SSRIS AND ADOLESCENT DEPRESSION

by

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The members of the Committee appointed to examine the Clinical project of LAURIE ANN HELMS find it satisfactory and recommend that it be accepted.

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Prescribing SSRIs for Adolescents with Depression

Abstract

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Nurse Practitioners in primary care are often on the front lines of diagnosing and treating depression. Many medications used to treat depression in adolescents have been studied but only one, Fluoxetine, is currently approved to treat major depression. In addition, there is a preponderance of media attention being focused on the question of how safe these medications are in adolescents and even focusing on those adolescents who have committed suicide while on these medications and overemphasizing the point that these medications may cause suicidality. Certainly, there is cause for concern, but should this concern keep providers from treating depression in adolescents in primary care? This question and the concern that many adolescent patients will go untreated because of fears that have been raised with the initiation of Food and Drug Administration’s (FDAs) black box warning labels on all SSRI medications lead to the review of the current research in this manuscript.

Discovered in this review of clinical trials was that there are risks and benefits that have to be carefully explored when deciding on when and how to treat this illness. There are risks involved in not treating this illness as well as potential risks in the use of medications. Recommendations for close monitoring, warning signs of problems, patient and family education as well as the need for close collaboration with mental health specialists are outlined to aid practitioners in treating depression in adolescents.
Prescribing SSRIs for Adolescents with Depression

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Abstract

Selective Serotonin Reuptake Inhibitors are the first line medications used to treat major depressive disorder (MDD) in adolescents. Questions regarding the safety and efficacy of these medications have raised concerns within the medical community as well as the general public. In hopes of answering these questions, a review of clinical trial data of the most commonly prescribed SSRIs was performed and recommendations for practice made.

Full Text

Depression is the most common problem encountered in primary care and major depressive disorder (MDD) is one of the most common psychiatric disorders of adolescence. Selective Serotonin Reuptake Inhibitors (SSRIs) are first line medications used to treat MDD in this population. Recent controversy over the safety and efficacy of SSRIs for use in adolescents has been the impetus for the Food and Drug Administration’s (FDA) initiation of black box labeling for these medications. This FDA warning has been cause for concern in the general public as well as amongst providers. The threat that these strong warnings will deter primary care providers from treating MDD in adolescents has been raised, illuminating the need for this comprehensive review of clinical trial data and the need for further research into effects of SSRIs in adolescents.

As with all primary care providers, Nurse practitioners (NPs) in primary care have access to the training, knowledge, and skills needed to treat depression. Nurse practitioners typically have strong relationships with their patients and treat the whole person. Focusing care on the physical, emotional and behavioral components makes NPs often the first to recognize signs of
depression among their clients. One study showed that almost one-third of the patients seen weekly by Nurse Practitioners (NPs) were seen for mental health problems. Many times adolescents present in primary care with complaints of fatigue, headaches or general somatic complaints that are often signs of depression. Recognition of depression in adolescents, as well as the knowledge of how to provide safe and effective treatment in primary care is essential. Left untreated, depression during adolescent years can lead to alcohol and tobacco abuse, academic and social derailment, unplanned pregnancy, eating disorders, mental illness in later years and high rates of attempted and completed suicide. Suicide is the third leading cause of death among adolescents. During adolescents years moodiness is common, but when it interferes with functioning in school, family and/or with peers, further investigation is necessary. Distinguishing between normal “moodiness” and major depression is essential and can be done by the nurse practitioner who is aware of the difference and the criteria for diagnosing major depressive disorder (MDD).

A diagnosis of MDD in the Diagnostic and Statistical Manual of Mental Disorders (DSMD-IV), requires the presence of five or more of the following symptoms for a period of two weeks: (1) depressed mood, (2) loss of interest or pleasure, (3) significant weight or appetite change, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue/loss of energy, (7) feelings of worthlessness or inappropriate guilt, (8) diminished ability to think or concentrate, and/or (9) recurrent thoughts of death or suicidal ideation/plan/attempts. Depressed mood or loss of interest or pleasure must be one of the five presenting symptoms.

