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Statin-Associated Psychiatric Adverse Events

A Case/Non-Case Evaluation of an Italian Database of Spontaneous Adverse Drug Reaction Reporting

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Abstract

Background: The inhibitors of HMG-CoA reductase ('statins') are widely prescribed hypolipidaemic drugs, which have been evaluated in several clinical trials involving hundreds of thousands of patients. From a safety perspective, both clinical trials and post-marketing surveillance have demonstrated that statins are generally well tolerated, with rare serious adverse drug reactions (ADRs) that affect mainly muscle, liver and kidney. However, recent interest has been focused on a potential risk of psychiatric ADRs associated with statins, including memory loss, depression, suicidality, aggression and antisocial behaviour. Special attention is currently being paid to the potential for statin-induced sleep disorders.

Objective: To investigate the hypothesis that statins may be associated with psychiatric adverse events using quantitative and qualitative signal analysis.

Methods: The Interregional Group of Pharmacovigilance database holds reports of suspected ADRs submitted since 1988 from eight Italian regions. In the present analysis, only reports ranked at least 'possible', according to WHO causality assessment criteria, were considered. Association between statins and psychiatric events was assessed by the case/non-case methodology, calculating the ADR reporting odds ratio (ROR) as a measure of disproportionality. Cases were defined as patients with at least one reported ADR combined with the system organ class (SOC) 'psychiatric disorders'. The non-cases comprised all patients who did not experience an ADR related to the SOC 'psychiatric disorders'. Index reports comprised all ADR reports involving at least one statin, while all ADR reports not involving statins as suspected drugs were used as controls.

Results: According to selection criteria, 35 314 reports were included in the analysis. A total of 71 psychiatric preferred terms combined with statins were identified in 60 reports. Among them, 14 reports (23.3%) noted a positive rechallenge. Both the unadjusted (0.8; 95% CI 0.6, 1.1) and adjusted ROR (0.7; 95% CI 0.6, 1.0) suggested a lower rate of reports of psychiatric events for statins as a whole class compared with all other drugs, although the difference was not significant. The five most frequently reported psychiatric events combined with statins were insomnia, somnolence, agitation, confusion and hallucination. Only insomnia was reported with higher frequency for statins compared with all other drugs (ROR = 3.3; 95% CI 1.9, 5.7), while confusion was reported with a lower frequency (ROR = 0.4; 95% CI 0.1, 0.9). Amongst statins available in Italy, only simvastatin (ROR = 0.5; 95% CI 0.2, 0.9) showed a significantly lower rate of reports of psychiatric events compared with all other drugs together.

Conclusion: A relatively small number of possible statin-associated psychiatric ADRs have been found in our database. No significant risks for a higher overall reporting of psychiatric ADRs associated with statins were identified in comparison with all other drugs combined. However, statin-associated insomnia resulted in a significant ROR that requires further investigation.

Background

The inhibitors of HMG-CoA reductase, commonly known as 'statins', are widely prescribed hypolipidaemic drugs that have been evaluated in several clinical trials involving hundreds of thousands of patients. This large body of studies and clinical experience have shown that statins are effective in reducing blood lipid levels and limiting the risk of complications associated with atherosclerosis. From a safety perspective, both clinical trials and post-marketing surveillance have demonstrated that statins are generally well tolerated, with rare severe adverse effects that mainly affect muscle, liver and kidney.[1] Since lipids account for about half of the dry matter of the CNS and are integral components of myelin sheaths and synapses, recent interest has been focused on potential risk of psychiatric adverse reactions to statins,[2] including memory loss, depression, suicidality, aggression and antisocial behaviour.[3-6] With regard to psychiatric safety, particular interest has been also raised about the possible influence of statin treatment on sleep. However, several publications, particularly during the 1990s, focused on possible statin-induced insomnia and sleep alterations, have generated conflicting or non-conclusive results.[7-11]

