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Psychiatric Adverse Reactions with Statins, Fibrates and Ezetimibe

Implications for the Use of Lipid-Lowering Agents

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Abstract

The HMG-CoA reductase inhibitors ('statins') have come into widespread use internationally. There has been a long history of their use in New Zealand and this use has increased in recent years. There has also been an increase in the number of reports to the New Zealand Centre for Adverse Reactions Monitoring (CARM) of suspected psychiatric adverse reactions associated with statins. The reactions mentioned in these reports include depression, memory loss, confusion and aggressive reactions. Convincing reports to CARM of recurrence of these reactions upon rechallenge add weight to recent studies reporting serious psychiatric disturbances in association with statin treatment. Aggressive reactions associated with statins are poorly documented in the literature. These observations emphasise the need to be vigilant in looking for these reactions as they can have a significant personal impact on a patient. The observation that other lipid-lowering agents have similar adverse effects supports the hypothesis that decreased brain cell membrane cholesterol may be important in the aetiology of these psychiatric reactions.

The effectiveness of HMG-CoA ('statins') in the treatment of dyslipidaemias has been extensively documented. Benefits from treatment have been reported over a range of outcomes, including cholesterol level reduction and blood pressure lowering in the primary and secondary prevention of coronary artery disease.[1,2] The magnitude of these achievements is remarkable, with the occurrence of major coronary events reportedly being reduced by 26–36% and death from any cause by 14–28% in statin users.[3] More recently, the potential benefits of statins for protection from Alzheimer's disease have also been postulated.[4] This success and the increasing focus on lipid-lowering guidelines have had the effect of promoting wider use, leading, over the past few years, to these drugs becoming the most prescribed medications in the world and possibly even in history.[5,6] Further strengthening their beneficial qualities, statins have generally been associated with a favourable safety profile with a relatively low overall frequency of undesirable effects.[7] Although these adverse events have usually been mild, on rare occasions more serious events have occurred, as evidenced by the recent market withdrawal of cerivastatin due to fatal rhabdomyolysis;[8] other reports of rhabdomyolysis and myopathy,[9] liver injury[7] and reports of an excess risk of peripheral neuropathy have also been associated with statin use.[10,11]

There has been recent interest in the effects of statins on brain function. However, there have been conflicting results, with positive effects in

Alzheimer's disease shown in some trials[4] whilst others have found no benefit.[12] Furthermore, an increasing number of reports raise the possibility that statins may be associated with deleterious cognitive,[3,13,14] mood and behavioural adverse effects including violence,[5] depression and even suicide,[15] which have been attributed to the statin effect of cholesterol level reduction on brain function.

Adverse events associated with statins have received increasing media attention in New Zealand. In particular, there has been ongoing public media concern, especially on 'talkback radio', around anecdotal reports of cognitive and other neuropsychiatric events attributed to statin use. There has been a recent increase in reports of adverse reactions with statins in general, which is related to their wider use, and at the same time there has been an escalation in the numbers of suspected psychiatric adverse reactions reported to the New Zealand Centre for Adverse Reactions Monitoring (CARM). These reports are consistent with others that have recently been published.[16] These reports and debate around the absence of such findings in formal studies have stimulated this review of the reports of psychiatric adverse effects of statins and fibric acid derivatives ('fibrates') held by CARM, as well as recent reports received for ezetimibe.

1. Psychiatric Adverse Drug Reactions Associated with Lipid-Lowering Agents Reported to the NZ Centre for Adverse Reactions Monitoring

1.1 Number and Type of Reaction

CARM has now received 203 reports of adverse events associated with statins that fall within the WHO Adverse Reaction Terminology System Organ Class grouping 'Psychiatric'. There are also 77 such reports associated with fibrates and five with ezetimibe. These are shown in table I. Reports held by CARM reflect the voluntary reporting experience over the entire life history of the use of a medicine in New Zealand. The higher overall numbers of reports for simvastatin and bezafibrate are due to these drugs being monitored in the Intensive Medicines Monitoring Programme (a prescription event monitoring system) and events detected by this programme that are considered to be adverse reactions then being entered into the CARM database.

Despite possible reporting bias for simvastatin due to recent media attention, and with the exception of clofibrate for which there are few reports, the proportion of reports for each lipid-lowering drug that describe psychiatric reactions are similar, in the range of 10–20% (see table I).

