Original Article

Evaluation Of Antidepressant Activity Of Statins Alone And In Combination With Fluoxetine In Acute And Chronic Behavioural Models Of Depression

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Abstract

Context: To study the role of statins (Atorvastatin, Simvastatin, and Pravastatin) as novel pharmacological option in treatment of depression.

Aim: To evaluate antidepressant activity of statins (HMG-CoA reductase inhibitor) in combination with Fluoxetine in acute and chronic forced swim test in rats.

Design: An experimental animal study.

Materials and methods: Male albino wistar rats of either sex with weight range 150-250 grams were used. Part 1 is Dose finding study in acute forced swim test with three doses of Atorvastatin (2.5 mg/kg, 5 mg/kg, 10 mg/kg), Simvastatin (2.5 mg/kg, 5 mg/kg, 10 mg/kg), and Pravastatin (10 mg/kg, 20 mg/kg, 40 mg/kg) each were done. Part 2 was conducted to study the effects of statins (Atorvastatin, Simvastatin, and Pravastatin) and Fluoxetine (10 mg/kg) per se and in combination, on immobility of rats in acute forced swim test were compared. In part 3 effects of statins (Atorvastatin, Simvastatin, and Pravastatin) and Fluoxetine per se and in combination on immobility of rats in chronic forced swim test were compared. Open field test was performed to discriminate between the general behavioural stimulation (false positives) and antidepressant effect of study drugs. All study drugs were given orally. In Part 2 & 3 maximum effective dose of statin from part 1 was utilised.

Statistics: ANOVA with post-hoc Tukeys test, significant effects were analyzed further using post hoc Newman-Keuls tests.

Results: In part 1 of dose finding study most effective doses for Atorvastatin, Simvastatin and Pravastatin were 10 mg/kg, 10 mg/kg and 40 mg/kg respectively. In this part acute forced swim test showed, no statistically significant reduction in duration of immobility by any of the statins (Atorvastatin, Simvastatin, and Pravastatin) as compared to control. In Part 2 acute forced swim test, When combined with Fluoxetine, Atorvastatin (157.83 ± 10.51) and Simvastatin (167.66 ± 7.71) showed significant reduction in duration of...
immobility when compared with control (183.66 ± 9.52) but not against Fluoxetine (161.33 ± 8.68) alone. In
part 3 chronic forced swim test, Atorvastatin (132.16 ± 7.19 sec) and Simvastatin (130.50 ± 5.68 sec)
significantly potentiated action of Fluoxetine. However Pravastatin did not significantly potentiated the action
of Fluoxetine. In open field test done before acute and chronic forced swim test (Part 2 & 3 respectively),
there was no statistically significant difference between test groups for line crossing, rearing, and defecation
suggesting that there was no general behavioural stimulation of rats and reduction in duration of immobility
with test drugs was due to antidepressant effect.

**Conclusion:** Present study shows that Atorvastatin, Simvastatin, and Pravastatin do not exhibit independent
antidepressant activity, but they can have synergistic effect with SSRI like Fluoxetine. Atorvastatin and
Simvastatin may help to reduce the dose of Fluoxetine thereby minimizing adverse effects of Fluoxetine

**Keywords:** Forced swim test, Ischemic heart disease, SSRI, Cholesterol, Wistar rat

**Key messages:** Atorvastatin and Simvastatin enhance antidepressant activity that of Fluoxetine. This can
be considered as rational combination therapy since they act on different receptor systems which form the
basis for their use in depression.

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**Introduction**

Ischemic heart disease (IHD) is leading cause of mortality worldwide and India is undergoing an
epidemiological transition and is on the threshold of an epidemic of cardiovascular disease. According to
the 2013 Global Burden of Disease Study, cardiovascular diseases are the fastest growing chronic illnesses between 2005 and 2015, growing at 9.2% annually responsible for >17 million deaths
globally each year (30% of all deaths) 80% of which occur in low-income and middle-income countries,
and this figure is expected to grow to 23.6 million by 2030 (1). IHD is the most common, serious, chronic,
life-threatening illness in the United States, where 13 million persons have IHD, >6 million have angina
pectoris, and >7 million have sustained a myocardial infarction (2). While the death rates have been
declining for the past three decades in the west, these rates are rising in India. Presently, 29.8 million
patients in India suffer from ischemic heart disease.

