

Full Length Research Paper

Comparison of the latency time of selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors

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Identification of the timing of the onset of antidepressant action has been a well-debated matter. Theoretically, all antidepressants have been known to have a therapeutic latency of two to three weeks. Objective of the study is to determine the therapeutic latency of different antidepressants. 159 patients from the Psychiatry Department, Oradea were taken in the study. The Hamilton-17 Depression scale (HAM-D-17) and the Montgomery-Asberg Depression (MADRS) were used. The time taken for the first symptom to disappear on either of the depression scales was described as the latency time. The latency time was found to be 6.62± 0.91 days in the general lot and was found to be influenced by several factors. Antidepressants have a therapeutic latency of less than 2 weeks. Paroxetine was found to have the smallest latency time while sertraline had the longest latency time.

Keywords: Depression, latency, antidepressants, depression scales.

INTRODUCTION

Depression is a prevalent psychiatric disorder with estimates reaching as high as 21%. For nearly 2500 years, depression has been described as one of the most common illnesses of humankind, but only recently it has commanded major public health interest. Without treatment, depression has the tendency to assume a chronic course, to recur, and to be associated with increasing disability over time.

Currently, different classes of antidepressants are available and have been demonstrated to be effective for the treatment of depression. Antidepressants are widely prescribed worldwide though many disadvantages are associated with the current classes of antidepressants. Some of the disadvantages include a long latency of action (2 to 3 weeks), many side effects (weight gain, sexual dysfunction) and high costs.

This latency of action is due to adaptive changes which occur in neurotransmitter receptor sensitivity in a delayed time course. Antidepressant treatment results in molecular and cellular responses that demonstrate an increase in neural plasticity. Neuroplasticity is a broad term that encapsulates changes in intracellular signaling cascades and gene regulation, modifications of synaptic number and strength, variations in neurotransmitter

release, modelling of axonal and dendritic architecture and, in some areas of the CNS, the generation of new neurons.

Neural plasticity upon antidepressant treatment is likely to involve adaptations of multiple intracellular signaling cascades and even interactions of these pathways. Some clinical trials have reported clinical improvement as early as the first week of treatment. Moreover, recent data using weekly or daily mood ratings demonstrate that maximum improvement occurs during the first 2 weeks, with some improvement within the first 3 days.

Traditionally, it has been thought that standard antidepressants take about 1 month for their action to fully unfold, and that they have a delayed onset of action of at least 2 to 3 weeks. Identification of the exact timing of the onset of antidepressant action has been a well-debated matter for the last 20 years. The order and timing of the alleviation of depressive symptoms has also rarely been studied.

Objectives of the study

The objectives of the study are:

Table 1. Dosage of antidepressants.

Antidepressant	Dose per tablet	Administration time versus number of table (morning)	Afternoon	Night
Escitalopram	10 mg	1	0	1
Paroxetine	20 mg	1	0	1
Sertraline	50 mg	1	0	0
Venlafaxine	75 mg	1	0	1
Duloxetine	30 mg	1	0	1

-To establish the therapeutic latency of different antidepressants from 2 different classes:

(1) Selective Serotonin Reuptake Inhibitors, namely escitalopram, sertraline, paroxetine, and

(2) Serotonin-Noradrenaline reuptake Inhibitors (venlafaxine, and duloxetine), and to make a comparison among them. The therapeutic latency of antidepressants will be considered as the time interval between the initiation of the medication and the disappearance of the first symptoms (number of days for the first symptoms to disappear).

-To establish the first symptoms to be influenced by each antidepressant.

MATERIALS AND METHODS

A group of 159 patients from the Psychiatry Department, Municipal Hospital, Oradea were taken in the study. All patients met the criteria for major depression (unipolar, single or recurrent episode) of the Diagnostic and Statistical Manual of Mental disorders, fourth edition. Patients with mild to severe forms of depression were included. Both male and female patients were taken in the study and all patients were at least 18 years. On the other hand, patients with comorbid psychiatric disorders were excluded. The antidepressants used in this study were from the Selective serotonin reuptake inhibitor (SSRI) and the Serotonin-noradrenaline reuptake inhibitor (SNRI) classes (Table 1). The usual recommended dosage range for the European Union for each antidepressant was used in order to avoid unwanted side effects. The same dose for each antidepressant was given to patients in order to have a more reliable result. Patients who needed higher doses of the given antidepressant during the study were excluded.