Case reports[12-15] and descriptive analysis of spontaneous adverse drug reaction (ADR) databases[4,16] suggest that statins may impair cognitive functions, leading to concern regarding their safety, particularly in the elderly.[17] Randomized controlled trials have failed to confirm this observation, perhaps because of methodological limitations. Furthermore, current data conflict to the extent that, in some studies, statins were suggested as being effective in reducing cognitive decline and dementia in patients with Alzheimer's disease. However, hypolipidaemic interventions in Alzheimer's disease have not met initial expectations fostered by these studies, and statin therapy is currently regarded as a doubtful therapeutic approach in the management of cognitive and other symptoms of Alzheimer's disease.[18]

In recent years, data-mining methods have been applied to identify safety signals within spontaneous ADR databases, and the use of such methodologies is rapidly evolving.[19] The aim of the present study is to test the hypothesis that psychiatric ADRs are associated with use of statins by using quantitative and qualitative signal analysis of reports to an Italian spontaneous ADR reporting database.

Methods

Data Source

The study was based on data obtained from spontaneous reporting in eight Italian regions that maintain a pooled ADR database (the Italian Interregional Group of Pharmacovigilance – Gruppo Interregionale di Farmacovigilanza; GIF): Veneto (since 1988), Lombardy (since 1993), Autonomous District of Trento (since 1994), Sicily (since 1996), Emilia Romagna (since 2000), Friuli Venezia Giulia (since 2002), Campania (since 2004) and Tuscany (since 2005). In 2005, the regions contributing to GIF had a population of about 34.4 million inhabitants (59% of the Italian general population). In 2007, the GIF collected more than 81% of Italian total spontaneous ADR reports.[20] The majority of reports in the whole database are from physicians (about 90%). Each ADR report is verified by the respective Regional Pharmacovigilance Centres for completeness of information on concomitant medications and classified according to the WHO criteria for causality assessment of ADR.[21] Only those reports with a 'certain', 'probable' or 'possible' assessment of causality, that were received by GIF up until June 2007, were included in the present analysis. The reported ADRs were coded using the WHO-Adverse Reaction Terminology. All drugs were grouped using the Anatomic Therapeutic Chemical (ATC) classification.

Data Analysis

Association between statins and psychiatric events was assessed by the case/non-case methodology, calculating the reporting odds ratio (ROR) as a measure of disproportionality. ROR compares the frequency of an ADR reported for a particular drug with the frequency of reports of the same ADR for all other drugs. ROR and 95% confidence intervals were calculated according to a case/non-case design.[22] Cases were defined as patients who experienced at least one ADR (preferred term) related to the system organ class (SOC) 'psychiatric disorders'. This class contains terms such as 'impotence' and 'libido alteration', which might also occur through non-psychiatric mechanisms.[23] For this reason, the present analysis was performed both by including and not including reports relating to preferred terms for sexual disorders. The non-cases comprised all patients who did not experience any ADR related to the SOC 'psychiatric disorders'. Index reports included all ADR reports involving at least one statin, while all ADR reports not involving statins as suspected drugs were taken as controls. Reports of vaccine-related adverse events have been excluded from the analysis. ROR computation was performed only for cases of statin-ADR combinations where there were at least two such cases in the database. Reports of cerivastatin-ADR combinations were excluded from the analysis since this drug was withdrawn from the world market in 2001.

For all patients included in the present analysis, the reported use of psychotropic drugs (first level ATC code 'N') was assumed as a proxy of psychiatric co-morbidity. This approach has been previously adopted for case/non-case analysis to overcome the intrinsic lack of information about co-morbidity, a relevant confounding factor affecting data collected in systems of spontaneous ADR reporting.[24] Unadjusted ROR as well as adjusted ROR were calculated by means of logistic regression. Variables included in the multivariate analysis were selected in terms of clinical and significant meaning that was revealed by univariate comparison between cases and non-cases. The final model comprised age, sex, seriousness of the ADR (defined by WHO critical term list), number of concomitant drugs and number of concomitant psychotropic drugs (as a proxy of psychiatric co-morbidity). Disproportionality was estimated for statins as a whole class, or as each separate statin, versus all other drugs. For comparisons between statins, reports with more than one statin as suspected drugs were excluded from the analysis. ROR was also computed for the five most reported ADRs with a particular focus on insomnia. In this evaluation, since the denominator was reduced to include only psychiatric events, a power analysis was performed when the ROR was at least 2-fold higher for statins. Insomnia was also investigated to

