2008 Position Paper on Using SSRIs in Children and Adolescents

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Introduction

This position statement provides an update on the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in the treatment of Major Depressive Disorder (MDD) and Anxiety Disorders in children and adolescents. This paper is not meant to be a comprehensive review of the treatment of anxiety and depression in young people, but a position paper regarding the role of SSRIs in children and youth. As new information regarding the use of SSRIs in young people has become available, the CACAP has updated its position statement on this topic. The current CACAP position is described below and will continue to be updated as new information pertinent to the clinical use of these compounds becomes available.

Overview of the Evidence

Major Depressive Disorder

At least 16 published and unpublished randomized double-blind, placebo controlled trials (RDBPCTs) in children and adolescents suffering from MDD are now available for review (Bridge et al., 2006; Cheung, Emslie, & Mayes, 2006). Currently, fluoxetine is the only SSRI that has evidence outlining that the benefits outweigh the risks and is approved for use in this population (Emslie et al, 1997; Emslie et al 2002; Whittington et al., 2004; March et al., 2004b).

Interestingly, studies in adult populations have not demonstrated substantial differences in efficacy, tolerability or safety of the different SSRIs. Sufficient research designed to address this issue are not available in children or adolescents. Thus it is difficult to assign class general conclusions from currently available information about specific SSRI medications in youth. Given this situation we recommend that class specific generalizations should not be made and that clinical application of SSRI medications be based on available individual SSRI data.

Available studies pertaining to SSRI medications in young people are of variable quality (Bridge et al., 2006). Some suffer from design, implementation or analytical problems that make results difficult to interpret. Some studies may have failed to demonstrate significant efficacy using primary outcomes but when secondary outcomes are analyzed they suggest significant differentiation from placebo or tricyclic comparators (Keller et al., 2001; Emslie et al., 1997). This means that the majority of trials were unable to demonstrate a measurable difference in the a priori (predefined) main endpoint of the trial. This is often the endpoint utilized to calculate the statistical power of the trial. Substantial variability in placebo rates across different studies (they range from about 30 percent to about 60 percent) may also confound study interpretation (Bridge et al., 2006; Cheung et al., 2006).

These difficulties notwithstanding, available data indicates that fluoxetine, possibly sertraline (Wagner et al., 2003) and citalopram can be considered to have demonstrated efficacy consistent with level 1 evidence for therapeutic effect (Bridge et al., 2006; Wagner et al., 2003; Wagner et al., 2004). If secondary outcome measures are used in the evaluation of paroxetine – one trial can be considered to be positive while two trials, both with substantial methodological difficulties can be considered to be negative. Neither venlafaxine nor mirtazapine have demonstrated potential efficacy in adolescent MDD. No SSRI has consistently demonstrated positive results in prepubertal children. The number needed to treat (NNT) for each SSRI studied has not been well established but literature suggests an approximate number of 10 and may be as low as 4 (for fluoxetine in the TADS trial) (Bridge et al., 2007; March et al., 2004b). This means that

for every 4 – 10 adolescents treated with an SSRI (for approximately 12 weeks) instead of a placebo, 1 extra person will achieve significant symptomatic approval.

Furthermore, while many studies have demonstrated reasonable response rates to treatment, rates of remission have been substantially less (Michael & Crowley, 2002). Additionally, there are relatively few continuation studies available. The TADS continuation data demonstrated no significant loss of efficacy over one year of treatment (March et al., 2007). Data from 36 weeks of treatment in the TADS trial confirmed that 86% of youth given the combination of fluoxetine and cognitive behaviour therapy continued to demonstrate noticeably improved symptoms (March et al., 2007). Furthermore, at 36 weeks, improvements in depressive symptoms were seen in approximately 80% of those given only CBT or fluoxetine (March et al., 2007). These data are consistent with another trial that found no difference in depressive symptoms at 28 weeks for youth given an SSRI and CBT vs. those given an SSRI and usual care (Goodyer et al., 2007).

Published maintenance studies of sufficient design to produce meaningful results are very limited. Recently, Emslie and colleagues randomized 102 children and adolescents (7-18 years old) who had improved depressive symptoms to receive fluoxetine (N=50) or placebo (N=52) in an open label, six month long maintenance trial (Emslie et al., 2008). In this trial, fluoxetine did demonstrate a benefit in preventing a relapse. The NNT was four, meaning that for every four youth (with improved depressive symptoms) given fluoxetine instead of placebo for six months, one extra person will have a relapse prevented (Emslie et al., 2008).

Unfortunately, restrictive entry criteria in clinical trials make it difficult to generalize their results to real-world populations. For example, severe symptoms, comorbidity, and acute suicidality are often exclusion criteria for participation in an RCT. The more favorable results with fluoxetine may be partially attributable to the fact that these trials included a placebo washout and selected more persistently depressed patients resulting in a lower placebo response. Furthermore, there is a trend in some trials for older adolescents to be responding more robustly than children and young adolescents. However, it should also be noted that in the child and adolescent trials, no antidepressant has been shown to be superior to placebo in achieving remission rates or more traditional measures of response used in adult studies (at least 50% reduction in standardized clinician depression rating scale such as HAM-D or the CDRS).

