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**Abstract**

Major depressive disorder (MDD) is a disease often underdiagnosed in adolescents. For adolescents in particular, MDD can have far-reaching implications on developmental, social and emotional functioning. Unfortunately, few guidelines detail consistent means by which to evaluate and treat these patients; significantly more information exists that solely pertains to the adult population. Governing bodies such as the American Academy of Child and Adolescent Psychiatry (AACAP) and Resource for Advancing Children's Health (REACH) recommend that primary care physicians be diligent in their psychiatric analyses and follow-ups with young patients who may be experiencing MDD. Both psychotherapy and medications, either as monotherapy or in combination, should be considered when treating MDD. Selective serotonin reuptake inhibitors (SSRIs), particularly fluoxetine, are considered the anti-depressants of choice despite their black box warning pertaining to increased suicidality in children and adolescents. In all cases, benefits of therapy should always be assessed alongside potential risks. Pharmacists can play a significant role in counseling patients on these potential risks and benefits for both the pharmacological and non-pharmacologic aspects of MDD treatment.

## Introduction

Major depressive disorder (MDD) is a debilitating disease that greatly affects adolescents, particularly when left untreated. The World Health Organization (WHO) defines adolescence as the growth period between childhood and adulthood when individuals are between the ages of 10 to 19.[1] Major depressive disorder is common in this age group with 11.2 percent of American adolescents suffering from MDD or dysthymic disorder.[2] Dysthymic disorder is a milder form of depression that occurs for at least two years (Table 1).[3] The average length of a depressive episode ranges from two to eight months. The recurrence rate of MDD is anywhere from 20 to 60 percent one to two years after remission, but increases to 70 percent after five years.[4] Although adolescents and adults can both be diagnosed with MDD, adolescents exhibit different signs and symptoms than their adult counterparts.[5] Adolescents may feel physically sick, get into trouble or perform poorly at school, become increasingly irritated or feel misunderstood.[5] In addition, they may become socially withdrawn or suffer from substance abuse.[6] Comparatively, adults may complain of feeling sad, fatigued, or frustrated and may struggle with activities of everyday life.[7]

Major depressive disorder is a complex and disabling disease that can negatively impact all aspects of a patient's life: developmentally, socially and emotionally.[6,8] Any patient suffering from MDD, regardless of age, needs to be treated with medication, psychotherapy or a combination of the two. Like adults with MDD, adolescents are at an increased risk for suicide if their depression becomes too severe.[6] Depressed adolescents are at an even greater risk than depressed adults for completing suicide, which is the third leading cause of death in American adolescents 15 to 19 years of age.[9] In addition to the increased risk of suicide, untreated MDD has long-term social and clinical implications. Adolescents who suffer from milder forms of depression, such as dysthymic disorder, may eventually meet the criteria for MDD as adults if their condition is left untreated.[6] Unfortunately, MDD is often underdiagnosed in this young patient population because they often do not fully meet the diagnostic criteria.[6] Diagnosis may also be complicated by the existence of comorbid conditions such as anxiety and learning/conduct disorders.[10] Patients who show signs and symptoms of MDD should receive proper diagnosis, psychiatric interventions and adequate therapeutic treatment based on their age and disease severity.[6] Although MDD affects a significant number of adolescents, there is variability between existing diagnostic and treatment guidelines, few medications are currently indicated for MDD treatment in adolescents, and limited research exists in this patient population.[11]

## Guidelines for Diagnosis and Treatment

There are a variety of guidelines available for the treatment of MDD in adolescents; however, these documents are inconsistent. Recommendations regarding medication use, psychotherapy and the duration of these therapies vary. The length of psychotherapy and duration of medication use depend on the severity of a patient's MDD. Unfortunately, there are no studies available in adolescents with information regarding which patients should receive therapy past the usual recommendations.[8] Currently, fluoxetine and escitalopram are the only antidepressants approved by the U.S. Food and Drug Administration (FDA) for use in adolescents with MDD.[11]