Table I. Main characteristics of patients with reports of statin-associated, and all other adverse drug reactions (ADRs)

Characteristic	Patients with statin-associated ADRs (n = 1323)	Patients with ADRs associated with drugs other than statins (n = 33 991)	p-Value
Age (mean ± SD)	62.1 ± 10.1	53.6 ± 20.8	<0.001
Female sex (%)	52.7	60.8	<0.001
Patients using psychiatric medications (%)	7.63	6.57	0.154
No. of psychiatric drugs (mean ± SD)	0.1 ± 0.4	0.08 ± 0.30	0.130
No. of suspected drugs (mean ± SD)	1.1 ± 0.4	1.1 ± 0.4	0.273
No. of concomitant drugs (mean ± SD)	5.6. ± 5.4	3.4 ± 4.4	<0.001
Serious ADRs (%)	27	41.8	<0.001

compare more lipophylic statins (lovastatin and simvastatin) with less lipophylic statins (atorvastatin, fluvastatin, pravastatin and rosuvastatin), as well as each statin subgroup against the pool of all other drugs. A p-value <0.05 was considered statistically significant. SPSS software package, version 14 (SPSS Inc., Chicago, IL, USA), was used for statistical computations. Continuous variables were reported as mean value ± standard deviation, while categorical variables were presented as percentage. Mean and proportional values were compared by means of Student's t-tests and chi-squared (χ^2) tests, respectively.

Results

According to selection criteria, 35 314 reports were included in the present analysis. The causality assessment was scored as certain in 1191 reports (3.4%), probable in 12 818 (36.3%) and possible in 21 305 (60.3%). Unlikely, unassessable and unclassifiable reports (n = 883) had been already excluded from the analysis. Table I shows the characteristics of patients reported with statin-associated ADRs (n = 1323) or ADRs associated with other drugs (n = 33 991). Significant differences were detected with regard to age, sex, number of concomitant drugs and proportion of serious ADRs. Of the 1323 reports on statins, 423 concerned simvastatin, 380 atorvastatin, 191 fluvastatin, 155 pravastatin, 137 rosuvastatin, 17 ezetimibe/simvastatin and 8 lovastatin, while 12 reports indicated more than one statin as suspected drugs. Reports of statin-associated ADRs (assumed as 100%; prevalence within the database, 3.75%) mainly concerned the musculoskeletal system (34%; 1.27%), followed by the body as whole/general (14.3%; 0.53%), the gastrointestinal system (11.6%; 0.43%), the central and peripheral nervous systems (9.7%; 0.36%), liver and biliary system, including serum transaminases alterations (7.6%; 0.28%), the skin and appendages (6.6%; 0.24%), psychiatric disorders (4.3%; 0.16%) and others (11.9%; 0.44%).

A total of 71 psychiatric preferred terms combined with statins were identified in 60 reports (table

Table II. Numbers and types of psychiatric adverse drug reactions (ADRs) in combination with statins

Drug	Psychiatric ADR (no. of reports)	Total
Atorvastatin	Insomnia (12), impotence (4), agitation (3), confusion (3), somnolence (3), amnesia (1)	26
Simvastatin	Insomnia (8), impotence (3), agitation (2), anxiety (2), hallucination (1), decreased libido (1), somnolence (1)	18
Fluvastatin	Insomnia (4), agitation (1), anorexia (1), confusion (1), abnormal dreaming (1), impotence (1), somnolence (1)	10
Rosuvastatin	Somnolence (2), confusion (2), anorexia (1), anxiety (1), insomnia (1), nervousness (1)	8
Pravastatin	Insomnia (4), agitation (1), impotence (1)	6
Ezetimibe/simvastatin	Insomnia (1), somnolence (1)	2
Lovastatin	Insomnia (1)	1
Total		**71**

