Major Depressive Disorder: Treatment-Resistant Depression and Augmentation of Other Medication Classes

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Major depressive disorder (MDD) is one of the most common reasons patients present for medical care worldwide. Nurses should be aware of the occurrence of and pharmacologic treatments for MDD and treatment-resistant depression (TRD). Holistic nursing plays a pivotal role in caring for patients with TRD.

Depression is a diagnosis of adolescents as well as adults (National Institute of Mental Health [NIMH], 2017). In 2016, an estimated 2.2 million adolescents ages 12-17 in the United States had at least one major depressive episode with severe impairment. This number represented 9% of the U.S. population in this age range. MDD can exist from a complication of surgery or be exacerbated by a surgical procedure or postsurgical complication (Ghoneim & O’Hara, 2016). According to Ghoneim and O’Hara, “...the suppression of the immune system in depressive disorders may expose the patients to increased rates of postoperative infections and increased mortality from cancer” (para. 3). Pain also can induce depression.

An individual must be symptomatic for at least 2 weeks to receive a diagnosis of depression (APA, 2018). According to the APA, the following symptoms can vary from person to person, ranging from mild to severe: feeling sad or depressed; lack of interest or pleasure in previously enjoyed activities; appetite changes (unintentional weight loss or gain); sleep difficulty (too much or little); lack of energy (fatigue); feeling of guiltiness or worthlessness; moving more slowly or pacing (others observe); difficulty with decision-making, concentration, and thinking; and/or suicidal thoughts. Genetics and biochemistry are common causes for depression, as are environmental factors and personality traits. Risk factors associated with treatment-resistant...
depression (TRD) include suicide risk, melancholic presentation, recurrent MDD, more than one hospitalization related to MDD, symptom severity, comorbid anxiety or personality disorders, and failure to respond to initial antidepressant at age 18 or younger (Dold & Kasper, 2017).

A 2016 report from the Substance Abuse and Mental Health Services Administration (NIMH, 2017) documents types of treatment as health professional only, medication only, and health professional and medication combined. An estimated 44% of affected persons receive combined care by a health professional and medication treatment. Treatment with medication alone was least common (6%). Approximately 37% of adults with a major depressive episode did not receive treatment.

APA (2018) reported an estimated 80%-90% of people experiencing depression respond well to treatment with antidepressants, yet 50% fail to respond fully. Symptom improvement may occur within the first 2 weeks of medication treatment, with full therapeutic benefits typically seen within 2-3 months. If a patient responds well to treatment, the APA recommends continued use of medication for 6 months or longer after symptom improvement. However, if the individual has various risk factors contributing to depression, as mentioned previously, longer-term treatment may be necessary. MDD thus may be a difficult-to-treat medical diagnosis.

**Treatment-Resistant Depression**

A narrative and systematic review of the literature completed by the Agency for Healthcare Research and Quality (2018) regarding TRD found no consensus definition. No evidence or agreement exists on the best approach to diagnose TRD or a preferred outcome. In addition, disagreements exist on definitions for adequacy of medication dose or duration of treatment. Recognition of this issue is essential when contemplating treatment. A patient with TRD (refractory depression) does not respond to antidepressant treatments (Palmisano, 2018). Mitchell (2018) identified various times when to determine an individual suffers from TRD. Frequently, the person can be diagnosed with TRD after two antidepressants fail to cause improvement. Research suggested a history of early-life trauma predicts poor response to antidepressant therapy, but results are variable and limited in adults (Williams, Debbattista, Duchemin, Schatzberg, & Nemeroff, 2016). Approximately 45% of individuals with MDD experience TRD.

A person with TRD often experiences an increase in suicidal ideation and attempts, with an estimated one-third of affected persons attempting suicide within their lifetime (Palmisano, 2018).

