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Expert Opinion

Escitalopram for the treatment of major depressive disorder in youth

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Introduction: Major depressive disorder (MDD) is a serious public problem, affecting 4 – 6% of adolescents at any one time. Although adolescent MDD needs early and appropriate intervention, concerns regarding the risk of suicidality associated with antidepressant treatment and efficacy of pharmacotherapy have led to decreased use of antidepressants in children and adolescents. After the approval of fluoxetine in 2003, escitalopram received FDA approval in 2009 for the acute and maintenance treatment of MDD in adolescent patients.

Areas covered: The paper addressed the following questions: Is escitalopram effective for adolescent MDD? How large is the magnitude of effectiveness? Does escitalopram treatment have any benefit in adolescents compared with the risk of suicidal behavior and treatment-emergent adverse events?

Expert opinion: The efficacy of escitalopram in adolescent MDD was demonstrated in a double-blind, randomized, controlled trial and extrapolated from a similar citalopram trial. The optimal dose is 10 mg/day and the magnitude of the antidepressant effect is modest. Escitalopram treatment is generally well tolerated by adolescents, but treatment-emergent agitation, suicidal behavior and manic symptoms should be closely monitored. Escitalopram can be used as one of the first-line treatment options for moderate to severe MDD in adolescents.

Keywords: adolescent, adverse events, child, citalopram, clinical trial, escitalopram, fluoxetine, major depressive disorder (MDD), selective serotonin reuptake inhibitors (SSRIs), suicidality

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1. Introduction

Major depressive disorder (MDD) is a serious disorder characterized by depressive mood, or loss of interest or pleasure. According to the DSM-IV-TR [1] a child/adolescent meets diagnostic criteria for MDD when he/she has a minimum of five of the following nine symptoms present during the same 2-week period: depressed mood or irritable mood or loss of interest or pleasure; markedly diminished interest or pleasure in activities; decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness, diminished ability to concentrate; recurrent thoughts of death; recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. At least one of the symptoms has to be either depressed mood or loss of interest or pleasure. It is important that the symptoms represent a change from previous functioning and cause clinically significant distress or impairment in social, occupational or other important areas of functioning. In adolescents, MDD increases the risk of suicide attempts and suicide, and tends to recur in adulthood [2]. Epidemiologic studies have found that MDD is common among adolescents with 4 – 6% point prevalence and up to 25% lifetime prevalence by the end of adolescence [3]. Retrospective reports about

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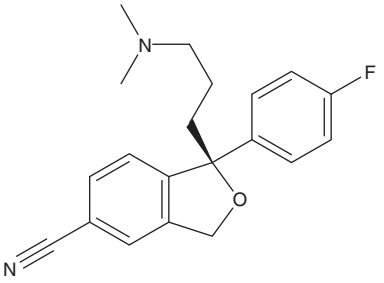
Box 1. Drug summary.

Drug name	Escitalopram
Phase	Launched
Indication	Major depressive disorder in adolescents
Pharmacology description	5 hydroxytryptamine uptake inhibitor
Route of administration	Alimentary, p.o.
Chemical structure	S-enantiomer of citalopram
	
Pivotal trial(s)	[29]

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the age of onset in adult studies indicate that > 50% of youths with MDD continue to have adult recurrence [3]. Adolescent depression is usually diagnosed according to adult diagnostic criteria, but there are important differences between adolescent and adult depression in terms of clinical presentation, comorbid disorders, risk of suicidal behavior and response to pharmacotherapy. Depressed adolescents have greater impulsivity, irritability, reckless behavior and behavior disturbances and fewer neurovegetative symptoms than do adults with depression [4,5]. Comorbid disorders with adolescent MDD include learning disability, attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorders anxiety disorders and substance abuse [6]. When a child or adolescent develops depressive symptoms, apart from major depression, the possibility of an underlying bipolar disorder should also be considered [7].

The concern over selective serotonin reuptake inhibitor (SSRI) use in children and adolescents began in 2003, when new data from clinical trials of paroxetine did not demonstrate efficacy in depressive children and showed an increased suicidality in children taking paroxetine compared with placebo [8]. In March 2004, the FDA issued a public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with 10 newer antidepressants (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram and venlafaxine) [9]. The FDA public health advisory recommended close observation for the emergence of suicidality in all patients treated with antidepressants, especially at the time of treatment initiation or dose increase. The FDA also mandated a black-box warning of increased risk of suicidal acts and behavior on the label of 10 antidepressants for their use in the pediatric population. This was based on data from trials in children conducted from the mid-1990s that indicated a risk ratio for suicidal acts (no suicides occurred) with antidepressants compared with placebo of 2.19 (95% CI 1.50 – 3.19; p = 0.00005) [10].