In the last three decades, the prevalence of CAD has increased from 1.1% to about 7.5% in the urban
population and from 2.1% to 3.7% in the rural population attributed to the genetic, metabolic,
conventional and nonconventional risk factors (3).

Risk factors for IHD are divided as Constitutional (age ≥45 years in males, ≥55 years in Females,
male gender, family history of IHD), modifiable risk factors (hyperlipidaemia, Hypertension, cigarette
smoking, diabetes, C - reactive protein) and additional risk factors (Inflammation, hyperhomocystinemia,
metabolic syndrome, lipoprotein (a), lack of Exercise; stressful life style; and obesity).

Depression has also emerged as an important risk factor for IHD. In IHD, depression is not only primary
risk factor (1.5-fold to two fold increase in the risk for incident IHD) but also secondary risk factor for
worsened prognosis and increased risk of mortality in these patients (4). This association is independent
of established risk factors for IHD (5). Depression, is associated with the number and length of cardiac-
related hospitalizations and all-cause mortality in IHD patients (6). Depression is a significant predictor of
mortality at 6 months in post-MI patients (7). Just as depression can be risk factor for MI it can also
occur as result of MI and be one of the outcomes of MI. At any given time, up to 20% of patients with
heart disease meet the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)
criteria for major depression, identifying better simultaneous treatments options for depression and
IHD in this population (8). By the year 2020 burden of depression will increase such that it will be the
second leading cause of disability throughout the world trailing IHD (9).
Pharmacotherapy of IHD includes drugs given to abort acute attack (nitrates, calcium channel blocker), drugs for prophylaxis ($\beta$ blocker, nitrates, calcium channel blocker) and drugs for prevention and treatment of risk factors (Antiplatelet, and Hypolipidemic drugs). Among the Hypolipidemic drugs statins are the most widely used cholesterol-lowering agents, which act by inhibition of 3-hydroxy 3-methylglutaryl coenzyme. In recent years the focus is shifted to the central nervous system (CNS) especially on cognition and neurological disorders associated with chronic use of statins (10).

Large scaled observational studies and population based studies have suggested a positive role of low cholesterol levels on psychological well-being (11, 12). Systematic review and meta-analysis suggests that statin use is associated with lower risk for depression (13). Some contradictory studies have shown lower serum cholesterol levels among some patients with recent impulsive or violent suicidal attempts (14). In amidst this clinical data controversy on statin use and depression we decided to conduct animal studies to check role of statin in depression. Earlier animal study has showed potentiation of antidepressant action of sub therapeutic dose of Fluoxetine by Lovastatin on chronic administration (15). Forced swim test is one of the most widely used preclinical paradigms for predicting antidepressant like activity of drugs after their administration. As such, the test has a number of uses and is included in almost every thorough analysis of rodent behaviour (16). Along with forced swim test, open field test is also commonly used to assess the sedative, toxic, or stimulant effects of compounds. Although doses of statins widely vary for various pleiotropic effects, doses of statins affecting various CNS functions like memory and learning in previous animal studies were chosen for this study. Dose of 5 mg/kg was chosen for Atorvastatin and Simvastatin (17). Similarly dose of 20 mg/kg was used for Pravastatin (18). All three statins Atorvastatin, Simvastatin and Pravastatin were administered orally. As there are no animal studies which have exclusively evaluated the antidepressant activity of these three statins Atorvastatin, Simvastatin and Pravastatin, one dose above and below the selected doses were used in dose finding study.

### Materials and methods

#### Animals

Hundred and eight Albino wistar rats of either sex (procured from Haffkine Biopharmaceuticals Corporation Limited, Mumbai) were used in this study. The wistar rats weighed 150-250 grams and housed in groups of 3-4 at the time of behavioural testing. Rats were maintained in a 12 h light/dark cycle, relative humidity 30-70%, with free access to food and water except during testing at 11:00 to 15:00 hours. Experiments were conducted in accordance with guidelines laid down by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Permission from Institutional Animal Ethics Committee was taken prior to the initiation of study.