CARM has recorded 364 psychiatric reaction terms in the 285 reports of adverse events associated with statins, fibrates and ezetimibe. These reaction terms are for disorders affecting mood, cognition, sleep and perception and are presented in table II.

Many of the mood disorders and some of the perception disorders resulted in significant morbidity for patients as reflected by the terms suicidality, aggressive reactions and paranoia, as well as the proportion of reaction terms that were recorded as being severe.

1.2 Reactions with Recurrence on Rechallenge

In 40 (statins 34, bezafibrate 3, gemfibrozil 1, ezetimibe 2) of the 285 reports, patients who experienced psychiatric reactions had documented recurrence of the effect upon rechallenge, adding further weight to the causal association between statin, fibrate or ezetimibe use and adverse psychiatric

Table I. Reports of psychiatric adverse reactions with statins and fibrates held by the New Zealand Centre for Adverse Reactions Monitoring (November 2005)

Drug	Reports including psychiatric adverse reactions (% of all reports)	All reports
Simvastatin	145 (21)	692
Atorvastatin	26 (19)	136
Fluvastatin	24 (21)	116
Pravastatin	8 (18)	44
Bezafibrate	54 (11)	480
Gemfibrozil	22 (11)	195
Clofibrate	1 (4)	25
Ezetimibe	5 (16)	31

Table II. Psychiatric reaction terms[a] (grouped into related types) for severe[b] adverse reactions associated with each antihyperlipidaemic drug class

Reaction type	Number [total (severe)] of reactions			Number [total (severe)] of reactions that were followed by a positive rechallenge		
	statins	fibrates	ezetimibe	statins	fibrates	ezetimibe
Mood disorders						
Depression, suicidal tendency, emotional lability, aggressive reaction, agitation, irritability, anxiety, nervousness, panic reaction, stimulation, euphoria	67 (9)	23 (1)	2 (0)	9 (1)	1 (0)	NR
Cognitive disorders						
Amnesia, confusion, impaired concentration, disorientation	30 (7)	3 (2)	2 (1)	10 (3)	NR	1 (0)
Sleep disorders						
Insomnia, nightmares, somnolence	51 (13)	12 (4)	1 (0)	12 (4)	1 (0)	NR
Perception disorders						
Depersonalisation, abnormal thinking, hallucinations, paranoia, compulsive reactions	14 (6)	2 (2)	NR	5 (4)	NR	NR
Other reactions						
Asthenia, fatigue, lethargy, malaise, somnolence, tiredness	107 (22)	49 (3)	1 (0)	13 (4)	4 (0)	1 (0)

a According to WHO Adverse Reaction Terminology System Organ Class.

b Reactions were graded as 'severe' or 'not severe' depending on their intensity; this decision is usually made by the person reporting the reaction. This different to the 'seriousness' of the reaction, which assesses its outcome, e.g. whether the adverse effect leads to extension of hospitalisation or is life-threatening.

NR = no reports.

experiences. A summary of characteristics of the positive rechallenge reports are presented in table III.

1.3 Reports of Aggressive Reactions

Of considerable concern for statin users are the reports that describe severe reactions, particularly the five aggressive reactions. These reports involved two females and three males aged 44–69 years who were taking simvastatin at dosages ranging from 10 to 40 mg/day, atorvastatin 10 mg/day or fluvastatin 20 mg/day. There is also one report of an aggressive reaction associated with ezetimibe treatment. The duration to onset was between 1 week and 2 months and in all instances there was improvement upon discontinuation of treatment. The case histories, all from reporters who were healthcare professionals, illustrated the magnitude of the personal impact. The cases will now be discussed in more detail.

Patient 1 was a 53-year-old man who had been taking simvastatin 40 mg/day for 2 months when he began to notice a change of personality. He became very angry and frustrated and was unable to think clearly to do tasks that should have been easy. He nearly hit his fellow worker and almost resigned from his job. The patient was receiving concomitant treatment with warfarin. Upon discontinuation of simvastatin therapy, his mental state returned to normal.

Patient 2, a 52-year-old woman, became very angry after 1 month on atorvastatin 10 mg/day and wanted to kill her friend and drown herself. These feelings subsided over 1–2 days after stopping statin

treatment. The patient had a past history of depression and anxiety. This patient was not receiving any other medications.

Patient 3 was a 44-year-old man, a known schizophrenic who became aggressive, irritable and angry and wanted to leave home after 2 months of receiving fluvastatin 20 mg/day. He was also receiving lithium, amoxapine, trifluoperazine and orphenadrine. The problems resolved upon stopping statin treatment.