In addition to concerns about the safety of antidepressant use among children and youth, relative lack of convincing data on the efficacy of antidepressant in children and adolescents caused clinicians to hesitate about prescribing antidepressants to depressive youth. Fluoxetine had been the only antidepressant that had an FDA indication for the treatment of depression in children and adolescents until escitalopram (**Box 1**) was approved by the FDA for the treatment of depression in adolescents on 19 March 2009 [11]. This review summarizes randomized placebo-controlled trials of antidepressants in children and adolescents and critically reviews data from four double-blind, placebo-controlled trials with citalopram and escitalopram for the treatment of major depression in children and adolescents.

2. Clinical trials of antidepressants in youth

The efficacy of tricyclic antidepressants (TCAs) in the treatment of children and adolescents has not been consistently demonstrated in double-blind, placebo-controlled trials [12-14]. A meta-analysis of 13 randomized placebo-controlled trials with TCAs showed no overall significant improvement with TCAs compared with placebo [15]. Subgroup analyses of this study suggested some benefit among adolescents (effect size = -0.47, 95% CI -0.92 to -0.02) and no benefit among children (effect size = 0.15, 95% CI -0.34 – 0.64). But treatment with TCAs was associated with higher incidence of vertigo, orthostatic hypotension, tremor and dry mouth.

There have been three double-blind, placebo-controlled trials (total n = 754) with fluoxetine which support its efficacy in the treatment of children and adolescents with MDD [16-18]. Of the three studies, the Treatment for Adolescents with Depression Study (TADS) was a multisite, controlled, publicly funded trial of 439 patients, aged 12 – 17 years, with MDD, which compared the effectiveness of fluoxetine (10 – 40 mg/day) and cognitive behavioral therapy (CBT), either alone or combination, with placebo for 12 weeks [18]. The primary outcome measures were the Children's Depression Rating Scale – Revised (CDRS-R) and the Clinical Global Impression – Improvement (CGI-I) score. After 12 weeks, fluoxetine alone (mean highest dose = 33.3 mg/day) were superior to both CBT and placebo alone, as measured by the CDRS-R. The combination was significantly superior to fluoxetine alone and CBT alone. There was no completed suicide. While clinically significant suicidal thinking as measured by the Suicidal Ideation Questionnaire – Junior High School Version (SIQ-JR) improved significantly in all four treatment groups, harm-related

adverse events occurred more frequently in fluoxetine-treated patients than in non-fluoxetine-treated patients (OR = 2.19, 95% CI 1.03 – 4.62). The harm-related adverse event was defined as involving harm to self, which can include a nonsuicidal event, such as cutting for relief of dysphoric affects, worsening of suicidal ideation without self-harm, or a suicide attempt of any lethality; or harm to others.

The efficacy of sertraline was evaluated in two parallel, double-blind, placebo-controlled trials of 376 children and adolescents, aged 6 – 17 years, with MDD [19]. When the data from the two studies were pooled in a prospectively defined combined analysis, it demonstrated that sertraline was statistically superior to placebo on the change in CDRS-R score from baseline to end point. The review of pediatric antidepressant trials by a British health agency, Medicines and Healthcare products Regulatory Agency (MHRA), includes the separate analysis of these two trials [20]. This analysis found that the two individual trials, did not demonstrate the effectiveness of sertraline in treating MDD in children and adolescents.

In the two trials there was a higher rate of discontinuation from sertraline (a total of 17) compared with placebo (a total of 4), especially amongst children. The rate of suicidal thoughts and self-harm, regardless of whether they led to treatment discontinuation, was 2.7% (5/189) in the sertraline group and 1.1% (2/184) in the placebo group.

There have been three multicenter trials of paroxetine for the treatment of children and/or adolescents with major depression, all of which were negative on the primary outcome measures [12,21-22]. Of these trials, only one study showed significant differences for paroxetine compared with placebo on some secondary measures [12]. On the basis of a CGI-I score of 1 or 2, the response rate of the paroxetine group (66%) was significantly greater than that of the placebo group (48%). Apter *et al.* [23] performed a blinded review of potential suicidal events and compared incidence rates between paroxetine- (n = 642) and placebo- (n = 549) treated pediatric patients during all five acute double-blind trials of paroxetine. The results showed that suicide-related events occurred more often in paroxetine (3.4%) than placebo groups (0.9%); (OR = 3.86, 95% CI 1.45 – 10.26; p = 0.003). Except one case, all suicide-related events occurred in adolescents of at least 12 years old. All suicide attempts occurred in MDD; few suicide-related events occurred in patients with a primary anxiety disorder. Therefore, paroxetine is not recommended as a treatment option for pre-pubertal children, but may be considered for adolescents as an alternative antidepressant based on individual circumstances.

