PSYCHOPHARMACOLOGY

A Review of Escitalopram and Citalopram in Child and Adolescent Depression

Carlo Carandang MD, ABPN (Dip), FAPA[1,2]; Rekha Jabbal BSP[3]; Angela MacBride BSP, ACPR[3]; Dean Elbe PharmD, BCPP[4]

Abstract

Objective: To review the basic pharmacology and published literature regarding escitalopram and citalopram in child and adolescent depression. **Methods:** A literature review was conducted using the search terms: 'escitalopram', 'citalopram', 'depression', 'randomized controlled trial', 'open label trial' and limits set to: Human trials, English Language and All Child (Age 0-18). Additional articles were identified from reference information and poster presentation data. **Results:** Three prospective, randomized controlled trials (RCT) were found for escitalopram in pediatric depression, and two RCTs were found for citalopram. One RCT each for escitalopram and citalopram showed superiority over placebo on the primary out come measure. Adverse effects in escitalopram and citalopram trials were generally mild to moderate. Suicidality was not assessed systematically in all RCTs reviewed, but did not appear to be elevated over placebo in escitalopram RCTs. One trial reported numerically higher suicide related events for citalopram compared to placebo (14 vs. 5, p=0.06). **Conclusion:** At present, escitalopram and citalopram should be considered a second-line option for adolescent depression. The US Food and Drug Administration approval of escitalopram for treatment of adolescent depression was based on a single positive RCT. This is less evidence than typically required for approval of a drug for a new indication.

Key words: *escitalopram, citalopram, depression, child, adolescent*

Résumé

Objectif: Analyser la pharmacologie et la littérature sur l'utilisation de l'escitalopram et du citalopram dans le traitement de la dépression des enfants et des adolescents. **Méthodologie:** Recherche d'articles contenant les termes suivants: escitalopram, citalopram, dépression, étude aléatoire contrôlée, étude ouverte, avec les limites suivantes: études humaines, anglais, tous les enfants (âgés de 0 à 18 ans). D'autres articles ont été ajoutés en se basant sur des références et sur des données provenant de présentations par affiche. **Résultats:** Deux études prospectives aléatoires contrôlées sur l'escitalopram dans la dépression pédiatrique et deux sur le citalopram ont été trouvées. Les mesures de début d'étude ont montré, dans une des études sur l'escitalopram et une des études sur le citalopram, que ces molécules étaient supérieures au placebo. Les effets secondaires de l'escitalopram et du citalopram étaient faibles à modérés. Ces études n'évaluaient pas systématiquement la suicidalité, qui ne semblait pas, en ce qui avait trait à l'escitalopram, être plus élevée qu'avec le placebo. Dans l'une des études, les événements suicidaires étaient plus nombreux avec le citalopram qu'avec le placebo (14 contre 5, p=0,06). **Conclusion:** L'escitalopram et le citalopram devraient, à l'heure actuelle, être utilisés comme médicaments de deuxième ligne dans le traitement de la dépression des adolescents. La Food and Drug Administration américaine a approuvé l'escitalopram pour traiter les adolescents dépressifs en se basant sur une seule étude prospective aléatoire contrôlée. En règle générale, il est nécessaire de disposer de davantage de données probantes pour ajouter une indication à un médicament.

Mots clés: *escitalopram, citalopram, dépression, enfant, adolescent*

[1]Mental Health and Addictions Program, IWK Health Centre, Halifax, Nova Scotia

[2]Division of Child and Adolescent Psychiatry, Dalhousie University, Halifax, Nova Scotia

[3]Child and Adolescent Addictions and Mental Health, Alberta Health Services, Calgary Zone, Calgary, Alberta

[4]Division of Child and Adolescent Mental Health, BC Children's Hospital, Vancouver, British Columbia

Corresponding email: delbe@cw.bc.ca

Introduction

None of the selective serotonin reuptake inhibitors (SSRIs) or other novel antidepressants are Health Canada approved for use in patients under 18 years of age. Escitalopram (Canada - Cipralex®; US – Lexapro®) was approved by the US Food and Drug Administration (FDA) on March 20, 2009 for acute and maintenance treatment of depression in adolescents 12 to 17 years of age (Yan, 2009). There was controversy surrounding this approval, and this review analyzes the published data on escitalopram and citalopram (Celexa®) in child and adolescent depression. To date, only one other antidepressant, fluoxetine, is FDA approved for acute and maintenance treatment of pediatric depression, in patients 8 to 18 years of age (Eli Lilly & Co., 2011).

Pharmacology

Escitalopram

Escitalopram (S-citalopram) is the active S-enantiomer of the racemic SSRI citalopram. It is available in Canada as 10 and 20 mg tablets (Lundbeck Canada, Inc., 2011). *In vitro* and *in vivo* studies have suggested that escitalopram is a highly potent and selective SSRI. Escitalopram acts by specific competitive inhibition of the membrane transporter of serotonin (Lundbeck Canada, Inc., 2011). Escitalopram has been found to be more than twice as potent as citalopram and is the most selective agent in its class (Rao, 2007; Lundbeck Canada, Inc., 2011).

