Research Paper

A Randomized Open-label Study to Evaluate the Effects of Escitalopram and Mirtazapine on Psychomotor Functions and Memory in Patients with Depression

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Abstract

Objective: To compare the effects of escitalopram and mirtazapine on psychomotor functions and memory and also to correlate the antidepressant efficacy of these drugs with psychomotor functions. **Materials and Methods:** This study was carried out at a tertiary care teaching hospital on 104 newly diagnosed literate patients with endogenous depression as per the inclusion and exclusion criteria. Patients were prescribed either escitalopram (20 mg OD) or mirtazapine (15 mg OD) or amitriptyline (75 mg BD). Psychomotor functions were assessed by digit-letter substitution, six-letter cancellation, choice reaction time, hand steadiness, and flicker fusion tests, and memory was assessed by PGI memory scale at the baseline and at the end of the 1st week, 1st month, and 4th month. Efficacy of drugs was measured by the Hamilton Depression Rating Scale (HDRS) at the baseline and each follow-up. The antidepressant efficacy of these drugs with various psychomotor function tests was correlated using Pearson's correlation test. $P < 0.05$ was considered statistically significant. **Results:** A total 95 patients, 32 in escitalopram, 32 in mirtazapine, and 31 in amitriptyline group, completed the study. Escitalopram and mirtazapine improved all psychomotor functions while amitriptyline significantly deteriorated ($P < 0.001$). All three drugs were equally efficacious ($P > 0.05$). A strong correlation was observed between psychomotor functions and HDRS score in patients treated with escitalopram (positive correlation), mirtazapine (positive correlation), and amitriptyline (negative correlation). **Conclusion:** Escitalopram and mirtazapine improve psychomotor function in patients with endogenous depression while amitriptyline deteriorates it. Thus, escitalopram and mirtazapine may be preferred to amitriptyline in clinical practice.

Keywords: Amitriptyline, depression, escitalopram, memory, mirtazapine, psychomotor functions

Introduction

Depression is a common mood disorder characterized by sadness, loss of interest or pleasure, feelings of guilt of low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration.[1] Globally, depression is ranked as the single largest contributor to nonfatal health loss. However, in India, the burden of depression, in terms of global disability-adjusted life years (DALYs), increased by 67% between 1990 and 2013. By 2025, DALYs attributable to depression are projected to rise by 2.6 million (22.5%) due to population growth and aging.[2]

Antidepressants are the mainstay of treatment of depression. As depression is a chronic condition and the treatment has to be given for a longer duration, the adverse reactions deserve attention, especially affecting the daily activities such as behavioral toxicity. Behavioral toxicity is defined as the extent to which a drug disrupts abilities necessary for the safe performance of cognitive and psychomotor tasks of everyday life.[3] Cognitive function is the brain's ability to acquire process, integrate, store, and retrieve information.[4] Psychomotor function includes sensorimotor processes such as reaction time and sensorimotor accuracy. Disturbance in these processes leads to patient maladjustment and may impair

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psychomotor performance, which plays an important role in driving and operating complex machinery. Various tests for the assessment of different aspects of the psychomotor function are available. This includes six-letter cancellation test (SLCT), digit-letter substitution test (DLST), flicker fusion test, hand steadiness test (HST), and choice reaction time (CRT) test. The effect of antidepressant drugs on psychomotor functions is variable. A meta-analysis of controlled studies of antidepressants showed that some tricyclic antidepressants could disrupt these functions.[5] Among selective serotonin reuptake inhibitors (SSRIs), sertraline significantly improves the psychomotor function as compared to desvenlafaxine and fluoxetine. On the contrary, fluoxetine deteriorates it over a period of 3 months.[6] Memory is a special faculty of brain, which retains the events developed during the process of learning and reproduces impressions once perceived. Memories are stored by increase in the sensitivity of synaptic transmission in the neurons due to previous neural activity which forms facilitated pathways. A significant and stable association was observed between depression and memory impairment.

The newer generation antidepressants such as escitalopram and mirtazapine are preferred by most clinical guidelines nowadays,[7-9] but very few studies have been conducted to demonstrate their effects on psychomotor functions and memory. Hence, the present study was undertaken to compare the effect of newer antidepressants such as escitalopram and mirtazapine with amitriptyline on psychomotor functions and memory and also to correlate their antidepressant efficacy with different psychomotor function tests.