#### Study drugs

Fluoxetine was procured from Sun Pharmaceuticals Ltd, Mumbai and administered in distilled water vehicle at a volume of 1 cc/kg. Atorvastatin, Simvastatin and Pravastatin procured from Ranbaxy Laboratories Ltd., Gurgaon was administered orally 3 times 24 hours, 5 hours and 1 hour prior to forced swim test. Statins (Atorvastatin, Simvastatin, and Pravastatin) were dissolved in Carboxymethylcellulose (0.5%) and vehicle groups received appropriate volume of Carboxymethylcellulose (0.5%).

#### Study design

Study was executed in three parts.

**Part 1**

It consisted dose finding study in acute forced swim test. Rats were grouped into 10 groups of 6 animals each with three doses of Atorvastatin (2.5, 5, 10 mg/kg), Simvastatin (2.5, 5, 10 mg/kg), Pravastatin (10, 20, 40 mg/kg) and 10th group was Vehicle control (Carboxymethylcellulose 0.5%). Objective was to study the effect of administration of three different doses of three statins on duration of immobility of rats in acute behavioural model of depression.
Part 3

This study was about response of Statins (Atorvastatin, Simvastatin and Pravastatin) in Chronic forced swim test. Dose of statins (Atorvastatin, Simvastatin and Pravastatin) causing maximum reduction in duration of immobility in part 1 was given daily to rats for 14 days. Similar eight groups as mentioned in part 2 were also used in part 3.

30 minutes after treatment with test drugs rats were forced to swim for 6 minutes daily. However, immobility time was observed 30 minutes after the final administration of drugs on Day 14. Open field test was performed on day 14, 5 minutes before subjecting animals to forced swim test like that of part 2 study.

Statistical analysis

Data were expressed as Mean±SD. Statistical analysis was done using the Graph Pad Instat version 3.06. Comparison of immobility time between different groups was done using ANOVA (analysis of variance) with Post hoc Tukeys test. P value <0.05 was considered as statistically significant.

The number of occurrences of each category of behaviour (immobility, swimming, climbing) was analysed using one-way (treatment) analyses of variance (ANOVA). Likewise, the weights of the rats immediately prior to testing were analysed using one-way ANOVA. Significant effects were analysed further using post hoc Newman-Keuls tests.

Results

In Part 1 of study all three doses of Atorvastatin, Simvastatin and Pravastatin did not show statistically significant reduction in duration of immobility as compared to control (Carboxymethylcellulose). Maximum reduction of duration of immobility with statins was seen for Atorvastatin, Simvastatin and Pravastatin at doses of 10 mg/kg, 10 mg/kg, and 40 mg/kg respectively. Among three statins (Atorvastatin, Simvastatin, Pravastatin), Atorvastatin in a dose of 10 mg/kg showed maximum reduction
in duration of immobility (170.16 ± 8.035 seconds) refer Table I.

TABLE I: Comparison of duration of immobility in Dose finding study in acute forced swim test (Part 1).

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Group (dose)</th>
<th>Mean±SD (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carboxymethylcellulose 0.5%</td>
<td>183.66 ± 9.52</td>
</tr>
<tr>
<td>2</td>
<td>Atorvastatin 2.5 mg/kg</td>
<td>179.83 ± 9.49</td>
</tr>
<tr>
<td>3</td>
<td>Atorvastatin 5 mg/kg</td>
<td>179.5 ± 8.89</td>
</tr>
<tr>
<td>4</td>
<td>Atorvastatin 10 mg/kg</td>
<td>170.16 ± 8.03</td>
</tr>
<tr>
<td>5</td>
<td>Simvastatin 2.5 mg/kg</td>
<td>183 ± 17.34</td>
</tr>
<tr>
<td>6</td>
<td>Simvastatin 5 mg/kg</td>
<td>175.66 ± 6.83</td>
</tr>
<tr>
<td>7</td>
<td>Simvastatin 10 mg/kg</td>
<td>171.33 ± 6.15</td>
</tr>
<tr>
<td>8</td>
<td>Pravastatin 10 mg/kg</td>
<td>189.16 ± 13.42</td>
</tr>
<tr>
<td>9</td>
<td>Pravastatin 20 mg/kg</td>
<td>187.66 ± 10.34</td>
</tr>
<tr>
<td>10</td>
<td>Pravastatin 40 mg/kg</td>
<td>176.66 ± 8.31</td>
</tr>
</tbody>
</table>

