Do Hospital and Community SSRI Usage Patterns in Children and Adolescents Match the Evidence?

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Abstract

Objectives: 1) To review SSRI prescribing patterns for children and adolescents in our hospital and provincial prescription database and 2) To evaluate whether prescribing practices are consistent with expectations, based on published evidence and practice recommendations. **Methods:** A PubMed online search was conducted to obtain all randomized controlled trials assessing efficacy of SSRI use in children and adolescents. The inpatient hospital pharmacy database at BC Children's Hospital (BCCH) and the BC Pharmacare database were used to identify all unique patients (under 19 years of age) seen in the inpatient department of psychiatry at BCCH or as outpatients in the province of BC receiving SSRI prescriptions between 2005-2009. **Results:** Fluoxetine, citalopram, escitalopram and sertraline have evidence supporting their efficacy in the treatment of depressive disorders. Fluoxetine, fluvoxamine, sertraline, paroxetine and venlafaxine have evidence for use in the treatment of anxiety disorders. Between 2005-2009, BCCH inpatient data revealed that fluoxetine is the most frequently prescribed SSRI, followed by citalopram, sertraline, fluvoxamine, venlafaxine, paroxetine and escitalopram. In the community outpatients, fluoxetine was most frequently prescribed SSRI followed by citalopram, venlafaxine, sertraline, paroxetine, fluvoxamine and escitalopram. **Conclusions:** Prescribing patterns for SSRIs at BC Children's Hospital are consistent with the available evidence in the pediatric population. Furthermore, with the exception of citalopram, provincial outpatient and inpatient prescriptions appear to follow published national guidelines. Hospital SSRI usage more closely reflects the available literature than outpatient community usage does.

Key words: *selective serotonin reuptake inhibitors, depression, anxiety, children, adolescents, efficacy, indications*

Introduction

In North America, depression in children and adolescents (≤18 years old collectively referred to as 'youth') has become more prevalent over the last generation and suicide is the 3rd leading cause of death in adolescents (Cheung, Emslie, & Mayes, 2005). At any given time, it is estimated that 2% of children and up to 8% of adolescents suffer from a depressive disorder (Birmaher et al., 2007). In addition, at least 10% of youth suffer from anxiety disorders (Keeton, Kolos, & Walkup, 2009). Antidepressant medications are often employed as a treatment for these disorders in youth. In the 1990's, prescription rates of these medications to children and adolescents were already rising three to five fold even though evidence of efficacy was not yet available in this population (Zito et al., 2002).

The most commonly prescribed pharmacological treatments for depression and anxiety in youth are Selective Serotonin Reuptake Inhibitors (SSRIs including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and for the purposes of this review, the serotonin/norepinephrine reuptake inhibitor, venlafaxine). Previously, these disorders were often treated with Tricyclic Antidepressants (TCAs); however SSRIs have mostly replaced these older antidepressants because in general they present a more tolerable adverse effect profile and a lower risk for death from overdose (Courtney, 2004).

In adults, the efficacy of SSRIs is well established for the treatment of depression and anxiety (Cheung et al., 2005). Prior to 1997, no published reports demonstrating superior efficacy of SSRIs over placebo in children and adolescents existed. Following initiation of randomized controlled trials (RCTs) with SSRIs in the pediatric population, there are now a few limited indications for SSRI medications in youth, specifically fluoxetine, fluvoxamine, and sertraline for obsessive-compulsive disorder (OCD) aged 6-17 (Food and Drug Administration, 2010). Until

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very recently, the only SSRI that was US Food and Drug Administration (FDA) approved for the treatment of depression in adolescents was fluoxetine (Food and Drug Administration, 2010). Recently, escitalopram was also approved for the treatment of major depressive disorder in the pediatric population (Food and Drug Administration, 2010). In children and adolescents, use of SSRIs was adopted by psychiatrists, pediatricians and general practitioners (GPs) prior to formal approval, for a variety of conditions, including ADHD and aggression (Rushton, Clark, & Freed, 2000), the former of which has no RCT evidence as an indication for SSRIs in any age group. Published guidelines (Garland, Virani, & Kutcher, 2009; Impact BC, 2010) recommend that fluoxetine should be the first line of treatment of the SSRI class of medications for depression and that several SSRIs (fluoxetine, sertraline, fluvoxamine for mixed anxiety or OCD, and paroxetine for social phobia) could be appropriate first choices for anxiety treatment. However, SSRI prescribing practices in children and adolescents may not follow published guidelines. In 2005, Bhatia and colleagues conducted a survey of Nebraska GPs, pediatricians and psychiatrists' prescribing practices for SSRIs (without the identification of target symptoms) in children and adolescents (Bhatia et al., 2008). GPs reported sertraline, followed by escitalopram and fluoxetine as their top three choices of the SSRIs. Pediatricians reported sertraline as their preferred first-line treatment, followed by fluoxetine and escitalopram. Psychiatrists reported practices closest to published guidelines with fluoxetine as their first choice for SSRI treatment followed by sertraline and escitalopram.

Given the concern that these medications are being used for a broad range of indications in children and adolescents despite limited evidence supporting efficacy in the pediatric population, there is a need to further evaluate these treatments. Therefore, our objective was to review SSRI prescribing patterns for children and adolescents in our children's hospital and provincial prescription database and to evaluate whether these are consistent with expectations, based on published evidence and practice recommendations.

