COMMENTARY

PHARMACOLOGICAL TREATMENT OF MAJOR DEPRESSIVE DISORDER IN CHILDREN AND ADOLESCENTS: THE PAROXETINE CONTROVERSY

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ABSTRACT

Controversy has surrounded the use of the selective serotonin reuptake inhibitor (SSRI) paroxetine in children and adolescents under the age of 18 years. Pending further review, paroxetine treatment for major depressive disorder (MDD) should not be initiated in youth under the age of 18 years. However, in the event that a youth with MDD has responded to paroxetine with good symptom resolution, it would be unwise to discontinue the drug. When discontinuation of paroxetine is desired, it should be undertaken with gradual tapering to prevent the emergence of rebound anxiety. As the evidence for efficacy in social anxiety disorder outweighs the evidence for use in MDD it may be appropriate to use paroxetine for social anxiety disorder in this age group with careful monitoring for the presence of suicidal ideation.

Key Words: paroxetine, major depressive disorder, social anxiety disorder

The recent controversy over the use of the serotonin reuptake inhibitor paroxetine specifically and antidepressant agents more generally, in children and adolescents under the age of 18 years, has been unsettling for practitioners and consumers alike.

The overall evidence for the use of selective serotonin reuptake inhibitors (SSRIs) in adults with major depressive disorder (MDD) has suggested that the balance of risks and benefits for these agents is favourable. Earlier concerns were raised about a possible association between SSRIs and suicidal ideation and attempts in adults.[1] However, a scientific review, as well as United States congressional hearings, eventually established that there was no causal link.[2]

In the wake of concerns raised about the issue in children and adolescents, this association may well be revisited. In children and adolescents, the evidence for the efficacy of the SSRIs in the treatment of major depressive disorder has been more modest and there is a tendency toward higher placebo response rates in pediatric trials than those seen in adult trials. Nevertheless, on the basis of two positive randomized control trials[3, 4] fluoxetine has received U.S. Food & Drug Administration (FDA) labeling as safe and effective for the treatment of MDD in children and adolescents.

Two additional double blind placebo-controlled studies of SSRIs in youth have been reported. The most recent of these is a study by Wagner et al[5] describing two randomized controlled trials using sertraline in children and adolescents aged 6 – 17 years with MDD with a 10% difference favouring drug over placebo.

The remaining study by Kellar et al[6] compared 275 outpatient youth aged 12 – 18 years with MDD who took either paroxetine, imipramine or placebo for 8 weeks in a double-blind placebo-controlled randomized trial. The response rate for paroxetine was

63% compared with 50% for imipramine and 46% for placebo. Only one of two prospectively defined primary outcome measures reached statistical significance.

On the other hand, a double-blind placebo-controlled trial of 319 outpatients aged 8 – 17 years with social anxiety disorder found response rates of 77.6% for paroxetine compared to 38.3% for placebo ($p < .001$) and a double-blind placebo-controlled trial of 203 outpatients aged 7 to 17 years with Obsessive Compulsive Disorder (OCD) found response rates to paroxetine of 64.9% versus 41.2% in the placebo group.[7] These latter two studies strongly suggest considerably more robust efficacy for paroxetine in childhood anxiety disorders when compared with the efficacy described for major depressive disorder.

Another issue that has been raised in the interpretation of research study data in childhood depression is the publication bias that results from the failure to publish negative placebo-control trials[8] and the selection bias in some of the pharmaceutically supported positive trials. In particular, Dr. Jane Garland, in a recent commentary on this issue, points out the weakness for efficacy in the two fluoxetine trials [3, 4] that led to FDA approval questioning whether there was efficacy for fluoxetine over placebo in the absence of comorbid anxiety after a reanalysis of the data in these studies. In addition, in the Kellar study cited above, comprehensive conclusions have been complicated by the fact that data with negative or mixed results were not included in the analyses of the multicentre trial sponsored by Glaxo-Smith-Kline of which Kellar's study was a part.

In June 2003 Professor G. Duff, Chairman of the Committee on Safety of Medicines (CSM) cautioned against the use of paroxetine in children and adolescents under the age of 18 years to treat depressive illness.[9] This followed new data from clinical trials that were received by the Medicines and Healthcare Products Regulatory Agency (MHRA) at the end of May 2003. The sponsoring company, Glaxo-Smith-Kline, submitted this data to have paroxetine approved for the treatment of OCD in children and adolescents rather than for depression.

Evidently the data did not demonstrate efficacy for depressive illness in this age group and showed an increase in the risk for harmful outcomes including episodes of self-harm and suicidal ideation; 3.2% of paroxetine treated subjects demonstrated these adverse effects versus 1.5% in the placebo group. There were no actual suicides.

