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Research paper

A randomized, double-blind, 6-week prospective pilot study on the efficacy and safety of dose escalation in non-remitters in comparison to those of the standard dose of escitalopram for major depressive disorder

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ABSTRACT

Background: Escalating doses of selective serotonin reuptake inhibitors are often used to treat patients with a suboptimal response to the standard dose. This study assessed the efficacy and safety of dose escalation of escitalopram, up to 30 mg, in non-remitters with major depressive disorder (MDD) after treatment with the standard dose.

Method: We recruited 98 patients with MDD (aged 18–65 years). After 4 weeks of open-label treatment with 10–20 mg of escitalopram per day, non-remitters [Montgomery–Åsberg Depression Rating Scale (MADRS) score > 10] were randomized 1:1 for double-blind treatment with either escitalopram (30 mg per day) or escitalopram (20 mg per day) plus placebo for 6 weeks. The primary efficacy outcome was a change in the total MADRS score.

Results: After 4 weeks of open-label treatment, 12 patients achieved remission, and 36 dropped out, leaving 50 non-remitters, of whom 44 (88%) completed the double-blind study. The primary outcome measure, the least-squares mean (standard error) change in the total MADRS score at week 6 was significantly different ($p = 0.046$) between the groups [−8.0 (1.2) in the placebo dose-escalation and −11.8 (1.2) in the escitalopram dose-escalation]. The dose escalation of escitalopram was well tolerated. However, the response and remission rates and quality of life showed no significant differences.

Limitations: Small sample size and short follow-up period

Conclusion: This study suggests that dose escalation of escitalopram up to 30 mg per day may be beneficial for the treatment of depressive symptoms in non-remitters after standard (10–20 mg/day) treatment.

1. Introduction

Depression is a very common and disabling mental illness affecting individuals of all ages and races. Unfortunately, major depressive disorder (MDD) is a highly recurrent and chronic condition with a complete recovery rate of only 20%, while the other 80% of patients have at least one recurrence during their lifetime (Burcusa and Iacono, 2007). Given the recurrent and debilitating nature of the illness,

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most patients with MDD experience a reduced quality of life (QOL) and pervasive impairments in psychosocial functioning (Judd et al., 2000). Selective serotonin reuptake inhibitors (SSRIs) are the initial antidepressants prescribed to the majority of patients diagnosed with MDD. However, up to 50% of patients fail to respond to standard SSRI treatment, and only 30% achieve the treatment goal of remission (Cain, 2007). For those who do not benefit from the initial course of antidepressant medication, additional therapeutic strategies are required to gain remission, including switching within and between classes of antidepressants (Rush et al., 2006) and using various augmentations and antidepressant combinations (Trivedi et al., 2006). Another option is dose escalation, which frequently precedes other strategies in patients with MDD, who fail to respond to standard doses of antidepressants recommended by treatment guidelines (American Psychiatric Association, 2000; Kennedy et al., 2001).

The clinical efficacy of dose escalation of SSRIs has been questioned in previous meta-analyses (Adli et al., 2005; Baker et al., 2003; Bollini et al., 1999; Jakubovski et al., 2016; Ruhe et al., 2006). Some of the meta-analyses suggested that dosing of antidepressant medications for MDD treatment resulted in flat dose-response curves within the therapeutic ranges for antidepressant medications (≥100 mg of imipramine equivalents) (Bollini et al., 1999) and for SSRIs (Adli et al., 2005). However, some methodological weaknesses were obvious in prior studies. In most of the studies, doses were increased too early and too abruptly, which may have obscured the effects of true dose escalation because of a delay in the effect of the standard dose, and patients who received an abrupt dose escalation, rather than dose titration, dropped out of the study early (Baker et al., 2003; Ruhe et al., 2006). Consequently, a meta-analysis that used dose-tolerant samples, rather than intention-to-treat samples, demonstrated potential dose-response relationships for SSRIs (Baker et al., 2003). Moreover, another systematic review suggested a modest benefit of increasing the SSRI dose for non-responders if the subjects previously received low-dose SSRI treatment for at least 4 weeks (Ruhe et al., 2006). A recent meta-analysis with meta-regression, using a continuous outcome (as well as a dichotomous outcome) for a treatment response, which is more sensitive to a change in the SSRI efficacy with the dose, showed that higher doses of SSRIs were slightly more effective, and this benefit appeared to only plateau at the higher end of the recommended dosing range (greater than 250 mg of imipramine equivalents, corresponding to >41.75 mg of escitalopram) (Jakubovski et al., 2016).

