International Journal of Pharmacological Research www.ssjournals.com
ISSN: 2277-3312 Journal DOI:10.7439/ijpr

Randomised study to compare the efficacy and tolerability of Duloxetine and Escitalopram in subjects with Major Depressive Disorder

Haridas Kiran*[1], Chauhan Naveen[1], Poddar Indrani[1], Pai M.R.S.M[1], Pai Keshava[2] and Thunga Ravish[2]

[1]*Department of Pharmacology, Kasturba Medical College, Mangalore- 575001.*
[2]*Department of Psychiatry, Kasturba Medical College, Mangalore- 575001.*

Corresponding author*
Dr. Haridas Kiran,
Department of Pharmacology,
Kasturba Medical College, Mangalore- 575001.
E-mail: drharidaskiran@gmail.com

Abstract
Management of depression presents a significant medical challenge. Drugs with improved efficacy and better tolerability are valuable additions to the present therapy of this disorder. Evidence suggests that therapy with a combined serotonin and noradrenaline reuptake inhibitor may be a more effective therapy of major depressive disorder (MDD) than a single neurotransmitter inhibitor. The present study assessed the efficacy and tolerability between duloxetine (dual neurotransmitter reuptake inhibitor) 40-60 mg/day and escitalopram (single neurotransmitter reuptake inhibitor) 10-20mg/day in 24 patients as an open labeled randomized study over a duration of 12 weeks. The primary efficacy measure was the mean total change in 17 items Hamilton rating scale for depression ($HAMD_{17}$) from baseline to end point using the last observation carrying forward. Tolerability was evaluated by assessing discontinuation rates, adverse event rates, vital signs, and laboratory tests. In the present study, the primary analysis detected a statistically significant difference at p=.025 using Fischer's test between duloxetine and escitalopram in both response and remission rates. There was no significant difference detected in efficacy of onset between the two study groups. Response rate, remission rate and efficacy of onset were highly significant at $p<0.05$ using Wilcoxon signed rank test within each group. There were a few adverse effects that were mild and self limiting with both molecules. Duloxetine is superior to escitalopram in response and remission of treatment of MDD in similar clinical setting. Both duloxetine and escitalopram are well tolerated molecules at comparable doses.
Keywords: Hamilton rating scale for depression ($HAMD_{17}$), Major depressive disorder (MDD).

1. Introduction
The years from 1990 through 1999 were termed the "Decade of the Brain" by the Library of Congress and the National Institute of Mental Health[1]. Since that decade, our understanding of depression has grown enormously. Despite this gain in knowledge, the incidence of depression continues to increase. The WHO estimates that, by 2020, major depression will represent the second most significant overall cause of disability after ischemic heart disease, and will be the leading cause of disability and disease burden in women[2]. The lifetime risk of major depressive disorder (MDD) is 7–12% for men and 20–25% for women[3] and the disorder is twice as common in women as in men[2]. Both serotonin and norepinephrine contribute to the pathology and treatment of depression. Serotonin affects areas of the brain controlling impulsivity, aggression, appetite, and sexual function, while norepinephrine plays a role in areas controlling vigilance and motivation. Both serotonin and norepinephrine have shared roles in relation to anxiety, irritability, cognitive function, mood, and emotion[4]. Selective serotonin reuptake inhibitors (SSRIs), which are at least as effective as other antidepressants, having superior tolerability profiles to compounds such as tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) and are safer in over dosage[5]. Escitalopram, the active *S*-enantiomer, is the most selective SSRI antidepressant, now approved worldwide for use in MDD[6][7][8]. Escitalopram appears unique among SSRIs in terms of its interaction with the serotonin transporter protein, on which the presence of two escitalopram-binding sites has been postulated: a primary high-affinity binding site and a secondary lower-affinity allosteric site. Binding of escitalopram to the allosteric site is thought to stabilize and prolong binding of the drug to the primary site[9]. Traditional SSRIs are generally selective for blocking the reuptake of serotonin, with ratios of blockade of serotonin to blockade of

norepinephrine of over 300.[10]

There is evidence suggesting that therapies with combined serotonin and norepinephrine reuptake inhibitory activity (SNRIs) may be more effective treatment for depression than therapy with SSRIs[11][12][13]. Venlafaxine, milnacipran, and duloxetine are SNRIs with ratios of 116, 9.15, and 7.23 for blockade of serotonin and norepinephrine respectively[10]. Duloxetine provides dual reuptake inhibition from starting dose. This advantage of enhancing multiple amines provides the required potential for a therapeutic advantage in rapid onset of efficacy. The goal of the acute treatment phase is complete remission of a patient's depressive symptoms. The recommended length of the acute treatment phase three months may vary for each individual patient but is approximately six to eight weeks[14]. The objective of this study is to evaluate the tolerability and the efficacy in terms of response and remission rates between appropriately powered comparators; duloxetine and escitalopram.

