DEPRESSION IN ADOLESCENTS: CURRENT TREATMENTS, SUICIDALITY AND EVALUATION OF NOVEL TREATMENT STRATEGIES

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Abstract

Multiple studies have examined the age of onset of major depression, indicating it is most frequent in adolescence and young adulthood. In this context, the offspring of depressed parents have a 2 to 4 time increased risk for depression compared with children of non-depressed parents.

Treatment for depression in adolescents can be divided into psychosocial, psychopharmacologic, somatic and combined psychosocial-psychopharmacologic, psychosocial-psychosomatic and psychopharmacologic-psychosomatic.

Depression in the children and adolescent population has been an area of research for over 20 years. Among novel therapeutic strategies, transcranial magnetic stimulation (TMS) has demonstrated the most favorable side effect profile. Until this time there are no published suicide attempts associated with this treatment and it may offer an option that is not associated with stigma of electroconvulsive therapy (ECT) or medications. Further research may provide more access to this therapy and hope to children, adolescents with depression and their families.

KEY WORDS: Depression, adolescents, novel treatment strategies.

Introduction

For many years depression was perceived as an adult disorder. The first reports describing youths with symptoms similar to depression, were described in the 17th century. The first time the National Institutes of Mental Health (NIMH) began to consider the issue in this age group was in 1975 when it organized a meeting to talk about the incidence and diagnosis of depression among children and adolescents. The results of this meeting clarified the diagnosis and the presence of depression in the child and adolescent population. (1). Since then, multiple studies have examined the age of onset of major depression, indicating it is most frequent in adolescence and young adulthood. While pre-pubesent onset is less common, it can occur. In this context, the offspring of depressed parents have a 2 to 4 times increased risk for depression compared with that of children of non-depressed parents. The most comprehensive epidemiologic data in adults comes from the National Comorbidity Survey (6), a nationally representative sample of over 8000 individuals from US households (ages 15 to 54) (6). While only 600 individuals from this sample were under age 18, the rates in this sample are consistent with other published data in adolescents. They found that the lifetime prevalence for major depressive disorder (MDD) in 15- to 18-year-olds was about 14%. An additional 11% were estimated to have a lifelong prevalence of minor depression, with higher rates among females than males. In support of this data, a more recent study from student health services on college campuses noted a marked increase in the requests for counseling for depression over the last decade. The authors also reported suicide as the second-leading cause of death among students (7). Adolescent depression can be chronic, recurrent, and serious. Symptoms of MDD in adolescents are similar to those in adults, and rates among females are higher (i.e., a 2-fold risk). There is also a high comorbidity with anxiety disorders, substance abuse, suicidal behaviors, antisocial behavior and educational disability (2, 3). Depression in children differs from depression in adolescents in that it occurs more frequently in males, is mood reactive with high levels of irritability and dysphoria, and has a high comorbidity with destructive behavioral disorders (4,5).

Current Treatment Strategies

Treatment for depression in adolescents can be divided into psychosocial, psychopharmacologic, somatic and combined psychosocial-psychopharmacologic, psychosocial-psychosomatic and psychopharmacologic-psychosomatic.

Psychosocial Treatment Strategies

The majority of psychosocial treatment studies focus on intervention trials with cognitive behavior therapy (CBT). This approach appears to be more effective than no treatment, wait list controls, or placebo controls in this age group. There is also evidence that CBT produced better results than alternate active treatments (8,9). While these results are promising, many patients continue to clinically have significant levels of depression following CBT, with the majority experiencing at least one recurrence of depression in the two years following treatment termination. As a result, 30% to 50% seek additional services following an acute trial with CBT (10). Much less is known about the efficacy of other forms of psychotherapy, such as interpersonal or family therapy.

Psychopharmacological Treatments

There are a limited number of blinded, randomized, controlled trials with psychopharmacological agents for depression in the child and adolescent population. To date, the only medications that have demonstrated safety and efficacy in double-blind, placebo-controlled trials for children and adolescents with MDD are the selective serotonin reuptake inhibitors (SSRIs). A single-site, 8-week, placebo-controlled trial reported by Emslie et al. (11), with fluoxetine (20 mg/day) was the first well documented SSRI reported to be effective. In addition, a multi-center study of 219 outpatient youths with MDD reported significantly greater improvement in depression as assessed by the Children's Depression Rating Scale-Revised (CDRS-R) with fluoxetine (20 mg) compared to placebo. Further, 52% of the fluoxetine group was rated much or very much clinically improved compared to 37% of the placebo group (12). In 2001, Keller et. al. reported paroxetine was well tolerated and effective for major depression in a double blind, placebo-controlled study of 275 adolescents. New data presented on June 19, 2003, by the Food and Drug Administration (FDA) led to the recommendation that paroxetine is not be used in children and adolescents under the age of 18 due to reports of a possible increased risk of suicidal ideation and suicide attempts.

Suicidality and SSRIs

Suicide is the third leading cause of death in adolescents (10-14 years) in United States and the leading cause of death in this age group in countries such as China, Sweden, Ireland, Australia and New Zealand (13,14,15).