There are limited publications available to support the use of high doses of escitalopram (above 20 mg) in the treatment of MDD (Wade et al., 2011). In this study, we investigated the efficacy and safety of dose escalation of escitalopram (to 30 mg per day) versus placebo following non-remission with 20 mg of escitalopram in the treatment of MDD. We aimed to evaluate whether this dose-escalation strategy is well tolerated and efficacious in decreasing depressive symptoms and increasing QOL of patients, as well as to determine whether dose escalation can be useful for patients who did not achieve MDD remission in response to standard doses of escitalopram.

2. Methods

2.1. Study design

This 6-week, randomized, parallel-arm, double-blind study of dose escalation of escitalopram in patients with MDD, who had not responded to treatment with a standard dose of escitalopram, was conducted at the Seoul National University Hospital in Seoul, Republic of Korea, from February 2013 to February 2016. The study consisted of the following two phases: an open-label phase during the first 4 weeks and a randomized, double-blind phase lasting 6 weeks (Fig. 1). After the initial assessment, all eligible participants received, open label, 10 mg of escitalopram per day for 1 week and then 20 mg per day for the remaining 3 weeks. After the 4-week open-label phase, subjects who did not achieve remission, defined as a total Montgomeryeatment with a standard dose of escitalopram, was conducted at zed (1:1), using an independently operated computer program, to receive either escitalopram (30 mg per day) or escitalopram (20 mg per day) plus placebo during a 6-week double-blind treatment period. The participants were provided white tablets containing either 10 mg escitalopram or placebo, respectively, in addition to 20 mg of escitalopram. Treatment compliance was calculated as the number of pills dispensed minus the number returned. During the study period, some supplementary medications, including lorazepam, clonazepam, diazepam, zolpidem, and propranolol, were allowed as needed.

The protocol was approved by the institutional review board at the Seoul National University Hospital and the Korea Food and Drug Administration. The study was performed in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients were provided written informed consent and were free to discontinue the study at any time. The study is registered at ClinicalTrials.gov (identifier: NCT01594866).

2.2. Subjects

Adult men and women (ages 18–65 years) with a primary diagnosis of MDD, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (text revision), were eligible for enrollment. Other inclusion criteria were a total MADRS score ≥18 at initial screening and baseline visits. Subjects were excluded from the study if they met the following exclusion criteria: (1) experienced hypersensitivity to escitalopram; (2) received any psychoactive medications such as antipsychotics, mood stabilizers, or selective monoamine oxidase inhibitors; (3) had symptoms of depression and were deemed resistant to two or more antidepressant treatments; (4) had psychiatric disorders other than MDD or a prior history of psychiatric disorders, such as manic or hypomanic episodes, schizophrenia, schizoaffective disorder, or substance abuse disorder; (5) had a significant risk of suicide based on the evaluation by an investigator or a score of ≥5 on item 10 of MADRS; or (6) had a history of neurologic disorders or medically unstable conditions (e.g., renal or hepatic impairment, cardiovascular, pulmonary, or gastrointestinal disorders). Pregnant or breastfeeding women were also excluded. As this was a pilot trial, we did not perform a power calculation. We aimed to randomize 50 patients in the blinded phase, considering the study period, cost, and the number of patients with MDD visiting the Seoul National University Hospital outpatient clinic.

2.3. Assessments

Initial screening was performed to identify subjects who met all inclusion criteria and did not meet any of the exclusion criteria. MADRS and Clinical Global Impression–Severity of Illness (CGI-S) scores were measured at the study entry (week −4), baseline (randomization, week 0), and post-randomization weeks 1, 2, 4, and 6. Clinical Global Impression–Improvement (CGI-I) scores were measured at baseline and post-randomization weeks 1, 2, 4, and 6. Hamilton Anxiety (HAMA) scale, Beck Depression Inventory (BDI), Clinically Useful Depression Outcome Scale (CUDOS), and World Health Organization Quality of Life, abbreviated version (WHOQOL-BREF) scores were examined at the study entry, baseline (randomization), and post-randomization weeks 2 and 6.

