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Chapter

Early Signal Detection: Data Mining of Mental Disorders with Statins

Maria-Isabel Jimenez-Serrania

Abstract

Statins are widely prescribed to treat dyslipidemias. It is well-known adverse reaction of these active ingredients related to rhabdomyolysis and myalgia, but there are other signals to be aware of, such as mental disorders. Pharmacovigilance tools help to trace known risks and detect early other unknown effects that appear over time. Data of all the reported suspected adverse drug reactions for statins from the international World Health Organization (WHO) repository Vigibase were analyzed with an adaptation of data mining Bayesian methodology to search for positive signals, threshold of false discovery rate (FDR) $< 0.05$, and listed candidates for priority clinical investigation. Among positive mental signals observed, some were currently stated as adverse reactions in technical factsheets as insomnia, depression, dementia, and nightmares, but others have not reached this condition as bipolar, psychotic, and emotional disorders or symptoms and suicide. Other diverse central positive signals that can be confounded with mental conditions obtained and not stated were senses impairment, such as blindness, deafness, balance disorder, and events related to suicide. Worrying positive signals proposed as candidates to further investigation are insomnia for pitavastatin, pravastatin, and simvastatin; dementia for atorvastatin and rosuvastatin; and suicide and psychotic disorders for atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.

Keywords: statin, adverse reaction, mental disorders, data mining, positive signals

1. Introduction

Statins or 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors are a worldwide used medication for dyslipidemias, both hypercholesterolemia, and hypertriglyceridemia [1].

These drugs are considered safe and cost-effective, but it is necessary to review the use and possible risk of adverse events. Some frequent adverse drug reactions (ADRs) related to statins affect muscle (myalgia, arthralgia, limb pain, and spasms), liver (elevation of transaminases or creatine kinase), and gastrointestinal system (constipation, flatulence, dyspepsia, nausea, and diarrhea) and are related to infections (nasopharyngitis) [2, 3].

ADRs related to musculoskeletal and connective tissue, such as myopathy, rhabdomyolysis, or myositis, are classified as rare [3]. The withdrawal of cerivastatin in
2001 was due to deaths attributed to drug-related rhabdomyolysis that led to kidney failure [4].

However, besides, there is a group of ADR related to mental status, cataloged as rare or very rare or frequency not known such as insomnia, sleep disorders, depression, cognitive impairment, memory impairment, and nightmares [3, 5]. Some of these events can be confusing and wrongly identified in older patients with mental deterioration [6].

This study aims to make available an early knowledge of signals of statins’ adverse reactions related to mental disorders to analyze in future clinical trials and provide a list of candidates for clinical trials.

2. Materials and methods

Nowadays, free access to national and international reporting ADR databases allows investigating new signals to be aware of possible risks. One of them is VigiBase®, the unique World Health Organization (WHO) global database for suspected ADRs maintained by the Uppsala Monitoring Centre (UMC) since 1968. This database disposes of a free-user interface VigiAccess™ that allows us to search for all data coming from over 110 countries, undersigning a statement of the responsibility for the appropriate use and interpretation of data [7].

For the present study, reported data of all the ADRs related to the chemical subgroup of the Anatomical Therapeutic Chemical (ATC) Classification System C10AA “HMG CoA reductase inhibitors” known as statins were searched in VigiAccess™ [8]. Data below the first heading adverse drug reactions (ADRs) for each active ingredient of interest—atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin—were extracted on October 2, 2019. Signals for cerivastatin—withdrawn in 2001—are included and analyzed as of contrast.

In this database, it is not possible to calculate the frequency of any ADR, but the data mining methodology, Bayesian confidence propagation neural network (BCPNN), can be used in these situations [9]. Nevertheless, this methodology is developed and used by the UMC as the WHO Collaborating Centre for International Drug Monitoring [10–12].

To detect signals of ADR, this method BCPNN was improved, by the UMC of the WHO with an extension to the multiple comparison settings. The calculated Bayesian estimator of false discovery rate (FDR) works like a p-value, offering a positive signal if FDR < 0.05 [13, 14].