Guidelines and treatment recommendations are currently available from the American Academy of Child and Adolescent Psychiatry (AACAP) and the Resource for Advancing Children's Health (REACH). The AACAP is a non-profit association whose members aim to treat and improve the quality of life in children and adolescents who suffer from mental health disorders. They provide treatment parameters for a variety of mental health disorders, including MDD.[12] The AACAP published their MDD parameters, which are based on the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), in 2007.[8] Guidelines for Adoles-

cent Depression in Primary Care (GLAD-PC) by REACH were also released in 2007. The GLAD-PC, a North American collaborative, was specifically developed for primary care physicians (PCPs) due to the differences between primary care and specialty care settings. The GLAD-PC: I discuss guidelines for the identification, assessment, and initial management of depression in youth ages 10 through 21. The GLAD-PC: II then outlines the treatment and ongoing management of adolescent depression. Few adolescents with MDD are actually seen by mental health professionals and instead seek help from their PCPs. The GLAD-PC helps PCPs, who may not be familiar with treating MDD in adolescents, properly diagnose and treat these patients.[13]

**AACAP Practice Parameters for the Assessment and Treatment of Children and Adolescents with Depressive Disorders**

The AACAP states that depression is a spectrum disorder that ranges from subsyndromal to syndromal. To be diagnosed with a syndromal disorder, adolescents must have a change in mood with either a depressed/irritable mood or a loss of interest/pleasure that accompanies a group of other symptoms for at least two weeks. These other symptoms include wishing to be dead, suicidal thoughts/attempts, changes in appetite or sleep and either decreased energy, concentration or self-worth. Although AACAP's diagnostic guidelines were based on DSM-IV, they are still similar to the recommendations in DSM-V (Table 1).[3,8] The AACAP recommends that physicians develop a relationship with their patient, his or her family, school personnel and other health care providers. The academy also suggests that physicians screen young patients at regular office visits to identify depressive disorders. If screening suggests the patient may be suffering from a depressive disorder, further evaluation is warranted including an assessment about harm to the patient or others. Additionally, this evaluation should include a family history of depressive disorders, ongoing or past negative events, such as abuse or divorce of parents and available support for the patient.[8]

Treatment with medication should always include an acute and continuation phase. Maintenance treatment may also be

**Table 1. Adapted from the DSM-V.[3]**

| DSM-V Diagnostic Criteria for MDD in Adults and Adolescents | |
|---|---|
| **Criteria A** | A patient must have **at least five** of the following symptoms occurring during the same two-week period and represent a change from previous functioning. One of the symptoms must either be depressed mood OR loss of interest/pleasure.<br><br>1) Depressed mood most of the day nearly every day.<br>2) Marked decrease in interest/pleasure most of the day nearly every day.<br>3) Significant weight loss or gain (5% of body weight in a month) or decrease in appetite nearly every day.<br>4) Insomnia or hypersomnia nearly every day.<br>5) Psychomotor agitation or retardation nearly every day (observed by others).<br>6) Fatigue or loss of energy nearly every day.<br>7) Feelings of worthlessness or excessive/inappropriate guilt nearly every day.<br>8) Diminished ability to think or concentrate or indecisiveness nearly every day.<br>9) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan. |
| **Criteria B** | Symptoms cause clinically significant distress/impairment in social, occupational, or other aspects of life. |
| **Criteria C** | Episode not attributed to physiological effects of substance abuse or another medical condition. |
| **Criteria D** | The occurrence of the major depressive episode cannot be explained by schizophrenia or a schizophrenia-like illness or another psychotic disorder. |
| **Criteria E** | There has never been a manic or hypomanic episode. |

appropriate in some patients. Treatment during the acute phase is to help relieve symptoms, while continuation treatment is to prevent relapse and to strengthen the acute phase. Maintenance therapy is recommended for patients who have a more severe or chronic disorder to prevent recurrence. Treatment at every stage should include patient and caregiver education on MDD, supportive management, and family/school involvement. Both parents and patients should be a part of the decision-making process for treatment. Adolescents with uncomplicated or brief depressive symptoms can often be successfully treated with education, case management and supportive care (psychotherapy) for four to six weeks. Patients who have a limited response to nonpharmacologic therapy or those with more severe depression may require both psychotherapy and antidepressant medications. The AACAP defines response to treatment as having no symptoms or having a significant reduction in depressive symptoms for at least two weeks.[8] Both psychotherapy and antidepressants can be used as monotherapy. Research attempting to prove a benefit exists in patients using combination therapy has been inconclusive.[14] However, clinicians state that patients do respond better to combination therapy; therefore, AACAP suggests patients receive both psychotherapy and medications, especially if they have moderate to severe or refractory MDD. The AACAP recommends patients use fluoxetine because it is indicated for use in adolescents (Note: these guidelines were published before escitalopram was an indicated therapy). Studies with selective serotonin reuptake inhibitors (SSRIs) other than fluoxetine had not shown a significant difference in treatment response compared to placebo when these guidelines were written.[8]

