BMJ Case Reports

Unexpected outcome (positive or negative) including adverse drug reactions

First-degree relatives with behavioural adverse effects on statins

David Reilly,[1] Stephanie Cham,[2] Beatrice Alexandra Golomb[3]

[1]NA, La Jolla, California, United States;
[2]Department of Medicine, UCSD, San Diego, California, United States;
[3]Department of Medicine and Family and Preventive Medicine, University of California, San Diego, La Jolla, California, United States

Correspondence to Dr Beatrice Alexandra Golomb, bgolomb@ucsd.edu

Summary

Irritability, aggression and other adverse behavioural effects have been associated with the use of statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) and other drug classes. A number of studies have also linked low cholesterol with aggression and violence. This paper presents the cases of two first-degree male relative patients (father and son) identified by self-referral to the University of California in San Diego Statin Effects Study. Both patients experienced behavioural adverse effects on statins including irritability and aggression, however neither patient recognised a significant change in their behaviour. This may be the first report of behavioural adverse effects manifested on statins by first-degree male relatives, which may suggest possible familial/biological predisposition. These cases also highlight the issue of externalisation by patients of the origin of interpersonal discord, which may serve as an obstacle to adverse effects reporting and lead to negative outcomes for patients, and for those around them.

BACKGROUND

Adverse behavioural changes including irritability/aggression have been reported with a number of drug classes. These include alcohol,[1] prescription psychiatric drugs,[2–5] steroid hormone-altering agents (anabolic steroids, retinoids),[6 7] varenicline[8] and antimalarial drugs.[9 10] Low cholesterol has been linked to violence/aggression in a number of studies,[11–14] and some reports have linked statin cholesterol-lowering drugs to behavioural adverse effects.[15 16] Statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) are among the best selling prescription drugs.[17]

Understanding potential effects of these drugs is important. We present a pair of cases in which behavioural adverse effects were manifested on statins by first-degree male relatives (father and son).

CASE PRESENTATION

Patients were identified by self-referral to the University of California in San Diego Statin Effects Study. Both patients described here gave informed consent. Both shared information on the drug use and timing to onset of adverse symptoms. Both gave permission for their family members to give input on their observations on the behavioural change.

Patient 1 is a 70-year-old married male. The patient had no significant medical history and received no significant medication until age 62, when he underwent double coronary artery bypass grafting (CABG). Following CABG, the patient initiated medication comprising atorvastatin, ramipril, perindopril and aspirin. No risk factors for statin-associated adverse events (AEs) were identified in this patient.[18]

At approximately 3 months of medication use, the patient's wife observed that the patient had become increasingly irritable and aggressive, stating that 'nothing made him happy; he was permanently angry'. She described him as having a 'permanent scowl' on his face and found him very quick to argue. The patient's wife reported that these behavioural changes constituted a marked departure from the patient's usual easygoing personality. Initially, she assumed these behavioural changes to stem from the stress of undergoing CABG surgery. As for the patient, he did not recognise any significant behavioural difference in himself and instead perceived his wife as being unreasonable; 'I kept saying, It's you being difficult. Not me'.

At approximately 1 year after atorvastatin initiation, the patient reported non-behavioural adverse effects comprising arthralgia, myalgia and myopathy to his physician. The physician responded by switching the patient from atorvastatin to simvastatin and the patient remained on simvastatin therapy for approximately 1 year, during which time behavioural and muscular adverse effects were neither resolved nor reduced in severity.

The personality change and impaired conation produced a negative impact on family and social function over the 2 years he remained on statins, with his wife stating 'he didn't want to go out anywhere and if we did, nothing would please him'. His relationship with his wife became increasingly difficult, with his wife reporting 'I didn't know how much more of this I could take from him'.

The patient elected to discontinue treatment with statins at 2 years. At approximately 5 weeks following discontinuation, the patient's wife reported recognition that the patient's 'personality was coming back' and that she noticed a 'definite change in his behaviour and wellbeing'. Muscle symptoms, as well as behavioural alterations, reversed. The patient did not rechallenge with statin therapy and presently receives no cholesterol-lowering therapy. He has experienced no behavioural or muscular adverse effects since discontinuation of statin treatment.