Recognition of depression is just the first step in addressing this illness, with initiation of treatment being the next. Ideally a referral to a mental health specialist is made, but many barriers exist to obtaining mental health services for patients in primary care, not the least of
which are shortages of mental health providers specially trained to deal with youth. Other barriers that exist are insurance restrictions, often leading to large out-of-pocket expenses, long appointment delays and stigma. Clearly the majority of the burden to recognize and often start treatment for this disease lies with primary care providers. Early recognition and early treatment equate to a better long-term prognosis. This emphasizes the need for astute decision-making skills in initiating treatment and close collaboration with mental health specialists.

**Review of the Literature**

Research examined included one of the first trials of fluoxetine (Prozac) in children and adolescents with depression.6 This study was a randomized, placebo-controlled trial. The study included ninety-six children and adolescents ages 7-17 years of age with nonpsychotic major depressive disorder. Forty-eight of the subjects were randomized to 20mg of fluoxetine and the other forty-eight were given placebo. Severity of depressive symptoms and primary outcome measurements were determined with the Clinical Global Impressions (CGI) scale and the Children’s Depression Rating Scale-Revised (CDRS-R). Equivalent response rates were found for patients aged 12 years and younger and those aged 13 years and older. Fifty six percent of the fluoxetine treated sample reported “much” or “very much” improvement on the CGI. In the placebo group, 33% rated improvement of “much” or “very much” on the same scale (Emslie et al.). The investigators concluded that fluoxetine at 20mg/day is safe and effective in children and adolescents with MDD.6

Two similar studies further supported the findings of Emslie, Rush, Weinberg and Kowatch et al. One was also a placebo-controlled, randomized clinical trial of fluoxetine for acute treatment of depression in children and adolescents.7 The subjects consisted of 122
children and 97 adolescents with MDD. Fluoxetine was associated with greater mean improvement in CDRS-R than placebo after one week and throughout the study period. Half of all fluoxetine-treated patients, 52.3% were rated “much” or “very much” improved compared to 36.8% of the placebo-treated group. This is consistent with the findings of previous investigators.

One of the largest and most recent studies with regards to treatment of depression in adolescents is the Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial. This study compared treatment with cognitive-behavioral therapy (CBT) alone, CBT with fluoxetine, fluoxetine alone, or placebo. A sample of 429 patients with a primary diagnosis of MDD volunteered for the study. Inclusion criterion was age 12 to 17 years, ability to receive care as an outpatient, a DSM-IV diagnosis of MDD at consent and again at baseline. Depressive mood had to be present for at least 6 weeks prior to consent. Response rate was measured with the CDRS-R total score, and for responder analysis a Clinical Global Impressions (CBI) improvement score.

The response rates for fluoxetine monotherapy in TADS were consistent with those seen in the previously described fluoxetine trials and demonstrate that fluoxetine monotherapy is an effective treatment for MDD in adolescents. It is interesting to note that besides the fact that CBT with fluoxetine was the most effective, fluoxetine alone was more effective than CBT alone according to the results measured on the CDRS-R. Investigators concluded that fluoxetine with CBT offered the most favorable tradeoff between benefit and risk for adolescents with MDD.

Harm-related adverse events defined as involving harm to self, such as cutting or worsening of suicidal ideation without self-harm, were studied in these groups of patients. Thirty-three (7.5%) of 439 patients experienced a harm-related adverse event. Of these
23 (69.7%) met the FDA’s definition for a serious adverse event defined as an event that required medical intervention or caused the patient to take a concomitant medication. Twenty-four (5.5%) of 439 patients experienced a suicide-related adverse event. This requires that the patient exhibit either worsening suicidal ideation or make a suicide attempt, or both. Examination of rates by treatment groups indicated that little or no increased risk for the CBT alone group, intermediate risk for the fluoxetine and CBT combined group, suggesting a protective effect for CBT. There were statistically significant elevated risks for harm-related adverse events only in the SSRI-treated participants. There were no completed suicides.

The safety and efficacy of sertraline (Zoloft) in pediatric patients with MDD was studied in two randomized double-blind placebo-controlled trials. These trials were conducted at 53 hospitals, general practice clinics, and academic centers in the United States, India, Canada, Costa Rica, and Mexico between December 1999 and May 2000.