Safety assessments were performed at initial screening and at subsequent visits, as described below. Adverse events (AEs) were assessed at the study entry (week −4), baseline (randomization), and post-randomization weeks 1, 2, 4, and 6 and were coded using the Medical Dictionary for Drug Regulatory Affairs, version 16.0. Vital signs, weight, and waist circumference were measured at the study entry (week −4), baseline, and post-randomization weeks 1, 2, 4, and 6.

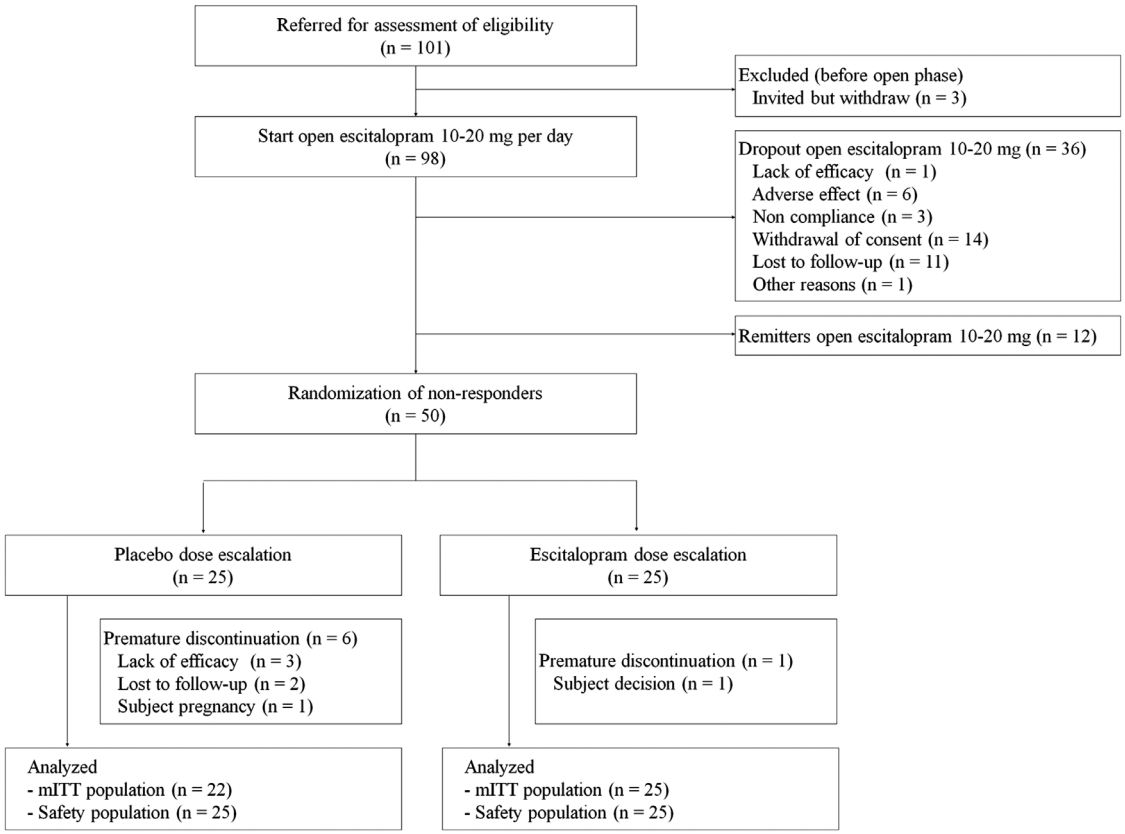

Fig. 1. Study design and disposition of subjects.

Electrocardiograms (ECGs) and laboratory tests were performed at the study entry (week −4), baseline (randomization), and post-randomization week 6.

2.4. Outcome measures

The primary efficacy outcome was a change in the total MADRS score from baseline to week 6 of treatment with 20 mg of escitalopram plus placebo or 30 mg of escitalopram. The secondary efficacy outcomes were the rate of response (e to week 6 of treatment with 20ents (AEs) were assessed at ission (total MADRS score ≤10). Changes in the severity of depression symptoms were measured using the CGI-S and CGI-I scales (CGI response was defined as sponse (e to week 6 of treatment with 20ents (AEs) were a(Guy, 1976) and the total BDI and CUDOS scores. The severity of anxiety symptoms was measured using the total HAMA score, and QOL was measured using the total WHOQOL-BREF score.

2.5. Statistical analysis

Efficacy analysis was based on a modified intention-to-treat (mITT) analysis set, including all randomized patients who received at least one dose of the study drug and had at least one post-baseline MADRS score. Safety and tolerability assessments were based on the safety analysis set, including all randomized patients who received the study drug and for whom post-dose data were available.