Patient 2 is a 40-year-old married male. He has a history of stage 1 hypertension controlled by an ACE inhibitor

Table 1 Characteristics of patients 1 and 2

		Case 1	Case 2
Sex		Male	Male
Age at first occurrence		62	39
Education		High school	Postgraduate
Lipid panel prior to statin initiation	LDL-C	NM	120 mg/dl
	HDL-C	NM	50 mg/dl
	TG	NM	140 mg/dl
	TC	NM	220 mg/dl
Statin drug #1		Atorvastatin 20 mg/day	Atorvastatin 20 mg/day
Statin drug #2		Simvastatin 20 mg/day	Atorvastatin 20 mg/day (rechallenge)
Time course to noted onset #1		Approx. 3 months	2–3 days
Time course to noted onset #2		NA*	3 days
Time course to first noted improvement #1		NA*	2–3 days
Time course to first noted improvement #2		4 to 5 weeks	2 days
Time course to full improvement #1		NA*	2–3 days
Time course to full improvement #2		4 to 5 weeks	2 days
Risk factors for adverse effects		None	Hypertension; family history of statin-associated AEs
Manifestations		Irritability	Irritability
		Aggression	Aggression
		Depression	Depression
		Conative impairment	
		Myalgia	
		Arthralgia	
		Myopathy	
Consequences			
Personal versus family recognition (at the time of symptoms)		Personal: Non-behavioural AEs only	Personal: Depression only
		Family: All AEs recognised by spouse	Family: Irritability and aggression
Personal narrative comments regarding case (retrospective)		*I kept saying, 'It's you being difficult. Not me.'*	*I was ready to lash out over something so tiny.* *I could not detect my own increased aggression. At the time I felt as if everyone around me was acting unreasonably, forcing me into retaliating in this way. I felt completely justified.*
Family members' narrative comments regarding case		*Nothing made him happy; he was permanently angry.* *He had a permanent scowl on his face.* *He didn't want to go out anywhere and if we did, nothing would please him.* *I didn't know how much more of this I could take from him.*	I began to feel scared; it was like he was a different person.

AE, adverse event; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NM, not measured; TC, total cholesterol; TG, triglycerides.
*Patient 1 did not have a wash-out period between use of statin 1 and statin 2; only data relating to AE resolution following discontinuation of statin 2 are available.

since late 2009. In late 2010, a lipid panel for the patient indicated hyperlipidaemia and the patient initiated atorvastatin. Two risk factors associated with adverse effects on statin therapy have been identified for this patient,[18] comprising hypertension and family history of AEs associated with use of the statin drug class. The patient's wife reports his usual personality as being calm, even-tempered, and soft-spoken.

In the case of patient 2, behavioural adverse effects, representing a marked departure from prestatin state, were observed within 2–3 days of statin initiation. The patient's wife reported that the patient became severely irritable over minor issues and was quick to become severely angry to the point of shouting. During one of these arguments, the patient's wife reported that she 'began to feel scared; it was like he was a different person'. The patient also reported a specific incident in which he was wrongly accused of not buying a bus ticket, 'I exploded in response to the accusation. When another passenger joined in, I shouted and stared him down, too'. When questioned retrospectively about this incident, the patient reported, 'I'm normally the kind of person who tries to help resolve arguments. But on that occasion, I came extremely close to physically lashing out'. The patient also pointed out that 'I could not detect my own increased aggression. At the time I felt as if everyone around me was acting unreasonably, forcing me into retaliating. I felt completely justified'.

The patient was able to detect concurrent signs of depression. He described these feelings to his mother, who reminded him of the adverse effects experienced by his father while receiving post-CABG medication. Patient 2 had heard of his father's experience on statin therapy but had assumed it to be associated with the stress of having undergone major surgery and not statin use. Nevertheless, patient 2 discontinued statin therapy and all symptoms of irritability, aggression and depression resolved completely within 2 to 3 days. Remaining unconvinced that statins were linked to these adverse behavioural effects, patient 2 rechallenged with atorvastatin in December of 2010. Within 3 days, the patient experienced a noticeable increase in difficulty in dealing with his wife coupled with feelings of depression. The patient discontinued statin use on day 4 and has not used them since. All behavioural adverse effects resolved within 2 days. The patient has

BMJ Case Reports 2011; doi:10.1136/bcr.09.2011.4758

since switched to niacin therapy and both the patient and his wife report no recurrence of adverse effects.

Table 1 summarises information including drug and dose, lipid panel data prior to treatment, time course of onset and resolution of clinically evident irritability, risk factors for statin-associated adverse effects, manifestations, consequences and personal versus family recognition of statin-associated adverse effects.