British Columbia's Children's Hospital (BCCH) is a tertiary-level care center and provincial leader for children's health care. Many of the province's most complicated cases of depression and anxiety in children and adolescents are treated by the BCCH Department of Psychiatry. Many children admitted to the inpatient units are treated with an SSRI.

Our hypotheses were 3-fold: 1) Patterns of SSRI use in children and adolescents at BCCH and in the province of BC follow scientific guidelines, 2) Observed deviations from guidelines would likely reflect marketing or other influences, and 3) Patterns of SSRI use at BCCH are closer to guidelines than in the province of BC as a whole.

Methods

Efficacy of SSRIs in children and adolescents

In order to obtain all studies evaluating SSRI use in children and adolescents, an online PubMed literature search was conducted using the following key words: children or adolescents or youth or pediatric; selective serotonin reuptake inhibitors or SSRI; fluoxetine or citalopram or desvenlafaxine or escitalopram or fluvoxamine or sertraline or paroxetine or venlafaxine; indications; evidence for use; efficacy. Only RCTs with an *a priori* specified primary outcome measure of efficacy of one or more SSRIs conducted in youth less than 18 years of age were included. Information about current Health Canada approved indications was obtained from the Health Canada website (Health Canada, 2010). Information about current US FDA approved indications for children was obtained from the FDA website (Food and Drug Administration, 2010).

All articles were classified into level of evidence categories based on the Centre for Evidence Based Medicine definitions (Cache limited, 2010).

BC Children's Hospital prescribing patterns

The inpatient hospital pharmacy database at BC Children's Hospital (BCCH) was used to perform a drug use evaluation. From the database, we identified all unique inpatients (youth under 19 years of age) seen in the department of child and adolescent psychiatry who received an SSRI (for any indication or duration) between the years 2005-2009. Information about diagnoses was not available in the pharmacy database and therefore was not obtained.

BC outpatient prescribing patterns

BC Pharmacare records were queried for antidepressant prescriptions for any indication or duration for youth under 19 years of age (Pharmacare, 2010). From this database, we identified all unique outpatients who received an SSRI between the fiscal years 2004/2005-2009/2010. Information about diagnoses for patients treated with SSRIs was not obtained.

Results

Efficacy of SSRIs

There are no Health Canada approved indications for SSRIs or venlafaxine in children and adolescents (Health Canada, 2009). Fluoxetine is approved by the FDA for the treatment of major depressive disorder in youth 8-17 years of age (Food and Drug Administration, 2010). Escitalopram was recently approved by the FDA for the treatment of major depressive disorder in adolescents aged 12-17 (Food and Drug Administration, 2010). Fluoxetine, fluvoxamine and sertraline have been FDA approved for treatment of OCD in youth 6-17 years of age for several years (Food and Drug Administration, 2010).

Table 1. Evidence for SSRI use in children and adolescents

SSRI /SNRI Evaluated	Indication	Study Groups	N (age range)	Length of study (weeks)	1^0 Outcome Superior to Placebo	Reference
Citalopram	Depression	C, Pl	244 (13-18)	12	No	VonKnorring 2006
	Depression	C, Pl	174 (7-17)	8	**Yes**	Wagner 2004b
	Autism	C, Pl	149 (5-17)	12	No	King 2009
Escitalopram	Depression	E, Pl	268 (6-17)	8	No	Wagner 2006
	Depression	F, Pl	96 (7-17)	8	**Yes**	Emslie 1997
	Depression	F, Pl	40 (13-18)	8	No	Simeon 1990
	Depression	F, CBT, F+CBT, Pl	439 (12-17)	12	**Yes**	March 2004b
	Depression	F, Pl	219 (8-18)	9	**Yes**	Emslie 2002
	Depression + AUD	F, Pl	50 (15-20)	12	No	Cornelius 2009
	Depression + ACUD	F, Pl	34 (12-17)	8	No	Findling 2009
Fluoxetine	Depression (relapse prevention)	F, Pl	168 (7-18)	12	**Yes**	Emslie 2008
	Depression (relapse prevention)	FF, FPl	40 (8-18)	32	**Yes**	Emslie 2004
	Anxiety	F, Pl	74 (7-17)	12	**Yes**	Birmaher 2003
	OCD	F, Pl	14 (8-15)	20	**Yes**	Riddle 1992
	OCD	F, Pl	103 (7-17)	13	**Yes**	Geller 2001
	OCD	F, Pl	43 (8-18)	8	**Yes**	Liebowitz 2002
	ADHD + depression/anxiety	A+F, A+Pl	173 (7-17)	13	No	Kratochvil 2005
Fluvoxamine	Anxiety	Fv, Pl	128 (6-17)	8	**Yes**	Walkup 2001
	OCD	Fv, Pl	120 (8-17)	10	**Yes**	Riddle 2001
	Autism	Fv, Pl	45 (5-17)	8	**Yes**	Hollander 2005
Paroxetine	Depression	P/I, Pl/I	275 (12-18)	8	**Yes**	Keller 2001
	Depression	P, Cl	121 (12-20)	8	No	Braconnier 2003
	Depression	P, Pl	286 (13-18)	12	No	Berard 2006
	Depression	P, Pl	206 (7-17)	8	No	Emslie 2006
	Social Anxiety disorder	P, Pl	322 (8-17)	16	**Yes**	Wagner 2004a
	OCD	P, Pl	207 (7-17)	10	**Yes**	Geller 2004
Sertraline	Depression	S, CBT, S+CBT	73 (12-18)	24	No	Melvin 2006
	Depression	S, Pl	276 (6-17)	10	**Yes**	Donnelly 2006*
	Depression	S, Pl	376 (6-17)	10	**Yes**	Wagner 2003
	Anxiety	S, CBT, CBT+S,Pl	488 (7-17)	12	**Yes**	Walkup 2008
	Anxiety	S, Pl	22 (5-17)	9	**Yes**	Rynn 2001
	OCD	CBT, S, CBT+S,Pl	97 (7-17)	12	**Yes**	March 2004a
	OCD	S, Pl	187 (6-17)	12	**Yes**	March 1998
	PTSD	S + CBT, Pl+CBT	24 (10-17)	12	**Yes**	Cohen 2007
Venlafaxine	Depression	V, Pl	33 (8-17)	6	No	Mandoki 1997
	Social Anxiety Disorder	V, Pl	293 (8-17)	16	**Yes**	March 2007
	Generalized Anxiety Disorder	V, Pl	320 (6-17)	8	**Yes**	Rynn 2007
Citalopram, Fluoxetine	OCD	C, F	29 (7-18)	6	**Yes**	Alaghband-Rad 2009
All SSRIs	Depression	SSRI, SSRI+CBT	208 (11-17)	12	No	Goodyer 2008
All	Depression (SSRI resistant)	SSRI, V, SSRI+CBT, V+CBT	334 (12-18)	12	**Yes**	Brent 2008