Materials and Methods

This was a prospective, randomized, open-label, parallel-group study carried out at the department of pharmacology and psychiatry in a tertiary care teaching hospital after getting approval from the institutional ethics committee (EC/Approval/215/15/dated 06/11/2015). Newly diagnosed patients with endogenous depression; aged 18–55 years of either gender; living in Ahmedabad city; and could read and write in Gujarati, Hindi, or English were included in the study after taking written informed consent.

Patients suffering from chronic diseases or diseases affecting psychomotor function, patients on any drug (s) known to affect memory and psychomotor function, having a history of alcohol or any other substance abuse, pregnant, and lactating women were excluded from the study.

Outcome

Change in psychomotor functions using various tests such as SLCT, DLST, critical flicker fusion test (CFT), and HST and memory scores at the end of the 4th month from the baseline are primary outcomes. Comparison of efficacy using Hamilton Depression Rating Scale (HDRS) and correlating antidepressant efficacy with psychomotor functions at the end of the study are secondary outcomes.

Study procedure

Patients were randomly assigned to any of the three treatment groups: escitalopram, mirtazapine, and amitriptyline. The patients were followed up at the end of the 1st week, 1st month, and 4th month of starting the treatment. The drug was dispensed by the investigator at each follow-up, and compliance was checked using a drug dispensing record sheet and checking the pill count. The baseline data such as demographic details, clinical examinations, laboratory investigations, any concomitant diseases and drug therapy, and details of the drug treatment were recorded in a predesigned case record form. The tests used for the evaluation of psychomotor function include SLCT,[10] DLST,[10] CFT,[11] CRT audio-visual,[12] and HST.[13] Memory was assessed by PGI memory scale. Efficacy was measured using HDRS.[14] Psychomotor functions tests, HDRS, and PGI memory scale were administered at the baseline and each follow-up.

Statistical analysis

A sample size of thirty in each group was calculated for 95% power and 5% level of significance. Data were analyzed using repeated measures ANOVA and paired and unpaired *t*-test. $P < 0.05$ was considered statistically significant. A correlation between change in HDRS and psychomotor functions was done using Pearson's correlation. Graph Pad version 6.0 (San Diego, CA, USA) was used for statistical analysis.

Results

Of 104 patients enrolled, 95 patients completed the study. The number of patients treated with escitalopram and mirtazapine was 32 each, while the number of patients treated with amitriptyline was 31. A total of 9 patients were lost to follow-up: 3 in escitalopram, 2 in mirtazapine, and 4 in amitriptyline group. The mean age of the patients was 40.33 ± 5.63 years and men: women ratio was 1.06:1 [Figure 1]. All the 95 patients were literate. The most common clinical presentation was depressed mood (100%), followed by lack of interest (92%), insomnia (86%), guilt (78%), lack of concentration (49%), and anxiety (25%). Majority of patients were homemaker, followed by factory workers and laborer and few were unemployed. Other occupations included teacher, computer operators, clerk, peon, post office worker, security guard, businesspersons, and tailor.

Effect of drugs on psychomotor functions

The psychomotor functions for all three groups were comparable ($P > 0.05$) at the baseline. Patients treated with escitalopram showed a significant increase in scores of SLCT and DLST at the 1st month as compared to the baseline ($P < 0.001$). In addition, a significant increase in scores was observed at the end of the 4th month as compared to the 1st month ($P < 0.001$). On the contrary, a significant decrease in scores of HST was seen at the 1st month from the baseline. However, in choice reaction test, a significant decrease in scores was observed as early as 1st week as compared to the baseline ($P < 0.001$) [Table 1].