2. Material and Methods

2.1 Subjects and design

This was a randomized parallel group open controlled study. All patients studied scored ≥ 15 on $HAMD_{17}$ which indicated moderate illness at screening and at second visit as an independent predictor of depression and they were randomly assigned (computer generated numbers) on a 1:1 ratio to duloxetine 40 mg/day or escitalopram 20 mg/day. Power of the study was 82%. Initially patients were administered 40 mg/day in two divided doses of duloxetine and 10 mg/day single dose of escitalopram. On failure to respond at one month the dose was increased to 60 mg/day and 20 mg/day respectively. Patients were followed up every 15 days for three months (12 weeks), and these visits were termed visit 1 through visit 7. Patients were included if they were in 18-65 years and fulfilled DSM IV criteria for major depression with or without somatic complaints. They were not selected on the presence, severity and type of pain. Patients were permitted to take non-prescriptive pain medications. The following exclusion criteria were applied: more than 65 years and less than 18 years; subjects who met DSM IV criteria for bipolar disorders; history of mania, grief episodes, schizophrenia, seizure, glaucoma; people with bleeding tendency; depressive pseudodementia; pregnancy and lactation; allergic to duloxetine and escitalopram; on concomitant medication with MAO inhibitors, fluvoxamine, ciprofloxacin, morphine, benzodiazepine, barbiturates, antihistamines, tricyclic antidepressant, warfarin, NSAIDs, antiarrhythmics, zopiclone, zolpidem, ongoing prophylactic treatment with lithium; had received treatment with any investigational drug within 30 days; lack of response to more than one antidepressant treatment during present depressive episode.

The efficacy parameters were assessed at all visits based on changes in $HAMD_{17}$. Onset of efficacy was defined as ≥ 20% decrease in total score from baseline at 2 weeks. Response rate was defined as ≥ 50% decrease in total score from baseline. Remission was defined as score ≤ 6 and fails to satisfy DSM IV criteria for major depression at last assessment. Tolerability was evaluated on the basis of spontaneously reported adverse events, physical examination including pulse rate, systolic and diastolic blood pressure (which were measured after the patient had rested for 5 minutes while in a supine position and again after 1 minute in standing position), vital signs, weight and laboratory investigations. The study protocol was approved by Institutional Ethic's Committee in accordance with the principles of the Declaration of Helsinki. Patients provided written informed consent.

2.2 Statistical Analysis

Response rate, remission rate and efficacy of onset analyses were performed using Fisher's test between the treatment groups. Wilcoxon signed rank test was used for evaluation of paired difference within the group. The term "significant" indicates statistical significance ($p \leq 0.05$).

3. Results

3.1 Patient characteristics and disposition

Patient disposition is shown in figure 1. Completion rates were similar between treatment groups at the end of therapy. The subjects satisfied DSM IV criteria for major depression. In this open randomized study, a total of 24 patients were administered duloxetine (40-60 mg/day) or escitalopram (10-20 mg/day) serially. Three patients assigned to treatment groups withdrew from the study. Demographic parameters of the study at baseline were depicited in table1.

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) diagram of patient disposition.