Abbreviations: A, atomoxetine; AUD, alcohol use disorder; ACUD, alcohol and cannabis use disorder; C, citalopram; Cl, clomipramine; CBT, cognitive behavioral therapy; E, escitalopram; F, fluoxetine; Fv, fluvoxamine; OCD, obsessive compulsive disorder; P, paroxetine; Pl, placebo; PTSD, post traumatic stress disorder; S, sertraline; SSRI, selective serotonin reuptake inhibitors; SNRI, selective norepinephrine reuptake inhibitors; V, venlafaxine

*Reanalysis of Wagner et al 2003 RCT sertraline study

Our literature review identified a total of 40 RCTs assessing evidence for SSRI use in youth. All studies are classified as evidence level 1a. These studies are summarized in Table 1. Of these, 27 reported a positive result for SSRI use. 13 RCTs showed no improvement in symptoms with SSRI treatment compared with placebo.

Depression

We found a total of 17 RCTs evaluating SSRI use in major depression. One publication (Donnelly et al., 2006) was a reanalysis of a prior sertraline trial (Wagner et al., 2003) and was therefore not included in our total. We also identified two trials (Emslie et al., 2004; Emslie et al., 2008) evaluating SSRI treatment for relapse prevention in depression.

Nine of these studies failed to show the drug tested to be superior to placebo in reducing the symptoms of depression in children and adolescents. Two additional trials showed efficacy for fluoxetine in relapse prevention during continuation treatment after recovery from acute depressive episode (Emslie et al., 2004; Emslie et al., 2008). Fluoxetine is generally accepted as a treatment for depression in children and adolescents. Our literature review identified 3 RCTs (Emslie et al., 1997; March et al., 2004b; Emslie et al., 2002) where fluoxetine was shown to be superior to placebo for the treatment of depression. In an earlier trial of 40 patients (Simeon, Dinicola, Ferguson, & Copping, 1990), although fluoxetine was superior to placebo on all measures except sleep, the primary outcome of efficacy was not positive as the result was not statistically significant. This was mainly due to the high placebo response rate and small to moderate treatment effects in children and adolescents as is the case in most depression trials. In general, trials require a larger sample size (at least 100, and in some studies 400 patients) to demonstrate statistically significant findings. Fluoxetine was found to improve total score in the clinical global impressions improvement (CGI-I) and severity (CGI-S) subscales in children compared with placebo (Emslie et al., 1997; Emslie et al., 2008; March et al., 2004b). In addition, fluoxetine significantly lowered depressive symptoms measured on the Childhood Depressive Rating Scale (CDRS) (Emslie et al., 1997; Emslie et al., 2002; March et al., 2004b). In three separate studies, children treated with fluoxetine had a mean CDRS improvement of 19.41, 20.1 and 22 points compared to 12.64, 10.5, and 14.9 with placebo treatment, respectively ($p<0.05$) (Emslie et al., 1997; Emslie et al., 2002; March et al., 2004). Two studies (Emslie et al., 2004; Emslie et al., 2008) assessed relapse of depression in an open label trial of fluoxetine after subjects were switched to a randomized treatment of either fluoxetine or placebo. In these studies, 34% and 42% of fluoxetine-treated youth relapsed (measured as a CDRS-R score of $\geq$40) compared with 60% and 69% of placebo-treated patients.

In addition to fluoxetine, there is some evidence that sertraline is effective in the treatment of childhood depressive disorders (Walkup et al., 2008; Rynn, Siqueland, & Rickels, 2001; March et al., 2004a; March et al., 1998). In one study (Wagner et al., 2003), results of two smaller 10-week studies were pooled. Here, sertraline was found to produce a statistically significant decrease on the CDRS-R total score compared with placebo, although the clinical significance of this finding (mean reduction of 2 points on the CDRS-R) may be considered minimal. In a reanalysis of the data from the above study, (Donnelly et al., 2006), sertraline treatment was associated with a statistically significant decrease on the CDRS-R when compared with placebo in adolescents (>12 years old) but not in children ($\leq$12 years old). Melvin and colleagues (Melvin et al., 2006) assessed sertraline treatment in youth in combination with and in comparison to cognitive behavioral therapy (CBT). Here, they found that CBT alone was superior to sertraline treatment after 6 months. The combination of sertraline and CBT was not found to be superior to either CBT or sertraline alone.