The primary efficacy variable was a change in the total MADRS score at week 6 from baseline. Comparisons between the escitalopram and placebo dose-escalation groups were performed using mixed-model repeated-measures (MMRM) analysis of all post-baseline total MADRS scores through the end of the study (week 6). The model included treatment, visit, treatment-by-visit interaction, and baseline MADRS scores by visit as fixed effects. Restricted maximum likelihood with an unstructured variance–covariance matrix was used for the estimation in the MMRM analysis. Based on a missing-at-random assumption, this analysis was performed using observed case data. The same MMRM approach was used for other continuous secondary efficacy outcome variables. Binary secondary efficacy outcome variables, with multiple post-baseline assessments (response, remission, and CGI-I response), were analyzed at all time points by logistic regression with a generalized estimating equation, adjusting the baseline measurement relative to the dependent analysis variable. For response and remission, the baseline total MADRS score was used as the baseline measurement, and for the CGI-I response, the baseline CGI-S score was used. Descriptive statistics were reported for safety outcomes. A *t*-test and chi-squared test were carried out to determine differences between the groups in the corrected QT interval (QTc) change from the study entry to post-randomization week 6 and in the prevalence of AEs.

3. Results

3.1. Subjects' characteristics

As shown in Fig. 1, of the 101 eligible patients, 98 patients started open-label escitalopram treatment, and 50 non-remitted patients were randomized for the double-blind phase. The remission rate during the initial open-label phase was 12.2% (12/98). The most common reason for dropout during the open-label phase (36 patients) was withdrawal of consent (n = 14, 38.9%). Of the 50 patients who were randomized for the double-blind phase, 43 (86.0%) completed the 6-week treatment. The reasons for discontinuation of treatment (n = 7) were the lack of efficacy (n = 3), inability to follow-up (n = 2), and pregnancy (n = 1) in the placebo dose-escalation group and subject's decision (n = 1) in the escitalopram dose-escalation group.

The baseline demographic and clinical characteristics were similar between the two treatment groups (Table 1). The mean age was 38.6

Table 1
Demographic and other baseline characteristics of the patients at study entry.

Variables	Placebo dose escalation (n = 25)	Escitalopram dose escalation (n = 25)
Age (years), mean ± SD	38.6 ± 13.2	40.4 ± 13.0
Sex (female), n (%)	18 (72.0)	20 (80.0)
Age at onset (years), mean ± SD	35.2 ± 13.2	36.6 ± 11.6
Duration of illness (years), mean ± SD	3.3 ± 5.2	3.8 ± 8.1
Current smoker, n (%)	5 (20.0)	2 (8.0)
Alcohol use, n (%)	12 (48.0)	11 (44.0)
MADRS total score, mean ± SD	20.6 ± 5.7	19.9 ± 5.7
CGI-S, mean ± SD	3.8 ± 1.0	4.0 ± 0.6
HAMA total score, mean ± SD	6.9 ± 2.9	7.1 ± 3.1
BDI total score, mean ± SD	18.9 ± 11.8	16.9 ± 9.7
CUDOS total score, mean ± SD	26.0 ± 14.5	23.4 ± 10.8
WHOQOL-BREF score, mean ± SD		
Physical domain	11.0 ± 1.7	10.7 ± 2.7
Psychological domain	9.5 ± 2.5	10.6 ± 4.4
Social relationship domain	11.8 ± 2.2	10.9 ± 2.5
Environmental domain	11.7 ± 2.2	11.4 ± 2.3
Baseline MADRS score sample size[a,b]	22	25
Baseline total MADRS score [b]	20.5 ± 5.6	19.9 ± 5.7

[a] mITT analysis set.
[b] at randomization
Abbreviations: BDI, Beck Depression Inventory; CGI-S, Clinical Global Impression–Severity of Illness; CUDOS, Clinically Useful Depression Outcome Scale; HAMA, Hamilton Anxiety; MADRS, Montgomery–Åsberg Depression Rating Scale; SD, standard deviation; WHOQOL-BREF, World Health Organization Quality of Life, abbreviated version.

and 40.4 years in the placebo and escitalopram dose-escalation groups, respectively. Most of the subjects were females (72% and 80.0% in the placebo and escitalopram dose-escalation groups, respectively). The mean body mass index was not significantly different between the groups. The mean baseline MADRS scores were similar between the 22 subjects in the placebo dose-escalation group and 25 subjects in the escitalopram dose-escalation group (20.5 and 19.9, respectively) in the mITT analysis set.