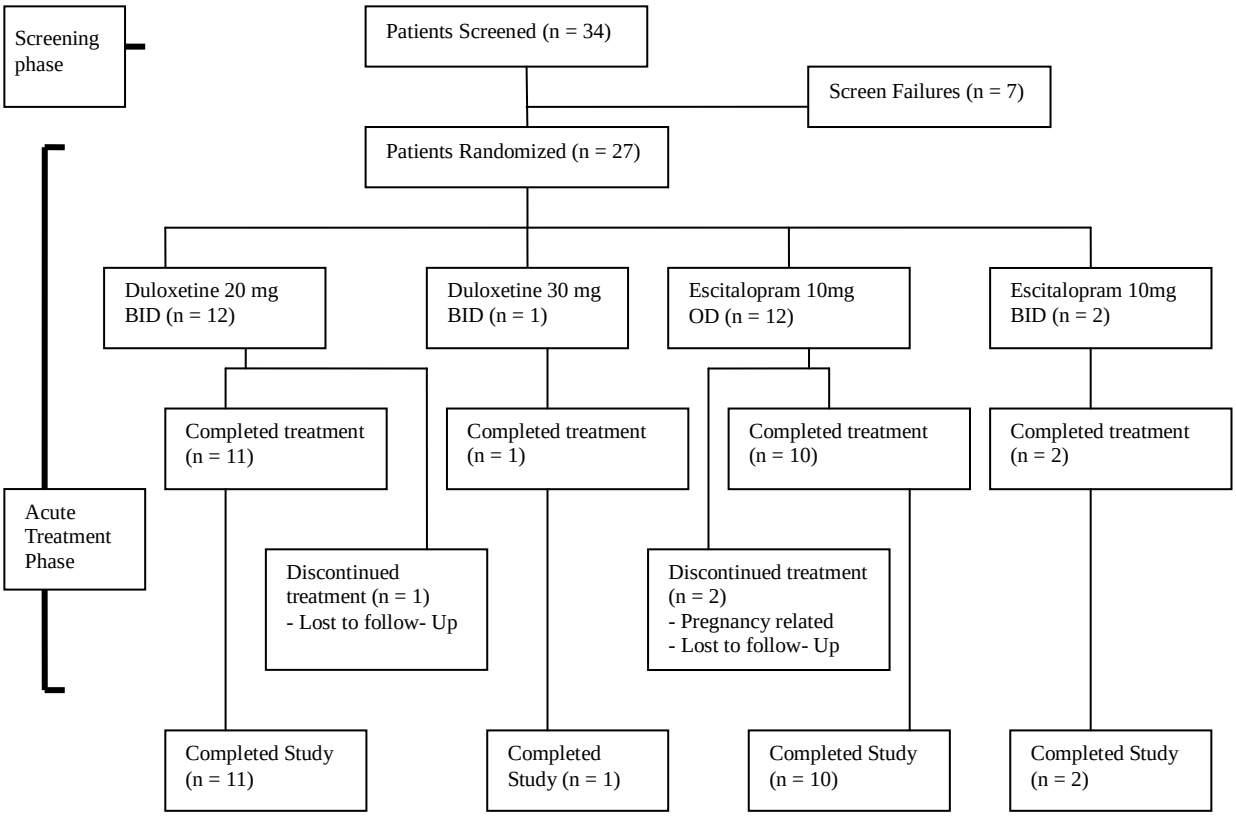


Table 1: Patient characteristics at baseline

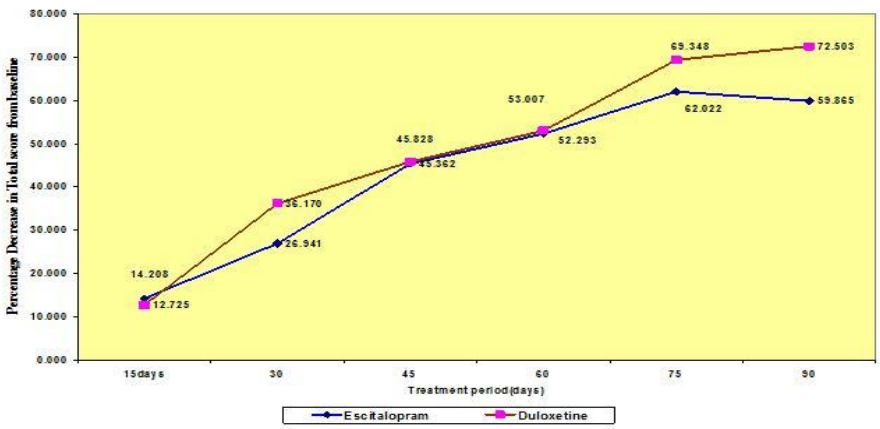
Demographic parameters	Duloxetine (n=12)	Escitalopram (n=12)
Sex		
Female	9 (75%)	7(58.3%)
Male	3 (25%)	5 (41.7%)
Age, mean years (SD)	38.57 (8.4)	34.89 (13.32)
Weight, mean kg (SD)	54.67 (6.80)	57.08 (7.21)
Psychiatric profile, mean (SD) $HAMD_{17}$ total	16.0 (2.74)	15.17 (2.23)
n = indicates number of randomized patients, $HAMD_{17}$ = 17–item Hamilton Rating Scale for Depression		
There were no statistically significant differences between treatment groups on any baseline demographic measures		

3.2 Efficacy – $HAMD_{17}$

Total reduction in score of $HAMD_{17}$ from base line

The changes in $HAMD_{17}$ are framed in figure 2, produced statistically significant greater mean reduction in $HAMD_{17}$ total score from baseline to the completion of study (12 weeks).

