POSITION PAPER

Update on the Use of SSRIs and SNRIs with Children and Adolescents in Clinical Practice

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Background

As concerns about the use of antidepressants in children and adolescents arose in 2003, there was uncertainty about the safety and efficacy of these medications in this patient population. To help clinicians better understand the available evidence, we published a position paper in 2008 on behalf of CACAP. This position statement provides an update to our earlier position paper on the use of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) in the treatment of Major Depressive Disorder (MDD) and Anxiety Disorders in children and adolescents. It is not intended to be a comprehensive review of the treatment options for anxiety and depression in children and adolescents. We will endeavor to update this position paper as new relevant information pertinent to the clinical use of these medications in this patient population becomes available. In addition to a review of new trials published from up to mid-2015, the following update was supported by a requested independent systematic review of research on safety and efficacy by the Canadian Agency for Drugs and Technology in Health (CADTH, 2015).

Overview of the Evidence

Major Depressive Disorder

Over 20 published and unpublished randomized double-blind, placebo controlled trials (RCTs) of SSRIs in children and adolescents suffering from MDD are now available for review (Cheung, Emslie, & Mayes, 2006; Bridge et al., 2007; Tsapakis, Soldani, Tondo, & Baldessarini, 2008; CADTH, 2015). Currently, fluoxetine has the most robust evidence demonstrating that benefits outweigh the risks for children and adolescents aged 8-18 (Emslie et al., 1997; Emslie et al., 2002; Whittington et al., 2004; March et al., 2004b), and is approved for use in this population by the US Food and Drug Administration (FDA). Health Canada has not approved its use in children and adolescents. In 2009, the FDA also approved escitalopram for treatment of adolescent depression; however, this approval was not consistent with the standard of two positive RCTs. Only one RCT (Emslie, Ventura, Korotzer & Tourkodimitris, 2009) and a prior trial of citalopram (Wagner et al., 2004) showed a positive outcome. Another escitalopram RCT did not show differences in the intention-to-treat primary outcome

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measure (Wagner, Jonas, Findling, Ventura & Saikali, 2006; Carandang, Jabbal, MacBride & Elbe, 2011).

Neither venlafaxine nor mirtazapine have demonstrated potential efficacy in adolescent MDD. Although two new SNRIs have been marketed, desvenlafaxine has not yet been studied in randomized, blinded, controlled trials, only in an open-label trial (Findling et al., 2014). Two recent child and adolescent RCTs of the SNRI duloxetine have been published, one with fixed and one with flexible dosing, both using fluoxetine and placebo comparators, where neither showed evidence of efficacy (Emslie et al., 2014; Atkinson et al., 2014).

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

Available studies pertaining to SSRI and SNRI medications in young people are of variable quality (Bridge et al., 2007). 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 response rates across different studies (they range from about 30 percent to about 60 percent) may also confound study interpretation (Bridge et al., 2009; Cheung et al., 2006, Bridge, Birmaher, Iyengar, Barbe & Brent, 2009). Furthermore, selection of patients for severity of depression, extended baseline observation and the use of placebo washout (e.g. Emslie et al., 1997; Emslie et al., 2002) may have facilitated separation of placebo and drug in the key early fluoxetine trials. In addition, two recent trials of duloxetine with fluoxetine as an active comparator, which did not incorporate a placebo washout period were unable to show a statistical or clinical difference over placebo at ten weeks (Emslie et al., 2014; Atkinson et al., 2014) Fluoxetine also failed to show efficacy in these trials (Emslie et al., 2014; Atkinson et al., 2014).

These difficulties notwithstanding, available data indicates that fluoxetine, possibly sertraline (Wagner et al., 2003), citalopram and/or escitalopram can be considered to have demonstrated efficacy consistent with level one evidence for therapeutic effect (Bridge et al., 2007; Wagner et al.,