Treatment emergent adverse events have included both physical and emotional/behavioural side effects. Physical side effects include headaches, gastric distress, insomnia/hypersomnia and others (Bezchlibnyk-Butler & Virani, 2007). These are variable in their occurrence and are generally only somewhat elevated over placebo. Emotional/behavioural side effect reported include: hyperactivity; irritability; hostility; disinhibition; emotional lability and self-harm (Bezchlibnyk-Butler & Virani, 2007). These adverse events occur in approximately 10-25% of youth (Bezchlibnyk-Butler & Virani, 2007). Discontinuation rates due to severe side effects also vary greatly across studies (from 0 to 9 percent), again making class specific generalizations difficult.

Suicidal behaviour has also been reported in children and adolescents in case reports and clinical trials (Cheung et al., 2006; Hammad, 2004; Hammad, Laughren, & Racoosin, 2006). The overall statistically significant ($p<0.05$) relative risk increase is 1.66 in MDD trials and 1.95 when all trials are pooled. This implies that approximately 2 people out of every 100 treated with an SSRI will have a "suicide-related" event (Hammad, 2004). There have been variable methods of reporting and recording "suicide-related" events. These have included: short term suicidal ideation; persistent suicidal ideation; self-harm without suicide intent; self-harm with suicide intent – all of which have been identified as "suicide-related" events. This variability of definitions makes it difficult to evaluate the incidence of actual suicide directed behaviours. There were no reported suicides in the RCT database.

Best available data from controlled trials and health record databases alike show that SSRI treatment significantly decreases suicidal ideation and suicide attempts in young people (Cheung et al., 2006; March et al., 2004b; Mosholder, 2008; Kutcher & Gardner, 2008). Population studies demonstrate an inverse cor-

relation between antidepressant use and youth suicide (Olfson et al., 2003; Gibbons et al., 2006). In addition, postmortem studies have not demonstrated a relationship between SSRI use and youth suicide (Leon et al., 2006; Isacsson, Holmgren, & Ahlner, 2005). Given all available data to date it appears far more likely that SSRI use decreases suicide rates rather than increases them. At the individual patient level however, SSRI use can be associated with emotional/behavioral side effects that require appropriate clinical management.

The potential small to moderate effect size for antidepressants for children and adolescents must also be evaluated in the context of the limited evidence base for other treatments. Systematic reviews have identified some evidence to support the efficacy of psychosocial treatments such as cognitive-behavioural therapy (CBT) or interpersonal therapy (IPT) for MDD; however, the effect size is small to moderate, and most of these findings are based on smaller, open or not-well-controlled trials (Michael & Crowley, 2002; Compton et al., 2004). The combination of CBT and fluoxetine may be superior to fluoxetine alone according to one controlled study (March et al., 2004b) but not in a natural clinical state study (Goodyer et al., 2007).

The bottom line: The risk benefit balance for fluoxetine in child and youth depression is favourable, while it less clear for most other SSRIs, except in older adolescents. Deliberate monitoring for efficacy and adverse effects is critically important.

Anxiety Disorders

There have been at least 12 published and unpublished well designed RDBPCTs in children and adolescents suffering from various anxiety disorders (Bridge et al., 2007). There have been six trials in OCD, five in mixed anxiety disorders and one trial in social phobia (Bridge et al., 2007). A summary of these trials indicates that the benefits outweigh the risk for most SSRIs (*fluoxetine, fluvoxamine, sertraline and paroxetine*), while there is insufficient data for the remaining SSRIs *(citalopram, escitalopram)* and data is negative for venlafaxine. The NNT for most SSRIs over placebo, with the endpoint being reduction in anxiety symptoms, can be estimated as being between three – six (Bridge et al., 2007). The moderate to large effect size is attributable both to the fact that placebo response appears to be lower in anxiety than depression for reasons that are not well understood, and the response to medication is also more robust.

As one would expect, the typical emotional and behavioral adverse effects describe above were also seen in the various anxiety disorder trials, with motor hyperactivity being the most common cause of discontinuation (Bezchlibnyk-Butler & Virani, 2007). However, the signal for increased suicidal thoughts and behaviours is less pronounced and more variable relative to the trials for depression (Bridge et al., 2007; Hammad et al., 2006). There appears to be 1 excess case of suicidal ideation or self-harm per 100 treated compared to placebo treated patients (Hammad et al., 2006).

When considering alternatives to pharmacotherapy, it is notable that CBT also has a larger effect size for anxiety disorders than for depression (Compton et al., 2004). Where head to head trials have been carried out, such as in OCD, medication and CBT are of similar efficacy overall with the combination clearly being more beneficial (March et al., 2004a).

The bottom line: The risk benefit balance for at least 3 SSRIs is favourable in anxiety disorders, and it is likely favorable for other SSRIs in the short term. Appropriate monitoring of SSRI treatment is indicated.

