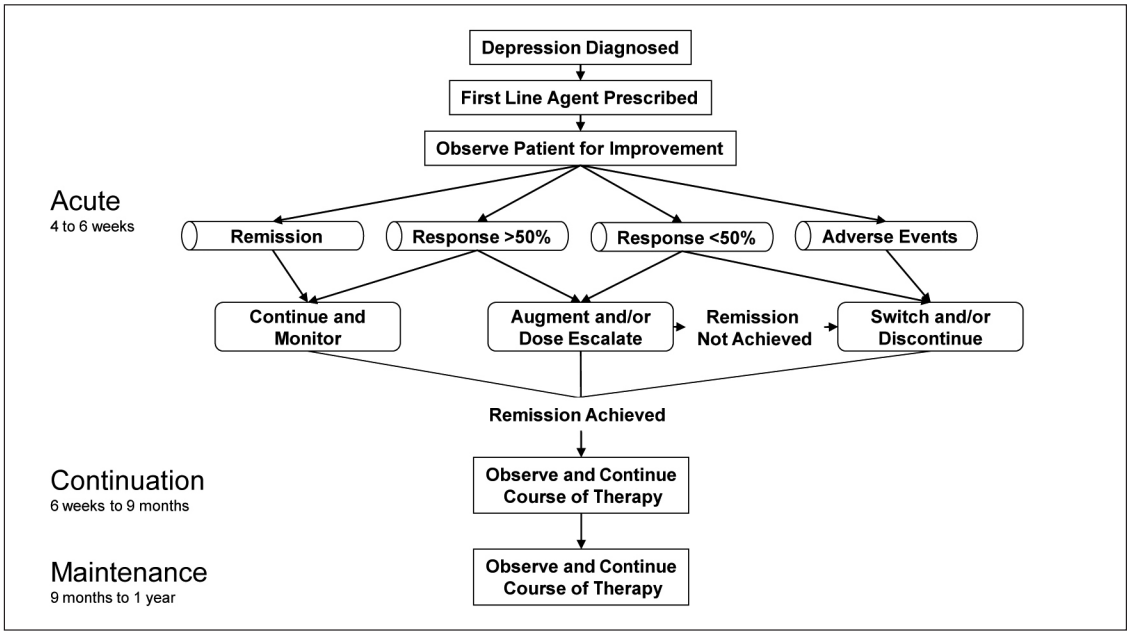

Figure 3. General treatment algorithm for MDD.[11,39,40]

to be predictive of a subsequent stable remission.[43] In addition to considerations surrounding time to treatment response, it should also be noted that the greatest likelihood for achieving remission and avoiding relapse in STAR*D occurred with first-line treatment.[11] After first-line treatment, each subsequent switch/step in therapy was associated with a worsening chance for achieving remission and a greater likelihood of relapse if/when remission was achieved.[12] These findings highlight the importance of establishing treatment response and achieving remission as early in the treatment process as possible, with minimal therapeutic steps.

Although the acute phase of treatment requires perhaps the most intensive clinical management of the treatment process for MDD, the continuation and maintenance phase are critical for sustaining treatment response and remission. In the continuation phase, patients who have been successfully treated in the acute phase should be continued on the medication that produced remission for an additional 4 to 9 months and carefully monitored for signs of relapse.[11] Patients who have had three or more prior major depressive episodes, who have chronic major depressive disorder, or who have risk factors for relapse should proceed to the maintenance phase of treatment after completing the continuation phase.[11] During the maintenance phase, patients should continue to receive the medication that produced symptom remission in the acute phase and maintained remission in the continuation phase at a full therapeutic dose for as long as it is deemed clinically necessary.[11]

Patient Management Strategies

Despite being a common and burdensome condition, MDD does not always receive the comprehensive level of care garnered by other chronic diseases. The resultant reality is that this disorder is often suboptimally managed in the primary care setting where it is frequently treated.[44] Considering the central role that pharmacotherapy plays in treatment and persistent medication adherence issues, community pharmacists are an integral part of the care team for MDD. As such, community pharmacists have an opportunity to impact the quality of care and treatment outcomes via participation in certain patient management interventions. Specifically, a collaborative care approach calls for the involvement of a multidisciplinary team in the delivery of care for MDD, requiring close contact between allied health care professionals, including pharmacists.