Apart from the antidepressants, patients were allowed a low-dose of benzodiazepine (bromazepam 1.5-3 mg/day or lorazepam 1-2 mg/day or alprazolam 0.5-1 mg/day or clorazepate 5-10 mg or clonazepam 0.5-1.0 mg). This combination of antidepressant-benzodiazepine was done in order to reduce the onset of the risk of suicide that has been associated with the use of

antidepressants during treatment. Patients who needed other medications in higher doses were rejected from the study.

Patients were evaluated on a daily basis. The Hamilton-17 Depression scale (HAMD-17) and the Montgomery-Asberg Depression (MADRS) were used as measuring tools in order to evaluate the severity of the depression before the initiation of treatment and then on a daily basis to detect the first symptom to disappear and the time taken for the first symptom to disappear. All patients were evaluated daily till at least the first symptom disappeared and till they were hospitalized.

Tests of statistical significance were calculated by Student method (t test) and χ^2 (chi 2). χ^2 test of significance (chi2) is the most commonly used when comparing frequencies or proportions, because it can be used for two or more samples. Null hypothesis states that there is no association between variables. The frequency is determined for each variable, as though the null hypothesis would be true. The alternative null hypothesis is the existence of a relationship between variables. The p value measures the probability that the null hypothesis is true. The condition of rejecting the null hypothesis, thus accepting the contrary hypothesis, namely that there is a correlation "not accidental" between the two parameters is: $p < 0.05$. Where $p < 0.01$, the correlation between the two parameters is highly statistically significant.

Sensitivity to change was evaluated by calculating the effect size (ES). ES is a method of standardizing a variable magnitude of change after a fixed period of time. It represents the average change for a variable expressed in units of standard deviations. This standardization allows comparison of the change of variables in a study. Moreover, ES can be used to compare the same variable between different studies.

RESULTS

The mean age of the patients was 56.2 ± 10.9 years. The mean duration of hospitalization was 9.33 ± 1.29 days. The therapeutic latency of all 5 antidepressants when both MADRS and HAMD-17 scales were considered

Table 2. The distribution of patients according to the antidepressants prescribed.

Antidepressants	Number of patients	%
Selective Serotonin Reuptake Inhibitors, SSRI		
Escitalopram	43	27.0
Paroxetine	38	23.9
Sertraline	26	16.4
Serotonin Norepinephrine Reuptake Inhibitors ,SNRI		
Duloxetine	30	18.9
Venlafaxine	22	13.8

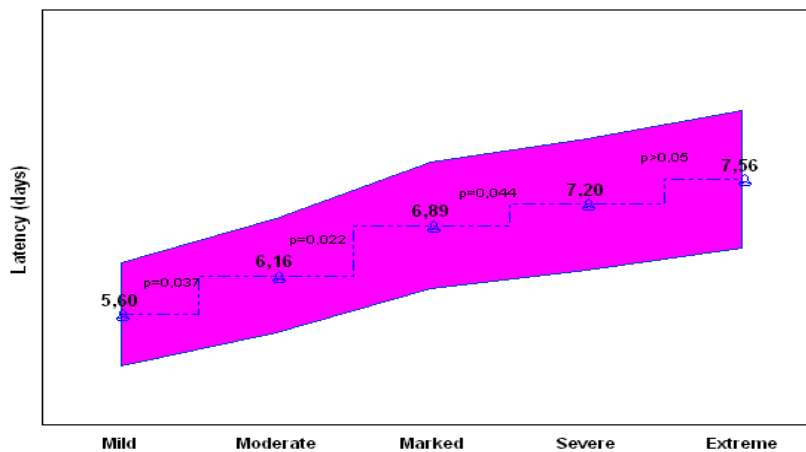


Figure 1. Latency time in relation to severity of depression.

together was calculated to be 6.62 ± 0.91 days (Table 2).