There have been two multicenter, double-blind, placebo-controlled trials of venlafaxine extended release (ER) for the treatment of major depression in 165 and 201 children and adolescents, aged 7 – 17 years [24]. Both trials were negative on primary outcome measure, which was the change from baseline in the CDRS-R score at week 8. A *post hoc* age subgroup analysis of the pooled data showed greater improvement on the CDRS-R with venlafaxine ER than with placebo among adolescents (aged 12 – 17 years), but not among children (aged 7 – 11 years). The most common adverse events were anorexia and abdominal pain. Hostility and suicide-related events were more common in venlafaxine ER-treated participants than in placebo-treated participants. There were no completed suicides.

There have been two unpublished controlled trials of mirtazapine for the treatment of children and adolescents, aged 7 – 17 years, with major depression [25]. Both trials failed to show a difference between mirtazapine and placebo on the primary efficacy measure of change from baseline to end point in the CDRS-R.

There have been no controlled trials of bupropion in pediatric depression. In an open-label study, 24 adolescents with comorbid ADHD and depression were treated for more than 8 weeks with bupropion sustained release (SR) [26]. Response rates defined as CGI-I score of 1 or 2 were 88% for depressive disorders and 63% for ADHD.

There have been only two double-blind, placebo-controlled trials of citalopram [27,28] and two double-blind, placebo-controlled trials of escitalopram [29,30] in children and/or adolescents with MDD. The efficacy of citalopram was demonstrated in one double-blind, placebo-controlled trial for children and adolescents in the USA [27] but not in a European trial [28] for adolescents. A multicenter, double-blind, placebo-controlled trial of escitalopram supported the efficacy of escitalopram as an acute treatment for MDD in adolescent patients [29]; however, a separate controlled trial of escitalopram in pediatric patients, aged 7 – 17 years, with MDD, failed to show the efficacy over placebo [30]. A subgroup analysis of the data indicated that escitalopram might be more effective than placebo in the adolescent group.

The efficacy of escitalopram in the acute treatment of MDD in adolescents was established, in part, based on extrapolation from the previously mentioned placebo-controlled study with racemic citalopram 20 – 40 mg/day [27]. Thus, we critically reviewed the two controlled citalopram studies and the two controlled escitalopram studies in detail. Three of the four studies are compared on the characteristics of the study subjects and on the efficacy results of the data in **Table 1** and **Table 2**.

3. Clinical trials of citalopram in youth

One of the two studies comparing citalopram and placebo was conducted in the USA, and another in Europe. The US study was an 8-week, randomized, double-blind, placebo-controlled study of 178 children and adolescent outpatients, aged 7 – 17 years, with MDD. Diagnosis was established with the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL) [27]. This study excluded patients with primary psychiatric disorders other than MDD, any psychotic features,

Table 1. Characteristics of placebo-controlled trials of citalopram and escitalopram in children and adolescents with major depressive disorder.

	Wagner *et al.* 2004 [27]		Wagner *et al.* 2006 [30]		Emslie *et al.* 2009 [29]	
Active medication	Citalopram		Escitalopram		Escitalopram	
Dose range (mg)	20 – 40		10 – 20		10 – 20	
Overall mean dose (mg/day)	25		12.3		13.2	
n	178		268		312	
Year study ended	2001		2004		2007	
Number of study site	21		25		40	
Age range (years)	7 – 17		6 – 17		12 – 17	
	Placebo	**Citalopram**	**Placebo**	**Escitalopram**	**Placebo**	**Escitalopram**
n (intent-to-treat)	85	89	133	131	157	154
Completion rate, n (%)	67 (78.8)	71 (79.8)	115 (86.5)	102 (77.9)	133 (84.7)	126 (81.3)
Age, (years, mean ± SD)	12.1 ± 2.8	12.1 ± 3.1	12.4 ± 3.0	12.2 ± 2.9	14.5 ± 1.5	14.7 ± 1.6
Female (%)	54.1	52.8	51.9	51.9	58.6	59.4
Mean age at onset (years)	9.8	9.8	10.3	10.0	12.3	12.4
Mean duration of depressive episode (months)	18.6	20.8	15.6	16.7	16.5	15.7
First episode (%)	82.4	78.7	-	-	72.0	70.3

a DSM-IV diagnosis of ADHD, posttraumatic stress disorder, pervasive development disorder, mental retardation, conduct disorder, or oppositional defiant disorder, any personality disorder that would interfere with study participation, a past year history of alcohol or substance abuse, a past year history of eating disorders or a suicide risk.

