

Severe irritability associated with statin cholesterol-lowering drugs

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Summary

Background: As use of a drug becomes widespread, the full spectrum of its effects becomes clearer. Although a link has been suggested between low or lowered cholesterol and irritability/aggression, less is known about possible links between irritability and statins.

Aim: To assess the possible connection of statin usage to severe irritability.

Design: Case series.

Methods: Six patients referred or self-referred with irritability and short temper on statin cholesterol-lowering drugs completed a survey providing information on character of behavioural effect, time-course of onset and recovery, and factors relevant to drug adverse effect causality.

Results: In each case the personality disruption, once evident, was sustained until statin use was discontinued; and resolved promptly with drug cessation. In four patients, re-challenge with statins occurred, and led to recrudescence of the problem. All patients experienced other recognized statin adverse effects while on the drug. Manifestations of severe irritability included homicidal impulses, threats to others, road rage, generation of fear in family members, and damage to property.

Discussion: Case series invariably raise more questions than they can answer. These case reports suggest that severe irritability may occur in some statin users. Although this adverse effect may be rare, potentially life-threatening adverse effects of drugs must be taken seriously.

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Introduction

The benefits of statins to heart disease and stroke are powerful and well documented. The success of these drugs has led to their increasingly widespread use, and statins now include the best-selling drug not only in the world, but in history.¹ No drug, however great the benefit, is without risk of adverse effects, and post-marketing surveillance often reveals effects, common or unusual, that

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may not have been previously evident.

The pre-statin literature provided tantalizing hints of a link between low or lowered cholesterol and violent death, as well as aggression.^{2,3} This connection has not been supported by studies using statin cholesterol-lowering agents, in which no excess of violent death has been observed,⁴ but these latter studies were not designed to assess this issue. Randomized controlled trials of statins have also not shown an excess of fatal rhabdomyolysis or peripheral neuropathy with statins, although other evidence supports such a connection. In primates, cholesterol reduction by diet (holding weight constant) led to increased aggression^{4,5} and reduced central serotonin activity,^{5,6} and low central serotonin is well known to be linked to violence in humans and animals.^{2,7-16} Statins have not previously been linked to violence or violent ideation. We have received reports of irritability on statins, resolving off statins and recurring with statin re-initiation. We describe several patients who report significant irritability on statin cholesterol-lowering drugs, that appears to be linked to their use.

□ **Methods**

Six patients were referred or self-referred for profound irritability or aggression on statin lipid-lowering therapy. In all instances, the irritability and its apparent connection to statin usage (by onset of significant behavioural change on statin, and its resolution off statin) was identified by the patient, and reported to their physician without any knowledge by them or their physician regarding a possible link between low or lowered cholesterol and irritability or violence. Each patient gave informed consent, and completed an IRB-approved questionnaire in which they gave information on statin agent/dose, symptoms, time-course, concurrent medications, and risk factors.

Criteria for causality were presumptively evaluated.¹⁷ ‘Probable’ causality requires occurrence after drug initiation, improvement on drug withdrawal, and absence of other explanations. ‘Definite’ causality requires, in addition, recurrence on rechallenge.¹⁷ A subjective element to causal associations has been reported;¹⁸ information by which the reader can judge presence of these elements is provided in the case histories.

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□ **Case histories**

Patient 1 is a 63-year-old single male who initiated statins (including simvastatin and pravastatin) five times over 5 years. Statins were discontinued after a maximum of 5 months on each occasion, due to adverse effects including significant irritability. All symptoms resolved on discontinuation. Most recently, he initiated atorvastatin and within 2 weeks again noted extreme irritability, violence, and anger (similar to but more extreme than in prior statin usages), citing as his chief complaint: ‘I wanted to kill someone’. The episodes worsened with statin use over the ensuing week. On several occasions he awoke with rage, ‘uncontrollable pent up tension’ and a desire ‘to kill someone’ and ‘smash things’. He damaged property, and stated that he believes had he been married he would be a widower. He stated that these behaviours constituted a marked departure from his usual personality, which he reports is even-tempered and mild. He had no prior history of

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aggression off lipid-lowering drugs. After 3 weeks on atorvastatin, he advised his doctor of his perceived marked personality change with the desire to kill. He was instructed to discontinue atorvastatin immediately. Anger, irritability and homicidal impulses resolved completely within 2 days.