On June 19, 2003, the FDA posted a "Talk Paper" which indicated that there was a review being undertaken of the use of paroxetine for the treatment of depression in children and adolescents under 18 years of age, citing possible increased risk of suicidal thinking and suicide attempts with the use of this agent for MDD in this age group. FDA cautioned (as had MHRA) against the use of paroxetine in this age group pending a review.[10] Despite the caution, an advisory clearly recommended against the sudden discontinuance of the drug and advised any changes for those taking the drug occur under medical supervision. Following the FDA advisory, a general advisory cautioned physicians regarding the increased risk of suicide in pediatric use of all SSRIs[11] and the Norepinephrine Serotonin Reuptake Inhibitor (NSRI) venlafaxine.[12]

A balanced perspective is required both in terms of general prescription of antidepressant drug therapy for children and adolescents as well as the specific use of paroxetine in youth prior to age 18 years. On the one hand, depression (particularly MDD) is a major contributor to morbidity and mortality in children and adolescents with significant risk for chronicity and recurrence.[13] The mean duration of a major depressive episode in youth aged 6 – 17 years is 7 – 9 months but symptom remission may not occur for 18 – 24 months and there is a 48% to 60% risk for recurrence, in this age group, over a 5-year period.

Suicide is a complication of depression; while the majority of suicide attempts are not lethal, suicide remains the leading cause of death in adolescents. The point prevalence for suicidal ideation in adolescents each year is 20% and 5 – 8% for suicide attempts.[14] It has been suggested that there is an inverse relationship between the use of

antidepressants and suicide rates in youth, particularly males and older adolescents.[15]

On the other hand, there has been a 3- to 5-fold increase in the prescription of antidepressant drug treatment for youth through the 1990's[16] in the United States and there is no reason to suspect a different trend in Canada.

The prevalence for antidepressant drug treatment has been nearly equivalent for 10 – 14-year olds and 15 – 19 year olds with boys younger than 15 years prescribed more of these agents than girls and the reverse for youth over 15 years.

In girls aged 15 – 19 years the pattern approaches what is seen in the adult population with the preponderance of recipients being female and receiving SSRIs related primarily to a diagnosis of depression. In 10 – 14 year old boys, antidepressant drugs are more frequently prescribed for Attention Deficit Hyperactivity Disorder (ADHD) than for depression and primary care providers provide the majority of these prescriptions. Moreover, data from the National Ambulatory Care Survey indicate that more than 30% of physician office visits for youths prescribed a psychotropic drug do not include a psychiatric diagnosis.[17]

In achieving a balance, there is definite utility in the parsimonious use of SSRIs for major depression and anxiety disorders in adolescents. Careful attention must be paid to the accurate diagnosis of MDD or anxiety disorder. Antidepressants must be used in the context of a therapeutic alliance with careful attention to issues of compliance and a commitment to maintain drug therapy over a 6 to 24-month period. The need for close and regular monitoring, once an antidepressant has been prescribed, cannot be overemphasized. Both the SSRIs and the NSRIs may have serious adverse effects including irritability, agitation, insomnia and behavioural disinhibition[18] which may contribute to suicidal thoughts and behaviour.

Regarding the use of paroxetine in youth under the age of 18 years, at this time the evidence for its efficacy in anxiety, particularly social anxiety disorder, outweighs the evidence for its use in MDD. However, in the event that a youth with MDD has responded to paroxetine with good symptom resolution, it would be unwise to discontinue the drug in the face of the recent MHRA and FDA cautions. Pending further review, paroxetine treatment for MDD should not be initiated in youth under the age of 18 years. This does not preclude its use for social anxiety disorder in this age group with careful monitoring for the presence of suicidal ideation. Discontinuation of paroxetine should be undertaken with gradual tapering to prevent the emergence of rebound anxiety.

More generally, there is much work to be done in the area of multicentre clinical trials for the use of antidepressants in MDD in children and adolescents. Study design must include placebo control trials in a naturalistic context with attention to selection biases for patients included in clinical trials as well as systematic evaluation of adverse drug events. Data analysis should be done independently of the sponsoring agency to eliminate potential conflict of interest.

There is a critical need for a comprehensive trial registry in evidence-based medicine with the publication of both positive and negative outcome placebo-control trials. Clinical decisions and recommendations will ultimately depend on full disclosure and a future mandate to obtain full disclosure. In addition, studies that compare treatment outcome for evidence based psychosocial treatments, including Cognitive Behavioural Therapy (CBT) and Interpersonal Psychotherapy (ITP) and drug interventions with combination therapies (CBT or IPT with pharmacotherapy) will help to elucidate the most effective treatments for MDD in youth.

These studies may also shed light on the narrower placebo versus drug response that has characterized the placebo-control trials for adolescent depression compared with the adult population.

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