An adaptation of this methodology can be plausible as same as other diverse methods can be trustworthy in global adverse drug reaction surveillance with a correct interpretation of the signals [15]. This one consists of contrasting all the ADRs of the ATC subgroups instead of all the pairs of ADR-drugs of the database. In this case, only the chemical subgroup C10AA “HMG CoA reductase inhibitors” [16] was considered in the analysis. This methodology approach has previously demonstrated robustness and consistency when all the ADR databases were applied to a specific group of drugs [17–19]. Details of the algorithm performed are reported (see Appendix 1).

All the positive signals among statins were obtained. Those related to mental disorders were extracted and grouped depending on the presence of the ADR in the summary of product characteristics (SPC) of each active ingredient implied and categorized according to high-level terms (HLTs) including preferred terms (PTs) of
the Medical Dictionary for Regulatory Activities (MedDRA) [20], the standard terminology used in VigiAccess™.

The first aggregation for statin positive signals obtained (FDR < 0.05 and Sp ≥ 0.99) was related to similar pathology following MedDRA, e.g., insomnia (that include general, middle, terminal, sleep disorder, and poor quality of sleep) and depression (that include general, major, depressed mood, and depressive symptoms) (see Appendices 2 and 3).

Finally, a ranking of positive signals for each statin is proposed as a list of priority ADR to further study.

The R® free software v3.4.1. R [21] and PhViD® Package v1.0.8 [22] were used to implement the methodology and to obtain positive signals. All the searches of evidence were made in the Medline database via Pubmed® [23].

3. Results

The total of positive signals with FDR < 0.05 and Sp ≥ 0.99 were 493, being 47 out of them related to a mental disorder (or confounding central symptoms): seven for atorvastatin (14.9%), three for fluvastatin (6.4%), three for lovastatin (6.4%), three for pitavastatin (6.4%), five for pravastatin (10.6%), eight for rosuvastatin (17.0%), and 29 for simvastatin (29.8%). All the results of algorithms related to a mental disorder and other confounding central disorders observed are available (see Appendices 2 and 3).

Subgroups of positive signals were second stratified and summarized considering the presence/absence of ADR in the summary of product characteristics. Mental disorders detected and reported in technical factsheets were insomnia, depression, dementia, and nightmares (Table 1), and not reported disorders were anxiety, bipolar disorder, and psychotic or emotional disorders/symptoms (Table 2). Finally, other diverse symptoms were identified to a greater or lesser extent with mental affection

<table>
<thead>
<tr>
<th>Statin</th>
<th>Insomnia and related</th>
<th>Depression and related</th>
<th>Dementia and related</th>
<th>Dreams disorders and related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerivastatin</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>10*, 11, 12, 13</td>
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<td></td>
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</tr>
<tr>
<td>Lovastatin</td>
<td>7*</td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
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<td>14*, 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>4*</td>
<td>8*</td>
<td>11, 12, 13*</td>
<td>16</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1*, 4*, 5</td>
<td>7*, 8*, 9*</td>
<td>14*, 15</td>
<td></td>
</tr>
</tbody>
</table>

1. insomnia and related (general); 2. middle insomnia; 3. terminal insomnia; 4. sleep disorder; 5. poor quality sleep; 6. depression (general); 7. major depression; 8. depressed mood; 9. depressive symptoms; 10. amnesia; 11. dementia (general); 12. dementia Alzheimer’s type; 13. memory impairment; 14. nightmares; 15. abnormal dreams; 16. daydreaming. Sensitivity ≥0.20.

*Stated in the summaries of product characteristics (SPCs).

Table 1. Positive signals (FDR < 0.05; specificity ≥0.99) for statins related to mental disorders reported as ADR in VigiAccess™.

3
such as impairment of senses (blindness, deafness, and vision blurred), and compromised life (suicide) (Table 2).