MDD is a leading reason for consultation in primary care, indicating a heightened need for involvement among allied specialists and providers.[45] As a result, collaborative care is an intuitive approach for the treatment of MDD, involving a greater role of medical and nonmedical specialists to augment primary care in the structured delivery of therapy using the principles of chronic disease management.[45] Specifically, this strategy integrates the services of mental health professionals, pharmacists, social workers, and a care coordinator to support primary care physicians (PCPs) in the management of patients with MDD.[45] With supporting data in the literature, collaborative care represents an effective means of improving the quality of primary care and ultimately patient outcomes in the treatment of MDD. A meta-analysis of 12,555 patients across 37 randomized studies showed that depression outcomes were improved at 6 months in a collaborative care setting compared with usual care (standardized mean difference, 0.25; 95% CI, 0.18-0.32), and evidence of longer-term benefit was found for up to 5 years (standardized mean difference, 0.15; 95% CI, 0.001-0.31).[45]

The pharmacist's role in collaborative care is primarily based on health coaching and consultation to improve medication adherence, but can also include assisting the PCP in medication choice, dose, and regimen.[46] To these ends, studies have demonstrated that pharmacist-based collaborative care interventions improve patients' attitudes toward antidepressant medications and that patients view regular interactions with their pharmacists as positive.[47] As a result, these interventions have been shown to significantly improve rates of antidepressant use by patients in primary care.[46]

...motivational interviewing is "...a collaborative, goal-oriented style of communication with particular attention to the language of change."

The regular consultation and interaction between pharmacists and patients with MDD described in the collaborative care approach is in keeping with the concept of the "therapeutic alliance" advocated by the APA.[11] This essentially entails establishing a rapport with the patient, being sensitive to his or her concerns, and recognizing his or her personal preferences in terms of therapy.[11] One proven technique that employs such a patient-centered approach to motivate change is motivational interviewing. More specifically, motivational interviewing is "…a collaborative, goal-oriented style of communication with particular attention to the language of change."[48] This means of patient interaction may be employed by community pharmacists to encourage behavioral changes in patients with MDD, particularly adherence to pharmacologic treatment and more open dialogue with prescribing physicians. While the overall approach of motivational interviewing involves empathetically exploring the patient's motivation for change and evoking these reasons via honest discourse with the patient, there are several different techniques that can be applied in different situations.[48] These techniques differ in their delivery but are all essentially based on the tenets of partnership, acceptance, compassion, and evocation. Furthermore, there are concrete strategies that assist the practitioner with the application of these principles, as found in the sample dialogue in Table 2.[48]

For general issues surrounding medication adherence, the Elicit-Provide-Elicit (E-P-E) and Decisional Balance techniques are likely to be beneficial.[48] The objective of the E-P-E technique is to find out what the patient already knows about their medication, fill in the gaps or correct misconceptions, and explore how the medication will fit into the patient's lifestyle.[48,49] The Decisional Balance technique involves asking patients to map out both the pros and cons of taking their medication. While the E-P-E technique tends to be time-saving, the Decisional Balance technique may require more time with the patient to conduct, and should only be used when the patient seems to be opposed to the treatment regimen.[49]

In dealing with adherence issues related to an absence of clinical response within the first few weeks of therapy, the use of reflective listening may be useful. Reflective listening involves listening carefully to understand the point of view from the patient's perspective and then paraphrasing the patient's meaning back to them as a means of demonstrating empathy and understanding.[48] For example, before explaining that it sometimes takes up to 6 weeks of medication therapy before patients experience any sort of noticeable benefit, it is helpful to validate the patient's disappointment in a lack of response. By feeling understood, the patient is more open to hearing an explanation regarding the timing of response to therapy.

Not only is the use of open questions helpful during the E-P-E technique, it is also helpful in exploring patient motivations and

Table 2. Motivational interviewing techniques to address nonadherence to pharmacologic treatment for MDD.[48]