2003; Wagner et al., 2004; Findling, Robb & Bose, 2013). 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. No SSRI or SNRI has consistently demonstrated positive results for depression in pre-pubertal children. The number needed to treat (NNT) for each SSRI studied has not been well established but literature reveals an approximate NNT of ten and which may be as low as four (for fluoxetine in the Treatment of Adolescent Depression Study (TADS) trial) (Bridge et al., 2007; March et al., 2004b; CADTH, 2015). This means that for every four to ten adolescents treated with an SSRI (for approximately 12 weeks) instead of a placebo, one 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 longer-term continuation studies available. The TADS continuation data demonstrated no significant loss of efficacy over one year of treatment (March et al., 2007a). 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., 2007a). Furthermore, at 36 weeks, improvements in depressive symptoms were seen in approximately 80% of those given only cognitive behavioural therapy (CBT) or fluoxetine (March et al., 2007a). 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. 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 (Zimmerman et al., 2015). For example, severe symptoms, co-morbidity, and acute suicidality are often exclusion criteria for participation in an RCT. As noted, 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 for inclusion, 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, in the combined fluoxetine trials, drug-placebo difference was greater in children compared with adolescents, and contrary to expectations, the placebo-response rate was lower in children. (Mayes et al., 2007; CADTH, 2015). 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 (at least 50% reduction in standardized clinician depression rating scales such as the Children's Depression Rating Scale (CDRS)) (Poznanski, Cook & Carroll, 1979).

Treatment emergent adverse events have included both physical and emotional/behavioural side effects. Physical side effects include headaches, gastric distress, insomnia/hypersomnia and others (Elbe, Bezchlibnyk-Butler, Virani & Procyshyn, 2014). These are variable in their occurrence and are generally only somewhat elevated over placebo.

Emotional/behavioural adverse effects reported include: hyperactivity; irritability; hostility; disinhibition; emotional lability and self-harm. These adverse events occur in approximately 10-25% of youth (Elbe et al., 2014). Discontinuation rates due to severe adverse effects also vary greatly across studies (from 0 to 9 percent), again making class specific generalizations difficult.

Manic switch due to underlying bipolarity, independent of medication treatment, is a risk in the naturalistic course of depression in young people. Although concerns about emergent mania are noted in drug labelling, the small numbers in trials do not give us a clear answer on relative risks. For example, in the initial fluoxetine trial (Emslie et al., 1997), one subject on placebo developed mania, while three of the fluoxetine subjects were reported as developing manic symptoms, which was not statistically different, and subsequent trials have rarely reported manic switch. Furthermore, a manic episode needs to be distinguished from the more common medication-induced activation which may be dose-related (Reinblatt, DosReis, Walkup & Riddle, 2009).

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 two people out of every 100 treated with an SSRI will have a "suicide-related" event compared to one person out of every 100 treat with placebo (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 completed suicides reported in the RCT database (Bridge et al., 2007).

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, 2004; Kutcher & Gardner, 2008). Population studies demonstrate an inverse correlation between antidepressant use and youth suicide (Olfson, Shaffer, Marcus & Greenberg, 2003; Gibbons, Hur, Bhaumik & Mann, 2006). In addition, post-mortem 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. There is limited information comparing SNRIs to SSRIs. In one trial, there was no statistically significant difference in suicidality with venlafaxine compared to SSRIs, although both cardiovascular and dermatological adverse effect rates were higher than with SSRIs (Brent et al., 2008). There was an indicator of higher suicide-related behaviours with venlafaxine compared to SSRIs in a meta-analysis of trial data (Hammad et al., 2006).

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 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:* *Based on data available to us in 2015, the overall approach to use of SSRIs has not changed from 2008. The risk benefit balance for fluoxetine in child and youth depression is favorable, while it is less clear for most other SSRIs, except in older adolescents. Deliberate monitoring for efficacy and adverse effects, especially for "suicide-related" thoughts and behavioural adverse effects (e.g. activation events) is critically important. Current data does not support the use of SNRIs as primary treatment in youth depression.*

Anxiety Disorders and Obsessive Compulsive Disorder

Over fifteen published and unpublished RCTs of SSRIs and SNRIs in children and adolescents suffering from various anxiety disorders or obsessive compulsive disorder (OCD) (Bridge et al., 2007). For SSRIs, there have been six trials in OCD, five in mixed anxiety disorders and one trial in social anxiety disorder (Bridge et al., 2007). For SNRIs, there have been two published trials for generalized anxiety disorder (GAD) (one each for venlafaxine extended-release (XR) (Rynn, Riddle, Yeung & Kunz, 2007) and duloxetine (Strawn et al., 2015)), and one for social anxiety disorder (venlafaxine XR) (March et al., 2007b). 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 the SNRI desvenlafaxine. Pooled results for venlafaxine XR showed positive results in one publication, but lower effect size than SSRIs, with a lower standard for response than most clinical trials (Clinical Global Impression-Improvement (CGI-I) score <3) and significantly higher behavioral and cardiovascular adverse effects compared to placebo (Rynn et al., 2007). A recent RCT of duloxetine in GAD demonstrated efficacy compared to placebo, but the effect size was considerably less than in a typical SSRI study (Strawn et al., 2015). For venlafaxine XR in social anxiety disorder, an NNT of five was observed, while treatment was deemed reasonably well-tolerated (March et al., 2007b).