If we perform a list of positive signals (FDR < 0.05; specificity ≥ 0.99; and sensitivity ≥ 0.20 and < 0.20) not stated in the factsheets of each active ingredient, differences among drugs are detected (Table 3). These all are candidates to be deeply studied in clinical trials. In addition, in terms of the number of reports, the most relevant signals with the highest number of pair [active ingredient-ADR] reports were simvastatin-ageusia (85 reports) and rosuvastatin-unilateral deafness (21 reports). Less sensitive signals, but alarming, were the pairs simvastatin-ADR related to suicide (477 reports), pravastatin-affectation of senses (375 reports), atorvastatin-affectation of senses (693 reports), and lovastatin-complete suicide (50 reports).

There are three signals reported in SPCs with an elevated number of pairs of ADR-drug counted: atorvastatin-amnesia with 1360 reports and simvastatin-insomnia with 1210 (see Appendix 2) and for the withdrawn cerivastatin-anxiety 2767 (despite being withdrawn since 2001) (see Appendix 3).

The fact to include all the statins (also the withdrawn cerivastatin) and all the ADRs reported for statins acts as a contrast to the method used. Positive signals of ADR that lead to the withdrawal of cerivastatin (i.e., rhabdomyolysis and transaminases increased) and typical ADR related to statins (i.e., myalgia and myopathy) are also detected (see Appendix 4).

4. Discussion

This is the first study of mental adverse drug reactions (ADRs) related to statins using neural networks based on the principles of Bayes law. Owing to there being no evidence of similar studies, not even with the classical Bayesian methodology BCPNN, it is necessary to review the background to establish a starting point to further investigation.
### 4.1 Positive mental disorders mainly presented as ADRs in SPCs

#### 4.1.1 Insomnia

Some studies reported insomnia with a higher frequency for statins compared with all other drugs [24], but this risk of insomnia with statins seems to be not significant.
for other studies of neuropsychiatric adverse effects of statins [25]. At the same time, multimethodological approaches using different algorithms and databases strongly suggest that statin use is associated with an increased risk for sleep disturbances including insomnia [26].

The situation of insomnia can lead to a loss of adherence to the treatment, more worrying in the elderly because they are less capable of sleeping correctly and can lead to polymedicate with sleep medicines [27].

In the present study, the positive signal of middle insomnia obtained with atorvastatin appears as the most relevant and already stated in SPCs, followed by signals also informed for fluvastatin, pravastatin, rosuvastatin, and simvastatin. For pitavastatin, the newest statin, middle insomnia is not studied individually or reported in SPCs; the signal obtained is positive with specificity and sensitivity.

The only statin without a positive signal of insomnia was lovastatin. This result is following a former clinical 5-year follow-up study where insomnia had a very low presence [28], but there is no other evidence found for the last 10 years about that.

The same situation of no recent evidence remains for all the rest of the statins, except for rosuvastatin information derived from the randomized controlled trial JUPITER, where the authors recommended monitoring patients on intensive therapy and performing adverse events trials for lipid-lowering agents [27].

In addition, simvastatin showed an elevated number of pairs of ADR-statins with 1210 events reported in the present research (see Appendix 2). This ADR is stated as very rare in their SPCs.

It would be interesting to dispose of a follow-up study to update the effect of insomnia with statins, special, lovastatin, and pitavastatin. If these last ones offer less generation of insomnia, they can be candidates for people—in special, the elderly—with sleep disorders.

4.1.2 Depression

In the present analysis, there is a clear positive signal of simvastatin and major depression and less sensitivity but also positive for depressed mood and depressive symptoms. In SPCs, depression is reported as ADR with unknown frequency.

Initially, the relationship between depression and metabolic disturbance, such as dyslipidemia, seems not to be clear. It has been observed that the increased appetite—in the context of a depressive episode—was the only symptom that was associated with metabolic (and inflammatory) markers [29]. The authors of this study considered that it could be a key feature of an immunometabolic form of depression.