The doses of SSRIs used in adolescents are similar to adult dosages. Low doses should be given initially and then titrated up to the lowest effective dose. Prescribing physicians should reassess the patients every four weeks and adjust doses when necessary. It is recommended that patients be treated for six to 12 months to avoid relapse. Physicians should also evaluate their patients to see if they are candidates for longer use; candidates include those with severe or refractory depression. Somatic treatments, such as electroconvulsive therapy or transcranial magnetic stimulation, in addition to pharmacotherapy and psychotherapy, may be necessary in patients with psychosis, seasonal depression or bipolar disorder. Moreover, comorbid psychological and physiological conditions should also be appropriately treated.[8]

**Guidelines for Adolescent Depression in Primary Care**

The recommendations from the GLAD-PC: I state that the PCP identifies adolescent patients who are at risk for depression and systematically monitor them for the development of a depressive disorder. The PCP should specifically assess psychosocial function in adolescent patients, as altered function can be an early sign of depression. Risk factors include personal or family history of psychiatric illness, substance abuse and suicidal behavior. Adolescents under psychosocial stress due to abuse, neglect or other traumatic events are also considered at increased risk for depression. To assess and diagnose patients, the PCP should evaluate both high-risk patients and patients who describe emotional problems as their chief complaint. Assessment should include direct interviews with the patient as well as family members or caregivers. The GLAD-PC also recommends diagnosis of depression based on the diagnostic criteria described in DSM-IV or in International Classification of Diseases, 10th Revision (ICD-10). During initial management, the PCP should educate the patient and family members about depression and its symptoms. A treatment plan should be established and goals should be set individually for key areas of function for the patient: home, school and peer settings. All management must include a safety plan that establishes an emergency contact in case of increased suicidality or crisis-type situations resulting from the depressive symptoms or treatment. The GLAD-PC notes that a safety plan should be established early because safety concerns are highest during diagnosis and initial management. The PCP should involve a concerned third party, such as a school nurse or other adult that can provide adequate support and supervision. It is also recommended that all materials that could cause serious harm or death be removed as a measure of precaution.[15]

According to GLAD-PC: II, the PCP should provide a six to eight week period of active support and monitoring for patients diagnosed with mild depression before making a treatment recommendation. The PCP should monitor patients every one to two weeks through follow-up phone calls in addition to frequent office visits. The PCP can provide support by making recommendations for exercise or leisure activities, peer support groups and patient self-management goals. Educational materials should also be provided to the patients and their families at this time.[16] If patients continue to present with symptoms, treatment with an SSRI antidepressant or psychotherapy should then be recommended. Fluoxetine is considered first-line treatment for all adolescents ages 10 through 21. Escitalopram is considered first-line treatment for adolescents ages 12 through 21.[16] Immediate treatment is recommended for adolescents with moderate to severe depression. Additionally, consultation with a mental health specialist should be considered in cases of adolescents with moderate/severe depression, coexisting substance abuse or psychosis. If a referral is made, the roles and responsibilities of both the PCP and mental health clinician need to be discussed and agreed upon by the involved clinicians, the patient and the patient's parents/guardian. It is important to note that the PCP should continue to follow-up with the adolescent after the referral.[17]

The guidelines note that appropriate psychotherapy methods include cognitive behavioral therapy (CBT) and interpersonal therapy (IPT). Cognitive behavioral therapy focuses on the patient's thoughts and behaviors to improve their mood. Parents or caregivers may be included in sessions of CBT. Key components of this therapy include incorporation of pleasurable behavior, reducing negative thoughts, and decreasing feelings of hopelessness by improving problem-solving skills. IPT focuses on interpersonal problems that may act to either cause or worsen depression. Goals of therapy include addressing specific interpersonal problems while improving interpersonal problem-solving skills and communication skills.[18] Parents and caregivers are invited to partici-

pate during specific phases of IPT, including the first session, during the middle phase of treatment and at the end of treatment.[17,18]

