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 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

Serotonin is normally released by activated platelets, causing enhanced platelet aggregation, which may contribute to the pathogenesis of acute myocardial infarction (MI).\(^1\) A genetic polymorphism of the serotonin transporter (the only mechanism for serotonin uptake into platelets) causes increased serotonin uptake and is associated with an increased risk of MI.\(^2\) Antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs) with high affinity for the serotonin transporter, attenuate platelet activation by depleting serotonin storage\(^4\) and have been shown to decrease platelet activity in patients with coronary artery disease.\(^5\)

The antiplatelet effects of SSRIs, most of which have high affinity for the serotonin transporter, have been implicated in an increased risk of gastrointestinal bleeding\(^6\) and lower risk of MI among users of SSRIs.\(^7\) Recently, van Walraven and colleagues\(^8\) described an increased risk of upper gastrointestinal bleeding with increasing serotonin transporter affinity of antidepressants.

We have previously described an association between SSRI use and reduced odds of MI. However, that study was limited in its ability to examine antidepressants other than SSRIs with nonselective serotonin uptake inhibition or the potential association between serotonin transporter affinity and MI protection because of the small number of antidepressant users included.\(^7\) Therefore, the specific aim of this study was to examine the association between both antidepressant type and the extent of the serotonin uptake inhibition of an antidepressant with the risk of MI in a general population.

Methods

Source Population and Identification of Subjects

Data were obtained from an ongoing case-control study of MI in the Philadelphia metropolitan area that is examining the effects of prescription and over-the-counter drug exposure on the risk of MI. Case subjects were patients aged 40 through 75 years with a first MI who were hospitalized between May 1998 and May 2001 at 1 of 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.

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acutecare hospitals in a 5-county region that are part of the Delaware Valley Case-Control Network. Acute MI was defined with the criteria from the Minnesota Heart Survey and verified in 86% of the cases that had sufficient information. Exclusion of those cases without complete information or charts available did not alter the results presented. Case subjects were excluded if they had a history of a prior MI, they did not have telephones or could not communicate on the telephone (eg, they did not speak English, were deaf, or were aphasic), they did not live in 1 of the 5 counties of the network, or they used multiple antidepressants at the time of enrollment. The participation rate among eligible cases was 60%. Control subjects were selected by random digit dialing and were not matched to case subjects except for meeting the same inclusion and exclusion criteria. The participation rate among eligible controls was 54%.

Data Collection
Exposure and covariate data were collected by a structured telephone interview for both cases and controls, who were unaware of the study hypothesis. To maximize the validity of exposure information, cases were interviewed only if they could be reached within 4 months of their MI. Similarly, controls were also interviewed only within 4 months of initially being identified. The index date was the date of MI for cases and the date of the telephone interview for controls. Detailed information was obtained regarding antidepressant use during the week before the index date, indication for antidepressant use, and other clinical characteristics. We did not measure depression or ask about symptoms related to depression except in asking antidepressant users for the indication for their medication.

Categorization of Antidepressants
Antidepressants were categorized by class (SSRI, tricyclic, and atypical) and by their affinity for the serotonin transporter with the dissociation constant ($K_d$) used as a continuous variable. Although prior studies of gastrointestinal bleeding used 3 categories of serotonin transporter affinity (low, moderate, and high),8 we found differences among classes of antidepressants on MI risk that made these groupings inappropriate without first stratifying on the basis of antidepressant class. In addition, there were no users of monoamine oxidase inhibitors or clomipramine (the only non-SSRI in the high-affinity group) in the study population.

Statistical Analysis
The odds ratio (OR) was used to estimate the relative risk of MI from use of antidepressants. The primary comparisons were between users of a particular class of antidepressant and nonusers of any antidepressant and by serotonin transporter affinity as a continuous variable within each antidepressant class. For these analyses, we used the log transformation of the dissociation constant. Higher values of this constant indicate lower affinity for the serotonin transporter (Table 1). Multivariable logistic regression analysis was used to control for possible confounding. The multivariable model included variables that are known risk factors for MI and any potential confounder that changed the unadjusted OR by more than 10% after adjustment.11 The variables used in the final model were age, gender, race, education, a validated physical activity score,12 aspirin use during the index week, number of cigarettes smoked per day, body mass index, and family history of coronary disease, diabetes mellitus, hypertension, and hypercholesterolemia. Other potential confounding variables tested (income, year and season of index week, vitamin use, lipid-lowering therapy, ACE inhibitor use, marital status, history of coronary disease, caffeine and alcohol consumption, type of insurance, β-blocker use, and nonsteroidal anti-inflammatory drug use) did not affect any of the ORs and were therefore not included. The analyses examining tricyclic, atypical, and SSRI antidepressants used the same multivariable model described above. Statistical analyses were performed with the SPSS (version 10.0) software program, and statistical significance was defined as a 2-sided probability value less than 0.05.

### 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

<table>
<thead>
<tr>
<th>Affinity for Serotonin Transporter</th>
<th>Type of Antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>High ($K_d &lt;1$ nmol)</td>
<td>SSRI</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>SSRI</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Sertraline</td>
<td>SSRI</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
</tr>
<tr>
<td>Moderate ($K_d = 1–10$ nmol)</td>
<td>SSRI</td>
</tr>
<tr>
<td>Citalopram</td>
<td>SSRI</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>SSRI</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Atypical</td>
</tr>
<tr>
<td>Low ($K_d &gt;10$ nmol)</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Atypical</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Atypical</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Atypical</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Atypical</td>
</tr>
</tbody>
</table>

$K_d$ 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.\textsuperscript{1,2} Recently, Fumeron et al\textsuperscript{3} 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.\textsuperscript{4} All of the high-affinity SSRIs represented in the present study have been shown to reduce platelet aggregation.\textsuperscript{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.\textsuperscript{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 antiplatelet 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,\textsuperscript{8} 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,\textsuperscript{16} 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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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).\textsuperscript{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.\textsuperscript{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 nonparticipants 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 level19 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 (ie, 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 that is itself associated with lower MI risk) could not explain these results. However, high-affinity SSRI related to access to medical care, strengthened rather than weakened the inverse association between high-affinity SSRI users and 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 this 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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