Variations of latency time

There were no significant differences in the latency times in female (6.64 days) and male (6.69 days) patients ($p > 0.05$). The latency time was shorter in patients less than 30 years; this was statistically significantly faster than in the other patients ($p < 0.001$). When marital status was considered, it was found that the shortest latency time was found in single patients; this was significantly shorter than in the other patients ($p < 0.001$). There were no differences in latency times in those with and without comorbidities. ($p > 0.05$). There was a progressive increase in latency time with increase in intensity of depression (Figure 1).

The therapeutic latency was found to be significantly shorter in patients with single/first depressive episode than in those with recurrent depressive disorder ($p = 0.018$).

Results from the Serotonin-Noradrenaline Reuptake Inhibitors (SNRI) group: Comparison between Duloxetine and Venlafaxine

Mean hospitalization days: duloxetine (9.44 ± 1.17 days); venlafaxine (9.32 ± 1.17 days). According to the evolution of the MADRS scores, the effect size of the treatment was more than 1.5 times in the venlafaxine group than in the duloxetine group ($ES = -3.46$ versus $ES = -2.27$). This implies that venlafaxine is more efficacious than duloxetine (Table 3).

Lassitude disappeared fastest in patients from the duloxetine group. Pessimistic thoughts disappeared in the shortest number of days (5.5 days) in patients from the venlafaxine group (Figure 2).

According to the HAMD-17 scale, from the duloxetine group, insight disappeared faster (2 days). Anxiety-psychoic took the greatest number of days to disappear as first symptom. From the venlafaxine group, agitation disappeared fastest, followed by insomnia-early in the morning (Figure 3).

Table 3. The evolution of the MADRS scores.

	Duloxetine (9,44±1,17 days)				Venlafaxine (9,32±1,17 days)			
	Initial (at admission)		Final (at discharge)		Initial (at admission)		Final (at discharge)	
	No. of Patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Normal	-	-	-	-	-	-	-	-
Mild	2	6,7	19	63,3	1	4,5	19	86,4
Moderate	25	83,3	11	36,7	19	86,4	3	13,6
Severe	3	10,0	-	-	2	9,1	-	-
Mean	25,53±3,16		18,37±2,28		26,45±3,32		14,95±1,87	
ES	-2,27				-3,46			

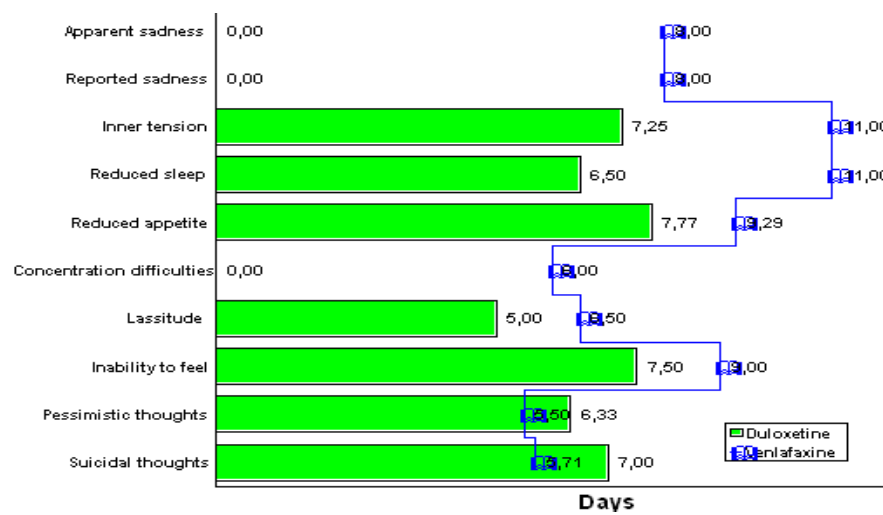


Figure 2. First symptom to disappear (MADRS).