Since 2003, concerns have been raised about the safety of the antidepressants for children and adolescents. This was based on unpublished data from studies linking the use of SSRIs to suicidal ideation and self-harm behaviors. In late 2003, these reports led the British drug regulatory agency to ban the use of all SSRIs except fluoxetine in treating depression among youth under the age of 18 (16). In 2004, the FDA reviewed 33 clinical trials involving nine different antidepressants used in over 4000 children and adolescents. The results of this analysis were presented in September 2004 and suggested that these medications increased the risk of suicidal thinking and behavior in this age group (17). Specifically, 4% of all youth taking medication reported suicidal thoughts and/or potentially dangerous behavior, compared to 2% of those taking placebo. On October 15, 2004, the FDA directed pharmaceutical companies to label all antidepressants distributed in the US with a black box warning, even though their analysis investigated only nine specific drugs. The warning states that the increased risk of suicidal thinking and/or behavior occurs in a small proportion of youth and is most likely to occur during the early phases of treatment. Although the FDA did not prohibit the use of antidepressants for children and adolescents, it called upon physicians and parents to closely monitor youth taking these medications for a worsening of depression or unusual changes in behavior. While the rate of completed suicide has been decreasing in USA from the late 1980s to 2003, it began increasing in 2004 (see Figure 1).

Epidemiological studies are trying to explain the relationship between the increase in number of SSRI prescriptions and decrease in completed suicide rates. For example Gibbons and colleagues reported on the relationship between antidepressant prescription rates and the rate of early adolescent suicide. The authors concluded that more SSRI prescriptions are associated with lower suicide rates in children and that these may reflect antidepressant efficacy. Preliminary results of a large cohort study examining the link between antidepressants and suicide in actively suicidal patients were recently reported by Dr. Jari Tiihonen of the University of Kuopio (Finland). The study suggests that the discrepancy between randomized clinical trials (showing an increase in suicidal ideation and attempts) and observational studies (showing a decrease in completed suicides) is due to antidepressant use increasing nonfatal suicidal behavior but decreasing fatal suicidal behavior. The study not only explains this discrepancy but also suggests a rational terminology for suicide research.

Cognitive Behavior Therapy and Antidepressants

The Treatment of Adolescents with Depression Study (TADS) sponsored by the National Institutes of Mental Health is the largest multicenter study to evaluate the effectiveness of four different treatment strategies for adolescents with major depressive disorder. This was a randomized, controlled trial conducted at 13 US academic centers between 2000 and 2003. The results of this study indicate that combined treatment with CBT and fluoxetine were superior to CBT or fluoxetine used alone or placebo. Placebo and fluoxetine alone were administered in a double-blind design while CBT alone and CBT with fluoxetine were administered

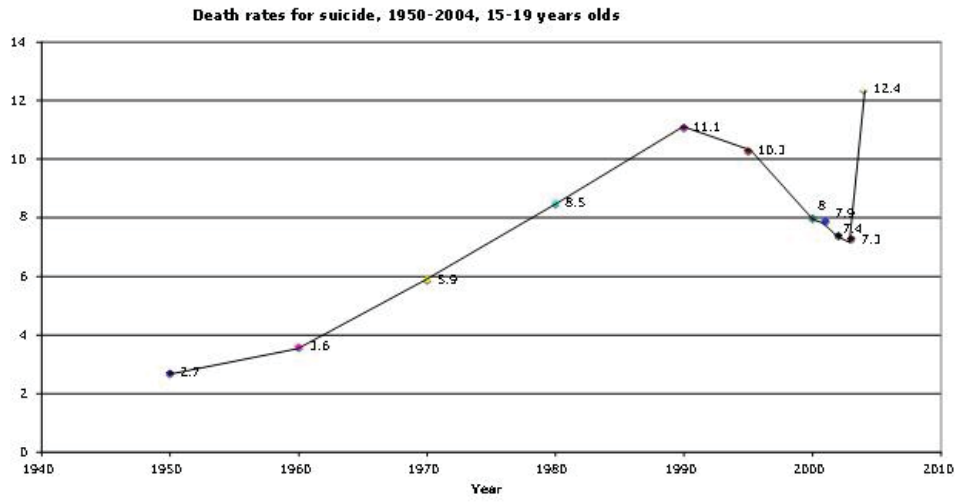

FIGURE 1. Death rates of suicide from 1950 to 2004, 15-19 years old

in an unblinded fashion. The TADS investigators reported that younger and less severely impaired adolescents were more likely to respond to acute treatment than older, more impaired or multiply comorbid adolescents. Overall, the combination of fluoxetine and CBT was effective in improving functioning, global health, and quality-of-life in depressed adolescents (19,20,21).