3.2. Efficacy outcome

The primary outcome measure, the least-squares (LS) mean (standard error) change in the total MADRS score at week 6, was −8.0 (1.2) in the placebo dose-escalation group and −11.8 (1.2) in the escitalopram dose-escalation group (Table 2). The difference between the two groups was statistically significant (p = 0.046) using MMRM analysis of the mITT analysis set. The difference in the LS mean change in the total MADRS score between the two groups was significant at every study visit (Fig. 2).

However, the placebo dose-escalation group did not differ significantly from the escitalopram dose-escalation group in several secondary efficacy variables, such as the MADRS and CGI-I response rates, MADRS remission rate, and HAMA, BDI, and CUDOS score changes at week 6 (Table 2). The LS mean change in the CGI-S score at week 6 was −1.1 in the placebo dose-escalation group and −1.8 in the escitalopram dose-escalation group (p = 0.043). QOL, measured using WHOQOL-BREF, showed improvements in the physical and social relationship domain scores at week 6 with the escitalopram dose

Table 2
Primary and secondary efficacy variables assessed at week 6.

Variables	Placebo dose escalation (n = 22)	Escitalopram dose escalation (n = 25)
MADRS score change, LS mean ± SE[a]	−8.0 ± 1.2	−11.8 ± 1.2
MADRS response rate, n (%)[b]	12 (54.5%)	20 (80.0%)
Adjusted OR (95% CI)		3.393 (0.894–12.876)
MADRS remission rate, n (%)[c]	10 (45.5%)	15 (60.0%)
Adjusted OR (95% CI)		1.800 (0.522–6.208)
CGI-I response rate, n (%)[d]	11 (50.0%)	14 (56.0%)
Adjusted OR (95% CI)		1.287 (0.397–4.171)
CGI-S score change, LS mean ± SE	−1.1 ± 0.2	−1.8 ± 0.2
HAMA score change, LS mean ± SE	−3.9 ± 0.5	−4.4 ± 0.4
BDI score change, LS mean ± SE	−5.6 ± 1.4	−7.1 ± 1.3
CUDOS score change, LS mean ± SE	−7.8 ± 2.2	−8.9 ± 2.1
WHOQOL-BREF score change, LS mean ± SE		
Psychological domain	0.9 ± 0.7	1.4 ± 0.6
Physical domain	1.5 ± 0.5	2.4 ± 0.4
Social relationship domain	0.8 ± 0.5	1.8 ± 0.4
Environmental domain	0.8 ± 0.5	1.6 ± 0.4

[a] Primary efficacy analysis.
[b] ≥rim decrease in MADRS, with the screening score (−4 weeks) as a reference.
[c] MADRS score ≤10 at endpoint.
[d] CGI-I score ≤2 at endpoint.
Note: Logistic regression analysis with a generalized estimating equation was used for response and remission.
Abbreviations: BDI, Beck Depression Inventory; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity of Illness; CI, confidence interval; CUDOS, Clinically Useful Depression Outcome Scale; HAMA, Hamilton Anxiety; LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; OR, odds ratio; SE, standard error; WHOQOL-BREF, World Health Organization Quality of Life, abbreviated version.

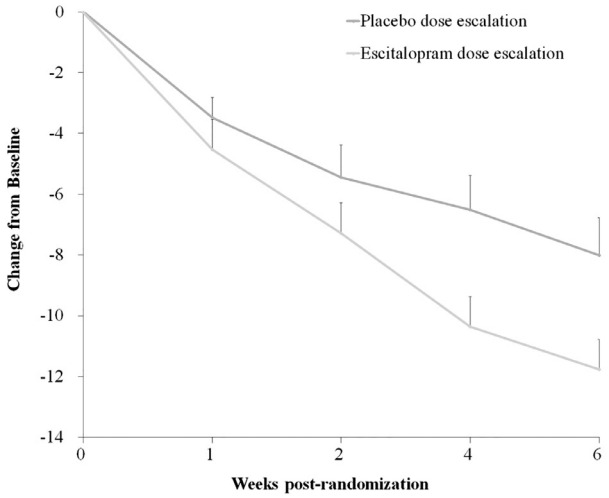

Fig. 2. Changes in the total MADRS scores from baseline, analyzed by MMRM in the mITT analysis set. Data represent least-squares means with a 95% confidence interval. Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intention-to-treat; MMRM, mixed model repeated measures.