Our literature search revealed 4 studies that assessed the efficacy of paroxetine in the treatment of depression in children and adolescents (Keller et al., 2001; Braconnier, Coent, & Cohen, 2003; Berard, Fong, Carpenter, Thomason, & Wilkinson, 2006; Emslie et al., 2006). None of these studies found paroxetine to be superior to placebo treatment based on primary outcomes measures of Hamilton Rating Scale for Depression (HAM-D), Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime (K-SADS-L), Montgomery-Asberg Depression Rating Scale (MADRS), or the CDRS-R. One study (Berard et al., 2006), did find a positive result with a secondary outcome measure (change in CGI-I scale), reporting a significantly higher response rate on the CGI-I in paroxetine treated youth compared to placebo-treated youth. In addition, 2 RCTs (Keller et al., 2001; Braconnier et al., 2003) used TCA (imipramine or clomipramine) treated youth as a control group to evaluate paroxetine treatment over 8 weeks. However, neither study found a difference in efficacy outcome between the treatment groups.

Venlafaxine was evaluated in one study in children with depressive disorders (Mandoki, Tapia, Tapia, Sumner, & Parker, 1997), however it was not found to be more effective for symptom reduction than placebo as measured by weekly depression rating assessments.

Anxiety

We identified 15 RCTs evaluating fluoxetine, paroxetine, fluvoxamine, sertraline and venlafaxine treatment in children and adolescents with anxiety disorders. Four RCTs (Birmaher et al., 2003; Riddle et al., 1992; Geller et al., 2001; Liebowitz et al., 2002) evaluating fluoxetine treatment had a primary outcome measure supporting efficacy. Birmaher and colleagues (Birmaher et al., 2003) evaluated anxious youths for 12 weeks and found that fluoxetine was effective in reducing anxiety symptoms when compared with placebo as measured by the

CGI-I, CGI-S and Pediatric Anxiety Rating Scale (PARS). Two other RCTs (Geller et al., 2001; Riddle et al., 1992) evaluated fluoxetine specifically for the treatment of OCD. One study (Geller et al., 2001) found that OCD symptoms measured using the Child Yale-Brown Obsessive Compulsive Scale (CY-BOCS), were significantly reduced with fluoxetine treatment compared with placebo. However, the other study (Riddle et al., 1992) did not find a significant improvement on the CY-BOCS but did find a significant improvement measured on the Clinical Global Impression-Obsessive Compulsive Disorder (CGI-OCD) with fluoxetine-treated youth compared with placebo treatment.

Four RCTs (Walkup et al., 2008; Rynn et al., 2001; March et al., 2004; March et al., 1998) evaluating sertraline as a treatment for childhood anxiety disorders were identified. On the PARS, sertraline treatment was found to significantly improve anxiety symptoms compared with placebo (Walkup et al., 2008). On the CY-BOCS, sertraline was found to significantly reduce OCD symptoms compared with placebo (March et al., 2004; March et al., 1998). However, in one study (March et al., 2004), sertraline was not found to be superior to placebo when remission rate of OCD symptoms was calculated. Sertraline is effective in treating anxiety disorders when combined with CBT. Walkup and colleagues (Walkup et al., 2008) assessed sertraline combined with CBT compared with sertraline and CBT alone and found that the combination therapy was the most efficacious in treating anxiety symptoms as measured by the CGI-I and the PARS.

In addition to fluoxetine and sertraline, paroxetine is also effective in treating childhood anxiety disorders (Wagner et al., 2004a; Geller et al., 2004). In children with social anxiety, paroxetine treatment improved symptoms on the CGI-I compared with placebo (Wagner et al., 2004a). In a study assessing OCD symptoms, paroxetine treated children had a significantly greater improvement in CY-BOCS total score compared with placebo (Geller et al., 2004).

There is also evidence to support fluvoxamine use in youth with anxiety disorders (Walkup et al., 2001; Riddle et al., 2001). Walkup and colleagues evaluated fluvoxamine use in youth with generalized anxiety disorder and found that treated patients improved significantly when compared with placebo on the PARS and on the CGI-I.

In addition to some of the SSRIs, venlafaxine is also useful in the treatment of childhood anxiety disorders (March, Entusah, Rynn, Albano, & Tourian, 2007; Rynn, Riddle, Yeung, & Kunz, 2007). When evaluated in children with generalized anxiety disorder, subjects treated with venlafaxine showed significant improvement in anxiety symptoms as measured by the PARS compared with placebo treated subjects (Rynn et al., 2007). When assessed specifically for the treatment of social anxiety disorders, venlafaxine-treated youth showed significant improvement on both the SAS-CA and on the CGI-I compared to placebo-treated youth (March et al., 2007).

SSRI use at BC Children's Hospital

From January 1st 2005 to December 31st 2009, for the BCCH mental health inpatient units, a total of 3895 prescription database entries for antidepressants were identified. This represented 664 unique patients who received an antidepressant. Fourteen different antidepressants were prescribed (amitriptyline, bupropion SR/XL, citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, mirtazapine, paroxetine, sertraline, trazodone and venlafaxine). SSRIs/venlafaxine comprised 82% of all antidepressant use (by unique patient) on the inpatient mental health units. The distribution of SSRI and venlafaxine use over these 5 years is presented in Figure 1. Fluoxetine was the most often prescribed (50% of all patients receiving an SSRI or venlafaxine during the evaluation period) followed by citalopram, sertraline, fluvoxamine and venlafaxine. Among the SSRIs, paroxetine and escitalopram were prescribed least often during this time period, though it should be noted that escitalopram first received a notice of compliance (NOC) from Health Canada in December 2004 and was not on the BCCH hospital formulary during the period of time evaluated.