Escitalopram has no or very little affinity for other receptors such as 5-$HT_{1A,}$ 5-$HT_{2,}$ dopamine D_1 and D_2 receptors, $\alpha_{1,}$ $\alpha_{2,}$ β-adrenoreceptors, histamine H_1, muscarinic cholinergic, benzodiazepine, gamma aminobutyric acid (GABA) and opioid receptors (Lundbeck Canada, Inc., 2011). Escitalopram does not bind to, or has low affinity for sodium, potassium, chloride or calcium ion channels (Lundbeck Canada, Inc., 2011).

In adults, following a single oral dose, escitalopram is rapidly absorbed with a mean maximum plasma concentration (C_{max}) of 18.8 +/- 4.5 ng/mL and a time to reach C_{max} (T_{max}) of approximately 3.0 +/- 1.5 hours (Rao, 2007). The area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) was 637 +/- 356 ng•h/mL (Rao, 2007). The bioavailability of escitalopram was estimated to be approximately 80% which indicates low hepatic extraction of drug (first-pass metabolism) prior to reaching the systemic circulation (Rao, 2007).

Periclou and colleagues (Periclou, Rao, Sherman, Ventura, & Abramowitz, 2003) compared the pharmacokinetics of a single oral dose of escitalopram 10 mg in adolescents (12-17 years of age; n=11) with that of healthy adults (18-35 years of age; n=12). The C_{max} was slightly higher, but not statistically significantly different in the adolescent group (13.1 +/- 2.76 ng/mL in adolescents; 10.39 +/- 1.92 ng/mL in adults, p=0.0621) (Rao, 2007; Periclou et al., 2003). The T_{max} was shorter in the adolescent group (2.9 +/- 0.5 hours in adolescents; 4.5 +/- 2.2 hours in adults, p=0.0249), and elimination half-life ($t_{1/2}$) was shorter in the adolescent group (19 +/-6.4 hours in adolescents; 28.9+/-9.4 hours in adults, p=0.0275) (Periclou et al., 2003). The AUC_{∞} was not significantly different between the two groups (311.7 +/- 105 ng•h/mL in adolescents; 387.1 +/- 157 ng•h/mL in adults) (Periclou et al., 2003). Based on this data the authors concluded that the differences in pharmacokinetic values were not clinically significant and therefore dosage adjustment of escitalopram was not required when used in adolescents.

To determine the pharmacokinetics of escitalopram at steady state a multiple-dose study was carried out using two different doses. Healthy young adult female and male volunteers were given escitalopram 10 mg/day for 24 days or 30 mg/day for 18 days, following a 6 day titration period. The C_{max} was approximately 21 and 64 ng/mL for the 10 and 30 mg/day doses, respectively (Rao, 2007). The AUC from 0 to 24 hours (AUC_{24}) was 360.2 +/- 218.7 and 1100.9 +/- 733.6 ng•h/mL for the 10 and 30 mg/day doses, respectively (nearly 3 times higher for the 30 mg dose) (Rao, 2007). Elimination half-life ($t_{1/2}$) was similar in the single and multiple dose studies (27-32 hours) (Lundbeck Canada, Inc., 2011). Based on the $t_{1/2}$, escitalopram can be dosed once daily with steady state plasma concentration achieved within 7-10 days (Rao, 2007). Food does not affect the absorption of escitalopram (Rao, 2007; Lundbeck Canada, Inc., 2011).

Escitalopram is widely distributed in the tissues following a single oral dose of 10 mg. The apparent volume of distribution (V_D) is about 12-26 L/kg (Lundbeck Canada, Inc., 2011). Escitalopram has low plasma protein binding (56%) and is unlikely to cause protein binding (drug displacement) interactions (Rao, 2007; Lundbeck Canada, Inc., 2011).

Escitalopram is metabolized in the liver to S-desmethylcitalopram (S-DCT) and S-didesmethylcitalopram (S-DDCT), via oxidative metabolism with N-demethylation (Rao, 2007). This process is mediated by cytochrome p450 (CYP) 3A4, CYP2C19 and to a lesser extent CYP2D6. The metabolites, S-DCT and S-DDCT, do not contribute to the clinical effects of escitalopram and have been shown *in vitro* to be much weaker serotonin reuptake inhibitors (Rao, 2007; Lundbeck Canada, Inc., 2011). The main routes of elimination are hepatic and renal. The metabolites undergo renal excretion with a small fraction being voided in the feces. Only 8-10% of the dose is excreted unchanged (Rao, 2007; Lundbeck Canada, Inc., 2011).