escalation, which were significantly greater than those with the placebo dose escalation. However, these findings were not significant after applying the Bonferroni correction (Table 2). Analysis using per-protocol samples showed different results from those of the mITT sample analysis (data not shown). The LS mean changes in the total MADRS scores at week 6 were not significantly different ($p = 0.105$) between groups (-8.5 in the placebo dose-escalation group and -11.5 in the escitalopram dose-escalation group).

3.3. Safety outcomes

At least one AE was reported by 44.0% (11/25) of the subjects in the placebo dose-escalation group and by 36.0% (9/25) of the subjects in the escitalopram dose-escalation group, with most AEs of mild or moderate intensity (Table 3). Daytime somnolence and headache were the most common AEs in both treatment groups. There was no significant difference in the prevalence of AEs between the groups. No subject experienced a serious AE during the study period, and no study participants discontinued treatment because of AEs in either group. There were no clinically meaningful differences in the clinical laboratory test values (clinical chemistry, hematology, and urinalysis) or vital signs between the placebo and escitalopram dose-escalation groups during the treatment period (data not shown).

There were no notable differences in the ECG readouts between the two groups during the study period. We investigated whether the escitalopram dose escalation had any impact on the QTc change over time. The mean (± standard deviation) QTc increased from baseline to the endpoint from 426.8 ± 22.0 to 429.2 ± 26.4 ms in the placebo dose-escalation group and from 424.6 ± 20.0 to 427.7 ± 29.8 ms in the escitalopram dose-escalation group, with no significant differences between the groups ($p = 0.932$). No participant showed a significant QTc increase (QTc > 500 ms and a change from baseline >60 ms) from the study entry to post-randomization week 6.

Table 3
Treatment-emergent adverse events in ≥4% of the subjects treated with escitalopram, *n* (%).

Variables	Placebo dose escalation ($n = 25$)	Escitalopram dose escalation ($n = 25$)
All adverse events	11 (44.0)	9 (36.0)
Daytime somnolence	3 (12.0)	4 (16.0)
Headache	4 (16.0)	3 (12.0)
Nausea	1 (4.0)	2 (8.0)
Dizziness	2 (8.0)	1 (4.0)
Diarrhea	0 (0)	1 (4.0)
Decreased appetite	0 (0)	1 (4.0)
Constipation	1 (4.0)	0 (0)
Sweating	1 (4.0)	0 (0)

4. Discussion

This study is the first assessment of the clinical effectiveness of dose escalation of escitalopram in patients with MDD, who did not achieve remission after 4 weeks of treatment with 10–20 mg of escitalopram per day. Consistent with our hypothesis, dose escalation of escitalopram to 30 mg per day, compared with that with placebo, improved depressive symptoms, measured by changes in the total MADRS score, but was not associated with increased response and remission rates. Although the key secondary outcomes (HAMA, BDI, and CUDOS scores) showed numerically better results with the escitalopram dose escalation, none were statistically significant. An enhanced QOL (i.e., physical and social relationship domains) was observed in the escitalopram dose-escalation group; however, the differences were not significant after multiple comparison correction. Dose escalation of escitalopram to 30 mg was well tolerated, and the dropout rate (4%) was much lower than that in the placebo dose-escalation group (24%). Our study suggests that dose escalation of escitalopram to 30 mg per day can be an effective strategy in the treatment of MDD in patients with a suboptimal response to standard dosing regimens.

This study showed that patients who did not achieve remission after 4 weeks of escitalopram (10–20 mg/day) significantly improved on a higher dose of escitalopram and showed reduced symptoms of depression. However, the differences in the response/remission rates between the groups were not significant. So far, there have been few published studies in support of dose escalation of escitalopram in the treatment of MDD. A previous open-label, pilot study, which investigated the efficacy, safety, and tolerability of escitalopram at doses of up to 50 mg for MDD, showed a possible efficacy of dose escalation of escitalopram above 20 mg in patients with MDD, who did not respond to citalopram treatment (Wade et al., 2011). It should be noted that we observed positive dose-response relationships only when symptom improvement was measured as a continuous value (i.e., MADRS score change and CGI-S change) but not as a categorical variable (response or remission, yes/no). The patients who continued treatment with a daily dose of 20 mg of escitalopram (placebo dose-escalation group) under double-blind conditions for an additional 6 weeks achieved a response rate of 54.5% compared with that of 80% in the escitalopram dose-escalation group. However, the difference in the response rates was not statistically significant. Possible explanations for the lack of significance with categorical data may be a relatively short study duration (post-randomization phase), small sample size, and low sensitivity of categorical outcome measures.