Figure 2: Effect of Duloxetine and Escitalopram on $HAMD_{17}$ Total Score



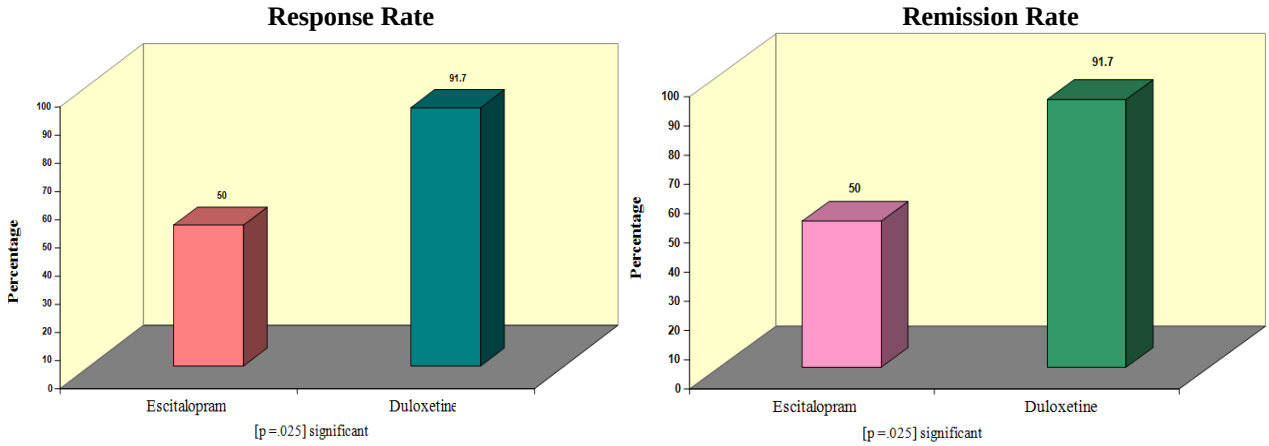
3.3 Efficacy of onset

Efficacy of onset (≥ 20% decrease in total score from baseline at 2 weeks) did not detect statistically difference between duloxetine (33.3%) and escitalopram (25%) groups but statistically significant ($p<0.05$) within the group.

3.4 Response and remission rates

The response and remission rates detected a statistically significant difference ($p<0.05$) between duloxetine and escitalopram groups as shown in figure 3.

Figure 3: The response and remission rates of duloxetine and escitalopram.



The efficacy parameters of response and remission were statistically significant within the groups as in table 2.

Table 2: The efficacy parameters of response and remission for duloxetine and escitalopram.

Duloxetine	**Paired differences**		**Z**	**P**
	Mean	**Std. Deviation**		
Day 0 – Day 15	2.0000	2.69680	2.226	0.026 sig
Day 0 – Day 30	5.5853	3.82476	2.941	0.003 hs
Day 0 – Day 45	7.3333	3.93893	3.066	0.002 hs
Day 0 – Day 60	8.6667	3.79793	3.066	0.002 hs
Day 0 – Day 75	10.7500	3.44106	3.068	0.006 hs
Day 0 – Day 90	12.0833	3.02890	3.074	0.002 hs
Escitalopram				
Day 0 – Day 15	2.1667	1.94625	2.714	0.007 hs
Day 0 – Day 30	4.0000	1.95402	3.077	0.002 hs
Day 0 – Day 45	5.9167	2.74552	3.075	0.002 hs
Day 0 – Day 60	7.3333	3.42008	3.077	0.002 hs
Day 0 – Day 75	8.5000	2.93877	3.068	0.002 hs
Day 0 – Day 90	9.0833	3.11764	3.068	0.002 hs

hs- highly significant($p<0.01$), sig- significant($p<0.05$)

3.5 Tolerability

3.5.1 Adverse events

There was no statistically significant difference in tolerability between duloxetine and escitalopram as shown in table 3 & table 4. Both were safe and well tolerated. There were no withdrawals from the study and the adverse effects were mild and self limiting. Nausea was the most common side effect with duloxetine and escitalopram seen in 8.3% of both groups study participants at visit 3 (30 days) and visit 5 (60 days) respectively. Anorexia was seen in 8.3% of study participants visit 4 (45 days) with escitalopram. Insomnia was seen in 8.3% of study participants at visit 4 (45 days) and 5 (60 days) with duloxetine and escitalopram, respectively. Headache was seen in 8.3 % of study participants with duloxetine at visit 5 (60 days).