Initiation of psychotherapy or behavioral therapy within 3 months of the screening visit was not allowed. Treatment with any antidepressant or anxiolytic within 2 weeks of baseline, or with any antipsychotic or stimulant within 6 months of screening was not permitted. Concomitant treatment with certain medications also was prohibited. The citalopram dose was 20 mg/day at baseline, with the ability to increase the dose to 40 mg/day any time after week 4. Primary outcome was the change from baseline in CDRS-R score at week 8 or upon termination. Secondary measures included Clinical Global Impression Improvement (CGI-I) and Severity (CGI-S) ratings. Of randomly assigned 178 subjects, four subjects assigned to the citalopram were lost to follow-up and did not receive study medication. Thus, the ITT population consisted of 89 subjects in the citalopram group and 85 subjects in the placebo group. Of these, 18 patients from each group discontinued this study prematurely.

Citalopram treatment showed significant improvement over placebo on the CDRS-R as early as week 1 ($p < 0.05$), which persisted throughout the study. According to the data reported to the MHRA, the change scores at week 8 for the citalopram and placebo patients were -21.7 versus -16.5 ($p = 0.038$) [20]. Additionally, more citalopram-treated patients (36%) met the predefined response criterion of CDRS-R ≤ 28 than placebo-treated patients (24%), which is a significant difference ($p < 0.05$). The prospectively defined response criterion of CDRS-R ≤ 28 was used as full remission in the Emslie *et al.* study of fluoxetine [17]. The rates of response for citalopram (36%) were similar to the remission rates observed for fluoxetine (41%) in clinical trials.

There were no differences between citalopram and placebo on CGI-I of 1 or 2 (47 vs 45%, respectively) and on CGI-S (4.4 vs 4.3 at baseline and 3.1 vs 3.3 at end point, respectively). It is unusual that CGI-I rates were not significantly different, while there was a significant difference in the predefined response rate of CDRS-R ≤ 28, which is more often considered an index of remission [31]. It is hard to explain the discrepancies between the results of CGI-S rates and CDRS-R. However, at a trial level, the low correlation between the mean baseline CDRS-R and mean CGI-S score ($r = 0.05$, $p = 0.91$) suggests that these two rating scales are measuring different aspects of illness severity [32].

Citalopram treatment was well tolerated. Adverse events in the citalopram group with frequency > 5% and with an incidence exceeding that in the placebo group were rhinitis, nausea, abdominal pain, influenza-like symptoms, fatigue, diarrhea and back pain. Psychiatric adverse events were reported infrequently by patients assigned to citalopram. No serious adverse events were observed.

The rate of discontinuation due to adverse events was comparable in the placebo and citalopram groups (5.9 vs 5.6%). Discontinuation due to agitation was reported only in two citalopram-treated patients, but discontinuation due to aggravated depression was reported only in two placebo-treated patients.

The second citalopram study was a multicenter (31 European recruiting sites), 12-week, randomized, double-blind, placebo-controlled, flexible-dose study [28]. The study began in Sweden in 1996, but extended to a total of seven countries because of poor recruitment and took more than 4 years

Table 2. Efficacy results of placebo-controlled trials of citalopram and escitalopram in children and adolescents with major depressive disorder.

	Wagner *et al.* 2004 [27]			Wagner *et al.* 2006 [30]			Wagner *et al.* 2006 [30]*			Emslie *et al.* 2009 [29]		
	Placebo (n = 85)	Citalopram (n = 89)	p	Placebo (n = 132)	Escitalopram (n = 129)	p	Placebo (n = 80)	Escitalopram (n = 77)	p	Placebo (n = 157)	Escitalopram (n = 155)	p
CDRS-R												
Baseline	58.8	57.8		56.6	54.5		57.2	55.4		56.0	57.6	
Change to wk 8 LOCF‡	-16.5	-21.7	0.038	-20.2	-21.9	0.310	-17.5	-20.1	0.233	-18.8	-22.1	0.022
Change to wk 8 OC				-20.8	-23.9	0.804	-17.8	-22.3	0.047	-21.9	-24.6	0.071
CGI-S												
Baseline	4.3	4.4		4.4	4.2		4.4	4.2		4.4	4.6	
Change to wk 8 LOCF	-1.0	-1.3		-1.3	-1.6	0.057	-1.0	-1.5	0.020	-1.4	-1.8	0.007
Change to wk 8 OC				-1.4	-1.8	0.014	-1.1	-1.7	0.004			
Response or remission rates (%)												
CGI-I ≤ 2	45	47		52.3	62.8	0.14				52.9	64.3	0.03
CDRS-R ≤ 28	24	36	< 0.05	37.9	45.7	0.32				35.7	41.6	0.15
CDRS-R: 40% decrease										48.4	59.1	0.06