Dold and Kasper (2017) reported resistance to antidepressive pharmacologic treatment is one of the most important clinical challenges in disease management. The clinician first should ensure the patient is not pseudo-resistant; according to Dold and Kasper, pseudo-resistance can occur when a person does not respond to the first antidepressant. The clinician should consider the following questions to exclude pseudo-resistant depression: (a) Was the antidepressant dose adequate in accordance with psychiatric society guidelines? (b) Was the duration of treatment long enough (at least 2-3 weeks)? (c) Was the patient adherent and the medication intake sufficient? (d) Were adequate drug plasma levels achieved (e.g., a patient with cytochrome P450 [CYP450] enzyme abnormalities could have metabolic oddities)? (e) Was clinical response masked by possible adverse effects of the antidepressant? (f) Were somatic co-morbidities and relevant psychiatric issues considered to ensure depression is the primary diagnosis? and (g) Were psychosocial stressors associated with the depressive symptoms?

**Risk Factors**

Serretti and Fabbri (2014) found various factors that predispose individuals to TRD. A clinician should be diligent in diagnosing TRD to ensure the individual is not suffering from pseudo-TRD. Pseudo-TRD can be related to subtherapeutic dosing (~20%), nonadherence (~40%), intolerable side effects (20%-30%), or wrong diagnosis (10%-15%). See Table 1 for risk factors predisposing individuals to TRD.

**Adolescents**

Statistics regarding depression in adolescents affirm the need for concern by healthcare providers. Roughly 12% of adolescents in the United States experience significant depression (NIMH, 2017). D’El Filippis and Wagner (2014) conducted a comprehensive review of studies focusing on TRD in children and adolescents. They commented on a study of 140 adolescents with major depression, in which 93% had full remission but 53% had a resurgence of depression. In a study of 276 adults with depression, about half reported depression in their adolescence. Study results also suggested a greater risk for suicidality if depression occurred before adulthood. Effective treatment of depressed adolescents is essential to future psychiatric well-being.

Zhou and co-authors (2014) conducted a systematic review examining TRD in adolescents. They defined TRD as found in “those who failed to respond to at least one psychological or pharmacological treatment for depression with an adequate dosage, duration, and appropriate compliance...” (p. 2). Authors noted 20% of adolescents experience major depression and 30%-40% fail to show significant improvement with initial treatment. Adolescents experiencing TRD are more likely to have a recurrent episode in adulthood, commit suicide, have seriously impaired social functioning, perform poorly in school, and have difficult relationships. Additional stressors associated with adolescence may complicate depression treatment. Depressed adolescents tend to have ancestors with mental disorders. Additionally, teens with depression often have a slower
Clinicians should investigate manic symptoms. Failure to respond to treatment within first few weeks may predispose person to TRD. Serotonin transporter genetic variants can be predictor of TRD.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Impact</th>
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<tr>
<td>Duration</td>
<td>Longer bouts of depression are associated with behavioral and cognitive changes, resulting in inability to return to baseline.</td>
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<td>Severity</td>
<td>Biological imbalances can occur with severe MDD.</td>
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<td>Bipolar depression vs. MDD</td>
<td>Clinicians should investigate manic symptoms.</td>
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<td>Symptomatic improvement</td>
<td>Failure to respond to treatment within first few weeks may predispose person to TRD.</td>
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<td>Comorbidities</td>
<td>Individuals with anxiety and personality disorders tend to have lower response rates and remission.</td>
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<td>Older age</td>
<td>Serotonin transporter genetic variants can be predictor of TRD.</td>
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MDD = major depressive disorder, TRD = treatment-resistant depression

Source: Serretti & Fabbri, 2014

response time to pharmacologic treatment than adults.

Adults

Research has supported the suggestion childhood traumatic experiences, including physical, sexual, and emotional abuse, neglect, and separation from caregivers, significantly increase the risk of developing mental and physical illnesses later in life (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016). The development of depression is thought to be a multifactorial, complicated interplay among numerous physiological, social, genetic, environmental, and biochemical factors (Arcangelo, Peterson, Wilbur, & Reinhold, 2017). A meta-analysis by Baumeister and colleagues (2016) found a significant association between childhood trauma and inflammatory markers, offering a potential molecular pathway by which early trauma confers vulnerability to developing psychiatric and physical disorders late in life.