Table 3: Adverse events of duloxetine and escitalopram

Adverse event	Duloxetine (40 mg/day) n (%)	Escitalopram (10mg/day) n (%)
Nausea	1 (8.3)	1 (8.3)
Anorexia	-	1 (8.3)
Insomnia	1 (8.3)	1 (8.3)
Headache	1 (8.3)	-

3.5.2 Vital signs & Body weight

Mean change from baseline to endpoint for vital signs & body weight as shown in table 4.

Table 4: Effect of duloxetine and escitalopram on vital signs & body weight

Variable Mean (SD)	Duloxetine (40 mg/day)	Escitalopram (10mg/day)
Weight (kg)	- 2.76 (0.19)	- 1.17 (0.22)
Heart rate (beats/min)	- 0.72 (9.92)	- 0.78 (10.24)
Systolic blood pressure (mm Hg)	0.11 (11.6)	0.14 (11.82)
Diastolic blood pressure (mm Hg)	2.14 (9.05)	2.43 (10.2)

4. Discussion

In the present study, primary analysis detected a statistically significant difference between duloxetine and escitalopram in response and remission rates. There was no statistically significant difference detected in efficacy of onset and tolerability. Response rate, remission rate and efficacy of onset were highly significant within both groups. There were no withdrawals from the study group. There were few side effects that were mild and self limiting.

In another study, Goldstein *et al*[15] conducted a randomized, placebo-controlled, double-blind trial in adults with MDD at 8 sites over 8-week treatment period. Patients were assigned to receive an escalating dosage of duloxetine, fluoxetine 20 mg daily, or placebo. In the duloxetine treatment group, dosages were initiated at 40 mg per day and increased to 120 mg per day by 3rd week. During the treatment phase, 34% of patients in both duloxetine and placebo groups and 36% taking fluoxetine discontinued treatment. One third of those who discontinued duloxetine did so because of adverse events, but a significant number of patients taking placebo discontinued it because of lack of efficacy. The above adverse events may have been contributed by higher dose of duloxetine in contrast to our study where dose was limited to 40-60 mg/day.

In another study, Detke *et al*[16] conducted a randomized, multicenter, double-blind trial that assigned 245 patients to either duloxetine 60 mg once per day or placebo for nine weeks. Patients who could not tolerate 60 mg/day were reduced to 40 mg/day of duloxetine. Patients in the duloxetine group had a greater reduction in $HAMD_{17}$ scores than patients in the placebo group and had significantly reduced scores of anxiety and pain on $HAMD_{17}$ subscales compared with patients receiving placebo. The present study also detected statistically significant reduction of $HAMD_{17}$ scores at similar dosing.

Another randomized, double-blind, placebo-controlled study evaluated duloxetine for the treatment of major depression in 267 patients at 21 U.S. sites over nine weeks.[17] Patients were initiated at 60 mg/day for duloxetine. Greater reductions from baseline in $HAMD_{17}$ scores were observed in patients receiving duloxetine than in those receiving placebo at the end of the study period. In present study greater reduction in baseline in $HAMD_{17}$ scores were observed in patients receiving duloxetine than in those receiving escitalopram.

The efficacy of escitalopram in the initial treatment of moderate-to-severe MDD has been evaluated in primary-care and specialist settings in several placebo-controlled trials and/or comparisons with citalopram[18] and other SSRIs (sertraline, paroxetine),[19][20] an extended-release formulation of bupropion (bupropion XL)[21] and an extended-release (XR) formulation of the serotonin/noradrenaline (norepinephrine) reuptake inhibitor (SNRI) venlafaxine.[22] The largest clinical trial database of tolerability information for escitalopram in MDD is documented in the manufacturer's prescribing information in which data were collated for 715 escitalopram and 592 placebo recipients involved in randomized, double-blind, placebo-controlled studies. The overall withdrawal rate due to adverse events was 6% for escitalopram and 2% for placebo.[6][7][8] In the present study also the adverse effects were mild and self limiting with both the study groups.