The PCP should reassess diagnosis and initial course of treatment if no improvement is seen within six to eight weeks of treatment for moderate to severe depression. Additionally, a mental health consultation should be reconsidered if there is no improvement noted after initial treatment or only partial improvement is seen after all primary care therapeutic approaches have been attempted. A reduction in symptoms of depression, improved ability to function and reports of improvement by the patient or parent/caregiver are all considered indicative of improvement. Several diagnostic aids in addition to DSM-IV and ICD-10 are mentioned in the GLAD-PC toolkit that can assist in reassessing patients and quantifying a reduction in symptoms. The Columbia Depression Scale—Teen Version is a survey that consists of yes or no type questions and incorporates inquiries about suicide ideation and attempts. The scale is based on a point system where "yes" is worth one point and "no" is worth zero points. There are two versions of the survey—one for parents and one for the adolescent. The scores are then assigned to the chance of depression, ranging from very unlikely to highly likely. In addition, the six question Kutcher Adolescent Depression Scale (KADS) is scored to indicate if a patient is "possibly depressed" or "probably not depressed." Moreover, a modified version of the Patient Health Questionnaire, 9th Revision (PHQ-9) is available to assess adolescent depression (note: research has not been conducted to validate the modifications). Modified PHQ-9 consists of a survey format that incorporates the frequency of symptoms (i.e. "not at all" through "nearly every day"). Points are assigned to the patient's responses that rank the severity of depression from mild to severe.[16]

After reassessing the patient, the PCP should address the choice and efficacy of initial treatment. If the patient does not respond to the maximum therapeutic dose of an SSRI antidepressant, treatment with a different SSRI antidepressant should be considered. The GLAD-PC toolkit for PCPs includes SSRIs not FDA-approved for adolescents (i.e. sertraline, citalopram, fluvoxamine, paroxetine) as alternatives.[16] If only psychotherapy or only antidepressant therapy was initially utilized, the clinician should consider adding the other therapy to the patient's treatment plan.[17] If the patient fails two trials of treatment with an SSRI and a course of CBT or IPT, the PCP should consult a mental health specialist to recommend a second-line medication such as citalopram or sertraline. If a patient fails a third medication trial, the PCP should reevaluate their diagnosis and consider a combination of medications.[16] Increasing the initial SSRI antidepressant dose above FDA-approved ranges is also suggested as a possible consideration for patients who only partially respond to therapy. The guidelines do not specify if this is a last-line option, but recommend that the dose be increased in consultation with a mental health professional. Assessments should include the presence of comorbid conditions such as substance abuse or bipolar symptoms that may affect treatment.[17]

According to GLAD-PC, ongoing management should include the tracking of goals and treatment outcomes. Goals of treatment include both an improved ability to function and cessation of depressive symptoms. Moreover, the patient's level of function should be assessed in various environments (i.e. home, school, and peer settings). Patients should be seen within one week of beginning treatment to initiate such tracking. Both GLAD-PC and AACAP experts recommend that antidepressant therapy should be continued for six to 12 months after complete resolution of depressive symptoms. The GLAD-PC cites AACAP in the recommendation that patients may be monitored for up to two years if patients suffer from recurrent depressive episodes.[8,17] If treatment includes an SSRI antidepressant, the PCP should monitor the patient for adverse events. The GLAD-PC references the FDA's recommendation for monitoring children and adolescents using antidepressants for clinical worsening, suicide risk and changes in behavior. These guidelines note that the optimal frequency of monitoring is controversial.[17]

## Pharmacological Treatment Options

Selective serotonin reuptake inhibitors are most commonly prescribed to treat depressive disorders due to their effectiveness over older generations of antidepressants such as the tricyclic antidepressants (TCAs). SSRIs directly inhibit the adenosine triphosphate (ATP) dependent carrier in presynaptic neurons. Without a functional reuptake pump, serotonin (5-hydroxytryptamine [5-HT]) is not broken down or recycled to produce more 5-HT. Instead, there will be an accumulation of this particular neurotransmitter in the synaptic cleft for continuous stimulation of serotonergic neurons. However, this process has no correlation to the duration of therapy since the onset of action for all antidepressants is typically delayed. If this were the case, adolescents would feel immediate relief within three days. Typically, maximum improvement in mood can take place within two weeks.[19] Another mechanism suggests that SSRIs induce desensitization of somatodendritic and terminal 5-HT$1_A$ autoreceptors, proteins responsible in inhibiting the release of 5-HT and other neurotransmitters from the presynaptic neuron.[20] Overstimulation of the autoreceptors would cause this desensitization. By attenuating the negative feedback responsibilities of these autoreceptors, 5-HT will accumulate to a greater extent, leading to an antidepressant response.