Patient 2 is a 59-year-old married male who over 3 years was successively placed on fenofibrate, gemfibrozil, pravastatin, niaspan, cerivastatin, and simvastatin, discontinuing each agent within 6 weeks (as little as 1 week on cerivastatin), due to side-effects deemed intolerable, including irritability or 'crabbiness.' Irritability resolved with discontinuation in each instance. Most recently he initiated simvastatin (5 mg); he developed severe irritability, which he described as entailing 'short fuse' and 'quick temper', becoming 'furious' at minor things. He twice developed homicidal impulses toward his wife, and in one instance chased her with intent to act upon them but was able to restrain himself. He recalled the similar (though less severe) reaction on prior lipid-lowering agents and discontinued treatment with prompt resolution. Irritability was barely perceptible at 2 weeks, and had resolved completely by 6 weeks. He had no prior history of aggression off cholesterol-lowering drugs. He remains off lipid-lowering drugs.

Patient 3 is a 76-year-old female who commenced simvastatin 10 mg for a total cholesterol of 254 mg/dl, and after some months on treatment, became aware that a significant change in her personality and psychological state had occurred. She experienced extreme irritability, impatience, a 'short fuse' and short temper. She found herself becoming increasingly confrontational about little things, and reacting unreasonably when annoyed. She states she had never previously been easily angered or had an irritable personality, stating that she was 'a different person than I had been in my life.' She began to avoid social encounters to avoid alienating others with her problematic personality. She discontinued simvastatin, and states the irritability and other effects resolved after three days. One month later she commenced atorvastatin; in three days she again began to re-experience personality change, and discontinued treatment.

Patient 4 is a 46-year-old female who experienced extreme irritability while taking atorvastatin 20 mg for 9 months. She was placed on atorvastatin for a total cholesterol of 325 mg/dl and within 6 weeks began experiencing side-effects. She reports mild pre-existing irritability due to a recent back injury, and was initially not conscious of its amplification, but became aware when 'anything' irritated and upset her to the 'exploding' point. She was very 'short' with her husband, and when responding to his requests that she speak louder or repeat herself she would 'blow up' at him. She states she treated her husband very badly. This reportedly contrasted with her normal even-tempered personality, in which only major complications bothered her. 'Suddenly any minor inconvenience made me mad instantly. I wasn't a nice person at all.' She identified a new physician, who discontinued atorvastatin immediately. The irritability dissipated progressively from the time of discontinuation and by the sixth week, she noticed it had gone.

Patient 5 is a 59-year-old male with diabetes, who enrolled in a major atorvastatin research study in 3/98, receiving either 10 mg or 80 mg atorvastatin (he remains blinded to which he received). His wife noted progressive changes in his temperament: He became angry and 'explosive' with people, developing 'road rage' and becoming angry with his family. Following one road rage instance that led him to return home without reaching his destination, he kept his family away, stating 'if someone had said something to me I would have put them in the hospital'. His wife states she became 'afraid to be around him' noting he became 'violent for no reason,' and had, in the time on

the drug (totalling 3 years) ‘become a completely different person,’ with violent episodes increasingly frequent and severe. He discontinued driving due to road rage, but still had angry episodes directed at other drivers while a passenger. The study physician was approached by patient and wife about the major personality change with timing of study participation. The physician reportedly stated the problems could not be related to atorvastatin, noting that others in the study had not reported similar problems. The patient became very angry and persisted in extreme anger after returning home. His wife states ‘he turned into a raging person, even when nothing provoked him.’ He discontinued atorvastatin. The anger dissipated over 2 weeks at which point he was back to his normal temperament. He states that while on atorvastatin, ‘I was very angry around people, even loved ones. I wasn’t like that before atorvastatin ... I was very hard on everyone, especially my wife’.