In this sense, it looks like inadequate nutrition leading to higher levels of cholesterol can be derived from some types of depression. On the other hand, using a genetic-based approach, it showed an increased risk of depression during statin [25].

Besides, some authors analyzed the association between statin treatment and antidepressant use, and they conclude that it is unspecific (equivalent association between statins and most other drugs) and that the association between statin use and depression diagnoses is mediated by residual confounding, bias, or by downstream effects of the statin prescription (seeing a physician more often) [30].

4.1.3 Memory impairment: dementia

Owing to the widespread use of statins, the severity of cognitive dysfunction, and its high prevalence in older people, some authors reflected that the patient
communications about possible cognitive impairment must be considered and evaluated appropriately, including after discontinuation of the statin [31].

In the present research, positive signals are observed about dementia, dementia Alzheimer’s type, and memory impairment for atorvastatin and rosuvastatin, as well as amnesia for atorvastatin.

Some authors considered that much of the evidence supporting statins in the prevention of dementia and Alzheimer’s disease are in persons exposed to statins at mid-life as opposed to late life [32]. They conclude that statins have an evident protective effect on cognition, related to the prevention of stroke and possible subsequent vascular dementia and preventing microvascular infarcts that lead to dementia without an acute stroke, and this idea is supported by others [32–34]. Other studies have demonstrated that the overall rate of cognitive decline was not different in statin users compared with never users [35]. Nevertheless, the American Academy of Neurology does not address statin use to prevent dementia [36].

Some studies are more skeptical, with good evidence that statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia [37]. Vascular dementia is the second commonest cause of this condition, and the authors consider a biologically plausible influence of the role in cholesterol associated with dementia. There is evidence of both the statin and nonstatin lipid-lowering drugs that were strongly associated with acute memory loss in the first 30 days following exposure in users compared with nonusers but not when compared with each other [38].

There is a conflict to determine if the balance of effects of lipids and lipid-lowering therapy falls on the branch of preventing or treating dementia or generating more risk [39].

The condition of amnesia with atorvastatin deserves a separate mention. In the present study, a positive signal only for atorvastatin was obtained (1360 cases notified). It was stated as low frequent in the factsheets, and there is no recent publication found in humans about that.

### 4.1.4 Dreams disorders: nightmares

A growing body of evidence indicates that statins may have potentially negative effects on nervous-system-associated diseases, including myopathies, peripheral neuropathy, intracerebral hemorrhage, cognitive impairment, depression, sleep disorders, nightmares, hallucinations, and headache [40, 41].

In a case report of atorvastatin, the authors hypothesized that the nightmares could be a direct effect of the statin on the central nervous system; they did not know if it was due to a pharmacokinetic (CYP3A4) or pharmacodynamic interaction. However, they recommend that if nightmares appear, it could be easy to avoid stopping statins [42].

Dreams disorders, not a severe condition, could lead to aversion and loss of adherence to the treatment. In the present study, pravastatin and simvastatin presented positive signals for nightmares and abnormal dreams, and fluvastatin only for nightmares. Rosuvastatin showed a positive signal with high sensitivity for daydreaming. Nightmares are reported in SPCs of all the statins with signals. On the contrary, daydreaming is not reported and could be especially compromising in older people with cognitive or mobility dysfunction.

A follow-up study of these symptoms can lead to prescribing statins less related to dream disorders ADR as atorvastatin, lovastatin, and pitavastatin.
4.2 Other positive signals related to mental disorders are mainly absent as ADRs in SPCs

4.2.1 Anxiety

It is striking that no one of these positive signals detected are reported in SPCs. As an example of contrast, cerivastatin showed an elevated number of reports [2, 43] of signals as anxiety or emotional disorder never stated in factsheets. Atorvastatin also showed an emotional distress signal.

A diagnosis of hyperlipidemia and the beginning of statin treatment could lead to anxiety about high cholesterol and its consequences. However, it is difficult to identify which anxiety is due to the onset of the treatment and associated with the fear of cardiovascular health, and which one is associated with a real ADR by statins.