In Part 2 of study, maximum effective doses of Atorvastatin (10 mg/kg), Simvastatin (10 mg/kg) and Pravastatin (40 mg/kg), when combined with Fluoxetine, Atorvastatin and Simvastatin showed significant reduction in duration of immobility when compared with control but not against Fluoxetine alone. There was no statistically significant difference in duration of immobility among all doses of three statins (Atorvastatin, Simvastatin, and Pravastatin). Results of part 2 are shown in Fig. 1. Locomotor activity of animals subjected to acute forced swim test was tested using open field test in all groups. There was no statistically significant difference between test groups for parameters line crossing, rearing, defecation suggesting that there was no general behavioural stimulation of rats and reduction in duration of immobility with test drugs was due to antidepressant effect. Results of the test are shown in Table II.

In part 3 of study response of statins (Atorvastatin, Simvastatin and Pravastatin) in chronic forced swim test was seen. Atorvastatin, Simvastatin and Pravastatin did not show significant reduction in duration of immobility as compared to control (Carboxymethylcellulose). When combined with Fluoxetine, Atorvastatin and Simvastatin showed significant reduction in duration of immobility when compared with control and Fluoxetine. However Pravastatin when combined with Fluoxetine did not show significant reduction in duration of immobility when compared with Fluoxetine alone. It means that Atorvastatin and Simvastatin potentiated action of Fluoxetine but Pravastatin did not. There was no statistically significant difference in duration of immobility among three statins. Results of part 3 are shown in Fig. 2.

Fig. 1: Duration of immobility in acute FST. (Part 2).
*P<0.05 Vs CMC, CMC: Carboxymethylcellulose, ATV: Atorvastatin, SMV: Simvastatin, PRV: Pravastatin, FLX: Fluoxetine. Data analysed using ANOVA with post hoc Tukeys test.
### TABLE II: Locomotor activity parameters in open field test for Acute forced swim test (Part 2).

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Group (dose)</th>
<th>Crossing</th>
<th>Rearing</th>
<th>Defecation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CMC 0.5%</td>
<td>63.83 ± 9.152</td>
<td>40.5 ± 5.167</td>
<td>1.5 ± 1.049</td>
</tr>
<tr>
<td>2</td>
<td>FLX 10 mg/kg</td>
<td>62.83 ± 6.882</td>
<td>36.33 ± 5.715</td>
<td>1 ± 0.894</td>
</tr>
<tr>
<td>3</td>
<td>ATV 10 mg/kg</td>
<td>68.16 ± 11.30</td>
<td>32.66 ± 5.125</td>
<td>1.33 ± 1.033</td>
</tr>
<tr>
<td>4</td>
<td>ATV 10 mg/kg + FLX 10 mg/kg</td>
<td>66.5 ± 7.969</td>
<td>34.66 ± 4.274</td>
<td>1.66 ± 1.033</td>
</tr>
<tr>
<td>5</td>
<td>SMV 10 mg/kg</td>
<td>70.33 ± 6.25</td>
<td>40.33 ± 5.78</td>
<td>1 ± 0.63</td>
</tr>
<tr>
<td>6</td>
<td>SMV 10 mg/kg + FLX 10 mg/kg</td>
<td>68.5 ± 5</td>
<td>33.16 ± 5.67</td>
<td>1.5 ± 0.83</td>
</tr>
<tr>
<td>7</td>
<td>PRV 40 mg/kg</td>
<td>57.5 ± 3.61</td>
<td>43.66 ± 4.88</td>
<td>1.16 ± 0.75</td>
</tr>
<tr>
<td>8</td>
<td>PRV 40 mg/kg + FLX 10 mg/kg</td>
<td>67.33 ± 8.66</td>
<td>45.33 ± 7.39</td>
<td>1.16 ± 0.98</td>
</tr>
</tbody>
</table>

p > 0.05 Vs CMC, CMC: Carboxymethylation, ATV: Atorvastatin, SMV: Simvastatin, PRV: Pravastatin, FLX: Fluoxetine.