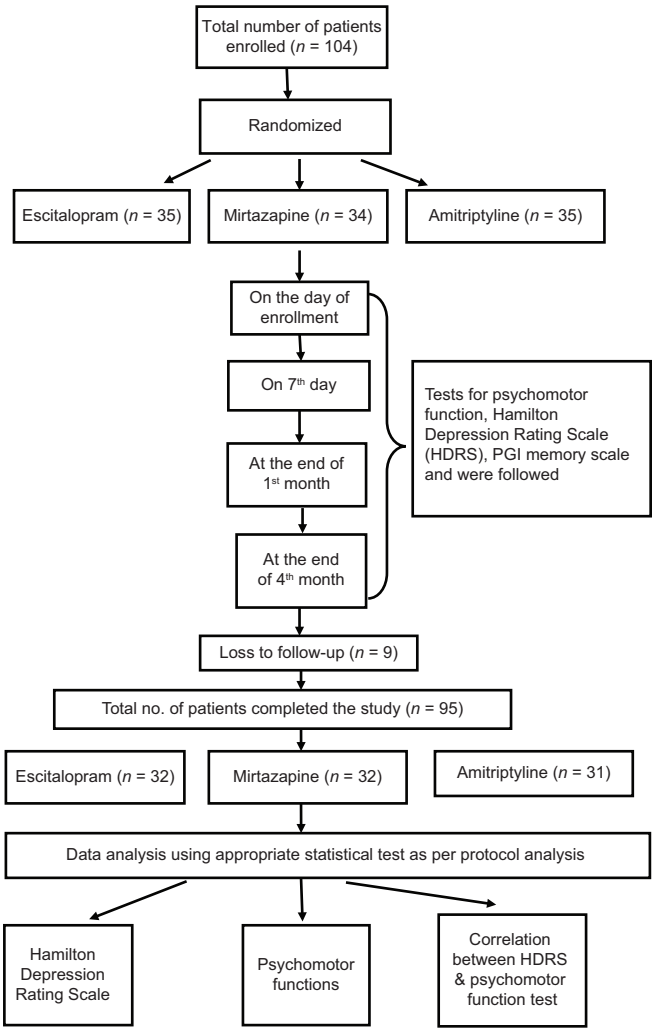

Figure 1: Details of patients enrolled (n = 95)

Similarly, in the mirtazapine group, patients showed a significant increase in scores of SLCT and DLST from the 1st month as compared to the baseline ($P < 0.001$). However, in flicker fusion test, the scores significantly increased only at the 3rd month ($P < 0.001$). On the contrary, a significant decrease in the score of HST was observed at the 1st month from the baseline. However, in choice reaction test, a significant decrease in the score was observed as early as 1st week as compared to the baseline ($P < 0.001$) [Table 1].

Conversely, amitriptyline-treated patients showed a decrease in the score of SLCT, DLST, and flicker fusion test at the 1st month and 4th month as compared to the baseline as well as the 1st month ($P < 0.001$). Moreover, a significant increase in the scores of choice reaction test and HST was observed from the 1st month as compared to the baseline ($P < 0.001$) [Table 1].

Comparison of three groups at the end of the 4th month

Effects of escitalopram and mirtazapine in all psychomotor functions were similar; both drugs increased the scores in SLCT, DLST, and flicker fusion test and decreased the scores in choice reaction test and HST. In addition, escitalopram

Table 1: Effect of escitalopram, mirtazapine, and amitriptyline on psychomotor functions at different follow-ups (n=95)

Pyschomotor test	Escitalopram (n=32)				Mirtazapine (n=32)				Amitriptyline (n=31)			
	Base line	1st week	1st month	4th month	Base line	1st week	1st month	4th month	Base line	1st week	1st month	4th month
SLCT	20.86±6.8	21.12±3.5	25.4±4.5*,†	31.45±3.2*,†,‡	22.5±6.85	26.4±5.4	26.6±5.3*	27.9±6.3*	21.65±3.2	21.5±4.5	16.3±4.1*,†	15.6±3.2*,†
DLST	22.12±5.2	21.34±4.5	26.42±5.3*,†	32.14±3.2*,†,‡	21.45±5.2	22.2±5.3	25.35.3*	26.2±4.3*,†	22.75±4.8	21.72±5.2	17.1±3.2*	15.4±3.2*,†
FFT	43.1±3.2	43.2±4.2	42.3±4.4	46.9±2.1*,†,‡	42.2±4.4	43.1±4.5	43.7±4.3	46.6±4.3*,†	43.5±4.6	43.6±4.2	40.1±4.1*,†	39.2±2.1*,†
CRT-audio	1.76±0.05	1.65±0.02*	1.45±0.03*,†	1.43±0.02*,†	1.89±0.04	1.84±0.03*	1.75±0.02*,†	1.72±0.01*,†,‡	1.58±0.04	1.60±0.02	2.01±0.03*,†,‡	2.35±0.02*,†,‡
CRT-visual	1.05±0.02	1.04±0.02*	0.95±0.03*,†	0.93±0.03*,†,‡	1.25±0.02	1.20±0.02*	1.18±0.03*	1.16±0.03*,†	1.02±0.03	1.05±0.02	1.25±0.03*,†	1.24±0.03*,†
HST	52.1±4.3	50.12±4.1	48.27±4.1*	46.36±4.5*,†	53.7±4.3	50.4±4.2	46.3±4.1*,†	45.0±3.9*,†	52.7±6.1	53.5±5.3	60.2±4.3*,#	61.3±4.5*,†