Patient 4, a 69-year-old woman, had a gradual onset of headaches and violent outbursts that were quite out of character for this normally placid person. She had been on simvastatin 20 mg/day for 2 months prior to the onset of symptoms. The symptoms stopped as soon as she discontinued the statin. She was not receiving any other medication.

Patient 5 was a 64-year-old man who, within 1 week of initiating simvastatin 10 mg/day, was reported to have become terribly aggressive, engaging in arguments with his wife, a situation that had not occurred previously. The symptoms resolved upon discontinuation of statin treatment. The patient was reported to be taking a number of other medications for non-psychiatric indications.

Patient 6 was a 64-year-old man who became very irritable and aggressive 4 days after initiating treatment with ezetimibe 10 mg/day in addition to simvastatin 20 mg/day. He recovered when ezetimibe was discontinued. He had taken the simvastatin for 3 years prior to this episode and continued to take it thereafter.

2. Reports to the WHO

The WHO International Drug Monitoring Programme holds adverse reaction reports from national pharmacovigilance centres worldwide. Its database, Vigibase, is analysed at quarterly intervals for adverse reaction/drug combinations that are statistically prominent compared with the background data, and then these are reported as information component (IC) values.[17] An IC025 value (95% lower confidence limit of the IC) of greater than zero indicates a degree of statistical prominence that should lead to further clinical evaluation of the reports. Vigibase holds relatively few reports of psychiatric adverse reactions associated with the use of lipid-lowering agents as a proportion of total reports compared with the data from CARM. Using the adverse reaction terms 'aggressive reactions',

Table III. Summary characteristics of cases of psychiatric reactions[a] occurring on rechallenge with cholesterol-lowering agents

Drug	Number of reports	Psychiatric reaction terms	Dosage (mg/day)	Onset time	Age (years)	Sex
Simvastatin	24	Anxiety, depression, emotional lability, euphoria, stimulation, confusion, amnesia, memory impairment, insomnia, paroniria, abnormal thinking, fatigue, malaise, tiredness	Range: 10–80; mode: 20	Range: 1 week to 1 year; mean: 5 months	Range: 51–79; mean: 63	16 female, 8 male
Atorvastatin	6	Depression, amnesia, confusion, paroniria, hallucination, asthenia, lethargy	Range: 10–20; mode: 20	Range: 1 week to 1 year; mean: 4 months	Range: 41–73; mean: 61	4 female, 2 male
Fluvastatin	3	Nervousness, insomnia, paroniria	Range: 20–40	Range: 1–2 months	63, 59 and 74	1 male, 2 female
Pravastatin	1	Malaise	10	3 days	51	1 male
Bezafibrate	3	Emotional lability, asthenia, fatigue, lethargy	Range: 200–600; mode: 600	1 week[b]	58[b]	1 female[b]
Gemfibrozil	1	Paroniria	300	1 week	59	1 male
Ezetimibe	2	Lethargy, amnesia	10	2 days, 3 months	58, 61	2 female

a According to WHO Adverse Reaction Terminology System Organ Class.

b Data were only available for one patient.

'agitation', 'amnesia', 'confusion', 'depression' and 'suicidality' in association with atorvastatin, simvastatin, gemfibrozil, bezafibrate and ezetimibe, it was noted that, as at February 2006, depression associated with gemfibrozil was markedly prominent statistically (IC025 3.09) compared with the background data. Amnesia with simvastatin and atorvastatin were statistically prominent (IC025 0.72 and 1.61). Depression associated with these two agents was also statistically prominent, but only weakly so (IC025 simvastatin 0.25, atorvastatin 0.1). Interestingly, none of the other adverse reaction/drug combinations that we studied achieved statistical prominence, although there are still relatively few reports of adverse events associated with ezetimibe and IC values have increased over previous quarters.

3. Discussion

A number of reports received by the CARM have documented significant psychiatric morbidity, and this has caused concern, despite the limitations and biases of reports received in the context of a spontaneous monitoring programme. The index cases that report recurrence upon rechallenge are particularly important in establishing a case for a causal association. These cases add weight to other published reports concerning statins and psychiatric adverse effects. Supportive of a relationship between the initiation of statin treatment and these adverse effects are a suggestive time course to onset; improvement upon treatment discontinuation; and the simultaneous occurrence in individual patients of other recognised adverse reactions associated with statins.