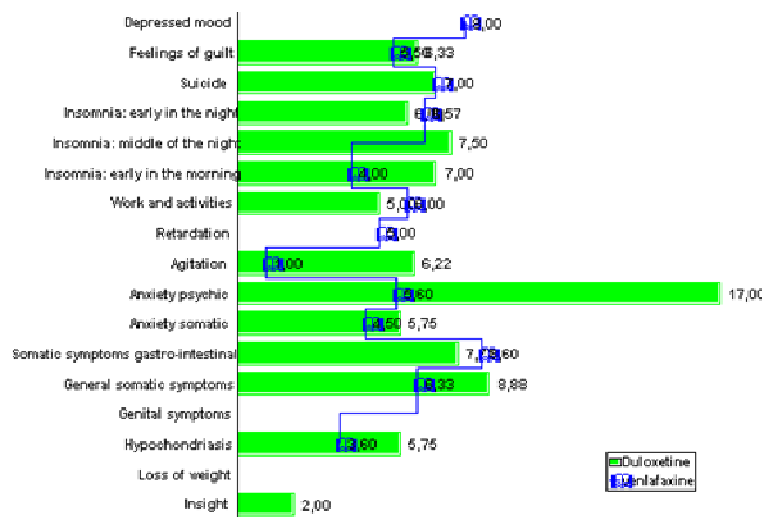


Figure 3. First symptom to disappear (HAM-D-17).

Venlafaxine had a shorter latency time (Figure 4) but results were not statistically significant ($p > 0.05$).

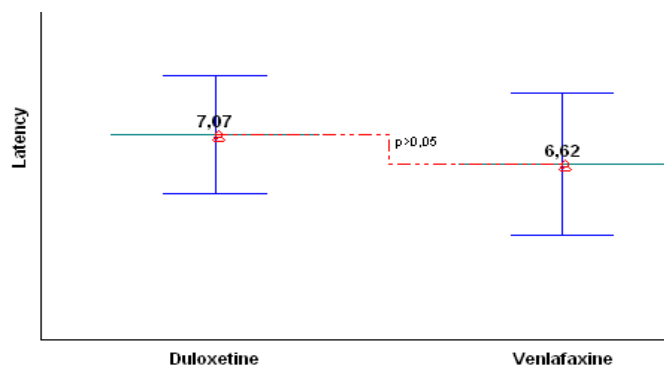


Figure 4. Latency time(number of days).

Table 4. Comparison between escitalopram, paroxetine and sertraline.

	Escitalopram				Paroxetine				Sertraline			
	Initial (at admission)		Final (at discharge)		Initial (at admission)		Final (at discharge)		Initial (at admission)		Final (at discharge)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Normal	-	-	1	2,3	-	-	-	-	-	-	-	-
Mild	3	7,0	30	69,8	3	7,9	27	71,1	5	19,2	16	61,5
Moderate	36	83,7	12	27,9	33	86,8	11	28,9	19	73,1	10	38,5
Severe	4	9,3	-	-	2	5,3	-	-	2	7,7	-	-
Mean	26,70±3,56		17,02±2,27		27,21±3,63		17,50±2,33		25,96±3,46		18,65±2,49	
ES (Effect size)	-2,72				-2,67				-2,11			

No.= number of patients.

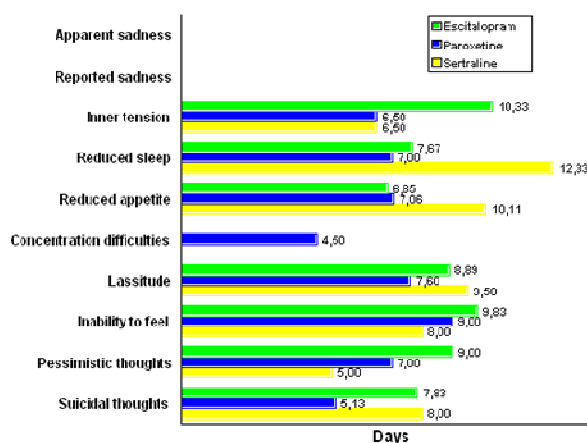


Figure 5. First symptom to disappear (MADRS).

Results from the Selective Serotonin Reuptake Inhibitor (SSRI) group: Comparison between escitalopram, paroxetine and sertraline

Mean hospitalization days: escitalopram: 9.44 ± 1.17 ; paroxetine: 8.74 ± 1.04 ; sertraline: 9.96 ± 1.23 days.

According to the evolution of the MADRS scale, the effect size of the treatment was slightly higher in the escitalopram group (-2.72), implying that escitalopram has a better efficacy than the other 2 SSRIs (Table 4).