*P<0.001 as compared to the baseline, †P<0.001 as compared to the 1st week, ‡P<0.001 as compared to the 1st month. Data are expressed as mean±SEM. Paired t-test is used. SLCT=Six-letter cancellation test, DLST=Digit-letter substitution test, CFFT=Critical flicker fusion test, CRT=Choice reaction test (audio or visual), HST=Hand steadiness test, SEM=Standard error of mean

significantly increased the scores in SLCT and DLST as compared to mirtazapine ($P < 0.01$). Furthermore, escitalopram significantly decreased the scores in choice reaction test as compared to mirtazapine ($P < 0.01$), while mirtazapine caused significant decrease in HST scores as compared to escitalopram ($P < 0.01$). In flicker fusion test, no significant difference was found between the two groups. However, in the amitriptyline group, there was a decrease in the scores in SLCT, DLST, and flicker fusion test and an increase in choice reaction test and HST [Table 2].

Effects of drugs on memory

The memory was assessed using PGI memory scale. All the groups were comparable at the baseline for memory. Patients treated with escitalopram showed improvement in memory score from the 3rd month onward. However, patients treated with mirtazapine showed no change in memory functions. On the other hand, patients administered amitriptyline showed deterioration in memory from the 3rd month onward [Table 3].

Hamilton Depression Rating Scale

Patients treated with escitalopram and mirtazapine showed a decrease in HDRS score from the 1st week onward ($P < 0.001$), while amitriptyline-treated patients showed improvement from the 1st month onward ($P < 0.001$) [Figure 2]. Moreover, a consistent significant improvement was observed at each follow-up as compared to their previous one in all treatment groups. However, at the end of the study, an improvement in HDRS score was similar in all three treatment groups ($P > 0.05$) [Figure 2].

Correlation between Hamilton Depression Rating Scale score and psychomotor function test

A strong correlation (r value near to 1) was observed between DLST, CRT, and HST and HDRS score in patients treated with escitalopram (positive correlation), mirtazapine (positive correlation), and amitriptyline (negative correlation). However, no or weak correlation was observed between SLCT and Fast Fourier Transform (FFT) and HDRS score with escitalopram- and mirtazapine-treated patients while a strong negative correlation was observed with amitriptyline-treated patients [Table 4].

Discussion

The study evaluated the effect of escitalopram, mirtazapine, and amitriptyline on different psychomotor function tests and also correlated the antidepressant efficacy of these drugs with psychomotor functions. Of 104 patients enrolled in the study, 95 completed the study, while 9 were loss to follow-up. Hence, the data of 95 patients were calculated as per the protocol analysis. In six-letter cancellation, digit-letter substitution, and flicker fusion tests, an increase in the scores indicates improvement in psychomotor function. Whereas, in CRT test and HST, a decrease in the scores indicate improvement in psychomotor function.

A significant improvement in all psychomotor functions was observed in patients treated with escitalopram as early as 1st week of treatment till the end of the study. Our results are supported by Alamkhan *et al*.'s double-blind, placebo-controlled study on 20–40 mg escitalopram.[15] An improvement in six-letter cancellation and digit-letter substitution scores indicates