Citalopram

Citalopram is a racemic mixture of two enantiomers S-citalopram and R-citalopram, the latter of which has over 100-fold lower affinity for the serotonin transporter (Hyttel, Bogeso, Perregaard, & Sanchez, 1992). As may be expected, like escitalopram, citalopram has minimal affinities for other neurotransmitters or reuptake transporters, and pharmacokinetics of citalopram are similar to those observed with escitalopram (Lexi-Comp Online, 2011). The pharmacokinetics of citalopram have not been fully characterized in adolescents. In adults, $t_{1/2}$ of citalopram is 24-48 hours (mean 35 hours), with peak levels occurring 1-6

hours (mean: 4 hours) after a dose and V_D of 12 L/kg (Lexi-Comp Online, 2011). Citalopram is taken once daily, and food does not affect absorption (Lexi-Comp Online, 2011). Metabolism of citalopram is similar to escitalopram, with additional minor involvement of CYP2D6. Plasma protein binding is higher than escitalopram at 80% (Lexi-Comp Online, 2011), though citalopram is still unlikely to cause significant protein binding/displacement interactions. Citalopram and its metabolites racemic desmethylcitalopram (DCT) and racemic didesmethylcitalopram (DDCT) are excreted in the urine in similar proportions as for escitalopram (Lexi-Comp Online, 2011). Some variability in citalopram disposition has been identified in adolescents based on gender, oral contraceptive use and cigarette smoking (Reis et al., 2002).

Efficacy data

A review of the literature was conducted using the search terms: 'escitalopram', 'citalopram', 'depression', 'randomized controlled trial', 'open label trial' and limits set to: Human trials, English Language and All Child (Age 0-18). Additional articles were identified from reference information, and poster presentation data provided by the manufacturer.

Tables 1 and 2 summarize the published pediatric depression literature on escitalopram and citalopram, respectively. The studies are ranked by Level of Evidence (Centre for Evidence Based Medicine, 2001). Three prospective RCTs were found for escitalopram in pediatric depression (Emslie, Ventura, Korotzer, & Tourkodimitris, 2009; Findling, Bose, Aquino, Korotzer, & Tourkodimitris, 2008; Wagner, Jonas, Findling, Ventura, & Saikali, 2006) and two prospective RCTs were found for citalopram in pediatric depression (von Knorring, Olsson, Thomsen, Lemming, & Hulten, 2006; Wagner et al., 2004).

Escitalopram literature for pediatric depression, consisting of 3 RCTs is summarized in Table 1. Wagner and colleagues (Wagner et al., 2006) studied 268 subjects with depression, 6-17 years of age (mean 12.3), randomized to receive either flexible-dose escitalopram 10-20 mg daily or placebo for 8 weeks. No statistically significant differences were seen between escitalopram and placebo on the a priori primary outcome measure of CDRS-R score. Response rates measured via CGI-I of 2 or less were 62.8% in the escitalopram group, and 52.3% in the placebo group. A post hoc analysis of study completers 12-17 years of age found a significant difference in favour of escitalopram on CDRS-R scores (p=0.047). Emslie and colleagues (Emslie et al., 2009) studied 312 subjects with depression, 12-17 years of age (mean 14.6), randomized to receive either flexible-dose escitalopram 10 to 20 mg daily or placebo for 8 weeks. Escitalopram treatment led to greater reduction in CDRS-R scores (primary outcome measure) than placebo, with effect size of 0.27 (small to medium effect size). Response rates measured via the Clinical Global Impressions-Improvement Scale (CGI-I) of 2 or less were 64.3% in the escitalopram group, and 52.9% in the placebo group. A 16-week double-blind extension of the previous 8-week trial (Emslie et al., 2009) was conducted by Findling and colleagues (Findling et al., 2008) which maintained observed statistically significant differences in CDRS-R reduction between escitalopram and placebo.

The citalopram literature is summarized in Table 2. The only RCT of citalopram/escitalopram conducted outside of North America for pediatric depression was headed by a European group (von Knorring et al., 2006). This group studied 244 subjects with depression, 13-18 years of age (mean 16), randomized to receive either citalopram or placebo for 12 weeks. No significant improvement was seen as measured by the Schedule for Affective Disorders and Schizophrenia for school-aged children - Present episode version (Kiddie-SADS-P) (primary outcome measure) and the Montgomery Åsberg Depression Rating Scale (MADRS). Mean daily citalopram dose in this trial was 26 mg (range 10-40 mg). As with other antidepressant trials in adolescents, placebo response rate (61%) in this study was much higher than those typically observed in adult antidepressant trials.

