Effect of Antidepressants and Their Relative Affinity for the Serotonin Transporter on the Risk of Myocardial Infarction

William H. Sauer, MD; Jesse A. Berlin, ScD; Stephen E. Kimmel, MD, MS

Background—Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), attenuate platelet activation by depleting serotonin storage and may decrease risk of myocardial infarction (MI). These drugs differ in their affinity for the platelet serotonin transporter and therefore may vary in their effects on MI protection.

Methods and Results—A case-control study of first MI in patients aged 40 through 75 years was conducted among 36 hospitals in a 5-county area during a 3-year period. Case subjects were patients hospitalized with a first MI, and control subjects were randomly selected from the same geographic area. Detailed information regarding medication use and other clinical and demographic data were obtained by telephone interview. Among the 1080 cases and 4256 controls who participated, there were 223 users of antidepressants with high serotonin transporter affinity, all of which were SSRIs (paroxetine, fluoxetine, and sertraline). After adjustment with multivariable logistic regression for age, gender, race, education, physical activity, quantity of cigarettes smoked per day, body mass index, aspirin use, family history of MI, and history of diabetes, hypertension, or hypercholesterolemia, the odds ratio for MI among current users of antidepressants with high serotonin transporter affinity compared with nonusers was 0.59 (95% CI 0.39 to 0.91; \( P=0.02 \)). Increasing serotonin transporter affinity was associated with reduced odds of MI among users of all SSRIs (\( P \) for trend <0.01) but not tricyclic (\( P=0.77 \)) or atypical (\( P=0.70 \)) antidepressants. There was no association detected between non-SSRI antidepressant use and MI.

Conclusions—Increasing serotonin transporter affinity correlates with greater MI protection with SSRI but not other antidepressant exposure. (Circulation. 2003;108:32-36.)

Key Words: serotonin uptake inhibitors ■ antidepressant agents ■ epidemiology ■ myocardial infarction ■ drugs
Results

Characteristics of Study Participants
There were 404 antidepressant users (76 exposed cases and 328 exposed controls) identified among the 1080 cases and 4256 controls who participated. Compared with nonusers of antidepressants, high-affinity SSRI users were more likely to be female and had more risk factors for coronary disease, including hypertension, family history, and hypercholesterolemia (all P<0.05; Table 2). Interactions were tested between each potential confounding variable and use of antidepressants with low, moderate, or high serotonin transporter affinity; none were significant (P>0.10).

Association of Antidepressant Serotonin Transporter Affinity and MI
There was a significant interaction between drug class and serotonin transporter affinity on MI risk (adjusted P for interaction 0.04). That is, the effect of serotonin transporter affinity on MI risk varied depending on the class of antidepressant drug used. Higher serotonin transporter affinity was associated with a reduced odds of MI among users of SSRIs (adjusted P for trend <0.01; Figure 1) but not among users of tricyclic agents or atypical antidepressants (adjusted P for trend 0.77 for tricyclics and 0.70 for atypicals).

Table 1. Antidepressants Categorized by Affinity for the Serotonin Transporter*8

<table>
<thead>
<tr>
<th>Antidepressants Categorized by Affinity for the Serotonin Transporter*8</th>
<th>Affinity for Serotonin Transporter</th>
<th>Type of Antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (K&lt;sub&gt;d&lt;/sub&gt; &gt;10 nmol)</td>
<td></td>
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<tr>
<td>Fluoxetine SSRI</td>
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<td>Paroxetine SSRI</td>
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<tr>
<td>Clomipramine Tricyclic</td>
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<tr>
<td>Sertraline SSRI</td>
<td></td>
<td></td>
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<tr>
<td>Fluoxetine SSRI</td>
<td></td>
<td></td>
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<tr>
<td>Moderate (K&lt;sub&gt;d&lt;/sub&gt; 1–10 nmol)</td>
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<tr>
<td>Citalopram SSRI</td>
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<tr>
<td>Imipramine Tricyclic</td>
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<tr>
<td>Fluvoxamine SSRI</td>
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<tr>
<td>Amitriptyline Tricyclic</td>
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<td></td>
</tr>
<tr>
<td>Venlafaxine Atypical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (K&lt;sub&gt;d&lt;/sub&gt; &gt;10 nmol)</td>
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<tr>
<td>Desipramine Tricyclic</td>
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<tr>
<td>Nortriptyline Tricyclic</td>
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<td>Protriptyline Tricyclic</td>
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<tr>
<td>Amoxapine Tricyclic</td>
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<tr>
<td>Doxepin Tricyclic</td>
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<tr>
<td>Trimipramine Tricyclic</td>
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<tr>
<td>Trazodone Atypical</td>
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<td></td>
</tr>
<tr>
<td>Nefazodone Atypical</td>
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<tr>
<td>Maprotiline Tricyclic</td>
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<tr>
<td>Bupropion Atypical</td>
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<tr>
<td>Mirtazapine Atypical</td>
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</table>

*<sup>10</sup>K<sub>d</sub> indicates dissociation constant.