Side effects associated with SSRI use occur due to the inhibition of other signaling transduction pathways; thus, leading to additional physiological responses.[20] Selective serotonin reuptake inhibitors generally improve mood, but they can also cause one to experience suicidal thoughts due to the inhibition of dopamine neurotransmission. Increasing concentrations of 5-HT with SSRIs downregulates dopamine receptors in the prefrontal cortex, the area of the brain responsible for cognitive behavior, personality, expression, decision-making and moderating social behavior.[20] Compromising mesocortical dopaminergic pathways could trigger impulsive and aggressive behavior toward oneself (e.g. suicide). To reverse the downregulation of dopamine receptors, researchers are currently investigating 5-HT$2_C$ receptors, proteins localized in the dorsal striatum, which are responsi-

ble for modulating striatal and prefrontocortical dopamine concentrations.[20] By discovering the correlation between these receptors and dopaminergic tone, scientists can better treat conditions such as depression.

**Black Box Warning**

In 2004, the FDA directed all manufacturers of antidepressants to add a black box warning (BBW) to SSRI labeling to alert health care providers of the increased risk of suicidality in children and adolescents being treated with these agents. The FDA also directed manufacturers to include information from pediatric studies regarding suicide risk in the labeling.[21] While suicide risk is highlighted for children, adolescents, and young adults, labeling states that all patients taking antidepressants should be monitored for clinical worsening, suicidality, or altered behavior during the initial months of treatment and during any dosage changes.[22,23] According to the warnings, the clinical need of the medication should be weighed against the clinical risks in any child, adolescent or young adult patient who is being considered for antidepressant therapy.[21]

Controversy still exists over this BBW. Some studies have shown statistically significant increases in suicidal thoughts and actions in adolescents on SSRIs, while others have not.[24,25,26] A study by Gibbons and colleagues showed that adolescent patients on SSRIs had a lower risk of suicide compared to patients on placebo.[26] Additionally, the government-funded Treatment for Adolescents with Depression Study (TADS) found that patients who received combination therapy of medications and psychotherapy had a lower suicide risk.[24] Interestingly, early in the trial, 29 percent of patients had suicidal thoughts. At the end of the study only 8 percent of patients on combination therapy had suicidal thoughts, compared to 15 percent of patients taking fluoxetine alone.[24] In another study, Ma and fellow researchers found that while the number of prescriptions for antidepressants is increasing, fewer patients are receiving them in combination with psychotherapy.[25] The AACAP recommends adolescents receive both medication and psychotherapy. This treatment combination is beneficial because it provides an opportunity for patients to develop coping skills and helps them develop a plan to continue treatment. The decrease in psychotherapy utilization may be a confounding factor contributing to the increased suicide rate associated with SSRIs.[8]

Some practitioners argue that the BBW discourages doctors from prescribing antidepressants to adolescents who really need to be treated with medication. Others argue that the risk of suicide, if MDD is left untreated, is higher than if a patient was placed on an SSRI. Regardless of reasoning, there is need for more research to discover whether or not suicidal activity is definitively linked to SSRI use in adolescents.[23]

Because a warning exists, the AACAP suggests that all patients receiving SSRIs be monitored for suicidal thoughts and actions. Patients with an especially high risk of suicide should be monitored particularly closely. These patients include those suffering from bipolar disorder, substance abuse, sexual abuse and patients with suicidal tendencies or a family history of suicide. The AACAP supports the FDA recommendation that patients be seen once a week for the first four weeks of therapy and then biweekly thereafter. Monitoring can be done via telephone or by a face-to-face meeting.[8]