Wagner and colleagues (Wagner et al., 2004) studied 178 subjects with depression, 7-17 years of age (mean 12.1), randomized to receive either citalopram or placebo for 8 weeks. Improvement was measured by the Children's Depression Rating Scale – Revised (CDRS-R) (primary outcome measure), where the difference in response rates between citalopram (36%) and placebo (24%) was statistically significant, with an effect size of 2.9 (large effect size). The rest of the literature on citalopram for pediatric depression consists of open-label trials and retrospective studies, as detailed in Table 1 (Schirman et al., 2010; Shirazi & Alaghband-Rad, 2005; Baumgartner, Emslie, & Crismon, 2002; Bostic, Prince, Brown, & Place, 2001).

Safety data

Escitalopram

Escitalopram is the therapeutically active enantiomer of racemic citalopram. The adverse effects of escitalopram are theoretically similar to but not as prevalent as those with citalopram. Safety data for escitalopram in pediatric depression was reviewed from three RCTs and one case report.

Wagner (Wagner et al., 2006) published an RCT in children and adolescents (6-17 years of age). The rate of premature discontinuation due to adverse effects was 1.5% for both treatment groups. In the escitalopram group, one patient discontinued due to indigestion and one due to insomnia, nausea, and shaking. Adverse events that occurred more

Table 1. Summary of escitalopram evidence in children and adolescents

Report Type & Level of Evidence	Year/Lead Author/Journal	# of pts (n), % males	Pt age (mean (SD) and range) (years)	Dosage
Prospective Double-Blind Randomized Trial (Level 1b)	2009; Emslie; J Am Acad Child Adolesc Psychiatry	n= 312 (41% male)	Esc group 14.5 (1.5) Pl group 14.7 (1.6) (range: 12-17)	Esc 10-20 mg vs Pl (mean dose Esc 13.2± 2.9 mg/day)
Prospective Double-Blind Randomized Trial (Level 1b)	2008; Findling; AACAP poster presentation (Extension trial of Emslie 2009)	n = 77 (41% male)	14.5 (1.5) (range: 12-17)	Esc 10-20 mg vs Pl
Prospective Double-Blind Randomized Trial (Level 1b)	2006; Wagner; J Am Acad Child Adolesc Psychiatry	n = 268 (48% male)	12.3 (3.0) (range: 6-17)	Esc 10-20 mg vs Pl (mean dose Esc 11.9± 2.3 mg/day)

Abbreviations

AACAP = American Academy of Child and Adolescent Psychiatry; AE = adverse events; Esc = Escitalopram; Pl = placebo

Abbreviations of Rating Scales used

CDRS-R = Children's Depression Rating Scale - Revised

CGAS= Children's Global Assessment Scale

CGI-I= Clinical Global Impressions - Improvement

CGI-S= Clinical Global Impressions -Severity

MC-SSRS= Modified Columbia Suicide Severity Rating Scale

SIQ-JR= Suidical Ideation Questionnaire - Junior High School Version

frequently in the escitalopram group were abdominal pain (5.4%), nausea (3.1%), vomiting (1.5%), headache (1.1%), and rhinitis (0.1%). There were two serious adverse events in the escitalopram group: pneumonia and accidental injury. There was one report of intentional self-harm behaviour in an escitalopram patient (self-inflicted laceration to wrist) compared to two in the placebo group. No clinically significant ECG results, laboratory, vital signs, or weight changes were observed.

Emslie (Emslie et al., 2009) reported adverse effects in a RCT in adolescents (12-17 years of age). Discontinuation rates due to adverse effects between the placebo group and the escitalopram group were 0.6% vs. 2.6% (p=0.21).