A Clinician's Perspective

When faced with a child or adolescent with mild depression or anxiety symptoms the most appropriate initial step would be supportive treatment including psychoeducation, sleep hygiene, practical problem solving including self-help materials, as well as family and school interventions if indicated, while conducting an extended baseline evaluation for persistence of depressive symptoms and functional assessment over several weeks. It is appropriate for clinicians to prescribe an antidepressant for children and adolescents experiencing persistent moderate to severe depressive or anxiety symptoms with clear evidence of functional impairment in addition to supportive treatment or a course of psychotherapy (Cheung et al., 2007).

As mentioned above, the likelihood of benefiting from an SSRI is greater for anxiety disorders than depressive disorders. It should be noted that at least 25% of patients with MDD will have a comorbid anxiety disorder, which would strengthen the indication in those patients.

Based on a compilation of the clinical trials, the NNT is about 10 for treating depression, six for treating OCD and three for treating other anxiety disorders. This can be compared with a number needed to harm (NNH) of 50 for a suicide related event and NNH of about 4-10 for any short or long term side effect (Bridge et al., 2007; Hammad, 2004; Bezchlibnyk-Butler & Virani, 2007).

When initiating an antidepressant in a child or adolescent, clinicians should have a realistic discussion with patients and their caregivers regarding the potential benefits and risks of treatment, including specific target symptoms, and potential harms including emotional and behavioral adverse effects. This discussion as well as a review of treatment alternatives (such as CBT and the evidence for its efficacy, safety and tolerability) should be documented. Given that the expected benefits from antidepressants are delayed and that the approximately half of depressed patients respond to nonspecific or placebo treatments, clinicians rarely need to prescribe an antidepressant on the first visit. Whether or not medication is prescribed, careful follow-up is indicated, and if medication is prescribed, telephone contact regarding any potential concerns should be encouraged, and the patient reevaluated within a week to 10 days.

Below is a suggested (abbreviated) approach to initiating and monitoring antidepressants in

Steps	Brief summary	Explanation
1.	Do no harm.	Do a proper risk benefit relationship analysis of the situation. Fully discuss the risks and benefits with your patient/family.
2.	Confirm diagnosis and severity of condition.	The diagnostic criteria should be clearly met and there be objective data of functional impairment. Medications should be reserved for the treatment of moderate to severe conditions. Also check for other potential causes of the depressive presentation (e.g., substance abuse, prodromal psychotic state).
3.	Risks for antidepressant adverse effects?	Check for signs and symptoms of that may imply an increased risk of adverse effects or switch to mania. For example, anxiety symptoms (especially panic), impulsivity/restlessness, agitation, history of mania/hypomania, and potential drug interactions.
4.	Suicidal ideation at baseline?	While measuring symptoms of depression at baseline, pay special attention to suicidality and document it.
5.	Open discussion.	Provide comprehensive information about the illness and the various treatment options to the patient and family. Appropriate literature should be available in your office and you should have a list of good websites to which you can direct their attention. Some useful sources of information are listed below.
6.	Starting an antidepressant.	Provide the patient and family with a detailed account of the possible adverse effects (both behavioral and somatic) and the expected timelines to improvement and document your discussion.
7.	Start low and go slow.	Consider a low test dose and ask the youth or their caregiver to contact you if they notice a problem in the first few days. Since starting an antidepressant is rarely an emergent situation and the time it takes to see a response is several weeks, you only need to increase the dose slowly (e.g., once a week until the expected minimally effective dose is reached). Were possible, wait the required 6-8 weeks to determine efficacy.
8.	Follow up.	See the patient weekly (where possible) for the first few weeks and allow for telephone check in when ever the dose is changed. Always ask about and document any adverse effects (use a monitoring form if possible).
9.	Placebo effect.	Take advantage of the placebo response (found to be high in most adolescent depression trials). That is, invoke a similar approach to patient care as done in studies including frequent face–to–face contact early in the course of therapy, the development of a trusting and supportive relationship, efforts to measure response objectively and subjectively, and careful elicitation of side effects, overall tolerance, ongoing concerns, and satisfaction with treatment.

children and adolescents (for more details, please see Kutcher, Gardner, & Virani, 2004).

Conclusion

SSRI treatments for young people with MDD and anxiety disorders are neither a panacea nor a contraindication. The best available evidence suggests that fluoxetine may be the medication of choice for use in both MDD and anxiety disorders. In most situations drugs such as venlafaxine and paroxetine would rarely be recommended and would not be used as first line treatments.

When properly applied and monitored, medication treatment may be of substantial benefit to some individuals. Initiation of antidepressant medications should be reserved for those who are moderately to severely depressed and requires careful monitoring. Both patients and caregivers need to be properly informed about both the potential for benefits and risks. We strongly suggest that medications should not be prescribed outside of a comprehensive treatment approach that includes supportive, problem-focused psychotherapeutic interventions, assessment and monitoring of suicide risk and education about the disorder and its treatment.

Information and practical suggestions regarding this approach and information for patients and caregivers can be found at one of the following websites:

- www.bcchildrens.ca/psychmeds
- www.nami.org
- www.teenmentalhealth.org
- www.cmha.ca/highschool/english.htm
- Guidelines for Antidepressant Depression in Primary Care (GLAD-PC) (Leon et al., 2006) available at: www.glad-pc.org/documents/GLAD-PCToolkit.pdf

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