**SSRI-Resistant Depression**

Some adolescent patients may not see any improvement after initial treatment with an SSRI. The National Institute of Mental Health funded a multi-site, clinical study to investigate treatment of adolescents with SSRI-resistant depression (TORDIA) that was conducted from 2000-2006.[27] The purpose of the study was to evaluate the efficacy of four different treatment strategies in adolescents who did not respond to initial treatment with an SSRI. Three hundred and thirty-four adolescents, ages 12 to 18 years, who had not responded to two months of initial treatment were randomized to one of the four treatment groups. Treatment groups included: switch to an alternate SSRI, switch to the selective serotonin-norepinephrine reuptake inhibitor (SSNRI) venlafaxine, switch to a new SSRI in combination with CBT, and switch to venlafaxine in combination with CBT. The groups treated with both venlafaxine and CBT or a new SSRI in combination with CBT had a higher rate of clinical response than the groups that did not incorporate CBT. There was no difference in clinical response between the adolescents who switched to a new SSRI and the adolescents who were treated with venlafaxine. However, venlafaxine was associated with a greater increase in diastolic blood pressure, pulse rate and skin problems. The TORDIA study was designed to detect a 10 percent difference between groups at a power of 80 percent for a sample size of 400 participants. Brent and colleagues stated that the sample size was not met due to a public health advisory that the FDA issued to health care providers regarding risk of suicidality in pediatric patients taking SSRIs. The warning was issued at the midpoint of the study in 2003. The authors noted that recruitment of participants became difficult when the concern about suicide risk in pediatric patients taking SSRIs increased; thus, the overall use of SSRIs declined.[27,28] Although the results were not statistically significant, TORDIA still provided clinically significant data regarding treatment options for adolescents who do not respond to initial SSRI treatment.

**Special Considerations with Antidepressant Treatment in Adolescents**

There is high variability in adolescent placebo response, which limits interpretation of clinical trials for pharmacologic treatment of adolescents with MDD. Trials comparing antidepressant treatment to placebo in adolescents have reported a wide range of placebo response from lower rates of approximately 20 percent to higher rates of 70 percent.[29-32] Variable placebo response to antidepressants is not restricted to the adolescent population. Reif and colleagues recently conducted a meta-analysis analyzing 96 studies and 9,566 patients (excluding children). The analysis did not differentiate between different classes of antidepressants. In patients taking antidepressants versus placebo, it was determined that the placebo response accounted for 68 percent of the effect in the drug groups. However, variations in the depression diagnosis (i.e. type and severity) and study design

were noted as cause for variation in recorded placebo responses.[33] Therefore, in future research, the effect of placebo treatment in depressed adolescents will be a necessary consideration. It is important to note that research regarding pediatric patients is often limited by small sample sizes due to fear of complications or violation of ethical standards.

Another important consideration in pharmacologic treatment is the developmental differences between adolescents and adults that can impact various pharmacokinetic parameters. In practice, pediatric dosing is often derived from the adult dose and adjusted according to body weight or body surface area for off-label uses of medications. Because this method does not account for developmental differences, it places patients at risk for either sub-therapeutic dosing and lack of effect or supra-therapeutic dosing and adverse events.[34] According to a systematic review conducted by Moreno and colleagues, adolescents may, theoretically, experience higher plasma concentrations of lipophilic drugs like antidepressants and antipsychotics because they have a higher body water/adipose ratio (i.e. lower percentage of body fat) than adults.[35] However, it is also believed that hepatic cytochromes have higher activity in adolescents around puberty than adults. Once puberty is reached, sex hormones are believed to compete for hepatic enzymes, meaning higher doses of antidepressants may be required to avoid sub-therapeutic dosing.[35]

Adolescents qualifying for discontinuation of therapy that are currently taking SSRIs or SSNRIs must be gradually weaned off their medications over a four-week time period.[36] Patients who are suddenly taken off their medications can experience discontinuation symptoms. The symptoms are characterized by a severe withdrawal effect resulting in headaches, nausea, tremor, anxiety and agitation. Research has indicated that the magnitude of withdrawal is inversely proportional to the half-life of the drug.[36] A shorter half-life would result in a faster elimination rate and more episodes of discontinuation symptoms. Fluoxetine, which has a very long half-life (one to three days after acute administration and four to six days after chronic administration), evokes the least amount of withdrawal symptoms for patients. On the contrary, other SSRIs (i.e paroxetine and sertraline) and SSNRIs (i.e venlafaxine, duloxetine) evoke more severe withdrawal symptoms.[36,37] Venlafaxine, with a short half-life of three to 13 hours, is rarely indicated for adolescents with depressive disorders because it tends to cause more frequent and robust withdrawal symptoms. In the literature, SSNRIs have not demonstrated better effectiveness than SSRIs.[36] Additionally, since they cause more adverse reactions than SSRIs, SSNRIs should be avoided and not recommended as first-line agents in adolescent patients with depressive disorders.