Pharmacologic Treatment

Several pharmacologic approaches are available for individuals with TRD. Mitchell (2018) recommended the following algorithm: optimization, switching, and augmentation. Optimization occurs when the clinician ensures the patient is taking the medication as prescribed, has been taking the medication for an appropriate length of time, and is receiving the ideal dosage. The typical length of initial therapy should be 6-8 weeks, but up to 12 weeks may be required. When optimization has been ensured, the clinician then should recommend switching to another medication within the same drug class and/or to a different drug class. Finally, if optimization and switching are ineffective, the clinician should augment with other medications to improve antidepressant effects in a process known as combination therapy. The clinician can combine two antidepressants first, then augment with other drug classes if not effective, including second-generation antipsychotics (SGAs) (Dold & Kasper, 2017).

Adolescents

Treatment options for adolescents suffering from TRD are limited due to lack of research. Indeed, few controlled studies exist for adolescents (Zhou et al., 2014). Comorbidities such as additional psychiatric disorders or medical problems, abuse, and non-adherence to prescribed therapies, may play a role in TRD (DeFilippis & Wagner, 2014). The practitioner also should consider CYP450 genetic variations which might have negative impact on the effectiveness of antidepressant medications. The diagnosis of depression also should be reexamined in adolescents with poor response to therapies.

DeFilippis and Wagner suggested clinicians should not assume an antidepressant failed to result in improvement before reaching the recommended maximum dosing. Once determined effective, the medication should be continued for at least 6-12 months in an effort to avoid relapse.

Treatment for adolescents with depression begin with supportive management followed by psychological therapy. Mild to moderately depressed adolescents should receive psychological therapy as first-line treatment (Zhou et al. 2014). Moderate-to-severe depression in adolescents likely requires pharmacological intervention, such as selective serotonin reuptake inhibitors (SSRIs). Examples of SSRIs include fluoxetine (Prozac®), citalopram (Celexa®), sertraline (Zoloft®), escitalopram (Lexapro®), and paroxetine (Paxil®) (NIMH, n.d.). Fluoxetine and escitalopram are the only antidepressants approved by the U.S. Food and Drug Administration (2014) for adolescents. Cognitive behavioral therapy (CBT) can be used in combination with pharmacological therapy to reduce suicidal ideation (Zhou et al., 2014).

The TORDIA (Treatment of SSRI-Resistant Depression in Adolescents) trial examined 334 patients ages 12-18 with TRD (defined as no response to SSRI with at least 8 weeks of treatment with a dosage of at least 40 mg of fluoxe-
tine or its equivalent). Participants were randomized to one of four treatment groups: switch to different SSRI; switch to a different SSRI plus CBT; switch to venlafaxine; or switch to venlafaxine plus CBT (DeFilippis & Wagner, 2014). The group switched to CBT plus either medication (another SSRI or venlafaxine) fared best with a 54.8% response rate. Authors recommend switching to an alternate SSRI and adding CBT for treatment of TRD in adolescents. They cautioned about the use of venlafaxine in this age group because of the risk for increased diastolic blood pressure, pulse, and skin problems compared to persons treated with an alternate SSRI. Because roughly half the non-responding 40% do respond to the change to a second SSRI, approximately 20% will fail to respond to this initial change in treatment. Unfortunately, DeFilippis and Wagner noted no studies provide recommendations for treatment for these adolescents.

Adults

Although several modalities exist for treating depressive disorders, pharmacotherapy remains the most common first-line treatment strategy (MacQueen et al., 2017). Unfortunately, around 20% of patients do not respond to any intervention, and many of those who do respond will relapse eventually (Carhart-Harris et al., 2016). This may be because a substantial number of depressed individuals continue to receive inadequate treatment (MacQueen et al., 2017). In addition, earlier onset of depression presentation is associated inversely with successful treatment outcome (Arcangelo et al., 2017). Younger patients with depression tend to have a more severe and complicated clinical course, with less likelihood of remission and increased likelihood of recurrence.

Selection of initial treatment options involves numerous factors, the most important being the patient’s target symptoms, comorbid medical or psychiatric conditions, concomitant medications, previous response to an antidepressant, and potential adverse effect and drug interaction profile. Given the relatively poor response rates to first-line antidepressant treatment, as well as negative consequences of untreated depression, clear guidance regarding treatment options for non-responders is important for clinicians (MacQueen et al., 2017). SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) are considered first-line therapy for depression; safety, tolerability, and lethality in overdose are considerations that tend to drive drug selection, not efficacy (Arcangelo et al., 2017).