Evaluation of treatment outcomes using symptom improvement (i.e., a continuous measure), rather than treatment response/remission (i.e., a dichotomous measure), is more sensitive to changes in SSRI benefits at different doses (Jakubovski et al., 2016). Systematic reviews and meta-analyses examined whether dose-escalation strategies are effective in non-responders for whom low-dose antidepressant treatments were ineffective (Adli et al., 2005; Jakubovski et al., 2016; Ruhe et al., 2006). An examination of dose escalation in low-dose SSRI non-responders suggested that SSRIs followed a flat dose-response relationship within the therapeutic range and that higher SSRI doses were only associated with a greater side-effect burden (Adli et al., 2005). In line with these findings, dose escalation of paroxetine in non-responders after 6-week treatment with paroxetine 20 mg per day had no clinical benefit (Ruhe et al., 2009). Furthermore, this study showed no significant increases in serotonin transporter occupancy upon dose

escalation of paroxetine, despite increased paroxetine serum concentrations (Ruhe et al., 2009). In contrast, another systematic review, which examined the efficacy of delayed dose escalation in SSRI non-responders, found a modest benefit of increasing the SSRI dose if subjects received previous low-dose SSRI treatments for at least 4 weeks (Ruhe et al., 2006). A recent meta-analysis of placebo-controlled trials of SSRIs showed a significant association between higher SSRI doses and their greater measured efficacies and found that the dose-response relationships of SSRIs did not follow a flat response curve within the SSRI therapeutic range (Jakubovski et al., 2016). This meta-analysis suggested a modest improvement in the efficacy of treatment with high doses (200–250 mg or 250 mg of imipramine equivalents) compared with that with low doses (100–200 mg of imipramine equivalents) (100 mg of imipramine = 16.7 mg of escitalopram) (Benkert et al., 1996; Bollini et al., 1999; Jakubovski et al., 2016). Jakubovski et al. (2016) differed in methodology from previous meta-analyses. The authors examined symptom improvement as a continuous measure, rather than examining clinical improvement (yes/no), as the primary outcome of the meta-analysis and evaluated the dosing effects of SSRIs not only using the treatment response as a dichotomous outcome but also as a continuous measure (Jakubovski et al., 2016). Finally, the lack of statistically significant differences between high-dose escitalopram treatment and placebo dose-escalation treatment is most likely due to the relatively small sample size of each arm (n = 25/25). A longer open-label phase before randomization and a post-randomization phase with a larger sample size may help better detect differences between dose escalation of escitalopram to 30 mg and that with placebo.

While many studies examining dose escalation of SSRIs in the treatment of MDD have focused on the severity of depressive symptoms and the rate of remission, few have explored the impact of treatment on QOL of patients (Ishak et al., 2011). In our study, high-dose escitalopram treatment seemed to be associated with an enhanced QOL in the physical and social relationship domains, although these associations were not significant after multiple comparison correction. QOL is operationally defined as the subjective evaluation of life domains such as health, work, family, social relations, and leisure activities, within a cultural and environmental context (World Health Organization, 2001). Depression has a significant association with a poor QOL (Ishak et al., 2011). In addition, QOL is linked to high relapse rates, ongoing suffering, and increased utilization of health services, which is related to the burden associated with MDD (Ishak et al., 2013). These findings support the notion that functional measures are still needed, in addition to symptom assessment, to determine the full impact of the illness (Cohen et al., 2013). It needs to be investigated in future large-scale studies whether high-dose escitalopram increases QOL, along with the improvement of depressive symptoms.