Table III. Reporting odds ratio (ROR) estimation for overall and serious adverse drug reactions (ADRs)

ADR	No. of pts with psychiatric ADRs (cases) [involving statins (%)]	No. of pts with non-psychiatric ADRs (non-cases) [involving statins (%)]	Unadjusted ROR (95% CI)	Adjusted[a] ROR (95% CI)
Overall ADRs	1775 [60 (3.4)]	33 539 [1263 (3.8)]	0.8 (0.6, 1.1)	0.7 (0.6, 1.0)
Serious ADRs	515 [12 (2.3)]	14 062 [345 (2.5)]	0.9 (0.5, 1.6)	0.9 (0.8, 0.9)[b]
Non-serious ADRs	1260 [48 (3.8)]	19 477 [918 (4.7)]	0.8 (0.5, 1.0)	0.8 (0.6, 1.1)[b]

a Adjustment was made for age, sex, seriousness of ADRs, number of concomitant drugs and number of concomitant psychotropic drugs.

b Adjustment not made for seriousness of ADRs.

pts = patients.

II). Among them, 14 reports (23.3%) referred to a positive rechallenge. The causality assessment was scored as 'certain' for 14 reports, 'probable' for 27 reports and 'possible' for 19 reports. Adverse events developed with a latency of 1 day to 4 years after initiating the treatment with statins. Median time to event onset was 15 days. About 52% of patients developed psychiatric symptoms within 2 weeks of treatment and 75% within 2 months. Outcome was assessed for 52 patients (86.6%): in the majority of them (47 patients; 78.3%) the adverse event completely resolved following statin withdrawal. In the remaining five patients (8.3%) the adverse event was resolving at the last documented follow-up. Time to outcome (event resolved) since drug withdrawal was assessed in 11 patients. In eight patients the reaction abated within 1 week, one case (insomnia) resolved in 10 days and two cases (the first was anorexia while the second presented with several symptoms, including confusion, amnesia and somnolence) within 2 months. The crude prevalence of concomitant psychotropic drugs in patients with statin-associated psychiatric ADRs was 3.34%.

Table III shows unadjusted and adjusted ROR values estimated for statins as a whole group and according to ADR seriousness. Both unadjusted (0.8; 95% CI 0.6, 1.1) and adjusted ROR (0.7; 95% CI 0.6, 1.0) suggested a non-significantly lower risk of reporting psychiatric events for statins as a whole class. After stratification by seriousness of ADRs, a lower risk of reporting was estimated for serious psychiatric ADRs (ROR = 0.9; 95% CI 0.8, 0.9).

The five most frequently reported psychiatric events combined with statins were insomnia, somnolence, agitation, confusion and hallucination. Only insomnia (ROR = 3.3; 95% CI 1.9, 5.7) was reported with a higher frequency for statins compared with other drugs (table IV), while confusion was reported with a lower frequency (ROR = 0.4; 95% CI 0.1, 0.9). Based on cell sizes and frequency of reports for insomnia, a power (1-β) of 96% [α = 0.05, N(cases) = 60; N(non cases) = 1715] was estimated. Statins with lipophylic properties presented a non-significant ROR for insomnia compared with those that were less lipophylic (adjusted ROR: 1.4; 95% CI 0.6, 3.4). The risk for insomnia

Table IV. Reporting odds ratio (ROR) estimation for the five most reported psychiatric adverse drug reactions (ADRs)