*Subgroup analysis for adolescents, ages 12 – 17 years.

‡Protocol defined primary outcome measure.

CDRS-R: Children's Depression Rating Scale – Revised; CGI-I: Clinical Global Impressions – Improvement; CGI-S: Clinical Global Impressions – Severity; LOCF: Last observation carried forward; OC: Observed cases.

rather than the planned 2 years. A total of 244 adolescents, inpatients and outpatients, 13 – 18 years old, with major depression were randomized to treatment with citalopram (10 – 40 mg/day; n = 124) or placebo (n = 120). Approximately one-third of the patients in both groups withdrew from the study. Thus, only 79 citalopram and 74 placebo patients completed the study.

The primary outcome measure was the change from baseline of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present Episode Version (Kiddie-SADS-P) total score. The secondary outcome measure was the proportion of responders and the percentage of patients in full remission. The response was defined as a score of 2 or less on the Kiddie-SADS-P depression and anhedonia items or a reduction of 50% or more of the Montgomery Åsberg Depression Rating (MADRS) total score. The remission was defined as MADRS total score of 12 or less. No significant differences between citalopram and placebo were found on the primary outcome measure or any other outcome measures.

A *post hoc* analysis revealed that more than two-thirds of all patients were receiving psychotherapy during the study. For those patients not receiving psychotherapy, there were statistically significant differences between citalopram and placebo in the percentage of MADRS responders (52 vs 22%, respectively; p = 0.019; last observation carried forward, LOCF) and remitters (45 vs 19%, respectively; p = 0.034; LOCF).

Common treatment-emergent adverse events in both groups were headache, nausea and insomnia. Serious adverse events were reported by 18 with citalopram and 16 with placebo. Hospitalization was the most common serious adverse event. Nearly one-third of patients had previous histories of suicide attempt. Suicide-related events, including suicidal thoughts and tendencies, were reported by 14 with citalopram and 5 with placebo (relative risk = 2.6, p = 0.06, Fisher exact test). The suicidal ideation single item of Kiddie-SADS-P showed worsening more frequently in the placebo (17.9%) than in the citalopram group (7.8%).

The authors of this study stated that methodological difficulties could be one explanation of the results because there is much less experience regarding studies with adolescents. The prolonged study period of more than 4 years, the larger number of participating countries and several adjustments to inclusion criteria and assessments might contribute to the overall variance in the study data. In addition, some important factors not controlled in the study might cause the high placebo response. The use of concomitant psychotropic medication was allowed and patients were initiating or undergoing psychotherapy during the study. Both inpatients and outpatients were included and less than two-thirds of patients completed the study. Owing to several methodological differences, this study is not easy to compare directly with the other three studies with citalopram or escitalopram. Therefore, we compared the results of the three studies with similar methodology in **Table 1** and **Table 2**.

4. Clinical trials of escitalopram in youth

Two large randomized, double-blind, placebo-controlled, flexible-dose, multicenter trials have been conducted with escitalopram [29,30]. In the first trial, 264 pediatric outpatients, ages 6 – 17 years, with MDD were enrolled in the USA [30]. Patients were diagnosed with an MDD episode of at least 4 weeks in duration according to DSM-IV criteria for MDD and confirmed by the K-SADS-PL. Patient's minimal baseline CDRS-R score was 40. The exclusion criteria were similar to those of a previous citalopram study [27]. Concomittant treatment with any psychotropic drug other than zolpidem or zaleplon was prohibited.

Following a 1-week, single-blind, placebo lead-in period, 268 patients were randomized to double-blind treatment. Of the 264 patients included in the safety population, a total of 261 patients formed the intent-to-treat (ITT) population and were included in the efficacy analysis. A total of 102 (77.9%) of 131 escitalopram-treated patients and 115 (86.5%) of 133 placebo-treated patients completed the study. The escitalopram dose was fixed at 10 mg/day for the first 4 weeks and could be flexibly titrated from 10 to 20 mg/day based on the clinical response and tolerability. The overall mean (± SD) escitalopram dose was 11.9 ± 2.3 mg/day.