The cardiac safety of some SSRIs, particularly citalopram and escitalopram, has been questioned with regard to QTc prolongation. A thorough QT-interval study found a dose-dependent QTc prolongation, with an increase of 18.5 ms for a 60-mg daily dose of citalopram and of 10.7 ms for a 30-mg daily dose of escitalopram, which is the (*S*)-enantiomer of citalopram (Temple et al., 2012). Although the risk of cardiac mortality is low at the individual level, QTc prolongation is potentially linked to lethal ventricular arrhythmias, such as Torsades de pointes (TdP), which is related to the risks of cardiac mortality and sudden death, especially in people with medical illnesses (Beach et al., 2018). For this reason, the Medicines and Healthcare Products Regulatory Agency in the UK issued a warning for escitalopram, recommending 20 mg daily as the maximum dose for adults and 10 mg daily as the maximum dose for those over the age of 65 or with hepatic impairment, although the US Food and Drug Administration issued no warnings for escitalopram. A case report showed the possibility of both QT prolongation and QRS widening with escitalopram overdose (Schreffler et al., 2013). However, a recent large cohort study suggested that high doses of escitalopram or citalopram did not significantly differ from comparable doses of fluoxetine, paroxetine, and sertraline in terms of the risk of sudden unexpected death, sudden cardiac death, or total mortality (Ray et al., 2017). A meta-analysis of patient-level data for 2407 patients on escitalopram (between 5 and 20 mg/day), compared with those for 1952 patients on placebo, showed a mean difference of only 3.5 ms, and only one out of the 2407 escitalopram patients had clinically significant QT prolongation (QTc > 500 ms or an increase of >60 ms from baseline) (Thase et al., 2013). In our study, we found a mean increase of QTc of 2.8 ms (all doses), with increases of 2.5 and 3.1 ms for escitalopram 20 and 30 mg, respectively. The mixed results suggest that escitalopram may carry some risk of mild QT prolongation but likely not enough to be clinically significant (Beach et al., 2018). Literature data suggest that drug-associated QTc prolongation is not sufficient to predict TdP in the absence of other cardiac risk factors, and studies based on efficacy and safety trials did not link drug-associated QTc prolongation with TdP (Hasnain and Vieweg, 2014). Further studies are needed to estimate the cardiac morbidity and mortality associated with a high dose of escitalopram and to investigate the risk factors associated with drug-associated TdP.

5. Limitations

This study has several limitations, which should be considered when interpreting the results. In our study, patients who did not achieve remission within 4 weeks of standard treatment were switched to high-dose escitalopram. This raises a possibility that some of the treatment effects observed during the 6-week high-dose phase represented a response that might have been reached with a longer treatment at the standard dose (Fava et al., 2002). For optimal comparison, an appropriate group of non-remitters may be selected by postponing randomization. The other study limitations included a relatively small number of patients and a relatively short study period, with no long-term assessment after dose escalation. These shortcomings may have resulted in an insufficient statistical power needed to detect differences in categorical outcomes between the doses tested. Moreover, the small sample size did not allow a thorough investigation of uncommon or rare adverse effects related to the high dose of escitalopram. Furthermore, there were contradictory findings between ITT and per-protocol analyses on the primary outcome measure, which may have resulted from different dropout rates between the two groups. A future larger randomized controlled trial should aim at minimizing protocol deviations and the dropout rate and use better statistical methods to deal with missing data. Additionally, this study did not include therapeutic drug monitoring of escitalopram. Investigation of the correlation between plasma concentrations and clinical effects of the drug would help determine the dose-response relationship for escitalopram. Nonetheless, this study shows potential benefits of high-dose escitalopram, along with its satisfactory tolerability and patients' adherence.

6. Conclusions

A significant improvement in depressive symptoms in response to dose escalation of escitalopram was observed, which suggests that high doses of escitalopram can offer practical clinical benefits to patients with MDD, who inadequately respond to a standard dosing regimen. A future larger randomized controlled trial needs to be conducted to examine the ideal timing and degree of dose escalation of escitalopram in the treatment of MDD to maximize the benefits while reducing any side effects that may result from higher doses.

CRediT authorship contribution statement

Eun Young Kim: Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Se Hyun Kim:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Hyun Jeong Lee:** Formal analysis, Writing - original draft, Writing - review & editing. **Nam Young Lee:** Formal analysis, Writing - original draft,

Writing - review & editing. **Hye Young Kim:** Formal analysis, Writing - original draft, Writing - review & editing. **C. Hyung Keun Park:** Formal analysis, Writing - original draft, Writing - review & editing. **Yong Min Ahn:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

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Overall data acquisition, statistical analyses, and interpretation of the study results were implemented with no input from Lundbeck Korea Co., Ltd.

Supplementary materials

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