ADR	Patients with statin-related psychiatric ADRs [n = 60] (%)	Patients with psychiatric ADRs related to drugs other than statins [n = 1715] (%)	Unadjusted ROR (95% CI)	Adjusted[a] ROR (95% CI)
Insomnia	28 (46.7)	372 (21.7)	3.2 (1.9, 5.3)*	3.3 (1.9, 5.7)*
Somnolence	8 (13.3)	325 (19)	0.6 (0.3, 1.3)	0.7 (0.3, 1.5)
Agitation	6 (10)	275 (16)	0.5 (0.2, 1.3)	0.5 (0.2, 1.3)
Confusion	7 (11.7)	361 (21)	0.4 (0.2, 1.0)	0.4 (0.1, 0.9)*
Hallucination	1 (1.7)	155 (5)	NA	NA

a Adjustment was made for age, sex, seriousness of ADRs, number of concomitant drugs and number of concomitant psychotropic drugs.

NA = not applicable; * $p < 0.05$.

Table V. Individual statins suspected of causing psychiatric events

Statin	Patients with psychiatric ADRs (cases)[a] [n = 1774] (%)	Patients with non-psychiatric ADRs (non-cases)[a] [n = 33 528] (%)	Unadjusted ROR (95% CI)	Adjusted[b] ROR (95% CI)
Simvastatin	12 (0.7)	411 (1.2)	0.6 (0.3, 0.9)	0.5 (0.3, 0.9)
Atorvastatin	24 (1.3)	356 (1.1)	1.3 (0.8, 1.9)	1.2 (0.8, 1.8)
Pravastatin	5 (0.3)	150 (0.4)	0.6 (0.2, 1.5)	0.6 (0.2, 1.4)
Rosuvastatin	6 (0.3)	131 (0.4)	0.8 (0.3, 1.9)	0.8 (0.3, 1.8)
Fluvastatin	9 (0.5)	182 (0.5)	0.9 (0.4, 1.8)	0.8 (0.4, 1.7)
Ezetimibe/simvastatin	2 (0.1)	15 (0.1)	2.5 (0.5, 11.1)	2.8 (0.6, 12.1)
Lovastatin	1 (0.1)	7 (0.02)	NA	NA

a Reports with more than one statin as suspected drug were excluded.

b Adjustment was made for age, sex, seriousness of ADRs, number of concomitant drugs and number of concomitant psychotropic drugs.

ADRs = adverse drug reactions; **NA** = not applicable; **ROR** = reporting odds ratio.

was significantly higher when comparing lipophylic statins with all other drugs (adjusted ROR: 1.9; 95% CI 1.2, 3.1). Less lipophylic statins showed a non-significant ROR for insomnia compared with all other drugs (adjusted ROR: 1.3; 95% CI 0.6, 2.8).

A further evaluation was performed which compared individual statins with all other drugs. Twelve reports indicated more than one statin as suspected drugs and were excluded from this analysis. Only simvastatin (ROR = 0.5; 95% CI 0.3, 0.9) showed a significantly lower rate of reports of psychiatric events compared with all other drugs (table V). The elimination of reports, which included terms associated with sexual dysfunction under 'psychiatric' events, did not result in significant changes in RORs, neither for statins as a whole class nor for statins as single agents (data not shown).

Discussion

The present study indicates that reports of ADRs associated with statin therapy show a prevalence of 3.75% within our Italian database. The overall frequency of reports of statin-associated psychiatric ADRs was low (prevalence within database: 0.17%) and resulted in a non-significant ROR. Only insomnia showed a significantly higher disproportional rate in patients taking statins. Several reports of statin-associated psychiatric ADRs documented the recurrence of adverse effects upon rechallenge, thus adding weight to the possibility of a causal relationship. These reports support the current literature regarding possible psychiatric ADRs associated with statin treatment. Although the possibility remains that these adverse events are coincidental, there is also a concern that they may not be readily recognized, and that the symptoms may be ascribed to idiopathic psychiatric disorders or, especially in the elderly, to the onset of cognitive function impairments.