The primary efficacy measure was the change from baseline to week 8 in CDRS-R total score, using the LOCF approach. The secondary efficacy measures were the CGI-I, CGI-S and the Children's Global Assessment Scale (CGAS). Two separate definitions of response were CDRS-R ≤ 28 and CGI-I ≤ 2.

There was no significant difference between drug and placebo on the primary efficacy measure. Regarding secondary efficacy measures, the mean change from baseline to end point in CGI-S and CGAS were significantly greater for escitalopram compared with placebo only for the observed cases analysis ($p = 0.014$ and 0.046, respectively), and not for the LOCF analysis ($p = 0.057$ and 0.065, respectively).

In the subgroup analysis for adolescent patients, aged 12 – 17 years, the change in CDRS-R total score was significantly different between the escitalopram and placebo groups for the observed cases analysis (-22.3 vs -17.8, $p = 0.047$) but not for LOCF analysis (-20.1 vs -17.5, $p = 0.233$). All secondary measures (CGI-S, CGI-I and CGAS scores) for both LOCF and observed cases analyses at week 8 showed a significant improvement in the escitalopram-treated adolescent subgroup compared with the placebo-treated adolescent subgroup.

The only adverse events at a rate > 10% in the escitalopram group were headache and abdominal pain. But there were no significant differences between treatment groups in the incidence rate of these adverse events. The rate of premature discontinuation due to adverse events was 1.5% (2 patients per group) for both treatment groups. In the placebo group, one patient discontinued because of a manic reaction, and a second patient discontinued because of ataxia, dizziness and somnolence. In the escitalopram group, one patient discontinued because of indigestion and a second patient discontinued because of insomnia, nausea and shaking. There were no completed suicides. Potential suicide-related events were identified in one escitalopram-treated patient and in two placebo-treated patients, which were not considered serious adverse events.

The second escitalopram study was a randomized, double-blind, placebo-controlled, flexible-dose, multicenter trial in adolescents, aged 12 – 17 years, with MDD as defined by the DSM-IV [29]. The duration of the current MDD episode must be ≥ 12 at screening. In addition, the patients are required to have a score of ≥ 45 on the CDRS-R and a score of ≥ 4 on the CGI-S at baseline. Exclusion criteria are similar to those of a previous escitalopram study. Additionally patients with a first-degree relative with bipolar disorder are excluded. Patients are excluded for a positive test for alcohol or other prohibited medication on the urine drug screening.

Following a 1-week, single-blind, placebo lead-in period, 316 patients were randomized to double-blind treatment. Of the 312 patients included in the safety population, a total of 311 patients formed the ITT population. A total of 126 (81.3%) of 154 escitalopram-treated patients and 133 (84.7%) of 157 placebo-treated patients completed the study. The escitalopram dose was fixed at 10 mg/day for the first 3 weeks with the potential to be increased to 20 mg/day at the end of week 3 or 4. The mean (± SD) escitalopram dose was 13.2 ± 2.9 mg/day.

The primary efficacy measure was the change from baseline to week 8 in CDRS-R total score, using the LOCF approach. The secondary efficacy measure was CGI-I score at week 8. Additional efficacy measurements were mean change from baseline in CGI-S and CGAS scores, CGI-I response rate (CGI-I score ≤ 2), CDRS-R response rate (at least 40% reduction in CDRS-R score from baseline) and remission (CDRS-R score ≤ 28). In addition to spontaneous reports, suicidality was assessed using patient self-report, the SIQ-JR and clinician rated Modified Columbia Suicide Severity Rating Scale (MC-SSRS).

Escitalopram treatment demonstrated significantly greater improvement in mean CDRS-R scores than placebo treatment ($p = 0.022$), with an effect size of 0.27. Significant differences in CDRS-R scores were first observed at week 4. Mean CGI-I scores at week 8 were significantly better for the escitalopram group than the placebo group ($p = 0.008$). The percentage of CGI-I responders was significantly greater for escitalopram- than placebo-treated patients ($p = 0.007$). The difference was first observed at week 3 and persisted through study end point. Remission rates (CDRS-R ≤ 28) at end point were 41.6% for escitalopram and 35.7% for placebo ($p = 0.15$).The rate of discontinuation because of adverse events was one patient for placebo versus four patients for escitalopram ($p = 0.21$). Of all adverse events, only six placebo patients and six escitalopram patients were considered to be self-harm but all of them were judged by the investigator to be nonsuicidal. Both

clinician- and patient-rated scales yielded equivalent incidence of suicidal ideation in both groups.