Data analysed using ANOVA with post hoc Tukeys test.

### TABLE III: Locomotor activity parameters in open field test for chronic forced swim test (Part 3).

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Group (dose)</th>
<th>Crossing</th>
<th>Rearing</th>
<th>Defecation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CMC 0.5%</td>
<td>61.66 ± 10.28</td>
<td>28.33 ± 3.029</td>
<td>1 ± 0.632</td>
</tr>
<tr>
<td>2</td>
<td>FLX 10 mg/kg</td>
<td>55.16 ± 10.02</td>
<td>32.33 ± 5.64</td>
<td>1.33 ± 0.81</td>
</tr>
<tr>
<td>3</td>
<td>ATV 10 mg/kg</td>
<td>62.66 ± 7.941</td>
<td>28.66 ± 6.02</td>
<td>1 ± 0.894</td>
</tr>
<tr>
<td>4</td>
<td>ATV 10 mg/kg + FLX 10 mg/kg</td>
<td>55.66 ± 8.68</td>
<td>33.5 ± 4.80</td>
<td>1 ± 0.849</td>
</tr>
<tr>
<td>5</td>
<td>SMV 10 mg/kg</td>
<td>61.33 ± 5.75</td>
<td>36 ± 4.96</td>
<td>1.16 ± 1.16</td>
</tr>
<tr>
<td>6</td>
<td>SMV 10 mg/kg + FLX 10 mg/kg</td>
<td>53.5 ± 5.089</td>
<td>35.66 ± 5.98</td>
<td>1.66 ± 1.21</td>
</tr>
<tr>
<td>7</td>
<td>PRV 40 mg/kg</td>
<td>57.5 ± 3.61</td>
<td>43.66 ± 4.88</td>
<td>1.16 ± 0.75</td>
</tr>
<tr>
<td>8</td>
<td>PRV 40 mg/kg + FLX 10 mg/kg</td>
<td>67.33 ± 8.66</td>
<td>45.33 ± 7.39</td>
<td>1.16 ± 0.98</td>
</tr>
</tbody>
</table>

P > 0.05 Vs CMC, CMC: Carboxymethylcellulose, ATV: Atorvastatin, SMV: Simvastatin, PRV: Pravastatin, FLX: Fluoxetine.

Fig. 2: Duration of immobility in Chronic FST. (Part 3).

Values expressed as Mean ± sD *P < 0.001 Vs CMC, $ P < 0.001 Vs FLX, # P < 0.01 Vs FLX, CMC: Carboxymethylcellulose, ATV: Atorvastatin, SMV: Simvastatin, PRV: Pravastatin, FLX: Fluoxetine. Data analysed using ANOVA with post hoc Tukeys test.
Locomotor activity of animals subjected to chronic forced swim test was tested using open field test in all groups. Test was conducted 5 minutes before subjecting animals to forced swim test. No statistically significant difference between test groups for line crossing, rearing, and defecation parameters suggests no general behavioural stimulation of rats and reduction in duration of immobility with test drugs was due to antidepressant effect. Results of the test are shown in Table III.

Discussion

There is increasing incidence of IHD associated with depression, hence intake of statins with or without antidepressant in patient of IHD is on a rise. There are no definitive evidences on whether statins cause depression or they protect against depression, and what is the effect of statin on efficacy of commonly used antidepressants like SSRIs.

Present study establishes that in acute and chronic forced swim test, statins alone group are not effective. In Part 2 acute FST of present study Atorvastatin, Simvastatin and Pravastatin only group were not effective in reducing duration of immobility, but when they combined with Fluoxetine that group was statistically significant compared to control group (Carboxymethylcellulose 0.5%) only, but not with Fluoxetine only group. The possible explanation behind this finding is that statins take 2-4 weeks to lower serum cholesterol which in turn can affect serotonergic neurotransmission, hence results are significant only against control but not against Fluoxetine group.