The study had few limitations that may have affected the results in terms of efficacy of onset and tolerability. The dosages of both active drugs were relatively low and period of study was short with less number of subjects.

Thus in a nut shell as per the present study duloxetine and escitalopram are well tolerated molecules at comparable doses. Duloxetine is superior to escitalopram in treatment of MDD of similar clinical settings. Newer molecules with better efficacy of onset, response rate, remission rate and tolerability are the need of this hour.

References

[1] Project on the Decade of the Brain. www.loc.gov/loc/brain/ [accessed 2014 Nov 20].

[2] Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatment (CANMAT). Clinical guidelines for the treatment of depressive disorders. *Can J Psychiatry* 2001; 46 Suppl1: 1S-92S.

[3] Sullivan PW, Valuck R, Saseen J, MacFall HM. A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions. *CNS Drugs* 2004; 18 (13): 911-32.
[4] Goodwin GM. How do antidepressants affect serotonin receptors? The role of serotonin receptors in the therapeutic and side effect profile of the SSRIs. *J Clin Psychiatry* 1996; 57(S4):9–13.
[5] Waugh J, Goa KL. Escitalopram: a review of its use in the management of major depressive and anxiety disorders. *CNS Drugs 2003*; 17 (5): 343-62.
[6] Forest Laboratories Inc. Lexapro™ (escitalopram oxalate) US prescribing information [online]. Available from URL: http://www.fda.gov [Accessed 2014 Nov19]
[7] H.Lundbeck AS. Cipralex: European summary of product characteristics [online]. Available from URL: http://www.cipralex.com/images/Cipralex/smpc.pdf [Accessed 2014 Nov 21]
[8] Lundbeck Canada Inc. Annotated prescribing information: escitalopram. Canada: Lundbeck Canada Inc., 2005.
[9] Chen F, Larsen MB, Sanchez C. The *S*-enantiomer of *R*, *S*-citalopram, increases inhibitor binding to the human serotonin transporter by an allosteric mechanism. Comparison with other serotonin transporter inhibitors. *Eur Neuropsychopharmacol* 2005 Mar; 15 (2): 193-8.
[10] Baldessarini RJ. Drugs and the treatment of psychiatric disorders, depression, and anxiety disorders. In: Hardman JG, Limbird LE, editors. Goodman and Gillman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill; 2001:437.
[11] Thase ME, Entsuah AR, Rudolph RL. Remisssion rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry 2001*;178:234-241.
[12] Tran PV, Bymaster FP, McNamara RK, Potter WZ. Dual monoamine modulation for improved treatment of major depressive disorder. *J Clin Psychopharmacol* 2003; 23(1):78-86.
[13] Nelson JC. Synergistic benefits of serotonin and noradrenaline reuptake inhibition. *Depress Anxiety* 1998; 7(suppl 1):5-6.
[14] American Psychiatric Association. Practice guidelines for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry* 2000; 157(suppl 4):1-45.
[15] Goldstein DJ, Mallinckrodt C, Lu Y, Detke MJ, Wiltse C, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry* 2002; 63:225–31.
[16] Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002; 63:308–15.
[17] Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *J Psychiatric Res* 2002; 36:383–90.
[18] Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int Clin Psychopharmacol* 2005 May; 20 (3): 131-7.
[19] Alexopoulos GS, Gordon J, Zhang D. A placebo-controlled trial of escitalopram and sertraline in the treatment of major depressive disorder [abstract no. 54]. *Neuropsychopharmacology* 2004; 29 Suppl. 1: 87.
[20] Baldwin D, Hindmarch I, Huusom AKT. Escitalopram and paroxetine in the short and long-term treatment of major depressive disorder (MDD) [abstract no. P01.135]. *Int J Neuropsychopharmacol* 2004 Jun 22; 7 Suppl. 1: S168.
[21] Wightman D, Horrigan JP, Modell JG. The tolerability and safety of bupropion XL versus escitalopram in the treatment of major depressive disorder [poster]. 13th Congress of the Association of European Psychiatrists (AEP); 2005 Apr 2-6; Munich.
[22] Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. *J Clin Psychiatry* 2004 Sep; 65 (9): 1190-6.