Several lines of evidence suggest a plausible pharmacological mechanism. In particular, Engelberg[25] observed that reduced serum cholesterol levels might decrease brain cell membrane cholesterol. This would lower lipid microviscosity and decrease the expression of serotonin receptors on the membrane surface, leading ultimately to a reduction in the control of serotonin activity on neurons. Since central serotonergic pathways are involved in behavioural control, reduced cholesterol levels could facilitate the occurrence of psychiatric adverse events. Some authors claim that the activity of the serotonin transporter, deputed to the reuptake of bioactive serotonin from synaptic clefts, can increase significantly during the first month of therapy with simvastatin, suggesting that, within this period, some patients might be vulnerable to impaired central serotonergic activity, with consequent risk of depression, violence and suicide.[26] However, despite the hypothesis of statin-induced psychiatric toxicity being supported by a plausible pharmacological mechanism, current clinical evidence re-

mains anecdotal in nature and more robust data are warranted.

In the present study, the case/non-case method was applied to an Italian ADR database to compare the ratio of reports of psychiatric ADRs (cases) with those describing non-psychiatric ADRs (non-cases), and to examine associations with statins. Since the present data have been obtained from spontaneously reported ADRs and the analysis has an exploratory value, our findings should be interpreted with caution, taking into account the biases that usually affect these evaluations. Biases result mostly from under-reporting and trends in reporting, the latter being fostered mainly by temporary special attention paid by physicians to the introduction of new drugs into the market, withdrawal of a drug from the market, specific guidelines and media claims. The trend in reporting bias, known also as notoriety bias,[27] has been shown to significantly affect disproportionality evaluation of spontaneous ADR reports by generating an over-reporting of specific adverse events. Such over-reporting may lead to a dilution of weak signals, leading to them not being recognised as possible ADRs when a disproportionality evaluation is performed. Thus, the withdrawal of cerivastatin from the market in 2001 had surely called the attention of healthcare professionals to statin-associated muscular toxicity, increasing their spontaneous ADR reporting of this particular type of event. On the other hand, in the present analysis, the under-reporting bias as well as the potential benefit of statins on cognitive disorders, as perceived by physicians, might have reduced the number of reports of statins associated with psychiatric events. However, this association is supported only by a few anecdotal reports, and therefore we can not assume that greater numbers would succeed in unravelling such a relationship in a population-based analysis. Our results may be affected also by an increase in the type I error rate because of multiple statistical testing. Nevertheless, since our analysis was 'exploratory' in nature, this kind of error might have limited impact on the study hypothesis, which needs further verification in confirmatory studies. Finally, the use of multiple testing does not overcome the problem of making valid statistical inferences for the hypotheses generated by data, as is usually noted in the design of case/non-case studies.[28]

In the present analysis, values of adjusted ROR for psychiatric events suggest a non-significant lower rate of reporting for statins. This finding is in accordance with the available medical literature, documenting these events only by case reports and case series. Thus, our results reflect the fact that psychiatric adverse reactions are likely to be associated with statin therapy with very low frequency. It is important to emphasize that an underestimation could have affected the present analysis. The low frequency of these events should be interpreted in the light of the above-mentioned high reporting rate of non-psychiatric ADRs, in particular those of muscular origin (34% of total statin-associated ADRs), recorded for all statins after cerivastatin withdrawal. Moreover, a possible perception by healthcare professionals of 'psychiatric safety' of statins, which in turn may produce a further under-reporting of psychiatric adverse events, can not be excluded. Indeed, the diffusion of scientific information about possible benefits of statins in cognitive disorders[29,30] might have contributed to a feeling of 'psychiatric safety'.