Duration of treatment	Efficacy Rating Scales (Bold = 1° Endpoint)	Efficacy Results	Adverse Events (AE)
1 week placebo lead followed by 8 weeks randomization	**CDRS-R** CGI-I CGI-S CGAS	**CDRS-R: mean improvement of -3.356 (P=0.022)** CGI-I: mean improvement of -0.344 (P=0.008) Responders (CGI-I ≤2): Esc: 64.3% vs Pl 52.9% CGI-S:mean improvement of -0.37 (P=0.007) CGAS: no mean change	MC-SSRS=no difference in suicidal behaviour (Pl=2.3% vs Esc=1.5%) or suicidal ideation (Pl=9.4% vs Esc=9.2%) SIQ-JR=no statistical difference (mean change from baseline Pl=-4.6 ±12.0 vs Esc=-2.9±10.2 (P=0.29)) 12 events considered to be self-harm (Pl=6 Esc=6) AE (% above Pl): insomnia (3.9), influenza-like symptoms (3.9), nausea/abdominal pain/diarrhea (2), vomiting (0.8) Decreased platelet count in Esc group (Pl=-2.2x109/L vs Esc=-7.6x109/L) Discontinuation due to AE: Pl=0.6% vs Esc=2.6% (P=0.21)
16 week extension of previous 8 week trial (Emslie 2009)	**CDRS-R** CGI-I CGI-S CGAS	**CDRS-R: mean improvement of -4.9 (P=0.005)** CGI-I:mean score of Pl=2.5±0.1 vs Esc=2.2 ±0.1 (P<0.05) CGI-S: mean improvement of -0.5 (P<0.05) CGAS: mean improvement of 3.6 (P<0.05)	MC-SSRS=increase in suicidal behaviour/ideation (Pl=10.9% vs Esc=14.5%) SIQ-JR= mean change from baseline Pl = -5.8±12.8 vs Esc= -3.0±11.7 Suicidality: 2 episodes in each Pl and Esc group (in extension group) AE (above Pl): nausea and insomnia Discontinuation due to AE: Pl=0.8% vs Esc=5.2%
8 weeks	**CDRS-R** CGI-I CGI-S CGAS	**CDRS-R: not statistically significant (P=0.31) (post hoc analysis of 12-17 year-olds P=0.047)** CGI-I: not statistically significant Responders (CGI-I <2): Esc: 62.8% vs Pl 52.3% CGI-S: not statistically significant (P=0.057) CGAS: not statistically significant (P=0.065)	Suicidality: 1 self-harm episode in Esc group; 2 self-harm episodes in Pl group AE (% above Pl): abdominal pain (5.4), nausea (3.1), vomiting (1.5), headache (1.1), rhinitis (0.1) Discontinuation due to AE: Pl 1.5% vs Esc 1.5%

Adolescents experienced insomnia (3.9%), influenza-like symptoms (3.9%), diarrhea (2%), nausea (2%), and abdominal pain (2%) in rates greater than placebo. In the escitalopram group, four patients experienced serious adverse events. One patient was sexually assaulted, one patient displayed self-injurious behaviour, one had suicidal ideation, and one displayed irritability. Furthermore, 12 adverse events were reported that were considered by the investigators to be suggestive of self-harm (six events in the placebo arm and six events in the escitalopram arm). All six escitalopram events were classified as being non-suicidal self-injurious behaviours. Using the Modified Columbia Suicide Severity Rating Scale (MC-SSRS) to prospectively measure suicidality; placebo treated patients compared to

Table 2. Summary of citalopram evidence in children and adolescents

Report Type & Level of Evidence	Year/Lead Author/Journal	# of pts (n), % males	Pt age (mean (SD)) and range (years)	Dosage
Prospective Double-Blind Randomized Trial (Level 1b)	2006; von Knorring; J Clin Psychopharm	n = 244 (% males not specified)	16 (1) (range: 13-18)	Cit 10-40 mg vs Pl (mean dose Cit 26 mg/day)
Prospective Double-Blind Randomized Trial (Level 1b)	2004; Wagner; Am J Psychiatry	n = 178 (47% male)	12.1 (3.1) (range: 7-17)	Cit 20-40 mg vs Pl (mean dose Cit 24 mg/day)
Prospective Open-Label Trial (Level 2b)	2010; Schirman; J Neural Transm	n = 78 (50% male)	13.9 (2.8) (range: 7-18)	Cit 20-40mg/day (mean dose of Cit 30.2 ±10.1mg/day)
Prospective Open-Label Trial (Level 2b)	2005; Shirazi; J Child Adolesc Psychopharmacol	n = 30 (47% male)	13.57 (2.5) (range: 8-17)	Cit 10-40 mg/day (mean dose Cit 20.8mg/day)
Retrospective Chart Review (Level 2b)	2002; Baumgartner; Ann Pharmacother	n = 17 (52.9% male)	13.2 (2.5) (range: 8-17)	Cit 10-40 mg/day (mean dose Cit 22.4 ± 7.3 mg/day)
Retrospective Chart Review (Level 2b)	2001; Bostic; J Child Adolesc Psychopharmacol	n = 21 (57% male)	15 (1.8) (range: 12-17)	Cit 10-60 mg/day (mean dose of Cit 26.5 ± 13.1 mg/day)

Abbreviations: AE = adverse events; Cit = citalopram; Pl = placebo

Abbreviations of Rating Scales used

BDI = Beck Depression Inventory

CDI = Children's Depression Inventory

CDRS-R = Children's Depression Rating Scale - Revised

CGAS = Children Global Assessment Scale

CGI-I = Clinical Global Impression - Improvement

CGI-S = Clinical Global Impression - Severity

GAF = Global Assessment of Functioning

HDRS = Hamilton Depression Rating Scale

IDS-C = Inventory of Depressive Symptomatology - Clinician Rated

Kiddie-SADS-P = Schedule for Affective Disorders and Schizophrenia for school-aged children - Present episode version