Scenario	Technique	Example
General Prevention of Medication Nonadherence	Elicit-Provide-Elicit	"What do you know about the benefit of this medication, how it works, and how you're supposed to take it?" [Patient response] "That's great! I can tell you have really read up on this. The only thing you didn't mention is the importance of taking it every day in order to experience a noticeable response." [Patient response] "What might get in your way of taking this medication on a regular basis?"
	Decisional Balance	After patient expresses doubts about efficacy or adherence in taking medication when filling his or her prescription the first time: Step 1 – Support Autonomy. "It really is your choice if you take this medication or not." Step 2 – Ask for Permission. "I'd like to make sure that you have all the information you need to make an informed decision. Would it be okay to go through a quick activity?" Step 3 – Elicit Cons. "What are the disadvantages of taking this medication? What else?" Step 4 – Elicit Pros. "What are the possible benefits of taking this medication? What else?" Step 5 – Evoke Patient Response. "Where does this leave you in your decision-making?"
Medication Nonadherence Related to Perceived Ineffectiveness	Reflective Listening & Validation	"You're disappointed that you haven't felt any improvement yet, and it's been two weeks. Plus you've noticed some side effects." [Patient Response] "I wonder if it would be helpful for us to quickly go over again what you know about how the medication works and the timeline for improvement that most patients can expect."
Medication Nonadherence Related to Untoward Effects or General Adverse Events	Open Questions for Assessing Barriers	"What might get in the way of taking this medication?" "Sometimes patients find it challenging to take medications as prescribed. How are you doing with this?"
	Open Questions for Exploring Options/Solutions	"On one hand you don't like the side effects, but you are hopeful about the benefits down the road. What do you think some possible solutions would be for you at this point?" "What do you think would be helpful at this point in considering your treatment plan?"
	Open Questions for Evoking Change Talk	"Why did the doctor prescribe this medication for you? In other words, what are the benefits for you?" "If you managed to get through the side effects and the medication was helpful for improving your mood, how would your life be different?"

barriers in a manner that allows for a richer dialogue.[48] Using open questions also creates an opportunity for reflective listening as described previously. Lastly, open questions can be effectively used to evoke change talk (ie, the benefit of the therapy) to strengthen commitment to the treatment plan, as well as elicit patient-driven solutions regarding how to address existing barriers. For example, through the use of open questions, a pharmacist may quickly ascertain that the barrier to taking medication is undesirable side-effects, and that the best solution may be to go back to discuss these symptoms with the prescribing physician.

Considering that community pharmacists regularly interact with patients at the counter and are well-respected and considered trustworthy by the public, they are in an ideal position to apply the aforementioned motivational interviewing techniques. Practitioners sometimes express concern regarding the extra time that this strategy may impose on a normally brief patient-provider interaction; however, in actuality, less time is needed to employ the MI approach compared with traditional patient education methods. This is due to the quick establishment of rapport and the efficiency of identifying the sticking point for a patient in medication adherence. Of course the methods described here are not exhaustive, but they provide a foundation on which to base patient-centered conversations designed to evoke intrinsic desire within the patient to recognize the benefits of antidepressant therapy and remain adherent to this therapy.

Conclusion

MDD imposes significant clinical and economic burden, realized primarily through functional impairment for those who suffer from the disease. As a means of addressing the morbidity and mortality associated with this disorder, pharmacotherapy represents a mainstay of treatment, strategically positioning community pharmacists to facilitate improved outcomes through their interactions with patients and assistance to prescribers in the capacity of medication management. Specifically, community pharmacists can be instrumental in mitigating nonadherence, counseling patients on matters regarding treatment response and adverse events, and suggesting alternative courses of therapy in the event that a switch in therapy is deemed necessary.

To help patients navigate the complicated and evolving landscape of antidepressant therapies and their appropriate use, pharmacists should be well versed in the APA's treatment guidelines for MDD. An understanding of treatment selection criteria is vital, especially considering comparable efficacy across a broad range of second-generation antidepressants. With factors such as patient-specific characteristics, patient preference, cost, and the ancillary benefits of particular agents all playing a role, community pharmacists are again well-positioned due to their routine contact with patients and inherent knowledge of pharmacology. Recently approved agents with novel mechanisms of action and/or combinations of neurotransmitter targets provide additional options in the clinician's armamentarium, and familiarity with emerging data surrounding these agents is crucial. Again, due to the comparable efficacy among previously available second-generation antidepressants, community pharmacists will be well served to stay current on the characteristics of newer antidepressant therapies that may provide a potential advantage. In addition to counseling patients with this information, pharmacists will be well-equipped to assist prescribing physicians as part of a collaborative approach to care.

Recent trends in patient management for MDD focus on strategies that maximize the potential of pharmacotherapy, again placing community pharmacists at the forefront of the care process. Likewise, strategies that involve multidisciplinary health care professionals in the care process have gained popularity among clinicians and other stakeholders over the past decade, further bolstering the role of the community pharmacist in facilitating treatment outcomes. These trends in the treatment of MDD, including a focus on medication adherence and engaging the patient in their own care, are ideally suited to the current roles and responsibilities of pharmacists at this interactive point of care.

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