This trial in adolescent patients was followed by an extension study that was initially an open-label escitalopram study, but it was subsequently amended to a double-blind, placebo-controlled, parallel-group, fixed-dose, 24-week study [33]. The duration was later amended from 24 to 16 weeks. Only 24.7% (77/311) of ITT patients completed this extension study. A preliminary report of 24-week data from the 8-week trial and 16-week extension trial showed that escitalopram-treated patients had a greater change in CDRS-R total score (primary efficacy measure) than placebo-treated patients (-23.1 vs -18.2, p = 0.005).

5. Conclusions

The antidepressants that have been demonstrated to be significantly superior to placebo on primary outcome measures in at least one double-blind, placebo-controlled trial for the treatment of pediatric depression are fluoxetine, citalopram and escitalopram. Of these SSRIs, fluoxetine is the only antidepressant that has FDA approval for the treatment of depression in both children and adolescents. Escitalopram was approved by the FDA for the acute and maintenance treatment of MDD in adolescent patients, aged 12 – 17 years. There have been two controlled trials of racemic citalopram and two controlled trials of escitalopram in depressive children and/or adolescents.

In a double-blind placebo-controlled flexible-dose 8-week trial of citalopram in children and adolescents with MDD, aged 7 – 17 years, citalopram treatment showed significant improvement over placebo on the CDRS-R score at week 1. A European double-blind, placebo-controlled, 12-week trial of citalopram in adolescent MDD inpatients and outpatients, aged 13 – 18 years, produced negative results, which could be explained by inappropriate methodology such as concomitant use of psychotropic drugs and psychotherapy.

In a double-blind, placebo-controlled, flexible-dose, 8-week trial of escitalopram in pediatric outpatients with MDD, no significant difference was shown between escitalopram and placebo in the change in CDRS-R score. In the *post hoc* analysis for adolescent patients, aged 12 – 17 years, the change in CDRS-R total score was significantly different between the escitalopram and placebo groups only for the observed cases analysis but not for the LOCF analysis. In a similarly designed recent trial of escitalorpam in adolescents with MDD, the efficacy of escitalopram over placebo was significant on the primary efficacy measure of the change in CDRS-R total score. Preliminary data from the 8-week escitalopram study and following 16-week study showed a significant difference between escitalopram and placebo on the same primary efficacy measure after 24 weeks of treatment, although only 24.7% of ITT patients completed the study.

Treatment with escitalopram was generally well tolerated in adolescents. The rate of discontinuation due to adverse events and suicidal events was low and not significantly different between the escitalopram and placebo groups. Escitalopram as well as fluoxetine can be selected for the first stage of antidepressant therapy in adolescents with MDD.

6. Expert opinion

The previously described clinical trials of escitalopram and citalopram demonstrated that escitalopram is effective for the treatment of depression in adolescents. But there are some aspects that clinicians should consider when interpreting the data of the trials.

First, while fluoxetine studies demonstrated the efficacy over placebo in children and adolescent depression patients, the efficacy of escitalopram was shown in only adolescent depression patients. An escitalopram study for pediatric patients showed some efficacy over placebo only among adolescents in the age-grouped *post hoc* analysis [30]. There do seem to be differences between children and adolescents in their responses to antidepressants. It is of interest that an age-grouped *post hoc* analysis of a venlafaxine ER study also showed a significant difference on the change in CDRS-R total score only among adolescents (-24.4 vs -19.9, p = 0.022) but not among children [24]. A sertraline study for pediatric depression showed a greater difference in the CDRS-R mean change between treatment groups in adolescents (sertraline, -21.55 vs placebo, -18.20; p = 0.01) than in children (sertraline, -24.05 vs placebo, -22.20; p = 0.19) [19]. In a meta-analysis of 15 randomized, controlled trials of pediatric MDD, age-stratified analyses showed that for children younger than 12 years with MDD, only fluoxetine showed benefit over placebo [34]. The differences in antidepressant response between children and adolescents seem to be partial because children show higher placebo response rates [32] and higher rates of adverse events compared with adolescents [35,36].