### Thoughts on Adolescent Depression

In 2003, the American Psychological Association (APA) issued a press release stating that adolescents who suffer from depression are susceptible to relapses of symptoms in adulthood. According to APA, intervention and prevention of adolescent depression are important to avoid such relapses.[38]

In 2005, the National Institute for Health and Clinical Excellence (NICE) and the National Collaborating Centre for Mental Health issued a press release stating that new standards had been developed regarding the treatment of depression in adolescents. According to NICE, mild depression should not be treated with antidepressants, and psychological therapy should be first-line treatment for moderate to severe depression. If antidepressant therapy is initiated, it should be provided along with psychological therapy. Health care professionals in close contact with adolescents should be trained to detect symptoms of depression. The standards also mentioned that there is the possibility of concurrent depression in parents that would need to be addressed in order to ensure effective treatment of their child's depression.[39]

In 2006, APA issued a press release highlighting a report regarding the gap in care for many adolescents. The gap was associated with limited access to appropriate services for mental health issues. The report called for research to further investigate the efficacy of treatments for depression as well as what doses and dosage intervals are appropriate in the adolescent population. The need for further research in the various combinations of pharmacologic treatment and psychotherapy was also highlighted. The American Psychological Association's report stressed the importance for research to investigate the role of outside influences such as family members or school employees on depressed adolescents' adherence to treatment. Additionally, APA cited a need for increased collaboration among U.S. federal agencies that fund treatment research as well as public disclosure of safety and efficacy data from the treatment research.[40]

### The Pharmacists' Role

Pharmacists have an important role in monitoring patient compliance and safety with antidepressant medications. It is imperative to inform patients to not abruptly discontinue their therapy. Adolescents and their parents should be informed of the aforementioned risks due to sudden discontinuation (i.e withdrawal symptoms). Discontinuation could result in a longer duration of therapy to not only correct the withdrawal symptoms, but to also treat the original depression state. Patients and their caregivers should also be advised that the physician will make all necessary medication adjustments as needed. Modifying medication therapy by oneself should be strictly prohibited; instead, one must consult with the physician. Since adolescents typically have faster metabolism than adults, they can experience even more severe withdrawal symptoms.[36] However, these effects and risks can be avoided with appropriate clinical management.

Pharmacists can also play an important role in providing nonpharmacologic counseling to adolescents experiencing recurrent episodes of suicidal ideation by encouraging patients and/or their parents to attend regular psychotherapy sessions. Furthermore, it is imperative to look for any signs of bipolar disorder, schizophrenia and/or a history of MDD in family members via examining family health history. The pharmacist should work collaboratively with the primary

physician to get any health information needed. If a family history of mental health disorders exists, then this may be a contributing factor to the patient's depression. Explaining this possible genetic link to patients could help to further the patient's understanding of their disease. Additionally, patient noncompliance of medication therapy is an area where pharmacists can make very positive interventions. Patient noncompliance can be due not only to lack of understanding about the importance of taking these antidepressants on a regular basis, but also can be due to the possible side effects from antidepressants. Thus, face-to-face follow-up visits with the pharmacist should be highly encouraged. These visits could occur weekly or biweekly. Seeing both a pharmacist as well as a physician could help to ensure efficacy and decrease the risk of adverse effects of antidepressant medications. It is imperative to also counsel parents about the importance of compliance with antidepressant medications, since caregivers/parents have great influence on an adolescent's life. Upon dispensing medications, pharmacists should also distribute medication guides, so that the patient can be fully aware as to what their therapy entails, and encourage the patient to call with any questions or concerns.[41]

## Conclusion

Although guidelines exist for the treatment of MDD in adolescents, these reports vary and are oftentimes not utilized in clinical practice. Treatment is inconsistent among physicians, and prescribers often choose to prescribe medications that are not indicated for the treatment of MDD in adolescents. More research needs to be conducted to further clarify the guidelines, add additional therapies to treatment options and to end the controversy that exists over whether or not to treat adolescent MDD patients with fluoxetine or escitalopram. Increasing the amount of patient and parent counseling will hopefully lessen the fear of adverse effects and social stigma concerns that surround antidepressants, allowing adolescents to receive the treatment that they need for MDD.[20] There are risks and benefits with taking medications to treat MDD; however, the benefits more often outweigh the risks. Effectiveness of medications can be achieved if dosing is gradually titrated, assuming that the patient is responding well to therapy. Most importantly, patients should avoid high-risk agents such as SSNRIs.[41] Finally, it is important for health care providers to communicate with one another and with their patients to address these risks and benefits for antidepressant treatment in adolescents. Due to their accessibility, pharmacists play a particularly important role in educating patients and caregivers on the importance of medication adherence and monitoring for signs of suicidal ideation.

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