In general, there is conflicting evidence of a relationship between statins and mood [44]. Some authors associate anxiety with an increased likelihood of discontinuation with statins [45]. In some groups of patients with head and neck cancer, preexisting hyperlipidemia was associated with an increased risk of new-onset anxiety/depression [46].

However, avoiding the diagnosis of the illness and chronic treatment, uncertainties about the pharmacological mechanisms, risks to health, side effects, costs, and skepticism are considered barriers to the uptake of statins [47].

The association between anxiety and nonadherence to preventive therapies remains unclear, and some authors have investigated whether the somatic symptoms of anxiety predict statin nonadherence [48].

4.2.2 Bipolar disorders

Bipolar disorder signals only appeared with rosuvastatin.

It has been observed that the continued use of drugs such as low-dose aspirin, statins, and angiotensin agents was associated with decreased rates of incident mania/bipolar disorder on both the outcome measures [49]. At least, as treatment, statins do not seem to exacerbate this cognitive dysfunction [50].

In patients with central nervous system metabolic disorders, it was hypothesized that statins may act as unmasking agents for latent neuromuscular disorders, as reported in cases of acute ataxia coincident with statin onset in individuals with bipolar disorder [51].

4.2.3 Psychiatric symptoms and psychotic disorder

It has an idea of the relation between the use of statins and preexisting psychotic disorders. The first meta-analyses published about that clarified that adjunctive therapy with statins could improve psychiatric symptoms, either negative symptoms or positive symptoms [52].

Data from the Norwegian spontaneous reporting system and from WHO’s, an international database covering the period of 1988–1995, include reports of adverse drug reactions relating to psychiatric disorders (15% of the reactions to statins in the Norwegian database). Reactions include aggression, nervousness, depression, anxiety, sleeping disorders, and impotence. The pharmacological mechanisms are not elucidated but may be an effect of falling serum cholesterol [53].
Another option is that statins show a strong association with inflammatory processes that may occur due to the disorder. This condition may cause increased inflammatory markers and concurrent psychiatric symptoms. Other factors such as gender, metabolic problems, or smoking can be associated with this increase in inflammatory markers [54].

This observation could be useful to elucidate the best statin for patients with different mental disorders. In the present study, psychiatric symptoms only appeared with simvastatin and psychotic disorder with simvastatin and lovastatin.

On the other hand, fluvastatin, pitavastatin, and pravastatin have no signals.

Some studies are in favor of statins used in combination with conventional psychotropic medications for various psychiatric disorders including depression, schizophrenia, and dementia [55].

4.2.4 Suicide

Atorvastatin, lovastatin, and simvastatin showed a signal of completed suicide (290 cases for atorvastatin and 283 for simvastatin). Simvastatin also presented signals for suicidal behavior, suicidal ideation (also rosuvastatin), and suicide attempt. It appears that statin, in particular, simvastatin, is a clear candidate for studying of suicidal conditions.

There are cases with simvastatin (various doses), atorvastatin (various doses), and lovastatin that reported mood/behavior change (violent ideation, irritability, depression, and suicide) that commenced following statin initiation and persisted or progressed with continued use. Problems resolved with drug discontinuation and recurred with rechallenge were attempted [56].

Aggressive reactions associated with statins are poorly documented in the literature, but 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 etiology of this psychiatric reaction [57].

4.3 Limitations of the study

The download of information on adverse drug reactions was carried out shortly before December 1, 2019, the date considered to be the start of the international pandemic by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Analyzing data before this date has the advantage of avoiding the potential and unknown interactions of the coronavirus or subsequent vaccines with pharmacological treatments.

It is known that the values of specificity and sensitivity are typically low with BCPNN methodology [23]. Nonetheless, it is acceptable with very high specificity and a low but conservative sensitivity as detected for typical positive signals for cerivastatin and other statins.