MADRS = Montgomery Asberg Depression Rating Scale

SCARED = Screen for Child Anxiety Related Emotional Disorders

SIQ = Suicide Ideation Questionnaire

Duration of treatment	Efficacy Rating Scales (Bold = 1° Endpoint)	Efficacy Results	Adverse Events (AE)
12 weeks	**Kiddie-SADS-P** **MADRS** BDI GAF	**Kiddie-SADS-P: decrease from baseline for both groups (no sig difference); responders for Cit = 60% vs Pl = 61%** MADRS: no significant difference BDI: no significant difference GAF: no significant difference	Suicide-related events: Cit=14 pts vs Pl=5 pts (p=0.06) AE (%above Pl): Fatigue (5), Nausea (4), Insomnia (2), Headache (1) Discontinuation due to AE: Pl=8% vs Cit=11%
8 weeks	**CDRS-R** CGI-I CGI-S	**CDRS-R: effect size of 2.9; Cit improvement F=6.58, df=1, 150 (p<0.05);** response rate Cit 36% Pl 24% (p<0.05) CGI-I: rating ≤2 Cit 47% vs Pl 45% CGI-S: Improvement from basline Cit -1.3 vs Pl -1.0	AE (%above Pl): Nausea (10), Rhinitis (7.6), Influenza-like symptoms (6.7), fatigue (4.4), diarrhea (4.4), abdominal pain (4.1), back pain (2.1) Discontinuation due to AE: Pl=5.9% vs Cit=5.6%
8 weeks	**CGI-I** CDRS-R CDI BDI SCARED	**CGI-I: significant improvement in 55.8% of all pts (85.1% in pts w/moderate illness, 47.3% in pts with marked illness,** 27.2% in pts w/ severe illness) CDRS-R: 43.1% showed ≥50% reduction in symptoms (p<0.001) CDI: significant reduction in depression severity (p=0.005) BDI: significant reduction in depression severity (p<0.001) SCARED: 50.% pts decreased score by ≥50% (p<0.001)	CDRS-R Item 13 (suicidality) = 44.8% decrease in suicidal ideation (p<0.001) SIQ = 21.6% decrease (p=0.054) AE reported: fatigue (31.6%), motor agitation (25.3%), decreased appetite (21.1%), headache (20%), gastric discomfort (16.8%), insomnia (15.8%), psychological agitation (14.7), hypersomnia (10.5%), sweating (10.5%) psychological & motor agitation more common in males (p<0.05) Discontinuation due to AE in 10 pts (10.8%)
6 weeks	**HDRS** **CGAS**	**HDRS: X=22.78; t=-14.12 (P<0.000)** **CGAS: X=26.02; t = 9.68 (P<0.000)** Moderate to large effect (≥50% change in HDRS & CGAS) in 91.7% of pts	AE reported by 3 pts (10%) delayed menstrual period, diuresis, nausea, diaphoresis Discontinuation due to AE in 6 patients (1=nausea & vomiting; 5=switched to mania)
12 weeks	**CGI-I** CDRS-R IDS-C SCARED	**CGI-I: 3/17 reported as "very much improved" & 9/17 as "much improved"** CDRS-R: 75% of pts had reduction of ≥50 % from baseline; 38% of pts had reduction of >70% IDS-C: 38% of pts had reduction of >50% from baseline SCARED: 50-75% of pts had >50% reduction from baseline	AE reported: drowsiness (29%), headache (24%), shakiness (18%), nausea (12%), dizziness (6%), decreased libido (6%), decreased appetite (6%) Discontinuation due to AE in 1 pt (6%)
128.5 ± 84 days	**CGI-I** **CGI-S**	**CGI-I: 76% much or very much improved** **CGI-S: reduction in severity 4.1±1.04 to 2.9 ±0.94 (p<0.0026)**	Mild AE reported by 33% of pts including headache, dizziness, nausea, sedation, agitation, & sweating Discontinuation due to AE in 3 pts (14%)

escitalopram treated patients, 2.3% vs. 1.5% had a worsening of suicidal behaviour, and 9.4% vs. 9.2% had a worsening of suicidal ideation. Changes in Suicidal Ideation Questionnaire – Junior High School Version (SIQ-JR) from baseline were non-significant between the two groups. Vital signs and weight gain were small and comparable between both groups. There were no abnormal electrocardiogram (ECG) findings at endpoint.

Findling (Findling et al., 2008) performed a double-blind extension of the originally conducted Emslie study (Emslie et al., 2009) that found discontinuation caused by adverse events for escitalopram to be 5.2% vs. 0.8% for placebo ($p<0.05$). Nausea and insomnia were the only side effects reported to be more frequent in the escitalopram group compared to placebo. In the extension portion of the study, four escitalopram patients experienced serious adverse events: one patient experienced severe weight loss, one patient had suicidal tendency, one with intentional overdose, and one with pleuritis. Treatment emergent adverse events thought to be suggestive of self-harm were noted in 5.7% of placebo patients compared to 7.1% of escitalopram patients in the lead-in and extension population combined. Percentages of patients reporting any increases in suicidal ideation and/or behaviour as indicated on the MC-SSRS were 10.9% vs. 14.5% for placebo vs. escitalopram. At endpoint, the SIQ-JR mean (±SD) change from baseline was -5.8 (±12.8) for placebo compared to -3.0 (±11.7) for escitalopram.