When a patient fails an adequate trial of a first-line antidepressant therapy, second-line therapy becomes necessary. In some cases, the apparent lack of treatment response is a result of faulty diagnosis, inadequate treatment, failure to appreciate and remedy coexisting general medical and psychiatric disorders, or other complicating psychosocial factors (Gautam, Akhilesh, Gautman, Vahia, & Grover, 2017). Guideline recommendations for second-line treatment include increasing the dose, switching to a different antidepressant, or adding a different drug. The last strategy may be divided into augmentation (non-antidepressant drug added to an antidepressant) and combination therapy (two antidepressants used together) (Kato et al., 2018). Guidelines clearly state that dose escalation of SSRIs does not work. Furthermore, a recent more rigorous meta-analysis found no high-level evidence that switching the antidepressant is effective when compared to simply continuing the initial antidepressant (Bschor, Kern, Henssler, & Baethge, 2018). If there is less than 50% improvement with 6-8 weeks of maximum tolerable dose and medication adherence is good, a change in antidepressant should be considered (Gautam et al., 2017). A 6-year study analyzed results after 8 weeks or more of 500 trials involving a drug versus placebo or comparing two different medications (Boseley, 2018). The most effective drug was amitriptyline (Elavil®), while the least effective but best tolerated was fluoxetine.

When patients fail to remit on initial treatment, early combination, or switching, using mirtazapine (Remeron®) results in a small benefit, without increased adverse effects (Kato et al., 2018). In adults age 60 and older who do not achieve remission from depression with first-line therapy, the addition of aripiprazole (Abilify®) is effective in achieving and sustaining remission (Lenze et al., 2015).

Augmentation of Other Medication Classes

If the dose of the antidepressant is optimized with some response but does not result in complete remission, then augmentation with another non-antidepressant may be appropriate. Lithium (Eskalith®), thyroid hormone, and stimulant medications have been the medications utilized to augment the initial antidepressant response (Arcangelo et al., 2017). This recommendation has not been studied well; only two reports have compared switching medications versus combination strategies among patients who failed first-line treatment. One compared combination versus switching versus continuing prior treatment (Ferreri, Lavergne, Berlin, Payan, & Puech, 2001), while the other compared dose escalation versus combination versus continuing the prior treatment (Licht & Qvitzau, 2002). This recommendation remains in the treatment guidelines, but is no longer common in practice (Arcangelo et al., 2017).

Second-Generation Antipsychotics

Sadock, Sussman, and Sadock (2019) reported some SGAs have been approved as adjunctive therapy with antidepressants to treat MDD without psychosis. Augmentation of SGAs has been recognized increasingly as an important treatment option (Wang et al., 2016). Wang and co-authors found patients with TRD demonstrated
SGA augmentation (olanzapine [Zyprexa®], risperidone [Risperdal®], and quetiapine [Seroquel®]) yielded greater clinical remission than placebo. A combination of oral olanzapine and fluoxetine (Symbyax®) has been approved and indicated to treat TRD. Importantly, olanzapine alone is not indicated to treat TRD (Sadock et al., 2019).

Initial adult dosage for Symbyax is 6 mg/25 mg olanzapine/fluoxetine once daily in the evening (Chew, Hales, & Yudofsky, 2017). Typical dosing for TRD is 6-18 mg olanzapine/25-50 mg fluoxetine daily. Currently, Symbyax has not been approved for TRD in pediatric patients. Common side effects include sedation, drowsiness, fatigue, dry mouth, weight gain, and increased appetite. Evening or bedtime administration can help eliminate daytime drowsiness and sedation. Providers should use caution with Symbyax in patients with significant weight gain due to the potential development of diabetes and hyperlipidemia, which then cause cardiovascular disease. This side effect can be minimized in patients who are encouraged to diet and exercise. Less common side effects include extrapyramidal symptoms and akathisia. Decreasing the dose can minimize the risk of developing the less common side effects.