5. Conclusions

Mental disorders detected and proposed in the present study to further investigation are insomnia for pitavastatin, pravastatin, and simvastatin; dementia for
atorvastatin and rosuvastatin; and suicide and psychotic disorders for atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.

Moreover, signals of central disorders as an affection of senses for pitavastatin (hearing loss), pravastatin (visual impairment), atorvastatin (blindness), and simvastatin (ageusia) can act as confounding symptoms of mental disorders, and they would be interesting to analyze in clinical trials as early symptoms for statin inter-change.

Surrendering to the low positive signals detected, fluvastatin, stands out as a candidate to contrast with the others.

Acknowledgements

To the European University of Miguel de Cervantes (UEMC, Valladolid, Spain), for giving me time and permission to perform this study.

Conflict of interest

The author declares no conflict of interest.

A. Appendix 1. Details of the algorithm performed

In this analysis, the algorithm was performed with the following arguments: value of the relative risk (RR) proven to be higher than 1 (RR < 1); minimum number of cases per pair (drug-adverse reaction) to be potentially considered as a signal (N = 1); rule of decision for the generation of signals: false discovery rate (FDR); limit or threshold for the decision rule: FDR > 0.05; statistics used for ordering the drug-ADR pairs: posterior probability of the null hypothesis (post.H0); and calculation of the distribution of the statistic of interest: by approximation to the normal distribution [1a, 2a] and using empirical estimation through Monte Carlo simulations (NB. MC = 10,000) [3a]. The estimator of FDR < 0.05 and specificity (Sp) ≥0.99 are considered to interpret the results. Sensitivity (Se) values are typically low in the BCPNN approach [4a], Se ≥ 0.20 is considered as reference.

The estimator FDR assures that at least 95% of the signals detected are positive (only 5% of false positives). Moreover, if the estimator of false negative rate (FNR) is 50% or lower, it implicates that, at least, half of the signals rejected are effectively negative. In the results presented, all the FNRs were lower than 49%.

B. Appendix 2. Detailed results of positive signals (FDR < 0.05; Specificity ≥ 0.99) of mental disorders related with statins reported as adverse drug reaction (ADR) in Vigiaccess™ database and analyzed by a contrasted approach of Bayesian confidence propagation neural network (BCPNN) extended to the multiple comparison setting for active ingredients groups

Interpretation of items: drug code: active ingredient reported; event effect: ADR reported; count: number of couples ‘active ingredient-ADR’ reported; post.H0: posterior probability of null hypothesis; FDR: false discovery rate; FNR: false negative rate; Se: Sensitivity (* ≥ 0.20); Sp: Specificity.

### Insomnia; middle insomnia; terminal insomnia; sleep disorder; poor quality sleep.

<table>
<thead>
<tr>
<th>Drug code</th>
<th>Event effect</th>
<th>Count</th>
<th>post.H0</th>
<th>FDR</th>
<th>FNR</th>
<th>Se</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>Insomnia</td>
<td>206</td>
<td>0.000</td>
<td>0.000</td>
<td>0.482</td>
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<td>0.000</td>
<td>0.484</td>
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<td>0.464</td>
<td>0.094</td>
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### Depression; major depression; depressed mood; depressive symptoms.

<table>
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<th>Se</th>
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<td>Lovastatin</td>
<td>Major depression</td>
<td>7</td>
<td>0.039</td>
<td>0.008</td>
<td>0.450</td>
<td>0.144</td>
<td>0.999</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Major depression</td>
<td>18</td>
<td>0.114</td>
<td>0.030</td>
<td>0.432</td>
<td>*0.209</td>
<td>0.994</td>
</tr>
</tbody>
</table>