DISCUSSION

To our knowledge this is the first report of behavioural adverse effects manifested on statins by first-degree male relatives (father and son). Both patients were exposed to the same statin dosage and both patients exhibited behavioural adverse effects comprising elevated irritability, increased propensity for aggression and onset of depression. The father additionally experienced conative impairment and non-behavioural adverse effects comprising myalgia, arthralgia and myopathy. Features indicative of probable causal relation to statin usage include occurrence on drug, resolution off, recurrence in the patient who rechallenged, previous reports of similar problems with this drug class,[15] concurrent development of other recognised (muscle) adverse effect in one of the patients (with concurrent resolution on discontinuation), and biological plausibility.[11 17–19] This is buttressed by a sizeable literature linking lower native cholesterol to higher violence and aggression/behavioural disturbance in humans, as well as in non-human primates.[11–13 19–23]

While behavioural side effects have previously been reported on statin therapy, these cases are of interest because they occur in first-degree relatives, suggesting possible familial vulnerability.

Additionally these cases share in common that both patients perceived the increased arguments and social difficulties at the time they received statin therapy to be the result of unreasonable behaviour by those around them. It required the resolution of these problems with drug discontinuation (bolstered in one by recurrence with rechallenge), coupled with reflection on their actions, to permit the inference that the source of the increased discord rested with them.

Other evidence underscores this key point: persons experiencing behavioural adverse effects may interpret their own lack of agreeableness, or short temper, as others' greater provocation. Many reports of behavioural adverse effects in our statin effects study have shared this theme. Additionally, such findings have been reported in a range of other settings. These include depression and its pharmacological redress[24]; premenstrual dysphoria and its resolution[25]; and the observation that 'problem physicians' disproportionately report 'problem patients'.[26] In each instance persons who are less agreeable or more short-tempered interpret disagreeableness and provocation from others to be greater. Indeed, criminal offenders characterised by repeat non-premeditated actions commonly perceive their own aggressing to be a justified response to provocation.

These case reports share limitations common to all case reports/case series. Findings rely on self-report. However concerns about bias and attribution 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; by concordance with other patients' reports; and by dechallenge, and in one case rechallenge support and a compatible literature. Indeed, these cases adhere to Naranjo criteria for probable or definite drug adverse effect causality.[27] These cases have no necessary implications for usual effects of statins on behaviour. Nonetheless, adverse effects of drugs are important to the individuals who experience them, irrespective of whether the drug produces similar effects on average, and even if it produces opposite direction usual effects.[28 29]

These findings extend prior reports of behavioural adverse effects on statins, suggesting the possibility of familial/biological predisposition. They highlight an underemphasised issue in behavioural adverse effect study: that of externalisation by patients of the origin of interpersonal discord. This consideration must be born in mind in approaches for behavioural AE surveillance, in the statin setting and beyond. Failure of patients to recognise adverse personality change in them has potential implications. Such failure can serve as an obstacle for reporting, leading behavioural adverse effects to be under recognised. Such failure may serve as an obstacle to rectifying the problem, with adverse implications to family, social and professional function, and to negative outcomes for patients, and those around them.

Learning points

- Irritability, aggression, and other adverse behavioural effects have been associated with statin use.
- Low cholesterol has been linked to violence and aggression in a number of studies.
- Patients experiencing adverse behavioural effects, on statins as in other settings, may externalise the origin of interpersonal discord.
- For patients and healthcare providers alike, lack of awareness of behavioural adverse effects associated with statin use can serve as an obstacle for reporting and for resolution of negative outcomes for patients and those around them.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Smart RG,** Mann RE. Causes and consequences of air rage in Canada: cases in newspapers. *Can J Public Health* 2003;**94**:251–3.
2. **Biswas PN,** Wilton LV, Shakir SA. The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13554 patients in England. *J Psychopharmacol (Oxford)* 2003;**17**:121–6.
3. **Healy D,** Herxheimer A, Menkes DB. Antidepressants and violence: problems at the interface of medicine and law. *PLoS Med* 2006;**3**:e372.
4. **Lion JR,** Azcarate CL, Koepke HH. "Paradoxical rage reactions" during psychotropic medication. *Dis Nerv Syst* 1975;**36**:557–8.
5. **Rampling D**. Aggression: a paradoxical response to tricyclic antidepressants. *Am J Psychiatry* 1978;**135**:117–8.
6. **Hartgens F,** Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med* 2004;**34**:513–54.
7. **Bigby M,** Stern RS. Adverse reactions to isotretinoin. A report from the Adverse Drug Reaction Reporting System. *J Am Acad Dermatol* 1988;**18**:543–52.

