



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Antidepressant Medications in Children and Adolescents

### Regulatory Status

No antidepressants are approved in Canada for individuals less than 19 years of age. In the United States, fluoxetine is approved for major depressive disorder (MDD) in individuals aged 8 years and older. However, the Product Monograph includes a strong warning about the potential for suicidality and various emotional and behavioral adverse effects.<sup>1</sup> The United Kingdom (UK) regulatory agency has determined that the harm to benefit balance is unfavorable in pediatric MDD for all antidepressants but fluoxetine.<sup>2</sup> Despite this, the UK fluoxetine monograph states that it is “not recommended” for people less than 18 years of age.

### Drug Utilization

In British Columbia, as in other jurisdictions, antidepressants are commonly prescribed to individuals under 19 years of age and these prescriptions have doubled between 1998 and 2003.<sup>3</sup> The main antidepressants being prescribed are the newer ones, selective serotonin reuptake inhibitors (SSRI), serotonin noradrenaline reuptake inhibitors (SNRI) and mirtazapine (see Table). **The growth in prescribing of these drugs is particularly disconcerting in light of reports suggesting that the drugs are not proven effective and are causing serious psychiatric adverse effects in some individuals.**<sup>2,4,5</sup>



follows. Note that a positive trial is one in which the pre-defined primary outcome is statistically significantly better for the drug as compared to the placebo. Of the 15 RCTs only 3 (2 fluoxetine and 1 citalopram) were positive.<sup>2,11</sup>

Six of the 15 RCTs are published, all claiming effectiveness: 2 pooled sertraline trials<sup>12</sup>, one paroxetine trial<sup>13</sup>, two fluoxetine trials<sup>14,15</sup>, and one citalopram trial.<sup>16</sup> However, the claims in 3 published trials (1 paroxetine and 2 sertraline) were not confirmed after independent analysis by the regulatory agencies.<sup>2,11</sup> In the paroxetine trial Keller et al<sup>13</sup> claimed efficacy for paroxetine and not for imipramine as compared to placebo; re-analysis by both the Medicine and Health Care Products Regulatory Agency<sup>2</sup> and the Food and Drug Administration<sup>11</sup> concluded this trial was negative for both antidepressants. The two sertraline trials were reported as positive when pooled together.<sup>12</sup> Upon re-analysis, the trials were shown separately to both be negative.<sup>2,11</sup> The following unpublished placebo controlled trials were negative: 2 paroxetine trials, 2 venlafaxine trials, 2 nefazodone trials, 2 mirtazapine trials and 1 citalopram trial.

In the 3 positive studies, the benefit was limited to a modest improvement in some symptoms, not remission of the disorder.<sup>14-16</sup> The 2 fluoxetine trials<sup>14,15</sup> have also been criticized on re-analysis.<sup>17</sup>

### Evidence of harm

Determination of the true rates of harm is hampered by inconsistent ascertainment, description and reporting of adverse effects. For example, in the published adolescent paroxetine trial<sup>13</sup>, 11/93 patients discontinued paroxetine due to “serious” psychiatric adverse effects, of which the most common was described as “emotional lability.” This was

SSRIs		SNRIs	
Chemical name	Brand name	Chemical name	Brand name
fluoxetine	Prozac	venlafaxine	Effexor
fluvoxamine	Luvox	nefazodone	Serzone
sertraline	Zoloft	<b>Other</b>	
citalopram	Celexa		
paroxetine	Paxil	mirtazapine	Remeron

### Evidence of effectiveness

A Cochrane systematic review of the tricyclic antidepressants (TCA) in children and adolescents shows little or no benefit for TCAs as compared to placebo.<sup>6</sup> Controversy about the SSRIs and SNRIs has arisen because only a selected 6 out of 15 randomized controlled trials (RCTs) studying these agents in child and adolescent depression have been published.<sup>7-11</sup>

Only the regulatory agencies have access to the full data set from the 15 RCTs and their conclusions are as



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then further defined as “suicidal ideation/gestures, conduct problems or hostility, e.g. aggressiveness...” Such responses led 7.5% of the initially mildly depressed outpatients placed on paroxetine to be hospitalized. None of the placebo-treated patients required hospitalization. This finding was dismissed in the discussion. The sertraline trials did not include a side effect checklist in the protocol, yet the medication was described as well-tolerated.<sup>12</sup>

Rates of suicidal ideation and attempts are low in most trials (2-3% with drug; 0-1% with placebo), and hence seldom reach statistical significance in individual trials. However, the direction of change is the opposite of that predicted if the medications are improving depression. Furthermore, observations in clinical trials and case reports from the past 12 years indicate that up to 25% of children placed on various SSRIs experience psychiatric adverse effects such as agitation, disinhibition, aggression, hyperkinesia and emotional lability.<sup>18</sup> **The recent labeling changes by Health Canada and the Food and Drug Administration emphasize these potential psychiatric and behavioral adverse effects in both children and adults.**<sup>4,19</sup>

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#### Summary

The published literature on this topic is an incomplete and inaccurate representation of the totality of evidence. The profession has had a difficult time coming to terms with this fact.<sup>7</sup> When we are guided by meta-analyses carried out on biased datasets, we are operating under the illusion of practicing evidence-based medicine. A recent article has termed this “evidence-biased medicine”.<sup>20</sup>

#### Clinical Implications

The prescription of an antidepressant to a child or adolescent is like an open trial with up to 80% of patients expected to improve. When improvement occurs, it is most likely due to a placebo group response, which includes spontaneous remission, response to supportive care, and other components. **Because of the unfavorable harm to benefit balance for antidepressants in this age group, first-line therapy is multiple supportive interventions: sleep hygiene, exercise, regular dietary patterns, consistent parenting, and practical problem-solving regarding schooling and life stressors.**<sup>21</sup> For those who do not respond, individual or group cognitive behavioral therapy or interpersonal psychotherapy should be arranged, if possible.<sup>21,22</sup> Medications are reserved for add-on therapy when the first two approaches are not working. When an antidepressant is prescribed, the patient must be monitored for signs of deterioration: behavioral and psychiatric changes, including increases in suicidal thinking, as emphasized by the new Health Canada labeling.<sup>4</sup>

This Letter contains an assessment and synthesis of publications up to June 2004. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 50 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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