Aripiprazole and brexpiprazole (Rexulti®) have been approved to augment antidepressants for treatment of MDD (Sadock et al., 2019). Aripiprazole, olanzapine, quetiapine, and risperidone have demonstrated superiority for adjunctive therapy for TRD treatment. Ziprasidone (Geodon®) with escitalopram has demonstrated significant efficacy as well (Dold & Kasper, 2017). Quetiapine XR (Seroquel XR®) has been approved for adjunctive therapy in addition to antidepressants if a patient has not responded to antidepressant monotherapy.

When augmenting with SGAs, the clinician should note the recommended dosing is lower than when used for bipolar disorder or schizophrenia (Dold & Kasper, 2017). Aripiprazole should be initiated at 2.5 mg per day, with a maximum dose of 15 mg per day. Quetiapine XR should be initiated at 50 mg per day, with a maximum dose of 300 mg per day.

If a clinician augments with SGAs, he or she should note SGAs require up to 8 weeks to reach full effectiveness (Sadock et al., 2019). Weight gain is common with olanzapine, which can cause drug-induced diabetes mellitus. These medications have not been studied in pregnant women and can be excreted in breast milk. Dold and Kasper (2017) identified akathisia as a common side effect of aripiprazole; weight gain and sedation are common side effects of quetiapine. They also reported individuals with depression receiving adjunctive therapy with SGAs are at higher risk of developing antipsychotic-induced adverse effects compared to people with schizophrenia. The current available evidence indicates clinicians should pay careful attention to evaluation of practical and individual risks and benefits at the time of the decision to prescribe SGA augmentation therapy (Wang et al., 2016).

Lithium

Augmentation of SGAs and lithium with antidepressant drugs is also a recommended first-line guideline treatment option for TRD (Dold & Kasper, 2017). Often lithium is a better option when the individual with MDD portrays high-risk suicidality behaviors or signs of bipolar disorder. Lithium is useful in over 50% of antidepressant nonresponders and usually is tolerated well, with full response to the adjunctive lithium occurring within several days to 3 weeks (Gautam et al., 2017). Benefits should outweigh risks when lithium is considered as adjunctive therapy (Dold & Kasper, 2017). It has a very narrow therapeutic index and is associated with weight gain. Thus, SGAs often are used as first-line adjunctive therapy for TRD.

Thyroid Hormone

Thyroid hormone supplementation, even in euthyroid patients, may increase the effectiveness of antidepressant treatment (Gautam et al., 2017). Triiodothyronine is the thyroid hormone used for MDD treatment as adjunctive therapy (Stahl, 2017). However, this represents off-label use.

Nursing Implications

Nurses should be aware of the occurrence of MDD and TRD. Holistic nursing plays a pivotal role in caring for patients with TRD. Nurses educate patients about the importance of medication adherence, especially if multiple medications are needed to treat patients with TRD. The algorithm of optimization, switching, and augmentation tends to be a good approach (Dold & Kasper, 2017). First-line therapy for antidepressant therapy includes SSRIs and SNRIs. When first-line therapy has failed, second-line therapy typically involves a switch to another medication within the same drug class or to a different drug class. If this therapy fails, the recommendation is to augment with another drug class and offer the individual combination therapy. Adjunctive medications include SGAs, lithium, and thyroid hormones. Dold and Kasper suggested augmenting with other drug classes can optimize effectiveness, improve treatment outcomes, allow complete remission of symptoms, and prevent reoccurrence.

Nurses also should be aware that comorbid medication conditions and surgery can exacerbate MDD or impact pain management (Ghoneim & O’Hara, 2016). Furthermore, the risk of developing TRD is increased for individuals who are minorities, have poor family and social support, lack economic or interpersonal resources, are nonadherent to therapy, and have decreased quality of life or lower function (DiBernardo et al., 2018). Finally, identification of unwanted or alarming medication side effects can impact adherence and patient outcomes.
Conclusion

MDD is a common reason for individuals to present for medical care and may be difficult to treat (Dold & Kasper, 2017). Many risk factors are associated with triggering depression, causing depression to occur from adolescence to geriatrics. Approximately 50% of individuals fail to respond fully to antidepressant therapy alone, which can lead to TRD (APA, 2018). Individuals suffering from TRD have an increased association with suicidal ideation and attempts, with 30% attempting suicide. Clinicians need to recognize the pharmacologic approaches for individuals with TRD.

REFERENCES