### Amnesia; dementia; dementia Alzheimer’s type; memory impairment.

<table>
<thead>
<tr>
<th>Drug code</th>
<th>Event effect</th>
<th>Count</th>
<th>post.H0</th>
<th>FDR</th>
<th>FNR</th>
<th>Se</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Amnesia</td>
<td>1360</td>
<td>0.000</td>
<td>0.000</td>
<td>0.486</td>
<td>0.010</td>
<td>1</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Dementia</td>
<td>143</td>
<td>0.003</td>
<td>0.000</td>
<td>0.467</td>
<td>0.082</td>
<td>1</td>
</tr>
</tbody>
</table>
Drug code | Event effect | Count | post.H0 | FDR | FNR | Se | Sp
---|---|---|---|---|---|---|---
Rosuvastatin | Dementia | 92 | 0.010 | 0.000 | 0.470 | 0.071 | 1
Atorvastatin | Dementia | 106 | 0.000 | 0.000 | 0.474 | 0.057 | 1
Rosuvastatin | Dementia | 53 | 0.030 | 0.006 | 0.453 | 0.134 | 0.999
Atorvastatin | Memory impairment | 913 | 0.000 | 0.000 | 0.480 | 0.034 | 1
Rosuvastatin | Memory impairment | 537 | 0.000 | 0.000 | 0.476 | 0.048 | 1

**Dreams disorders: nightmares; abnormal dreams, daydreaming.**

| Drug code | Event effect | Count | post.H0 | FDR | FNR | Se | Sp
---|---|---|---|---|---|---|---
Pravastatin | Abnormal dreams | 34 | 0.057 | 0.012 | 0.445 | 0.161 | 0.998
Simvastatin | Abnormal dreams | 111 | 0.035 | 0.007 | 0.451 | 0.140 | 0.999
Rosuvastatin | Daydreaming | 5 | 0.100 | 0.025 | 0.435 | 0.197 | 0.995
Fluvastatin | Nightmare | 40 | 0.015 | 0.002 | 0.458 | 0.114 | 1
Pravastatin | Nightmare | 105 | 0.000 | 0.000 | 0.476 | 0.047 | 1
Simvastatin | Nightmare | 387 | 0.000 | 0.000 | 0.484 | 0.017 | 1

**C. Appendix 3. Detailed results of positive signals (FDR < 0.05; Specificity ≥ 0.99) of other mental and central disorders not stated in SPCs related to statins reported as ADR in Vigiaccess™ database and analyzed by a contrasted approach of Bayesian confidence propagation neural network (BCPNN) extended to the multiple comparison setting for active ingredients groups**

Interpretation of items: drug code: active ingredient reported; event effect: ADR reported; count: number of couples ‘active ingredient-ADR’ reported; expected count: couples ‘active ingredient-ADR’ expected; post.H0: posterior probability of null hypothesis; n1/E: ratio between the count observed and the count expected of the corresponding couple; drug margin: number of reports of a drug; event margin: number of reports of an event; FDR: false discovery rate; FNR: false negative rate; Se: Sensitivity (* ≥ 0.20); Sp: Specificity.

**Loss of special senses not reported in SPCs: blindness, unilateral blindness, deafness, unilateral deafness, anosmia, ageusia, balance disorder.**