In a review of data from placebo-controlled, age-grouped, published clinical trials of SSRIs, activation and vomiting SSRI adverse events were two- to threefold more prevalent in children than in adolescents, which were a frequent reason for discontinuation from SSRI clinical trials in preadolescents [35]. The risk of manic conversion during antidepressant treatment was highest among children aged 10 – 14 years [36]. Contrary to these results of clinical trials, in two combined fluoxetine trials, drug–placebo difference was greater in children compared with adolescents [37]. The reason why depressed children responded better to fluoxetine compared with other SSRIs is unclear but could be associated with number of study sites, severity of depression, comorbidity or properties of fluoxetine, such as its long half-life. A review of data from 12 randomized, controlled trials of second-generation antidepressants in youth with MDD showed that the single best predictor of placebo response was the number of study sites, and baseline severity of illness was a significant inverse predictor of placebo response [32].

Second, the drug–placebo difference was modest. The effect size compared with placebo in the escitalopram trial in

adolescents was 0.27. In a meta-analysis of 13 controlled trials with all antidepressants in depressive youths, pooled analyses of continuous measures of mean improvement in depression symptomatology also showed an effect size of 0.20 [34]. In pediatric patients, the effects of antidepressants are strongest in non-obsessive compulsive disorder (OCD) anxiety disorders, intermediate in OCD, and more modest in MDD [34]. However the TADS study showed exceptionally high effect size (0.68) for fluoxetine alone on the CDRS-R compared with other studies. The TADS study included many subjects with comorbid psychiatric disorders (52% of total subjects) and the baseline severity was relatively high, the mean baseline CDRS-R of 60 [18]. Considering that severity of depression is inversely related to placebo response [32], it is difficult to determine whether fluoxetine is superior to other SSRIs or the study designs caused the difference in effect size.

High placebo response rate means that a large portion of the patients could improve on nonspecific clinical contact, such as education regarding sleep hygiene, practical coping skills, and family interventions. When deciding on medication versus other therapy, clinicians need to take a more personalized approach, including the severity and subtype of the depression, risk of suicidality, how family members have responded to medication, recurrence of a depression or its chronicity, lack of response to psychotherapy, family preferences, and psychosocial stressors [38].

Third, infrequent adverse events, such as suicide-related events, treatment-emergent agitation and precipitation of mania, are not easy to be explored in each clinical trial. The clinical trials with escitalopram reported several adverse events but were not able to find any difference in the rate of these events between the medication and placebo group. Of them, rate of suicide-related events have been the most controversial issue. Suicidal ideation and suicide are also a symptom of depression. In addition, suicide-related events are difficult to define or classify. Suicidal ideation, suicidal gesture, self-harm behavior and suicide attempt all have different meanings. Despite the methodological difficulty, there is emerging evidence of possible suicide-related events from antidepressants [39]. Thus, clinicians should closely monitor for suicidal idea and behavior, agitation, irritability and other behavioral changes particularly during the initial few months of treatment.

Finally, determining proper dosage of escitalopram in adolescents has not been fully explored. This seems more of an issue for children, but in young adolescents lower dose might also be effective with fewer adverse events. There is one pharmacokinetic study of escitalopram in adolescents [40]. In this study, the half-life of escitalopram was 19.0 h in adolescents and 28.9 h in adults, and mean maximum plasma concentration (C_{max}) was ~ 26% higher in adolescents than adults. Shorter half-life of escitalopram and risk for treatment-emergent adverse events in adolescents indicate that twice-daily dosing might be rational for adolescents. Other antidepressants such as sertraline and venlafaxine also have shorter half-lifes than fluoxetine. Moreover, there are age-related differences in pharmacokinetics of most antidepressants. Inappropriate drug dosing may have contributed to the failure to detect efficacy for some antidepressant studies or to the suboptimal tolerability. Thus, pharmacokinetic and dose-ranging studies are recommended before initiation of definitive efficacy trials of antidepressants in children and adolescents with MDD [41].

Although the FDA requires a black-box warning on antidepressants describing an increased risk of suicidality in children and there is less evidence for the efficacy of antidepressants in youths than in adults, antidepressant medication is still an effective treatment especially for severely depressed adolescents. When deciding on initiation of medication, initial assessment and continued monitoring are very important. Of all antidepressants, fluoxetine has the greatest evidence of efficacy in treating depression in children and adolescents. Escitalopram and citalopram have increasing evidence of efficacy and could be used as one of the first-line options in adolescents with MDD considering several factors such as patient's age, potential drug interactions, previous history of response, tolerability issues and family preference.

For choosing the appropriate patients for escitalopram treatment, future studies should pay attention to finding the clinical predictors of treatment effects, including age of patients, severity, duration and subtype of depression and dosing strategies.

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