Suicidal thoughts, reduced sleep, lassitude disappeared fastest in the paroxetine group (Figure 5).

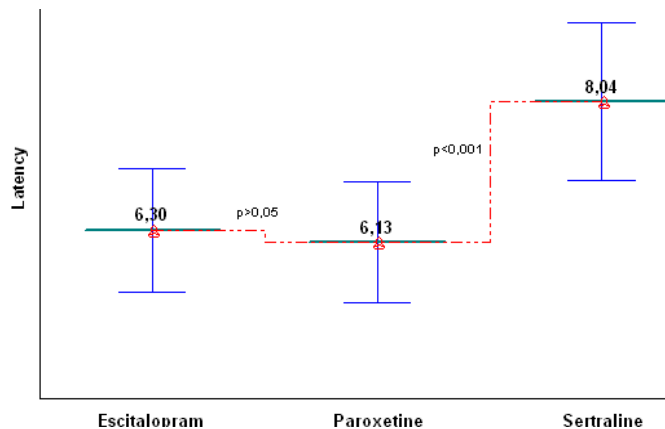


Figure 6. Latency time (number of days).

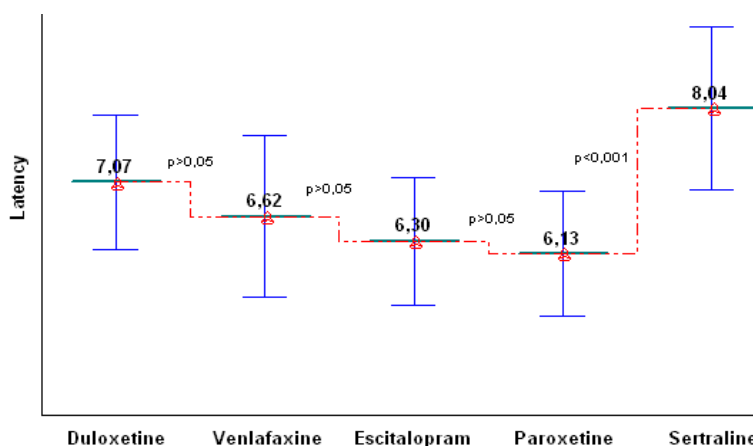


Figure 7. Latency time (number of days).

Table 5: Comparison of results from the 5 antidepressants.

Antidepressant	Latency time (number of days)
Duloxetine	7.07±0.88
Venlafaxine	6.62±1.06
Escitalopram	6.30±0.85
Paroxetine	6.13±0.82
Sertraline	8.04±1.07

The therapeutic latency was shorter in the paroxetine group (6.13 days) but not statistically significant as compared to escitalopram (6.30 days) ($p > 0.05$) (Figure 6). Sertraline had the longest latency time within the SSRI class (8.04 days).

Comparison of results from the 5 antidepressants

Among the 5 antidepressants, sertraline had the longest latency time (Figure 7, Table 5).

The smallest latency time was found in patients with single/first episode of depression in the venlafaxine group (4.40 days). This was insignificantly smaller than in patients from the duloxetine group ($p > 0.05$). The smallest latency time was found in the paroxetine group in the case of recurrent depressive disorder (5.97 days). This was insignificantly smaller than that of venlafaxine and escitalopram ($p > 0.05$) (Figure 8).

In mild depression, the smallest latency time was found in the paroxetine group. In moderate depression, the smallest latency time was found in the escitalopram

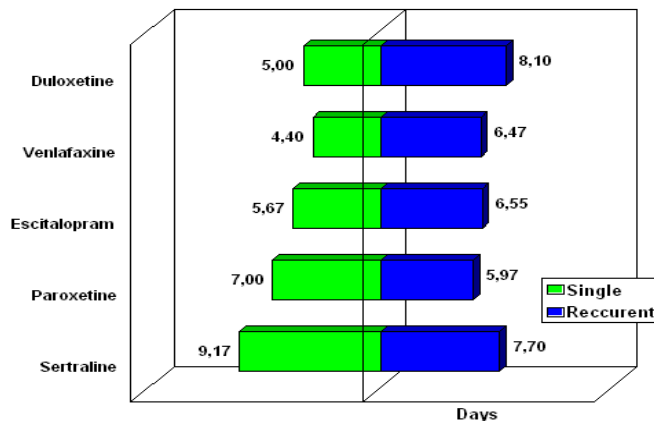


Figure 8: Latency time (number of days) in relation to diagnosis.

