

Position Statement on Antidepressant Use in Children

Pediatric Pharmacy Advocacy Group

BACKGROUND

Childhood depression and suicide are among the most prevalent of pediatric mood disorders and are among the leading causes of morbidity and mortality in children respectively. Although depression, specifically major depressive disorder (MDD), is the most severe form and has not been consistently linked to suicide, it remains an important contributor associated with suicidal behavior and completed suicide.¹⁻² The estimated prevalence of MDD in children is approximately 2 percent, increasing to as much as 4 to 8 percent in adolescents.³⁻⁴ Since 2000, death attributed to self harm has remained the fourth leading cause of pediatric mortality; third in children above ten years of age. It is exceeded only by unintentional injuries, assault, and malignant neoplasms.⁵⁻¹⁰ Nonetheless, this places suicide secondary to depression as one of the leading medically preventable, or at a minimum, treatable causes of childhood mortality.

MDD is defined by a history of one or more major depressive episodes in the absence of manic, hypomanic, or mixed episodes of mood disturbance meeting DSM-IV criteria. One must display at least 5 of the following symptoms: depressed or irritable mood, markedly diminished interest or pleasure in almost all activities, change in appetite or weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, impaired concentration, indecisiveness, recurring thoughts of death or suicide. In addition, one of the symptoms must be either depressed mood or loss of interest or pleasure present for most of the day, nearly everyday, for ≥ 2 weeks. The symptoms must cause clinically significant distress or impairment marking a change from previous functioning, must not be caused by the direct effects of a substance or medical condition, nor be accounted for by bereavement.¹¹

Treating MDD is complicated due to unclear acceptance as to a standard for treatment of this disorder. The majority of established treatment options can be generalized into one of three categories: cognitive behavioral therapy (CBT, also known as psychosocial intervention), pharmacologic therapy (including, but not exclusive to monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), serotonin selective reuptake inhibitors (SSRIs), mixed reuptake inhibitors, etc.) or combinations of these therapies. With each treatment avenue consideration must be given to the cost, convenience, effectiveness, duration, social impact, risks (i.e side effect and safety) and benefits.

DESCRIPTION OF THE ISSUE

The question of an increased incidence of self-harm and potential suicidal behavior in adolescents treated with paroxetine was first raised in 2003 by the United Kingdom (UK) Committee on Safety of Medicines.¹² Reanalysis of the data from multiple clinical trials indicated higher rates of possible suicide-related events in adolescents treated with several newer antidepressants.¹³ After reviewing the data in February 2004, the U.S. Food and Drug Administration (FDA) advisory committee commissioned a reevaluation and reanalysis of data from all pediatric antidepressant trials. That meta-analysis found a significantly higher risk of suicidal behavior in adolescents treated with 10 antidepressants ([bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone (discontinued from the US & European markets), paroxetine, sertraline, escitalopram, and venlafaxine] than in those who received placebo.

Subsequently, in March of 2004, the FDA issued a public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with these medications.¹⁴ The March 2004 advisory recommended close observation for the emergence of suicidality in all patients treated with antidepressants, especially at the time of treatment initiation or dose increase. This warning prompted reports in the medical^{15, 16} and mainstream media^{17, 18} leading to questions on whether antidepressants could worsen depression or increase the risk of suicide in adults as well as pediatric patients. In October, 2004, the FDA Advisory committee required the addition of a black box warning on antidepressants regarding the risk of prescribing them in pediatric patients. Following the FDA's warning, the debate over the standard treatment of pediatric depression, especially MDD, only intensified and has been accompanied by an outpouring of literature.¹⁹⁻³⁹

RATIONALE

In August 2004 the Treatment for Adolescents with Depression Study (TADS), a landmark randomized, placebo controlled trial (n = 439) was published.²² The findings from this 12 week trial suggested an elevated risk for harm-related adverse events (suicide related or non-related, to self or others) in SSRI-treated groups compared the to non-SSRI treated groups; however, none

of the odds ratios for suicide related events were statistically significant. This trial suffered from limitations such as no CBT in the placebo group, no standardization of the CBT, and failure to blind fluoxetine therapy in the combination group. Further criticisms of the study included not stratifying subjects based on prior history of suicidal ideation, no consideration of the resource allocation and expense for CBT, and inconsistent results of monotherapy to placebo comparisons. Based on poor design, the results of the study have lead to further questions rather than providing insight into the possible relationship(s) between antidepressant use and associated self-harm / suicidality in children.²⁴⁻²⁸

A number of subsequent studies have been published analyzing the patterns of antidepressant use in children and adolescents including a long term follow up study of TADS carried out to 36 weeks.⁴⁰ These studies further evaluate links to suicidality, characterize prescribing habits in clinical practice, and measure the effects and tolerability of antidepressant treatments.^{31-32,34-40} One important study from the United Kingdom described an important and steady increase of antidepressant use in pediatric patients from 1992 to 2003.²⁹ Evidence of increased risk of non-fatal self harm was found only among those 18 or younger who used SSRI's as compared with TCA users. There were also no differences between individual TCAs, but among SSRIs, paroxetine was found to carry the greatest risk.³⁰ A four year nationwide Danish study of all persons 10-17 years of age treated with antidepressant agents could not demonstrate an association between SSRI treatment and completed suicide.³¹ More recently in April 2007, a meta-analysis designed to evaluate the clinical relationship between suicide and antidepressant treatment concluded that relative to placebo, antidepressants were efficacious for pediatric patients with MDD, and that the benefits outweighed the risks from suicidal ideation and suicide attempt across all indications.³²

The published data suggests a common theme of increased suicidality and pharmacologic treatment in the setting of depression and MDD. Therefore, a prominent question in the entire debate is, why or what is the possible mechanism behind this phenomenon? There certainly are no clear answers, but there are a few theories including inadequate antidepressant dosing, unrecognized co-morbidities at the initiation of therapy, activating adverse effects, and nonadherence to drug therapy.³³

CONCLUSION

Based upon available published data and experience, it is the position of the Pediatric Pharmacy Advocacy Group (PPAG) that antidepressant pharmacotherapy can be an important treatment strategy for pediatric MDD patients. The PPAG recognizes the need for judicious selection of the proper antidepressant agent(s) based upon the individual child's needs and implementing measures that assure optimal antidepressant dosing linked to patient response and tolerance. When deemed appropriate and feasible by the patient's healthcare team, concomitant cognitive behavioral psychosocial intervention is an important component and enhancer of an MDD management program. Until more information is available regarding the true relationship(s), if any, between antidepressant drugs and childhood self-harm/suicidal ideation, all children and adolescents should be closely monitored (for approximately 1 to 2 months) for these and other serious potential adverse outcomes upon initiating antidepressant therapy, whenever dose/therapy adjustments are introduced or during periods of disease aberrations. Of the antidepressant agents currently available in the US, published data support fluoxetine as first line pharmacologic MDD therapy in children and adolescents.²² Other SSRI's, mixed reuptake inhibitors, and tricyclic antidepressants should be considered second, third and last line therapy, respectively. Selection should be based upon prior treatment failure, side effect profile and other precluding factors such as co-morbid diseases, clinically relevant drug interactions, and drug formulations issues..

Childhood and adolescent depression is a complex constellation of psychological, somatic, and social signs, symptoms, and disturbances. There is no definitive treatment for pediatric MDD, but early diagnosis and most importantly, intervention with first line therapies, are imperative in order to strive towards the recovery of children and all those touched by their lives.

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