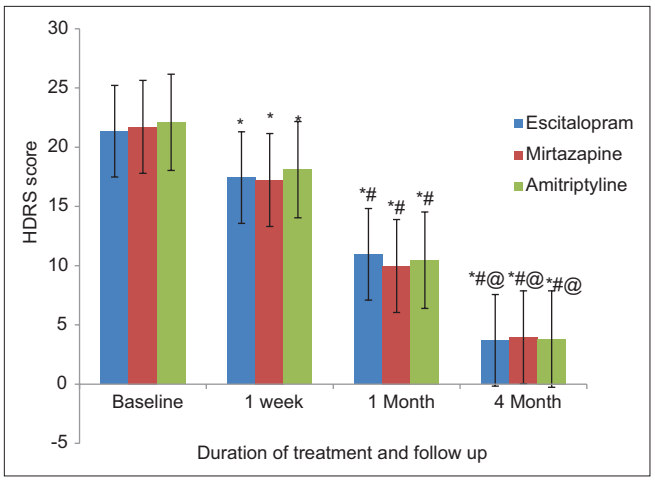

Figure 2: Effect of escitalopram, mirtazapine, and amitriptyline on Hamilton Depression Rating Scale at different time intervals ($n = 95$). Values are expressed in mean ± standard error of mean.*$P < 0.001$ as compared to the baseline. #$P < 0.001$ as compared to the 1st week. @$P < 0.001$ as compared to the 1st month

Table 2: Comparison of effect of escitalopram, mirtazapine, and amitriptyline on psychomotor functions at the end of the study ($n=95$)

Psychomotor function test	Escitalopram ($n=32$)			Mirtazapine ($n=32$)			Amitriptyline ($n=31$)		
	Baseline	4th month	Mean difference (mean±SD)	Baseline	4th month	Mean difference (mean±SD)	Baseline	4th month	Mean difference (mean±SD)
SLCT	20.6±6.8	31.45±3.2	10.59±3.6*	22.5±6.85	27.9±6.3	5.4±0.55	21.6±6.8	15.6±3.2	6.0±3.6
DLST	22.12±5.2	32.14±3.2	10.02±2*	21.45±5.2	26.2±4.3	4.75±0.9	2278±5.2	15.4±3.2	7.38±2
CFFT	43.1±3.2	46.9±2.1	3.8±1.1	42.2±4.4	46.6±4.3	4.4±0.1	43.5±3.2	39.2±2.1	4.3±1.1
CRT-audio	1.76±0.05	1.43±0.02	0.3±0.03*	1.89±0.04	1.72±0.01	0.17±0.03	1.58±0.05	2.35±0.02	0.77±0.03
CRT-visual	1.05±0.02	0.93±0.03	0.12±0.01*	1.25±0.02	1.16±0.03	0.09±0.01	1.02±0.02	1.24±0.03	0.22±0.01
HST	52.1±4.3	46.36±4.5	5.74±0.2	53.7±4.3	45.0±3.9	8.7±0.4†	52.7±4.3	61.3±4.5	8.60±0.2

Data are expressed in mean±SEM. Unpaired *t*-test used. *$P<0.01$ as compared to mirtazapine group, †$P<0.01$ as compared to escitalopram group. SLCT=Six-letter cancellation test, DLST=Digit-letter substitution test, CFFT=Critical flicker fusion test, CRT=Choice reaction test, HST=Hand steadiness test, SEM=Standard error of mean, SD=Standard deviation

Table 3: Comparison of effect of escitalopram, mirtazapine, and amitriptyline on patient global impressions memory score at different time intervals in the study (*n*=95)

	Escitalopram (*n*=32)	Mirtazapine (*n*=32)	Amitriptyline (*n*=31)
Baseline	62.9±0.7	61.9±2.4	62.0±1.5
1st week	62.8±2.4	61.6±2.4	61.9±2.4
1st month	63.1±1.5	62.4±2.5	60.8±3.2
3rd month	64.5±2.0*,#,@	63.1±2.0	59.8±1.5*,#
4th month	65.0±2.3*,#,@	62.9±2.3	58.7±1.7*,#,@

Values are expressed as mean±SEM. One-way ANOVA is used. *P<0.001 as compared to the baseline, #P<0.001 as compared to the 1st week, @P<0.001 as compared to the 1st month. SEM=Standard error of mean

Table 4: Correlation coefficient (*r*) between psychomotor function tests and Hamilton Depression Rating Scale

Psychomotor function test	Escitalopram (*n*=32)	Mirtazapine (*n*=32)	Amitriptyline (*n*=31)
SLCT	0.5745	0.2530	−0.8732
DLST	0.9842	0.9434	−0.9158
FFT	0.0125	0.0002	−0.9455
CRT-audio	0.4485	0.9384	−0.8285
CRT-visual	0.9232	0.9741	−0.7814
HST	0.9750	0.9172	−0.8403