SSRI use in British Columbia Outpatient Settings

Pharmanet data captures all outpatient medication use, identifying the number of unique patients receiving prescriptions. The break down of SSRI use in BC outpatient settings for children and adolescents is presented in Figure 2. Fluoxetine was the most often prescribed SSRI to youth followed by citalopram, venlafaxine, sertraline, paroxetine, escitalopram and fluvoxamine.

Discussion

Few medications have substantial evidence for use in the treatment of childhood depressive and anxiety disorders. While there is FDA approval for some of the SSRIs for pediatric depression and anxiety, none of these medications are approved by Health Canada for use in the pediatric population. Unlike adults, in children and adolescents, the number needed to treat (NNT) to achieve clinically significant responses is relatively high when evaluating SSRI treatment for depression (NNT=10) and somewhat lower for treatment of anxiety disorders (NNT=4). This may require larger cohort studies than would otherwise be expected to draw positive clinical conclusions.

In this review, we have summarized the RCT evidence available for the use of SSRIs in children and adolescents. This literature has also contributed to the development of recent national guidelines (Garland et al., 2009; Impact BC, 2010) for SSRIs treatment in children and adolescents. Of the SSRIs, fluoxetine has the most evidence for use in youth for the treatment of both

Figure 1. Unique SSRI Prescriptions to Children and Adolescents at BC Children's Hospital Psychiatry Inpatient Units by year from 2005-2009

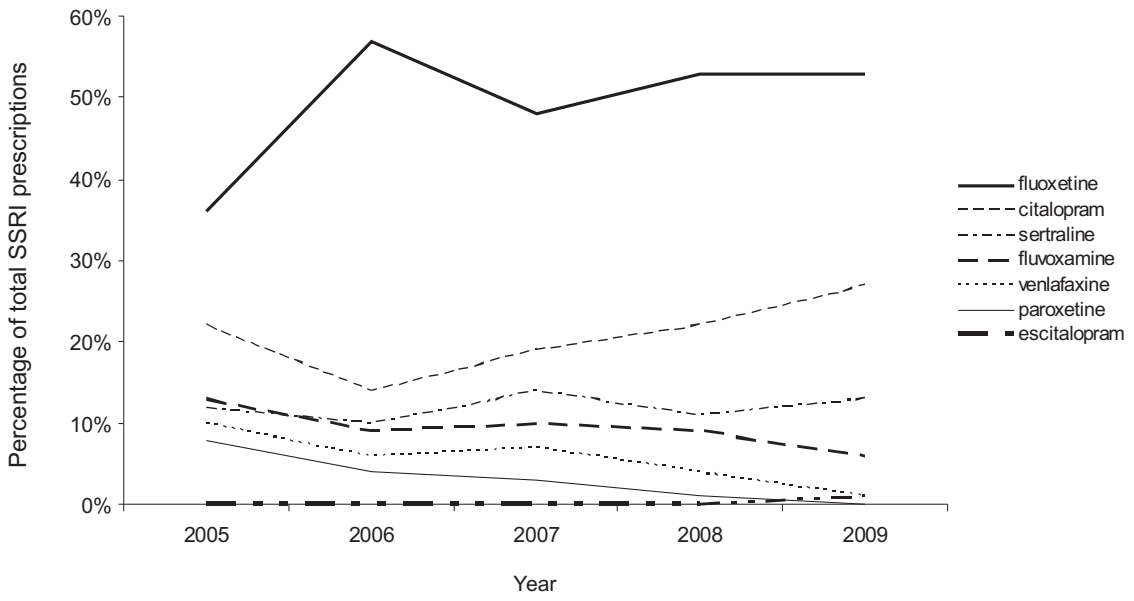
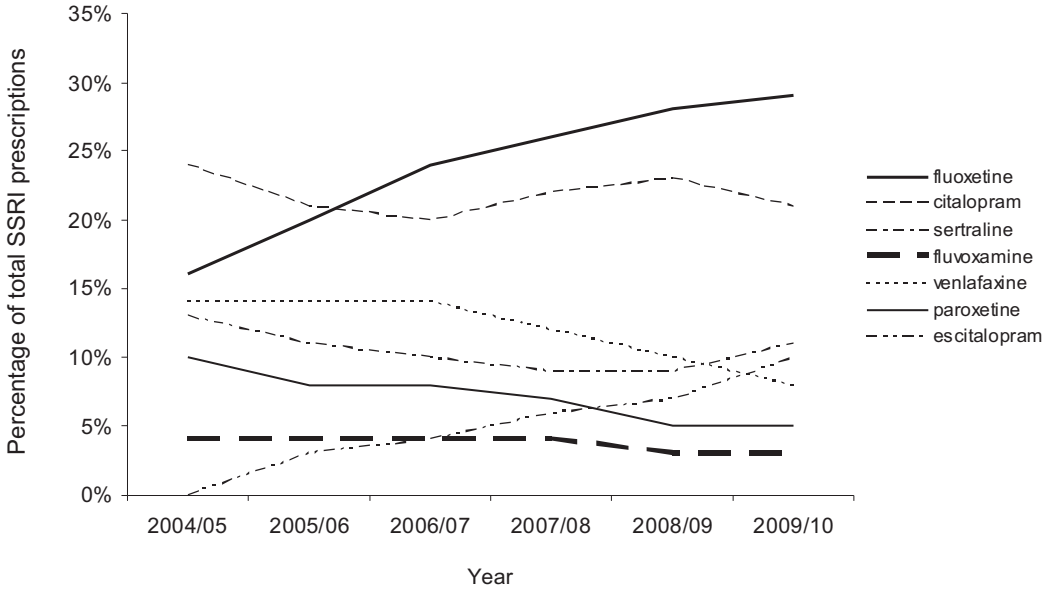