8. **Moore TJ,** Glenmullen J, Furberg CD. Thoughts and acts of aggression/violence toward others reported in association with varenicline. *Ann Pharmacother* 2010;**44**:1389–94.
9. **Angles A,** Bagheri H, Montastruc JL, *et al*. [Adverse drug reactions (ADRs) to antimalarial drugs. Analysis of spontaneous report from the French pharmacovigilance database (1996-2000)]. *Presse Med* 2003;**32**:106–13.
10. **van Riemsdijk MM,** Sturkenboom MC, Pepplinkhuizen L, *et al*. Mefloquine increases the risk of serious psychiatric events during travel abroad: a nationwide case-control study in the Netherlands. *J Clin Psychiatry* 2005;**66**:199–204.
11. **Golomb BA**. Cholesterol and violence: is there a connection? *Ann Intern Med* 1998;**128**:478–87.
12. **Golomb BA,** Stattin H, Mednick S. Low cholesterol and violent crime. *J Psychiatr Res* 2000;**34**:301–9.
13. **Zhang J,** Muldoon MF, McKeown RE, *et al*. Association of serum cholesterol and history of school suspension among school-age children and adolescents in the United States. *Am J Epidemiol* 2005;**161**:691–9.
14. **Repo-Tiihonen E,** Halonen P, Tiihonen J, *et al*. Total serum cholesterol level, violent criminal offences, suicidal behavior, mortality and the appearance of conduct disorder in Finnish male criminal offenders with antisocial personality disorder. *Eur Arch Psychiatry Clin Neurosci* 2002;**252**:8–11.
15. **Golomb BA,** Kane T, Dimsdale JE. Severe irritability associated with statin cholesterol-lowering drugs. *QJM* 2004;**97**:229–35.
16. **Olson MB,** Kelsey SF, Matthews KA, *et al*. Lipid-lowering medication use and aggression scores in women: a report from the NHLBI-sponsored WISE study. *J Womens Health (Larchmt)* 2008;**17**:187–94.
17. IMS Health. Top 20 Global Products, 2010, Total Audited Markets. Available from http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-line%20Market%20Data/2010%20Top-line%20Market%20Data/Top_20_Global_Products.pdf. (accessed 9 August 2011).
18. **Golomb BA,** Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs* 2008;**8**:373–418.
19. **Kaplan JR,** Shively CA, Fontenot MB, *et al*. Demonstration of an association among dietary cholesterol, central serotonergic activity, and social behavior in monkeys. *Psychosom Med* 1994;**56**:479–84.
20. **Golomb BA,** Tenkanen L, Alikoski T, *et al*. Insulin sensitivity markers: predictors of accidents and suicides in Helsinki Heart Study screenees. *J Clin Epidemiol* 2002;**55**:767–73.
21. **Hillbrand M,** Foster HG. Serum cholesterol levels and severity of aggression. *Psychol Rep* 1993;**72**:270.
22. **Hillbrand M,** Spitz RT, Foster HG. Serum cholesterol and aggression in hospitalized male forensic patients. *J Behav Med* 1995;**18**:33–43.
23. **Mufti RM,** Balon R, Arfken CL. Low cholesterol and violence. *Psychiatr Serv* 1998;**49**:221–4.
24. **Kramer PD**. *Listening To Prozac*. New York: Viking 1992.
25. **Gise LH**. *The PMDD Phenomenon: Breakthrough Treatments for Premenstrual Dysphoric Disorder (PMDD) and Extreme Premenstrual Syndrome (PMS)*. New York: McGraw-Hill Professional 2002.
26. **Hinchey SA,** Jackson JL. A cohort study assessing difficult patient encounters in a walk-in primary care clinic, predictors and outcomes. *J Gen Intern Med* 2011;**26**:588–94.
27. **Naranjo CA,** Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–45.
28. **Kolata G**. When drugs cause problems they are supposed to prevent. New York Times 2010;A18; http://www.nytimes.com/2010/10/17/health/policy/17drug.html.
29. **Bramness JG,** Skurtveit S, Mørland J. Flunitrazepam: psychomotor impairment, agitation and paradoxical reactions. *Forensic Sci Int* 2006;**159**:83–91.