Three hundred seventy six patients were randomly assigned to double blind treatment with either sertraline or placebo. The CDRS-R was used as the instrument to measure improvement. This study demonstrated that sertraline-treated patients exhibited significantly greater improvement on the CDRS-R over the ten-week course of the study than those receiving placebo. Week-by-week analysis showed that significant differences in favor of sertraline were apparent as early as week one on the Clinical Global Impression of Improvement (CGI-I) scales and week three on the CDRS-R and the Clinical Global Impression of Severity of Illness (CGI-S) rating. A review of sertraline’s safety data was conducted by the FDA and concluded that: “These reports do not provide any safety signals that indicate that the Agency needs to do anything except continue to actively assess the evolving benefit-risk profile of these products (sertraline).”
A randomized, placebo-controlled trial of citalopram (Celexa) found it to be effective and safe for the treatment of depressive symptoms in children and adolescents.9 Outcome measures were scored on the Children's Depression Rating Scale-Revised (CDRS-R). In the group treated with citalopram, CDRS-R scores decreased significantly more than the placebo treatment group beginning at week one and at every observation point to the end of the 8-week study.9

The final sample consisted of 89 patients assigned to citalopram and 85 patients assigned to placebo. Citalopram treatment showed statistically significant improvement compared with placebo on the CDRS-R. At endpoint more citalopram-treated patients met the prospectively defined criterion for response than did placebo-treated patients. The rate of discontinuation due to adverse events was comparable in the placebo and citalopram groups. Investigators concluded that citalopram treatment significantly improved depressive symptoms compared with placebo within one week in this population of children and adolescents. No serious adverse events were reported.

The most controversial SSRI for use in adolescent depression is paroxetine (Paxil, Seroxat). The US Food and Drug Administration reviewed safety and efficacy data for the use of paroxetine in pediatric populations in 2003.10 The pooled results of three unpublished trials involving pediatric patients with major depressive disorder failed to show paroxetine to be more efficacious than placebo. In addition, the pooled results showed that suicidal thoughts, suicide attempts and episodes of self-harm were more frequent among the paroxetine users than the placebo group.10

The controversy over the safety and efficacy of SSRIs in childhood and adolescent depression increases with the addition of unpublished data. Whittington, Kendall, Fonagy and Cottrell, et al bring this to light in their meta-analysis of data from randomized controlled trials
that evaluated an SSRI versus placebo in participants aged 5-18 years. Studies included in the meta-analysis were either published in peer-reviewed journals or were unpublished and included in a review by the Committee on Safety of Medicines. The findings consistently suggest that fluoxetine has a favorable risk-benefit profile. Addition of unpublished data to published data from trials of paroxetine indicates that risks outweigh benefits. Addition of unpublished data of citalopram suggests unfavorable risk-benefit profiles.

Research into the safety and effectiveness of using SSRIs to treat MDD in adolescents is limited by the fact that the studies done have been relatively short term, eight to twelve weeks for most. High placebo response rates, on average 33% for fluoxetine alone, were reported in all of the reviewed studies. This raises the question of whether or not simply acknowledging the illness and initiating treatment has enough power to cause improvement in depressive symptoms in some individuals. The presumption that large trials are inherently better than smaller ones may also be questioned, as a clinically significant response rate should be evident even in small trials. This presumption has been demonstrated in the various size trials of fluoxetine, but other SSRIs have not been studied enough to show this same consistency.

Implications for Practice

The most compelling evidence for effectiveness of SSRIs in treating adolescent depressions exists with fluoxetine (Prozac). Fluoxetine is currently the only SSRI approved for treatment of MDD in adolescents. Adolescents with MDD may not respond well to fluoxetine and in some instances, may even have a worsening of the depression.

In this case, and when referral to a mental health specialist is not available, a trial of another SSRI may prove helpful. In clinical practice, practitioners can and do prescribe SSRI's other than fluoxetine to adolescents with MDD. This underscores the fact that clinical experience
plays an important role in the decisions made in practice. As with any off-label use of medication, thorough documentation with rationales must be performed. The decision to prescribe a given medication should be based on a careful consideration of the potential risks and benefits in the context of the individual patient.