Figure 2. Unique SSRI prescriptions to Children and Adolescents in BC Pharmacare Database by Year 2004/05-2009/10



depression and anxiety and should be considered by physicians as a first-line treatment. Although other SSRIs have positive RCT evidence to support use in depression (sertraline, citalopram and escitalopram) and anxiety (sertraline, fluvoxamine, paroxetine), our literature review revealed mixed results.

Based on current SSRI prescription guidelines (Garland et al., 2009; Impact BC, 2010; Zinck, Bagnell, Bond, & Newton, 2009) we would expect fluoxetine to be the most widely used SSRI in youth, followed by sertraline, citalopram, fluvoxamine, venlafaxine, paroxetine and escitalopram. Overall, SSRI prescriptions to children at BCCH are consistent with BC and Canadian guidelines, with the exception of citalopram, which was prescribed at a higher rate than was expected based on our literature search.

In the outpatient prescription data, SSRI usage was as follows: fluoxetine, followed by citalopram, sertraline, escitalopram, venlafaxine, paroxetine, fluvoxamine, and desvenlafaxine. Although the use was similar to prescription trends seen at BCCH, inpatient prescribing patterns appear to follow published guidelines more closely than do outpatient prescribing patterns.

Deviations in prescribing practices from expectations based on national guidelines in both the inpatient and outpatient setting could be due to a variety of reasons. Of note, fluoxetine, citalopram and sertraline are less expensive medications to purchase in Canada and therefore may be more appealing to consumers. In addition, recently introduced medications are frequently promoted by industry and are often available by sample at no cost to consumers.

It is not surprising that fluoxetine is the most prescribed medication in its class, especially considering its superior body of evidence in both depression and anxiety disorders, low cost and long half-life, which may minimize discontinuation effects in teenagers with erratic compliance. The increased rate of citalopram prescriptions at our hospital may be related to a number of contributing factors including effective marketing and low cost compared with other SSRIs. The profile of this medication at our institution may have also been influenced by the presence of a citalopram clinical trial being conducted in the mood and anxiety disorders clinic over the evaluated time period. In addition, citalopram and escitalopram may be preferred over other SSRIs when prescribed in conjunction with other medications because they are less likely to inhibit cytochrome p450 (CYP) enzymes and lead to drug interactions (Bezchlibnyk-Butler & Virani, 2007).

In view of the fact that physicians' prescribing practices to youth do not always follow published guidelines or reflect our comprehensive review of the literature, it is important that risk-benefit balance of medication usage patterns be evaluated in this population. Furthermore, in 2004, Health Canada issued an advisory warning against the use of paroxetine, fluvoxamine, and venlafaxine due to adverse effects seen in the pediatric population (Courtney, 2004) and therefore these medications would not be considered as a first-line treatment for children and adolescents.

Weaknesses in this review

For the purposes of this review, we were not able to segregate SSRI usage by diagnosis for either the hospital or community settings. Our interpretation of the data is based on the assumption that SSRIs were prescribed for depression, anxiety and OCD, in that order, in the pediatric population. In addition, the conclusions we have drawn to explain SSRI usage may be only some of the reasons for why prescribing practices do not consistently reflect scientific evidence.

Conclusions

Prescribing patterns for SSRIs at BC Children's Hospital are consistent with the available evidence in the pediatric population. Furthermore, provincial outpatient and inpatient prescriptions appear to follow published national guidelines, with the exception of citalopram, which may be related to a number of unique factors that were present during the evaluated time period. In both the outpatient and inpatient setting, strong marketing practices may contribute to prescription rates that deviate from evidence-based guidelines. Finally, it appears that SSRI usage by psychiatrists in the inpatient setting more closely reflects the literature than does usage in the outpatient setting. With many of these medications having only limited evidence to support their use, it is important that physicians consider the benefits and the risks when prescribing these medications, especially in this vulnerable population.

Acknowledgements/Conflicts of Interest

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References

Alaghband-Rad, J., & Hakimshooshtary, M. (2009). A randomized controlled clinical trial of citalopram versus fluoxetine in children and adolescents with obsessive-compulsive disorder (OCD). *European Child and Adolescent Psychiatry, 18*(3), 131-135.

Bezchlibnyk-Butler Z., & Virani A. (2007). Clinical handbook of psychotropic drugs for children & adolescents. Second edition. Hogrefe & Huber; Cambridge, MA.

Berard, R., Fong, R., Carpenter, D. J., Thomason, C., & Wilkinson, C. (2006). An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *Journal of Child and Adolescent Psychopharmacology, 16*(1), 59-75.