The dissociation constants listed are derived from reference 10.
Association Between SSRI Use and MI

Table 3 displays the risk of MI by type of antidepressant. SSRI use was associated with a significantly reduced risk of MI compared with other antidepressant users (data not displayed in table; adjusted OR 0.51; 95% CI 0.29 to 0.90; \(P = 0.02\)) but not when compared with nonusers of any antidepressant (adjusted OR 0.72; 95% CI 0.49 to 1.05; \(P = 0.09\)). However, use of high-affinity SSRIs (paroxetine, fluoxetine, and sertraline) was associated with a significant reduction in risk of MI compared with use of other antidepressants (adjusted OR 0.38; 95% CI 0.21 to 0.70; \(P < 0.01\)) and no antidepressant use (adjusted OR 0.59; 95% CI 0.39 to 0.91; \(P = 0.02\)). Gender was the only potential confounder included in the multivariable model that weakened the association between high-affinity SSRI use and MI.

Association Between Other Antidepressant Use and MI

Users of low and moderate serotonin transporter affinity antidepressants did not have significantly altered odds ratios for MI compared with no antidepressant use. Use of tricyclic and atypical antidepressants, all of which were low or moderate serotonin transporter affinity antidepressants in the present study, was not associated with an altered risk of MI (Table 3).

Discussion

Study Results

This study demonstrates a significant reduction in risk of MI associated with current use of high-affinity SSRIs compared with both nonuse of antidepressants and use of other antidepressants. In addition, the extent of serotonin inhibition among SSRIs correlated with the degree of reduced odds of MI. Other antidepressants, regardless of serotonin transporter affinity, were not associated with an altered odds ratio of MI relative to those not using antidepressants.
Potential Role of Serotonin Reuptake Inhibitors in Prevention of MI

Serotonin is normally released when platelets are activated by proaggregatory factors, causing platelet effects, which may contribute to the pathogenesis of MI. 1-3 Recently, Fumeron et al 4 described the association between the LL genotype of the SLC6A4 polymorphism of the serotonin transporter gene, which results in increased platelet serotonin uptake, and higher risk of MI compared with other genotypes.

Antidepressants that prevent the uptake of serotonin into platelets may thereby inhibit the only mechanism for platelet storage of serotonin. 5 All of the high-affinity SSRIs represented in the present study have been shown to reduce platelet aggregation. 5,13-15 We know of no studies that have suggested altered platelet activity attributed to the other antidepressants with low or moderate serotonin transporter affinity; however, one study demonstrated no effect of nortriptyline on platelet activity. 14

If the mechanism of reducing MI is related to the effect of antidepressants on platelet serotonin, and if antidepressants in the higher-affinity groups have a greater antplatelet effect than lower-affinity ones, then these drugs might be expected to have the greatest effect on MI risk. The potential effects of high serotonin transporter affinity antidepressants on platelet biology therefore form the basis for the a priori hypothesis that the extent of serotonin reuptake inhibition correlates with reduction in serotonin-mediated platelet aggregation and thus reduced risk of MI in users of these agents. The results of the present study, as well as those described in a previous study examining gastrointestinal bleeding in users of antidepressants with moderate and high serotonin transporter affinity, 5 would suggest that the platelet inhibition caused by antidepressants is related to their affinity for the serotonin transporter.

The reduced risk of MI associated with increasing serotonin transporter affinity was seen only among users of SSRIs and not other antidepressants. This may be due to a nonlinear effect on platelet inhibition by antidepressants with increasing affinity for the serotonin transporter. The lack of effect of increasing serotonin transporter affinity in the non-SSRI antidepressants may also reflect potentially harmful effects of these drugs, 15 negating any potential MI protective effects from platelet inhibition. Because there were no users of non-SSRI antidepressants in the highest-affinity group, we are unable to clarify the potential biological basis for this observation. Regardless of the reason for differences between SSRIs and non-SSRI antidepressants, the pharmacodynamic property of serotonin inhibition is a plausible biological explanation for the reduced risk of MI associated with SSRIs. 7,16