Miriyala and Coffey (2008) described a case of renal failure in a 17 year-old female following a 10 month course of treatment of major depressive disorder with escitalopram. Approximately three weeks after taking a one week break from the medication, the patient experienced nausea, vomiting, abdominal pain, and diarrhea. After treating these symptoms unsuccessfully for three weeks, the patient was taken to hospital and was diagnosed with acute renal failure with no specific cause. Escitalopram was discontinued four days after the diagnosis was made. Eosinophiluria and eosinophilia were found during the workup, suggestive of drug-induced allergic interstitial nephritis. At time of discharge one week later, the patient's serum creatinine was approaching normal and her symptoms had improved.

Citalopram

Safety data for citalopram in pediatric depression was reviewed from two RCTs, two prospective open-label trials, and two retrospective reviews.

von Knorring (von Knorring et al., 2006) reported adverse effects in an RCT of citalopram in adolescents 13-18 years of age. Discontinuation rates due to adverse effects for the citalopram and placebo groups were 11% vs. 8%. Treatment emergent adverse events were reported by 75% of citalopram patients compared to 71% of placebo patients. Most adverse events were considered mild to moderate, with headache, nausea and insomnia the most common, though not significantly different between groups. Fatigue occurred significantly more frequently with citalopram compared to placebo (6% vs. 1%, $p=0.02$). Thirty-four serious adverse events occurred, with 18 in the citalopram group compared to 16 in the placebo group, and the most common event was hospitalization due to psychiatric disorder. No deaths occurred. Suicidality was assessed at trial entry, with nearly one-third of patients having had previous suicide attempts. Treatment emergent suicidality was reported by 14 patients receiving citalopram compared to 5 patients receiving placebo ($p = 0.06$). Most patients reporting treatment emergent suicidality recovered and continued in the study. No clinically significant changes between citalopram and placebo groups for laboratory measures, ECG data, vital signs or body weight were identified.

Wagner (Wagner et al., 2004) reported adverse effects from a citalopram RCT in children and adolescents 7-17 years of age. Discontinuation rates due to adverse effects for the citalopram and placebo groups were 5.6% compared to 5.9%. Treatment emergent adverse events occurring more often in the citalopram group than the placebo group and at rates greater than 5% were rhinitis, nausea, abdominal pain, influenza-like symptoms, fatigue, diarrhea and back pain. Adherence rates to study medication was not detailed in this trial, and many of the adverse effects noted to occur more commonly in the citalopram group are in keeping with SSRI discontinuation syndrome. No serious adverse events were documented. Suicidality as an adverse event was not specifically addressed in this trial. No clinically significant changes between citalopram and placebo groups for laboratory measures, ECG data, vital signs or body weight were identified.

Schirman (Schirman et al., 2010) reported adverse effects in an open-label trial of citalopram in children 7-18 years of age. Ten of 95 patients (10.5%) discontinued the trial early due to adverse effects, including two patients who developed hypomanic symptoms. The most common adverse effects reported included fatigue, motor agitation, decreased appetite, headache, gastric upset, insomnia, agitation, hypersomnia and sweating. Psychological and motor agitation were more common in males than in females ($p<0.05$). While overall population suicidality scores measured by the suicidal ideation questionnaire (SIQ) declined by 21.6% ($p=0.054$), the numbers of patients experiencing treatment emergent suicidality were not provided. No suicide attempts were documented during this trial.

Shirazi (Shirazi & Alaghband-Rad, 2005) reported adverse effects in an open-label trial of citalopram in children 8-17 years of age. Five of 30 patients (16.7%) discontinued the

trial early due to manic switch, and one patient discontinued due to nausea and vomiting. The authors reported screening for manic symptoms at trial entry via the Diagnostic Interview of Children and Adolescents. Other adverse effects reported were considered mild and included single reports of delayed menstrual period, diuresis, nausea and diaphoresis. The authors state that no suicidal thoughts or behaviours occurred; however, systematic screening for suicidality was not reported.

Baumgartner (Baumgartner et al., 2002) reported adverse effects in a retrospective review of citalopram in children 8-17 years of age. One of 17 patients (6%) discontinued citalopram due to intolerable adverse effects, and one patient required dosage reduction due to adverse effects. Documented adverse effects included drowsiness (29%), headache (24%), shakiness (18%), nausea (12%), dizziness (6%), decreased libido (6%) and decreased appetite (6%).