Bhatia, S. K., Rezac, A. J., Vitiello, B., Sitorius, M. A., Buehler, B. A., & Kratochvil, C. J. (2008). Antidepressant prescribing practices for the treatment of children and adolescents. *Journal of Child and Adolescent Psychopharmacology, 18*(1), 70-80.

Birmaher, B., Brent, D., Bernet, W., Bukstein, O., Walter, H., Benson, R. S., et al. (2007). Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(11), 1503-1526.

Birmaher, B., Axelson, D. A., Monk, K., Kalas, C., Clark, D. B., Ehmann M., et al. (2003). Fluoxetine for the treatment of childhood anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(4), 415-423.

Braconnier, A., Coent, R. L., & Cohen, D. (2003). Paroxetine versus clomipramine in adolescents with severe major depression: a double-blind, randomized, multicenter trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(1), 22-29.

Brent, D., Emslie, G., Clarke, G., Wagner, K. D., Asarnow, J. R., Keller, M., et al. (2008). Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression. *Journal of the American Medical Association, 299*(8), 901-913.

Cache Limited (2010). *Oxford centre for evidence-based medicine—levels of evidence.* Retrieved 04/23, 2010, from http://www.cebm.net/index.aspx?o=1025

Cheung, A. H., Emslie, G. J., & Mayes, T. L. (2005). Review of the efficacy and safety of antidepressants in youth depression. *Journal of Child Psychology and Psychiatry, 46*(7), 735-754.

Cohen, J. A., Mannarina, A. P., Perel, J. M., & Staron, V. (2007). A pilot randomized controlled trial of combined trauma-focused CBT and sertraline for childhood PTSD symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(7), 811-819.

Cornelius, J. R., Bukstein, O. G., Wood, S. D., Kirisci, L. Douaihy, A., & Clark, D. B. (2009). Double-blind placebo-controlled trial of fluoxetine in adolescents with comorbid major depression and an alcohol use disorder. *Addictive Behaviors, 34*(1), 905-909.

Courtney, D. B. (2004). Selective serotonin reuptake inhibitor and venlafaxine use in children and adolescents with major depressive disorder: a systematic review of published randomized controlled trials. *Canadian Journal of Psychiatry, 49*(8), 557-563.

Donnelly, C. L., Wagner, K. D., Rynn, M., Ambrosini, P. Landau, P., Yang, R., et al. (2006). Sertraline in children and adolescents with major depressive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(19), 1162-1170.

Emslie, G. J., Kennard, B. D., Mayes, T. L., Nightingale-Teresi, J., Carmody, T., Hughes, C. W., et al. (2008). Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. *American Journal of Psychiatry, 165*(4), 459-467.

Emslie, G. J., Wagner, K. D., Kutcher, S., Krulewicz, S., Fong, R., Carpenter, D. J., et al. (2006). Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(6), 709-719.

Emslie, G. J., Heiligenstein, J. H., Hoog, S. L., Wagner, K. D., Findling, R. L., McCracken, J. T., et al. (2004). Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(11), 1397-1405.

Emslie, G. J., Heiligenstine, J. H., Wagner, K. D., Hoog, S. L., Ernest, D. E., Brown, E., et al. (2002). Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(10), 1205-1215.

Emslie, G. J., Rush, J. A., Weinberg, W. A., Kowatch, R. A., Hughes, C. W., Carmody, T., et al. (1997). A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Archives of General Psychiatry, 54,* 1031-1037.

Findling, R. J., Pagano, M. E., McNamara, N. K., Stansbrey, R. J., Faber, J. E., Lingler, J., et al. (2009). The short-term safety and efficacy of fluoxetine in depressed adolescents with alcohol and cannabis use disorders: a pilot randomized placebo-controlled trial. *Child and Adolescent Psychiatry and Mental Health, 3*(11), 1-13.

Food and Drug Administration (2010). *Atypical antipsychotic drugs information.* Retrieved 11/23, 2009, from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094303.htm

Garland, E. J., Virani, A., & Kutcher, S. (2009). 2008 Position paper on using SSRIs in children and adolescents. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 18*(2), 160-165.

Geller, D. A., Wagner, K. D., Emslie, G., Murphy, T., Carpenter, D. J., Wetherhold, E., et al. (2004). Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(11), 1387-1396.

Geller, D. A., Hoog, S. L., Heiligenstein, J. H., Ricardi, R. K. Tamura, R., Kluszynski, S., et al. (2001). Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(7), 773-779.

Goodyer, I. M., Dubicka, B., Wilkinson, P., Kelvin, R., Roberts, C., Byford, S., et al. (2008). A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. *Health Technology Assessment, 12*(14), 1-4.

Goodyer, I., Dubicka, B., Wilkinson, P., Kelvin, R., Roberts, C., Byford, S., et al. (2007). Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behavior therapy in adolescents with major depression: randomized controlled trial. *British Medical Journal, 335*(7611), 142-150.

Health Canada (2010). *Drug product search.* Retrieved 02/02, 2010, from http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

Hollander, E., Phillips, A., Chaplin, W., Zagursky, K., Novotny, S., Wasserman, S., et al. (2005). A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology, 30*(1), 582-589.

Impact BC (2010). Practice Support Program—Mental Health Youth—Tools & Resources. *Impact BC Health Improvement Action.* Retrieved 02/05, 2010, from http://www.impactbc.ca/practicesupport/mentalhealthyouth/toolsandresources

Keeton, C. P., Kolos, A. C., & Walkup, J. T. (2009). Pediatric Generalized Anxiety Disorder. *Pediatric Drugs, 11*(3), 171-183.