Prior to making a diagnosis of MDD, it is essential to rule out organic causes of depression such as anemia, hypothyroidism, mononucleosis or other diseases. In addition to ruling out organic diseases, it is important to differentiate other mental health disorders from depression. The differential diagnosis of MDD includes bipolar disorder, somatoform disorder, anxiety, and attention deficit hyperactivity disorder. Hamrin and Pachler state that 40% to 70% of children and adolescents with depression have comorbid psychiatric disorders, most frequently anxiety disorder, disruptive behavior disorder, attention-deficit/hyperactivity disorder, or substance abuse. This high incidence of comorbidities must not be lightly taken. In the previously described trials it is important to note that subjects were carefully screened and those with psychiatric co-morbidities were excluded as were those with eating disorders, problems with substance abuse and those considered at risk for suicide. A patient that is determined to be at risk for suicide must immediately be referred to an emergency mental health setting.

Use of a depression inventory tool such as Beck’s Depression Inventory (BDI) or CDRS-R should be used not only to aide with diagnosis and documentation but can also be re-administered after initiation of therapy to help to evaluate efficacy of treatment. The BDI is commonly used in primary care as it is easy to administer and can be quickly scored.

Nurse practitioners place a very high value on patient education and stand on the front lines for delivering the teaching necessary to help patients and families be aware potential problems to watch for. This education should include the following:
• Discussing the potential risks and benefits of SSRI medications.

• Reviewing the risks of not treating depression in adolescents including longer episodes of depression and higher rates of recurrence.

• Discussing the risk of lack of response or even worsening of depression with the potential for suicidal ideation. Discussing that the risk of suicidal ideation is real with or without antidepressants and this has to be considered.

• Emphasizing the importance of frequent follow up in the first couple months of treatment with SSRIs. Observing for clinical worsening, suicidality and unusual changes in behavior should be done weekly during the first four weeks of treatment and then every other week for the next four weeks and again at twelve weeks, and as clinically indicated.13

• Informing the patient and family of the warning signs that indicate a worsening of the patient’s condition and/or suicidal ideation.

• Discussing the importance of taking the medication as prescribed and the potential impact that the use of other substances, such as alcohol, illicit drugs or medications, may have.

Research to explain the reason behind why fluoxetine clinical trials alone showed efficacy for treatment of MDD in adolescents should be initiated. Was this difference due to the pharmacological differences or the differences in study designs? Research into the safety of long-term use has not been done and is needed. Further research into prescribing practices of clinicians and the outcomes of these practices is warranted.
Conclusion

The importance of knowing how best to treat adolescents with depression in primary care settings cannot be overemphasized. Ideally, psychotherapy is the first line treatment but all too often, access is limited. Some counseling can be done in routine office visits but limited time and knowledge can make this prohibitive. It is acknowledged that NPs in busy practices have a challenge treating these patients. Initiation of pharmacotherapy with SSRIs is within the scope of the NP but specific guidelines for pharmacological treatment of adolescents with MDD in primary care have not been published. Paramount to safe treatment with these medications is communication, education, and close follow up with the patient and family along with close collaboration with mental health specialists. An advantage that NPs have is they view patient education as a priority in care, which is an invaluable asset when treating this population of patients.

Continuing education about counseling techniques that can be used in primary care, as well as updates on the use of psychotropic medications help to instill confidence in caring for this population. Continuing education activities can be found online at www.medscape.com/cmecenter.directory/nurses. A search for specific conferences available can be made at www.conferenceseek.com.

It is encouraging to note that in July 2004, a committee consisting of family medicine providers, pediatric providers and psychiatric providers convened at Columbia University to formulate, through expert opinion and synthesis of available research, Guidelines for Adolescent Depression in Primary Care (GLAD-PC). These guidelines, although desperately needed, have yet to be published but will hopefully be available soon to provide for better and more consistent treatment of this illness by primary care providers.
References