In Part 3 Chronic FST Atorvastatin and Simvastatin potentiated action of Fluoxetine compared to control group as well as Fluoxetine only group but Pravastatin potentiated action of Fluoxetine only when compared to control group but not with Fluoxetine only group. Fluoxetine significantly reduced duration of immobility as compared to Control and when combined with Atorvastatin and Simvastatin refer Fig. 1 and 2. The basis for potentiation of Fluoxetine action by Atorvastatin and Simvastatin is to modulate serotonin function. Current immune-mediated concepts on aetiology of depression include increased proinflammatory cytokines, and final activation of tryptophan and serotonin degrading enzyme Indoleamine 2, 3-deoxygenase, which may cause a reduction of serotonergic neurotransmission in Major Depressive Disorder. Considering the anti-inflammatory and immunomodulatory properties of statins, adjunctive use of statins with SSRIs may block or reverse a cascade of immune-mediated serotonin depletion in depression (15) and potentiate Fluoxetine effects. There is an association between cholesterol lowering treatment and normalization of initially low intraplatelet 5-HT; and a directly adverse impact of elevated cholesterol levels on 5-HT transporter or receptor function; (15, 19) Even earlier studies involving supplementation with lovastatin increased the antidepressant efficacy of Fluoxetine in laboratory animals, as shown by reduced immobility and increased swimming in rats, (15) and the action of lovastatin may involve the serotonergic pathways, supporting the proposal that statins increase serotonergic function (20).

In vitro studies have demonstrated that statins can induce tPA (tissue plasminogen activator) and inhibit plasminogen activator inhibitor-1, the major inhibitor of tPA. It is therefore possible that statins could act through the tPA - plasminogen pathway to increase BDNF (Brain Derived Natriuretic Factor) and achieve an antidepressant effect (21). Another possibility for this synergistic interaction could be blocking of NMDA receptor causing antidepressant activity by Atorvastatin and Simvastatin. This is seen similarly in study done by Santos T et al (20) by Pittenger C et al (22). Pravastatin failed to potentiate antidepressant activity of Fluoxetine, Pravastatin being a hydrophobic statin could not cross BBB and affect brain lipids and hence did not show potentiation of antidepressant action of Fluoxetine (23, 24, 25, 26). Whereas Simvastatin & Atorvastatin are most and intermediate lipid soluble statins which cross BBB easily.

Statins can have synergistic effect with Fluoxetine and can reduce dose of Fluoxetine in patients of depression. This may help to minimize adverse effects of Fluoxetine like gastrointestinal disturbances (27). Open field test was done to rule out general behavioural stimulation. A reduction in duration of immobility seen with Fluoxetine and statins was due
to their antidepressant activity and not due to general behavioural stimulation, which may lead to false positive results.

Considering the high rate of partial or non-response to antidepressants such as SSRI which is used as first-line agents for the treatment of depression, statins as adjuncts to SSRIs may facilitate serotonergic function and thereby improve treatment outcomes. Statins may help to reduce the incidence of depression in IHD patients and will reduce the increased morbidity and mortality due to depression in IHD.

The present study, however, do not address the question of whether the onset of antidepressant efficacy would be shortened; indeed, there are currently no animal screening methods that reliably model the lag in efficacy in humans that characterize all current antidepressant treatments. Limitations of this study are that it lacks studying the receptor level mechanism of action of statins as antagonist. Direct evidence of correlation between brain cholesterol level and serotonergic transmission in brain could not be established as CSF/brain levels of serotonin were not measured. Measurement of blood levels of cholesterol as a proxy would be of limited utility because brain levels are much more tightly regulated.

Randomized, controlled clinical trials are needed in future to estimate the impact of adding statins to SSRIs in patients of IHD suffering from depression. Studies involving the estimation of CSF levels of serotonin will be more feasible for correlating effect of statins on serotonergic transmission. More studies on additional pleiotropic effects of statins which will broaden the clinical indications of statins are needed.

Conclusion

Present study showed that although statins Atorvastatin, Pravastatin and Simvastatin did not exhibit independent antidepressant activity, however Atorvastatin and Simvastatin have synergistic effect with SSRI Fluoxetine. From this it can be deduced that Atorvastatin and Simvastatin may help to reduce the dose of Fluoxetine thereby minimizing adverse effects of Fluoxetine.

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References