SLCT=Six-letter cancellation test, DLST=Digit-letter substitution test, FFT=Flicker fusion test, CRT=Choice reaction test, HST=Hand steadiness test

improvement in sensory processing and recording recognition memory of brain, respectively, due to increased serotonin neurotransmission.[16] However, flicker fusion test primarily examines the attention, although it can be affected by other factors such as pupil size and retinal function. Therefore, partly, the flicker fusion test results may be due to pupillary dilation, which has been reported in the majority of studies with SSRI.[16] Motor component of psychomotor functions such as CRT and hand steadiness improved because of positive effect on concentration by serotonin level. Similarly, patients treated with mirtazapine showed a significant improvement in all psychomotor functions. Our observations are synonymous with Brunnauer *et al*.[17]

Conversely, patients treated with amitriptyline deteriorated all psychomotor functions. Amitriptyline, apart from inhibiting reuptake of 5-HT and NE, also antagonizes histaminic H_1 and muscarinic receptors, which is responsible for sedation and psychomotor impairment. As amitriptyline has shown detrimental effects on sensory (DLST and SLCT) and central processing (flicker fusion test) mechanism, this could also be the reason for impairment of fine motor performance with amitriptyline during HST and choice reaction test.[18]

All the three antidepressant drugs were found to be equally efficacious in improving the symptoms of depression. However, the improvement was fastest as early as 1st week in escitalopram- and mirtazapine-treated patients. A meta-analysis by Watanabe *et al*. comparing different antidepressant drugs also showed response rate as early as at the 1st week in escitalopram- and mirtazapine-treated patients.[19] The possible explanations for the apparently superior efficacy of escitalopram versus conventional SSRIs can be escitalopram decreases its own dissociation rate from the serotonin transporter, possibly via the allosteric site, leading to more prolonged inhibition of the transporter and higher extracellular serotonin levels.[20] A persistent increase in extracellular serotonin levels may be essential for the antidepressant effect.[21] However, mirtazapine increases the release of both norepinephrine and serotonin levels in brain.[22] This allows mirtazapine to be the most potent antidepressant drug with rapid onset of action than any other antidepressant drugs.[23]

Patients treated with escitalopram showed improvement in memory score from the 3rd month onward. However, patients treated with mirtazapine showed no change in memory functions. On the other hand, patients administered amitriptyline showed deterioration in memory from the 3rd month onward. Improvement in memory observed in the escitalopram group is probably related to increased neurogenesis (integration of new neurons) in dentate gyrus of hippocampus in brain, which is crucial for the formation of episodic and spatial memory. However, anticholinergic property of amitriptyline is responsible for deterioration in memory.

Further, a positive correlation was observed between all psychomotor functions and HDRS in patients treated with escitalopram and mirtazapine. This denotes that improvement in psychomotor function is related to improved symptom of depression following drug therapy. However, patients treated with amitriptyline showed a negative correlation between all psychomotor functions and HDRS, which denotes that treatment with amitriptyline improves depressive symptoms at the cost of psychomotor and cognitive deuteriation. SLCT and FFT require sensory processing and central integration. Histamine is a vital neurotransmitter required for sensory processing and central integration.[24,25] Escitalopram and mirtazapine have lack of affinity for histamine receptors and this could be the reason for weak or no correlation between SLCT and FFT and HDRS scores. However, central cholinergic activity of amitriptyline could probably a reason for strong negative correlation.

Like any other studies, the present study had some limitations. Some of the psychomotor tests such as SLCT and DLST are subjective in nature, and the result may vary according to the education level of the patients. However, the importance of the present study cannot be undermined. It is one of the few studies conducted in India on comparative effect of antidepressants on psychomotor function. This work may prove to be a foundation for future research on depressive illness and may also help clinicians in deciding treatment options.

Conclusion

There is no statistically significant difference between escitalopram, mirtazapine, and amitriptyline as antidepressants. Escitalopram and mirtazapine improve the psychomotor functions in patients with endogenous depression while amitriptyline significantly deteriorates it. Thus, escitalopram and mirtazapine may be preferred to amitriptyline in clinical practice.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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