Specific rates of psychiatric adverse events associated with different statins are probably related to the ability of each drug to cross the blood-brain barrier. Accordingly, it is has been supposed that statins with a high degree of lipophilicity, namely simvastatin and lovastatin, may be associated with a higher rate of CNS disturbances in comparison with hydrophilic derivatives.[15] Although the majority of available reports have referred to lipophilic statins,[4,12-14,16] no conclusive evidence exists that a particular statin is more likely to be associated with psychiatric ADRs than any other. In the present study, a significant ROR was observed only for simvastatin, suggesting a lower risk of psychiatric ADR reporting in comparison with other statins. Therefore, in contrast to evidence in the anecdotal literature that simvastatin is the most frequently reported statin involved in psychiatric ADRs, our results suggest that in Italy simvastatin has a lower

rate of psychiatric ADR reporting than other statins. Further evaluations of larger databases are needed to suggest a possible explanation for these divergent findings.

Serious adverse psychiatric events, including severe aggressive behaviour, associated with statin therapy have been reported anecdotally in previous papers.[4,6] Manifestations of this behaviour included homicidal impulses, threats to others, road rage, generation of fear in family members and damage to property.[6] However, these behaviours were not associated with statin therapy in our database. This finding should be interpreted in light of the lack of awareness among caregivers of the potential for a relationship between severe aggressive behaviour and statin therapy. Alternatively, the possibility, albeit unlikely, that our multi-regional reporting system was not able to detect these events or that the Italian population may be resistant to statin-induced serious psychiatric toxicity can not be excluded. We suspect that violent behaviour may represent a rare event of statin therapy, which is more likely to occur in susceptible individuals. This putative association should be confirmed in large database studies. Of note, other serious psychiatric adverse reactions (hallucination, confusion, depression) were recorded in our database. Although rare, these events may be potentially life-threatening and need to be considered by physicians during the process of diagnosis.

Among the reported adverse events, only insomnia was associated with a significant ROR with a higher power value. Sleep disturbances and impairments of daytime performance have been attributed to statins, particularly to lovastatin. Schaefer[31] first reported a higher prevalence of sleep complaints in hypercholesterolaemic patients receiving lovastatin (17.6%), than in patients receiving pravastatin (0%). In controlled studies comparing the effects of lovastatin and pravastatin on sleep, Vgontzas et al.[32] found that prolonged administration of lovastatin, but not pravastatin, increased the wake time after sleep onset. As already discussed, it has been suggested that these differences may depend on the high lipophylicity of lovastatin and its ability to cross the blood-brain barrier. In keeping with this view, a decrease in sleep time was observed after administration of simvastatin, which is also has a high degree of lipophilicity, to hypercholesterolemic patients who had previously reported a normal sleep pattern.[25] Of note, conflicting evidence was obtained in another controlled study in which lovastatin and pravastatin did not exert significant effects on sleep parameters in hypercholesterolaemic patients.[33] The present study shows that statins as a whole class, particularly those with lipophilic properties, are associated with a higher reporting rate of insomnia in comparison with other drugs, and that lipophilic statins are associated with a non-significant higher ROR for this ADR in comparison with less lipophilic ones. These findings support the hypothesis of a possible risk of sleep disturbance associated with statins that might depend, at least in part, on their ability to cross the blood-brain barrier.

In summary, a relatively small number of statin-associated psychiatric ADRs were found in our database. In some cases, these reactions are serious and may be life-threatening. Their recognition and management deserve particular attention by caregivers. Insomnia was the only psychiatric event resulting in a frequency of reporting that was significantly higher for statins in comparison with the combination of all other drugs.

Conclusions

Several cases of statin-associated psychiatric ADRs were found in the GIF database, in line with the current awareness of possible CNS toxicity with these drugs. The hypothesis of a statin-associated psychiatric toxicity is justified by pharmacological and biochemical rationales, but the supporting clinical evidence remains mainly anecdotal in nature. Although a signal associating statins with insomnia was found, the overall incidence of reports on statin-related psychiatric adverse events was low and similar to that estimated for the pool of all other drugs. However, these findings may result from the exploratory nature of our analysis, using a database of spontaneous ADR reporting. Therefore the findings must be interpreted with caution because of the limitations of such studies. Accordingly, the present

findings require further investigation to evaluate the actual risk of statin-associated psychiatric ADRs.

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