Bostic (Bostic et al., 2001) reported adverse effects in a retrospective review of citalopram in adolescents 12-17 years of age. Three of 21 patients (14%) discontinued citalopram due to intolerable adverse effects (headache: two patients, dizziness: one patient). Seven patients (33%) reported mild adverse effects that included: headache, dizziness, nausea, sedation, agitation and diaphoresis. None of the patients had symptoms of manic activation. No comment was made regarding suicidality by the authors.

FDA Approval Process & Legal Action

While only one RCT for escitalopram was statistically superior to placebo on the primary outcome measure, according to Forest Laboratories, Inc. (US manufacturer of Lexapro®) the FDA decision to approve escitalopram was based on two RCTs – the escitalopram RCT with positive results (Emslie et al., 2009) and an earlier trial with citalopram (Wagner et al., 2004). "Escitalopram is the only active enantiomer of the racemic drug citalopram, so we considered it reasonable to [deem] the positive citalopram study along with the positive escitalopram study as sufficient evidence to support the approval," said Karen Mahoney, an FDA spokesperson (Yan, 2009). A 2002 application for a pediatric indication for citalopram had previously been rejected by the FDA, and the US patent for citalopram expired in 2003 (Yan, 2009).

The FDA approval decision for escitalopram came shortly after filing of a federal civil suit alleging Forest Laboratories, Inc. had illegally marketed escitalopram and citalopram for off-label use in children and adolescents from 1998 to 2005. The suit also alleged the company suppressed publication of a negative citalopram trial, and reports of increased suicidality in pediatric patients (Yan, 2009). This lawsuit was joined with another lawsuit regarding another Forest Laboratories, Inc. product levothyroxine, and was eventually settled in September 2010 for the sum of $149 million (Forest Laboratories, Inc., 2010).

The citalopram trial (Wagner et al., 2004) that formed part of the basis for escitalopram FDA approval was alleged to have been written and submitted by a medical "ghostwriter" on behalf of Forest Laboratories, Inc. (Freedman & Roy, 2009). In April 2009, one month after the FDA approval for escitalopram in adolescents was granted, Forest Laboratories, Inc. admitted that a medical communications company, Prescott Medical Communications Group was not acknowledged as a contributor to the article at the time of publication. This practice is not allowed by the American Journal of Psychiatry, and an editor's note regarding correction of this matter was published in August 2009 (Freedman & Roy, 2009).

Discussion and recommendations

The research groups that have studied citalopram and escitalopram for pediatric depression in RCTs are not independent groups, with the exception of the von Knorring group from Sweden (von Knorring et al., 2006). However, the RCT by this group was a negative trial. The other principal investigators on the studies analyzed here are co-authors on each others studies (Wagner et al., 2006; Wagner et al., 2004) and one group performed the double blind extension (Findling et al., 2008) of the other group's RCT (Emslie et al., 2009). From these data, escitalopram and citalopram should not be considered for first-line treatment of adolescent depression, given the lack of replication of positive studies by independent groups. Each positive RCT lasted for only 8 weeks duration (Wagner et al., 2004; Emslie et al., 2009), and there was only one 16 week extension (Findling et al., 2008). Hence, the indication for escitalopram for maintenance treatment of adolescent depression is premature. According to Forest Laboratories, Inc., "the FDA approved escitalopram for maintenance treatment because the efficacy in adolescents 'can be extrapolated from adult data' and from the drug's pharmacokinetic parameters" (Forest Laboratories, Inc., 2010). While not required for licensing approval, a glaring omission is the lack of head to head trials of escitalopram or citalopram with fluoxetine, the gold-standard treatment for pediatric depression.

Pediatric psychopharmacology is a burgeoning field, and no longer requires extrapolation from adult studies, given the differential response and safety issues when comparing a pediatric population with an adult population. For example, tricyclic antidepressants (TCAs) do not work in the pediatric population (Hazell, O'Connell, Heathcote, & Henry, 2002) whereas TCAs are effective treatments for depression in adults.

Health Canada should not follow the FDA decision, and should demand that standards and process be met until sufficient evidence supporting safety and efficacy is provided for a pediatric indication. Given the broad awareness of the circumstances leading to the FDA approval of escitalopram for adolescents and a Canadian escitalopram patent expiry date of September 2014, application by Lundbeck Canada, Inc. to Health Canada for an escitalopram pediatric

indication seems unlikely. Unlike in the US, completion of studies leading to pediatric or geriatric indications are not incentivized by six-month patent extensions in Canada.

Conclusion

In conclusion, the available evidence does not support first-line treatment of adolescent depression with either escitalopram or citalopram. It is our opinion that the US FDA approval of escitalopram was premature, given the available evidence. Escitalopram and citalopram should be considered second-line treatments for adolescent depression, along with sertraline. Dosage adjustment of escitalopram is not required when used in adolescents.

Acknowledgements / Conflicts of Interest

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