The NNT for most SSRIs and SNRIs over placebo, with the endpoint being reduction in anxiety symptoms, can be estimated as being between three to six (Bridge et al., 2007; CADTH 2015). 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. However, there is some inconsistency, in that a recent study comparing clomipramine, fluoxetine and placebo found a high placebo response (77%) and no significant difference between treatment conditions, suggesting that even in anxiety disorders, selection of patient population and other factors may affect trial outcomes in young people. (da Costa et al., 2013).

The emotional and behavioral adverse effects observed in the MDD trials were also seen in the various anxiety disorder trials, with motor hyperactivity being the most common cause of discontinuation (Elbe et al., 2014). Activation events, correlated with serum levels of fluvoxamine, were reported in 45% of drug treated versus 4% of placebo treated patients, mostly occurring by week four of treatment for anxiety disorders (Reinblatt et al., 2009). In a recent report of sertraline-associated adverse effects in a multimodal anxiety study (CAMS; Rynn et al., 2015) children who received sertraline had a significantly higher rate of adverse effects overall than adolescents (16.2% versus 3.7%, p<.05) and had more disinhibition. It is notable that the signal for increased suicidal thoughts and behaviours is less pronounced and more variable in anxiety trials relative to the trials for depression (Bridge et al., 2007; Hammad et al., 2006; CADTH, 2015). There appears to be one 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 medication and CBT are of similar efficacy overall with the combination clearly being more beneficial (March et al., 2004a; Walkup et al., 2008; Piacentini et al., 2014).

> *The bottom line: The risk benefit balance for at least three SSRIs is favorable in anxiety disorders, and it is likely favorable for other SSRIs in the short term. Appropriate monitoring of SSRI treatment is indicated. SNRIs should be considered as second or third line treatments given the limited available trial data to support their use.*

A Clinician's Perspective

When faced with a child or adolescent with mild depression or anxiety symptoms the most appropriate initial step should 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 (Garland, 2004). It is appropriate for clinicians to prescribe an SSRI 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 (Garland, 2004; 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 for SSRIs ranges from four to ten for treating depression, about six for treating OCD and about three for treating anxiety disorders. This can be compared with a number needed to harm (NNH) of about 50 for a suicide related event and NNH of about four to ten for any short or long term side effect (Bridge et al., 2007; Hammad, 2004; Elbe et al., 2014). For SNRIs, there is currently no evidence supporting efficacy in adolescent depression, while for efficacy in anxiety disorders, the NNT is about five to six.*

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 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 ten days.

Below is a suggested (abbreviated) approach to initiating and monitoring antidepressants in children and adolescents (for more details, please see Kutcher, Gardner & Virani, 2004).

Conclusion

SSRIs and SNRIs for children and adolescents with MDD and/or anxiety disorders are neither a panacea nor contra-indicated. The best available evidence suggests that fluoxetine may be the medication of choice for use in both MDD and anxiety disorders. In most situations given limitations and uncertainty in the available data, SNRIs are not recommended as first line treatments.

When properly applied and monitored, medication treatment may be of substantial benefit to some individuals. Initiation of SSRI 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 these disorders and their treatment.

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 should 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). Where 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 whenever 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.

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

For Clinicians

- Guidelines for Adolescent Depression in Primary Care (GLAD-PC) (Leon et al., 2006; Cheung et al., 2007) available at: http://www.thereachinstitute.org/images/GLAD-PCToolkit_V2_2010.pdf

For Parents, Caregivers and Youth

- www.mindcheck.ca
- www.keltymentalhealth.ca/finding-help/medications/antidepressants-anti-anxiety
- www.teenmentalhealth.org
- www.cmha.ca/highschool/english.htm

Acknowledgements / Conflict of Interest

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