Electroconvulsive therapy

Multiple studies describe the effects of electroconvulsive therapy (ECT) in adults. Despite the fact that its mechanism of action remains unclear, we have many psychiatric disorders that are well established indicators for ECT (e.g., major depression with psychotic symptoms, bipolar disorder, schizophrenia and catatonia). ECT is associated with multiple adverse effects. The mortality rate with ECT is estimated at 0.01-0.03% per patient (i.e., 1-3 per 10,000), with the majority of deaths due to cardiovascular complications. Consequently, patients with coronary artery disease, hypertension, vascular aneurysms, and cardiac arrhythmias require special observation and attention. ECT is also associated with post treatment confused states including temporary memory loss; a high cost; limited availability; and substantial stigma. This has frequently caused reluctance on the part of patients or their families to consent to this treatment (22, 23 , 24, 25). While ECT can be effective for severe depression in children and adolescents when other measures fail (26), data concerning its safety and efficacy in this population are limited. For example, one trial involving 16 adolescents who received ECT for treatment-resistant bipolar disorder reported it was effective, well tolerated, and cost efficient (26). In another report, adolescents given ECT for severe bipolar disorder did not demonstrate long-term cognitive impairment (27). The American Psychiatric Association (APA) has published specific guidelines for obtaining consent for ECT in this age group . Thus, before referring children for ECT, a psychiatrist experienced in treating this population and not otherwise involved with the patient should agree with the recommendation for ECT, which is usually considered when other treatments have failed.

Alternative Treatments

While CBT is effective, it is associated with a high rate of relapse. Furthermore, antidepressant medication use may be reduced by the new FDA restrictions. Thus, it is important to look for other alternative treatment approaches. While the literature on therapeutic neuromodulators in adults is encouraging, data in the child and adolescent population are very limited. Bright light therapy (BLT), vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) are potential alternative strategies. While TMS was originally introduced as a neuropsychological probe (28), it has emerged as a promising treatment for depression. TMS produces a localized, alternating magnetic pulse that induces neuronal depolarization in a small section of the cortex below stimulation coil placement. It can be delivered as multiple stimulations in a rapid fashion over a brief period of time, referred to as repetitive TMS (rTMS) (29). rTMS has demonstrated a favorable safety and tolerability profile. Numerous reviews and meta-analyses indicate that rTMS may have clinically important antidepressant properties (29, 30, 31). A large multi-center, sham-controlled trial was recently completed (O'Reandon et al in press), and another multi-center trial funded by NIMH is in progress. The first study demonstrated favorable efficacy, safety, and tolerability profiles, for real sham TMS. Decrease in depressive symptoms with rTMS has also been reported in depressed patients referred for ECT due to severity of their symptoms or unsatisfactory benefit from medication trials (31,32,33). Because TMS appears to be a safe and efficient treatment in adult depression, it is important to explore its potential in a child and adolescent population. Hirshberg and colleagues (35) reported that the number of published cases involving rTMS in the adolescent population is small. They suggested that rTMS may be considered for treatment of bipolar and unipolar disorder as well as schizophrenia in adolescents. They cautioned, however, that until controlled data are available, clinicians should limit this procedure to individuals who have had multiple medication trials with insufficient efficacy or intolerable side effects. In this context, preliminary results of an early trial indicated that five of the seven youth with MDD benefited from TMS and only one reported minimal side effects (39). The same study acknowledged that TMS was still experimental and that its safety in children and adolescents should be systematically evaluated before conducting larger studies in this population. Another review presented data from 48 reports involving a total of 1034 children. Thirty-five of the studies used single pulse TMS (980 children), 3 studies used paired TMS (20 children), and 7 studies used rTMS (34 children). Three studies used both single pulsed and repetitive TMS, but the number of subjects involved in these studies was not reported. Of note, no seizures were reported in patients who underwent single pulse, paired

pulse, or repetitive (low and high frequency) TMS. Further, these findings are consistent with those reported by Gilbert et al. (36,37) in 304 children who experienced no major adverse effects or seizure episodes with rTMS. Due to the limited safety and efficacy data for younger children, some have suggested that rTMS should only be used for adolescents who have refractory depression or epilepsy (38). Regarding safety, rTMS appears to carry similar risks when administered as a single, paired, or repetitive pulse stimulation in adult studies. Thus, headaches, scalp pain, and a small risk of seizures are all described. To our knowledge, while no safety studies of rTMS have included children or adolescents, caution is warranted in regulating the dosing of rTMS in children because of their lower seizure thresholds (35).

Conclusion

Depression in the children and adolescent population has been an area of research for over 20 years. Despite numerous studies, this topic continues to generate many unanswered questions pertaining to diagnosis, treatment approach, suicide and medications, treatment outcome, treatment length and maintenance strategies. These questions raise the issue of novel or alternative treatments including rTMS. Thus far, TMS has demonstrated favorable side effect profile, there are no published suicide attempts associated with this treatment and it may offer an option that is not associated with stigma of ECT or medications. It is time to conduct research with unconventional treatments. Such research should provide information regarding safety, feasibility and effectiveness of alternate treatments. We believe that such research may provide hope to children, adolescents with depression and their families.

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