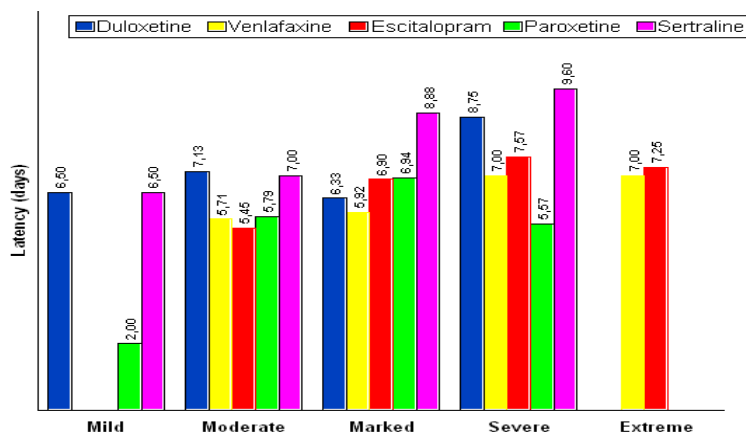


Figure 9: Latency time in relation to severity of depression.

group. This was insignificantly smaller than that of venlafaxine and paroxetine ($p > 0.05$). In marked depression, the smallest latency time was found in the venlafaxine group. In severe depression, the smallest latency time was found in the paroxetine group. In extremely severe cases, the latency time of venlafaxine was smallest (Figure 9).

DISCUSSION

The therapeutic latency of antidepressants in this study was less than the theoretical value of 2-3 weeks. A faster onset of action of antidepressants has been demonstrated by many independent groups (Szegeedi et al., 2003; Cornutiu et al., 2007). Cornutiu et al. (2007) demonstrated that the therapeutic latency of escitalopram in a lot of 48 patients was 8.28 days for depressive spectrum disorders and was dependent on the clinical intensity of the depression.

The therapeutic latency of the antidepressants in the general lot was found to be influenced by several factors

such as age, diagnosis, severity of depression, marital status. The shortest latency time was found to be in patients from younger age groups (less than 30 years old), in mild depression, in single/first depressive episode.

This shorter latency time could perhaps be explained by the neurobiological mechanisms. Most antidepressants exert their initial effects by increasing intrasynaptic levels of serotonin and/or norepinephrine, but clinical antidepressant efficacy is observed only after chronic administration (over days to weeks). This suggests that a cascade of downstream events is ultimately responsible for their therapeutic effects.

Changes in growth factor levels may underlie changes in neurogenesis with increasing age. Neurotrophic factors, growth factors and their receptors are abundant during development and decline with age (Wise 2003; Shetty et al., 2005). Since neurogenesis may be more preserved in younger patients, the latency of action of antidepressants may be shorter in such patient groups.

Recurrent depressive episodes and more severe depressive episodes may also be related to a more

significant decrease in neurogenesis and thus affect the latency of antidepressants adversely. Structural imaging has demonstrated decreased hippocampal size in patients with major depression, especially those who have suffered multiple episodes (MacQueen et al., 2003).

Psychosocial stress may also affect latency time adversely. Divorce or loss of spouse is a chronic type of stress and regulates neurogenesis negatively.

CONCLUSION

Paroxetine had the shortest latency time while Sertraline had the longest latency time (8.04 days). In extremely severe depression, venlafaxine appeared to have the smallest latency time. Venlafaxine appeared to be more efficacious than the other antidepressants. In published studies using SSRIs as active comparators, venlafaxine therapy has been found to be comparable or superior to therapy with sertraline (Mentonen et al 2000) and paroxetine (Ballus et al 2000).

The therapeutic latency of the 5 antidepressants in this study has been found to be less than the theoretical value. The latency time has also been found to be influenced by both biological and psychosocial factors. These practical points could be useful in order to guide patients on the number of days they would have to wait in order to start experiencing clinical improvement in their symptoms. Moreover, the antidepressants could be prescribed according to the clinical profile of the patients.

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