The case reports of aggressive reactions highlight the importance of identifying the potential for this type of reaction. Whilst three of the six cases had possible underlying psychiatric factors that might have suggested a different risk for aggression compared with those without such factors, all patients' reactions were reported to be completely out of character compared with their usual personality, with resolution after drug withdrawal.

The presence of psychiatric events in statin, fibrate and ezetimibe users is in keeping with the link between lowered cholesterol levels and various adverse psychiatric reactions, including violence and aggression, which are further reinforced by findings in systematic reviews.[5,7,15,17,18] Since each of these medicine groups lower cholesterol by a different mechanism, cholesterol reduction itself is therefore implicated in causing the psychiatric adverse effects.

3.1 Mechanism

Cholesterol is crucial to brain functioning. Despite the brain's relatively small proportion of body mass (2%), it contains 25% of the body's nonesterified cholesterol,[10] which is 5- to 10-fold more than is present in other organs.[14] Statins penetrate the blood-brain barrier, with simvastatin being associated with the highest permeability,[19] and thus, statins could bring about local cholesterol-lowering effects. Glial-derived cholesterol is reported to be vital for the formation of synapses, is a major component of myelin and is an important part of cellular membranes, with roles in membrane exchange and regulator expression, including the expression of neurotransmitter substances.[10] Engelberg[20] suggested a chain of events where reduced serum cholesterol levels might decrease brain cell membrane cholesterol, which in turn would lower lipid microviscosity and decrease the expression of protein serotonin receptors on the membrane surface, ultimately leading to reduced serotonin entry into cells. Since serotonin pathways function as a behavioural restraint system that inhibits impulsive behavior, reduced cholesterol levels could facilitate aggressive and violent behaviours.[16]

This mechanism suggests that any strategies to reduce serum cholesterol levels are potentially implicated in the occurrence of adverse effects attributed to cholesterol lowering and, therefore, diet should theoretically also provide the same outcomes. However, recent evidence from a randomised trial of the effects of cholesterol-lowering dietary treatment on psychological functions[21] did not support any adverse effect on mood, although there was a relative impairment in cognitive function. It has been demonstrated that cholesterol lowering therapy evokes cholesterol-induced serotonergic changes

that are more marked in the first 2 months of therapy than later.[16] There is also some speculation about whether it is the rapid lowering of cholesterol levels or extremely low cholesterol levels that may be at the heart of the effects.[15] In either of these circumstances, diet alone may not be capable of achieving a sufficient degree of cholesterol reduction to manifest the effects observed with drug therapy. The absence of the observation of consistent dose effects in our data adds further weight to the adverse events being due to the intended therapeutic cholesterol-lowering effect, the consequences of which may be more profound in a susceptible subgroup of patients. When use of lipid-lowering therapy at higher doses is observed, these may have been utilised with the intention of achieving the desired therapeutic cholesterol end point.

The presence of a plausible mechanism raises some concern about why psychiatric events and, in particular, aggressive and violent events have not been identified in major statin studies. It has been suggested that this failure to detect such adverse reactions may be in part due to the rarity of the events, typical clinical trial selection and exclusion factors, as well as not recognising the need to expressly measure this type of event. It is also surprising to have clearly documented cases of recurrence of effects upon rechallenge when some of these reactions are not statistically prominent in the WHO database. Although the possibility remains that the reports are coincidental, there is also a concern that these reactions are not readily recognised and that the symptoms may be attributed to idiopathic psychiatric disorders or, in older persons, the onset of dementia.

4. Conclusion

The reports we have presented support the literature regarding psychiatric adverse reactions in association with treatment with statins and fibrates. These findings have not been previously documented for ezetimibe. Although many of the reports in the CARM database occurred within the first few months of taking medicines compatible with possible cholesterol reduction, it is the reports of aggressive reactions that are most convincingly consistent with the mechanism described. These compelling cases, when added to the accumulating literature related to statins and the effects of cholesterol reduction, contribute to the identification of a potentially important and clinically significant observation. Although it has not been possible to estimate the incidence of these events, the low level of observations to date suggests that they occur infrequently, which should be weighed against the benefits these agents can achieve. However, the occurrence of these events does highlight the need to create awareness in prescribers of the potential for these effects, albeit in a relatively small group of patients. Failure to do so may lead to late recognition of these adverse reactions in individual patients. In the case of aggressive and violent behaviours, there could be an adverse societal impact beyond the patient.

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