Patient 6 was a 45-year-old married male who commenced lovastatin for cholesterol 250 mg/dl. He developed what he described as a ‘quick temper,’ which led him to exhibit temper with his wife and daughter and to experience road rage. He noticed that each time he ran out of medication and failed to refill it for several days, the quick temper resolved. He discontinued medication, with full resolution of irritability. Over the ensuing 8 years, he was tried successively on niacin, simvastatin several times, and atorvastatin twice. Each time he instituted treatment he experienced recurrence of irritability. He describes the irritability by noting that it is characterized by a hypersensitivity to little things, ready susceptibility to provocation, and a feeling ‘not of paranoia but as though one is under attack, under external threat’; that one ‘reacts with fight or flight’, and ‘doesn’t have enough calm.’ After the final rechallenge with atorvastatin, he stated he would never resume statins, noting that there was a ‘huge difference’ when he stopped it. As an example, he states that on the day the (re)interview occurred he was nearly run into by another car. ‘Before, I would have pursued them down the road. Now, off cholesterol drugs, I no longer follow other cars’.

[Table 1](#) summarizes information on drug and dose, total cholesterol prior to and on treatment, time-course of onset and resolution of clinically evident irritability, other medical conditions, irritability status or psychiatric history off cholesterol drugs, other statin symptoms, and presumptive causality status. No commonality among concurrent medications was identified, and no subjects were on drugs such as isotretinoin (Accutane) or anabolic steroids, that are thought to possibly contribute to violence (medications not shown). It is noteworthy that among those reporting severe irritability, other literature-documented statin adverse effects were often also reported.

View this table: **Table 1** Summary of cases

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Discussion

Case series inevitably raise more questions than they can answer, and limitations of case-series data are well recognized. The base population is unknown and rates cannot be estimated. There is no control group, so risk ratios cannot be defined—

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indeed, it cannot be asserted that the small number of cases implies an increased rate in statin users overall, even if the association is causal in these individuals. The absence of blinding of the subject to treatment could influence the outcome. Concerns about bias from this source are somewhat reduced by these subjects' lack of awareness of any hypothesis linking low/lowered cholesterol to irritability at the time they observed and reported these effects in themselves. Additionally, the time-course of onset and recovery appear more consistent with a drug effect than with an effect of suggestibility (which might be expected to occur at the time of drug initiation or discontinuation), as are the greater severity and/or faster time to onset with more potent statins, noted in four of the subjects.^{1,2,3,6} The opportunity for confounding is also present. The off-on-off(-on) character of the finding somewhat reduces the opportunity for confounders to explain the findings. Nonetheless, lack of randomization, blinding, and control groups represent significant limitations inherent to case series. On the other hand, case series may function as important early warning signals of potential major problems.

This is the first case series in which severe anger and irritability have been associated with statins. Most instances show a time-course that suggests a relationship to statins, with variable time to noted onset, but continued progression of problems until statin discontinuation, followed by prompt resolution, in days to weeks. (The variable time to onset and widely different cholesterol levels at which different individuals experience symptoms are consistent with findings for other established statin-associated adverse effects, such as non-CK elevating mitochondrial myopathy^{19,20} or polyneuropathy.²¹ It is also, of course, true for adverse effects to which elevated cholesterol disposes, such as myocardial infarction.) Four cases^{1,2,3,6} meet existing literature criteria for definite (or strongly probable) drug adverse effect causality:¹⁷ the effect arose on statins, recovered off statins, and recurred with rechallenge with the same or a different statin, and had no alternative explanation. In the two remaining cases, the effect arose on drug, progressed throughout continued treatment, resolved promptly on cessation, and was accompanied by other symptoms known to relate to statins, including muscle symptoms^{19,22-33} neuropathy,^{21,34-37} memory problems³⁸⁻⁴¹ and other central nervous system changes.^{42,43} In some cases, homicidal impulses were noted; others entailed expression of violence to family members, strangers, or those who share the road. Property damage was done in more than one case, and persons were imperilled or threatened in several. In one case, there were possible susceptibility factors that may have predisposed persons to irritability problems on statins (post-traumatic stress disorder), but other cases showed no evident predisposition, and reported a serene temperament prior to experiencing problems on statins. The co-occurrence with other accepted statin adverse effects (such as myopathy,¹⁹ memory problems³⁸ and neuropathy²¹) in several cases further supports a connection to the drug, and suggests the possibility of a susceptible subset and/or related mechanism linking irritability to other statin adverse effects.