Prior Investigations Into the SSRI–MI Protection Relationship

There have been several studies examining the potential for MI protection associated with SSRI use. In the SADHART study, a randomized trial investigating the safety and efficacy of sertraline in patients with post-MI depression, there was a nonsignificant reduction in MI risk in the treatment group. 17 Although the SADHART study was not powered to detect any meaningful reduction in MI risk, the results are consistent with what we observed in the present study. Cohen et al 16 used an administrative database to study the risk of MI for users of all antidepressants. In that study, tricyclic agents were associated with an increased risk of MI, and SSRIs were associated with a nonsignificant protective effect (OR 0.8). 16 However, the study was limited by its inability to adjust for confounding comorbidities, including depression. Furthermore, the small number of exposed cases substantially impeded its ability to detect a meaningful effect of SSRI use on MI risk. In a recent study of SSRIs that included antidepressants with both high and moderate serotonin transporter affinity, there was no detectable altered MI risk observed in users of these agents compared with users of other antidepressants. 18 However, that study used a definition of exposure that would include some subjects not currently taking an SSRI and included an atypical agent as an SSRI, both of which could have biased the results toward no effect on MI risk. In addition, all subjects with risk factors for cardiac disease were excluded, thereby limiting the generalizability of the results.

We previously described an association between SSRI use and reduced odds of MI in a population of smokers. That study had insufficient numbers of users of other antidepressants to perform the analyses used in the present study. The results of the present study are consistent with the previous observation because 99% of the SSRI group of our prior study consisted of high-affinity SSRIs, and subsequent analyses excluding the very small number of moderate-affinity SSRI users in the prior study did not substantially alter the results of that study.

Potential Limitations

Nonparticipation could bias the results of the present study if nonparticipant cases were more likely to use high-affinity SSRIs.
for treatment of depression than were participants. This bias is unlikely because use of other antidepressants, which would be expected to have a similar participation rate, is not associated with reduced odds of MI. In addition, the significant association between increasing serotonin transporter affinity and reduced risk of MI among SSRI users would be unaffected by differential participation of antidepressant users. Alternatively, if nonparticipant control subjects were less likely to use a high-affinity SSRI, there could be a false association with these agents and reduced MI risk. However, the prevalence of use of these agents in the control group was similar to what is described on a national level and therefore cannot explain these results.

Differential recall of antidepressant use could create a false association if control subjects were more likely than case subjects to accurately report high-affinity SSRI exposure. However, high-affinity SSRI use was associated with reduced odds of MI compared with users of other antidepressants, who would have the same issues of differential recall, which makes this unlikely. Similarly, the association of serotonin transporter affinity and MI risk among SSRI users should not be subject to recall bias.

Uncontrolled confounding is another potential limitation of the present study. If high-affinity SSRI users are a low-risk group because of other unmeasured characteristics, there would be a false association between high-affinity SSRI use and lower risk for MI. However, high-affinity SSRI users had more traditional risk factors for MI, except that they included a higher proportion of women than did the nonuser group, and adjustment for all known potential risk factors, including variables related to access to medical care, strengthened rather than weakened the inverse association between high-affinity SSRI use and MI, with the exception of gender. Confounding by indication (i.e., if high-affinity SSRIs were used for a condition that is itself associated with lower MI risk) could not explain these results because the primary indication for high-affinity SSRIs (depression), if it had any effect, should increase the risk of MI.20,21 This would bias the results toward a falsely harmful effect of high-affinity SSRIs. Because we did not have information on the severity of depression, we could not adjust for that potential confounder. However, depression severity is likely to be nondifferential among the high-affinity SSRI users, given equivalent efficacy in this class, and could not explain the results.

Finally, if SSRI users were more likely to experience sudden cardiac death, then a false association with MI protection could be seen, because cases only included nonfatal MI. However, unlike the tricyclic agents, SSRIs are not arrhythmogenic and did not change ECG parameters in randomized trials.14,17

Conclusions
Use of SSRIs with high affinity for the serotonin transporter is associated with reduced odds of MI, and the extent of serotonin inhibition among SSRIs correlates with the degree of reduction in MI risk. Although adequate treatment of depression itself could translate into a reduced risk of MI, the present results suggest that the relative reduction in platelet serotonin uptake caused by SSRIs is the reason for the risk reduction. Further investigation is needed to confirm these findings, to evaluate the effect of varying levels of antidepressant serotonin transporter affinity on platelet inhibition, and to evaluate further potential differences among antidepressants regarding cardiovascular risk.

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References
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