Keller, M. B., Ryan, N. D., Strober, M., Klein, R. G., Kutcher, S. P., Birmaher, B., et al. (2001). Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *Journal of American Academy of Child and Adolescent Psychiatry, 40*(7), 762-772.

King, B. H., Hollander, E., Sikich, L., McCracken, J. T., Scahill, L., Bregman, J. D., et al. (2009). Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior. *Archives of General Psychiatry, 66*(6), 583-590.

Kratochvil, C. J., Newcorn, J. H., Arnold, L. E., Duesenberg, D., Emslie, G. J., Quintana, H., et al. (2005). Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry, 44*(9), 915-924.

Liebowitz, M. R., Turner, S. M., Piacentini, J., Beidel, D. C., Clarvit, S. R., Davies, S. O., et al. (2002). Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(12), 1431-1438.

Mandoki, M. W., Tapia, M. R., Tapia, M. A., Sumner, G. S., & Parker, J. L. (1997). Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacology Bulletin, 33*(1), 149-154.

March, J. S., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., et al. (2009). The Treatment for adolescents with depression study (TADS): outcomes over 1 year of naturalistic follow-up. *American Journal of Psychiatry, 166*(10), 1141-1149.

March, J. S., Entusah, A. R., Rynn, M., Albano, A. M., & Tourian, K. A. (2007). A randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. *Biological Psychiatry, 62*(1), 1149-1154.

March, J. S., Foa, E., Gammon, P., Chrisman, A., Curry, J., Fitzgerald, D., et al. (2004a). Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: The Pediatric OCD treatment study (POTS) randomized controlled trial. *Journal of the American Medical Association, 292*(16), 1969-1976.

March, J. S., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., et al. (2004b). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for adolescents with depression study (TADS) randomized controlled trial. *Journal of the American Medical Association, 292*(7), 807-820.

March, J. S., Biederman, J., Wolkow, R., Safferman, A., Mardekian, J., Cook, E. H., et al. (1998). Sertraline in children and adolescents with obsessive-compulsive disorder. *Journal of the American Medical Association, 280*(20), 1752-1756.

Melvin, G. A., Tonge, B. J., King, N. J., Heyne, D., Gordon, M. S., & Klimkeit, E. (2006). A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(10), 1151-1161.

Pharmacare (2010). *Policy, outcomes evaluation and research, pharmaceutical services division, ministry of health services.* Unpublished manuscript.

Riddle, M. A., Reeve, E. A., Yaryura-Tobias, J. A., Yang, H. M., Claghorn, J. L., Gaffney, G., et al. (2001). Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(2), 222-229.

Riddle, M. A., Scahill, L., King, R. A., Hardin, M. T., Anderson, G. M., Ort, S. I., et al. (1992). Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*(6), 1062-1069.

Rushton, J. L, Clark, S. J., & Freed, G. L. (2000). Pediatrician and family physician prescription of selective serotonin reuptake inhibitors. *Journal of the American Academy of Pediatrics, 105*(6), 82-90.

Rynn, M. A., Riddle, M. A., Yeung, P. P., & Kunz, N. R. (2007). Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. *American Journal of Psychiatry, 164*(2), 290-300.

Rynn, M. A., Siqueland, L., & Rickels, K. (2001). Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *American Journal of Psychiatry, 158*(12), 2008-2014.

Simeon, J. G., Dinicola, V. F., Ferguson, H. B., & Copping, W. (1990). Adolescent depression: a placebo-controlled fluoxetine treatment study and follow up. *Programming Neuro-Psychopharmacology & Biological Psychiatry, 1990*(14), 791-795.

Von Knorring, A., Olsson, G. I., Thomsen, P. H., Lemming, O. M., & Hulten, A. (2006). A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *Journal of Clinical Psychopharmacology, 26*(3), 311-315.

Wagner, K. D., Jonas, J., Findling, R. L., Ventura, D., & Saikali, K. (2006). A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(3), 280-288.

Wagner, K. D., Berard, R., Stein, M. B., Wetherhold, E., Carpenter, D. J., Perera, P., et al. (2004a). A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Archives of General Psychiatry, 61*(11), 1153-1162.

Wagner, K. D., Robb, A. S., Findling, R. L., Jin, J., Gutierrez, M. M., & Heydorn, W. E. (2004b). A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *American Journal of Psychiatry, 161*(6), 1079-1083.

Wagner, K. D., Ambrosini, P., Rynn, M., Wohlberg, C., Yang, R., Greenbaum, M. S., et al. (2003). Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *Journal of the American Medical Association, 290*(8), 1033-1041.

Walkup, J. T., Albano, A. M., Piacentini, J., Birmaher, B., Compton, S. N., Sherrill, J. T., et al. (2008). Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *New England Journal of Medicine, 359*(26), 2753-2766.

Walkup, J. T., Labellarte, M. J., Riddle M. A., Pine, D. S., Greenhill, L., Klein, R., et al. (2001). Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *New England Journal of Medicine, 344*(17), 1279-1285.

Zinck, S., Bagnell A., Bond K., & Newton A. S. (2009). The Cochrane Library and the treatment of major depression in children and youth: an overview of reviews. *Evidence-based child health: a Cochrane review journal, 4*(1), 1336-1350.

Zito, J. M., Safer, D. J., dosReis, S., Garnder, J. F., Soeken, K., Boles, M., et al. (2002). Rising prevalence of antidepressants among US youths. *Pediatrics, 109*(5), 721-727.