A possible link between low or lowered cholesterol and violence has been previously reviewed.^{2,3} A community cohort study merging national databases in Sweden reported a link between low cholesterol and subsequent arrests for violent crimes against others, adjusting for covariates,⁴⁴ while studies of institutionalized criminals and psychiatric patients have shown a link between lower serum cholesterol values and increased frequency or severity of violence.⁴⁵⁻⁴⁷ Meta-analyses of pre-statin randomized trials found a notable relation between randomization to lipid-lowering treatment and violent death in men (in primary prevention), which was significant in some meta-analyses^{48,49} (reviewed in reference 2). However, major statin studies and meta-analyses of statin

trials have failed to suggest an excess of violent death with statin drugs.⁴ Although it has not been expressly measured in most studies, the occurrence of severe, or subjectively homicidal irritability like that reported here is likely to be rare. Selection factors in trials, including run-in periods and selection against persons with violent predispositions (alcohol, psychiatric problems and non-compliance) may contribute to failures to detect, since it is these populations in whom the increased risk was selectively expressed in pre-statin trials.⁵⁰ Additionally, such problems may not be identified (because not elicited) in trials, and their rarity might limit identification in trials even if an effort to elicit problems were made. (Again, increased fatal rhabdomyolysis with statins has not been observed in clinical trials, though it is a well-accepted complication.) More modest, non-homicidal manifestations of anger or irritability may be more common, but irritability has not been assessed in clinical trials. One previous study reported a link between cholesterol-lowering drugs and worsening test scores of aggression, significant after 1 year of drug therapy but not after 3 months,⁵¹ but did not provide details of case histories. Of note, in the present series, some subjects experienced irritability problems on non-statin as well as statin lipid-lowering drugs; thus the effect is not presumed to be specific to statins.

Statins have vitally important cardiovascular benefits, and the findings presented here do not suggest that prescribing practices should be modified. Nonetheless, it is essential that a full understanding of risks as well as benefits be sought, so that if significant adverse effects occur (even if rare), the possible connection to drug can be recognized, and reasoned risk-benefit assessments can adjudicate whether treatment should be continued or modified. In the context of the larger literature, additional numerous reports we have received of more modest manifestations of irritability on statins that resolve with discontinuation and recur with reintroduction, and the widespread use of statin cholesterol-lowering drugs, the possibility of rare but serious adverse personality and behaviour effects of statins should not be dismissed. The importance of recognizing this possible adverse effect is underscored by the fact that severe irritability carries novel implications, in that treatment of one person could potentially impinge on the health or well-being of others.

Statins are currently taken daily by millions of individuals in the US (105 million worldwide in 2002^{1,52}). With continuing usage, rare events such as rhabdomyolysis and neuropathy have been noted. We reported here some new rare events, which are sentinel by virtue of their behavioural toxicity. It is unknown how common these events are or whether they represent a chance association (though co-occurrence with other statin adverse effects, resolution off statins, and recurrence with rechallenge militate against this). However, clinicians should keep these possible adverse effects in mind when prescribing statin agents.

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□ Footnotes

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