| Drug code | Event effect | Count | post.H0 | FDR | FNR | Se | Sp
---|---|---|---|---|---|---|---
Lovastatin | Ageusia | 44 | 0.000 | 0.000 | 0.481 | 0.028 | 1
Pravastatin | Ageusia | 29 | 0.043 | 0.008 | 0.449 | 0.148 | 0.999
Simvastatin | Ageusia | 85 | 0.124 | 0.034 | 0.430 | 0.217 | 0.993
Pravastatin | Anosmia | 11 | 0.044 | 0.009 | 0.449 | 0.148 | 0.999
Atorvastatin | Balance disorder | 468 | 0.034 | 0.007 | 0.451 | 0.139 | 0.999
Simvastatin | Balance disorder | 289 | 0.014 | 0.002 | 0.459 | 0.111 | 1
Atorvastatin | Blindness | 169 | 0.000 | 0.000 | 0.473 | 0.059 | 1
<table>
<thead>
<tr>
<th>Drug code</th>
<th>Event effect</th>
<th>Count</th>
<th>post.H0</th>
<th>FDR</th>
<th>FNR</th>
<th>Se</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Blindness</td>
<td>28</td>
<td>0.003</td>
<td>0.000</td>
<td>0.466</td>
<td>0.086</td>
<td>1</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Blindness unilateral</td>
<td>56</td>
<td>0.045</td>
<td>0.009</td>
<td>0.449</td>
<td>0.149</td>
<td>1</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Blindness unilateral</td>
<td>33</td>
<td>0.084</td>
<td>0.020</td>
<td>0.439</td>
<td>0.184</td>
<td>0.996</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Deafness</td>
<td>215</td>
<td>0.000</td>
<td>0.000</td>
<td>0.480</td>
<td>0.034</td>
<td>1</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Deafness</td>
<td>32</td>
<td>0.002</td>
<td>0.000</td>
<td>0.468</td>
<td>0.079</td>
<td>1</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Deafness unilateral</td>
<td>37</td>
<td>0.041</td>
<td>0.008</td>
<td>0.449</td>
<td>0.146</td>
<td>0.999</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Deafness unilateral</td>
<td>21</td>
<td>0.109</td>
<td>0.028</td>
<td>0.433</td>
<td>*0.203</td>
<td>0.994</td>
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<tr>
<td>Pravastatin</td>
<td>Diplopia</td>
<td>84</td>
<td>0.000</td>
<td>0.000</td>
<td>0.485</td>
<td>0.015</td>
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<tr>
<td>Lovastatin</td>
<td>Diplopia</td>
<td>39</td>
<td>0.002</td>
<td>0.000</td>
<td>0.468</td>
<td>0.078</td>
<td>1</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Visual impairment</td>
<td>367</td>
<td>0.000</td>
<td>0.000</td>
<td>0.488</td>
<td>0.003</td>
<td>1</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Visual impairment</td>
<td>139</td>
<td>0.021</td>
<td>0.004</td>
<td>0.456</td>
<td>0.123</td>
<td>1</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Visual acuity reduced</td>
<td>91</td>
<td>0.000</td>
<td>0.000</td>
<td>0.479</td>
<td>0.038</td>
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<tr>
<td>Pravastatin</td>
<td>Vision blurred</td>
<td>146</td>
<td>0.000</td>
<td>0.000</td>
<td>0.479</td>
<td>0.038</td>
<td>1</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Vision blurred</td>
<td>617</td>
<td>0.124</td>
<td>0.034</td>
<td>0.429</td>
<td>*0.218</td>
<td>0.992</td>
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<tr>
<td>Pravastatin</td>
<td>Sudden hearing loss</td>
<td>5</td>
<td>0.029</td>
<td>0.005</td>
<td>0.453</td>
<td>0.133</td>
<td>0.999</td>
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<td>Pravastatin</td>
<td>Sudden hearing loss</td>
<td>2</td>
<td>0.148</td>
<td>0.043</td>
<td>0.424</td>
<td>*0.237</td>
<td>0.990</td>
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<tr>
<td>Atorvastatin</td>
<td>Tinnitus</td>
<td>511</td>
<td>0.000</td>
<td>0.000</td>
<td>0.477</td>
<td>0.0435</td>
<td>1</td>
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<td>Pravastatin</td>
<td>Tinnitus</td>
<td>81</td>
<td>0.034</td>
<td>0.006</td>
<td>0.452</td>
<td>0.138</td>
<td>0.999</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Dysgeusia</td>
<td>110</td>
<td>0.000</td>
<td>0.000</td>
<td>0.482</td>
<td>0.026</td>
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<tr>
<td>Lovastatin</td>
<td>Dysgeusia</td>
<td>67</td>
<td>0.006</td>
<td>0.001</td>
<td>0.464</td>
<td>0.093</td>
<td>1</td>
</tr>
</tbody>
</table>

**Other mental health problems not stated in SPCs:** anxiety, bipolar disorder, psychiatric symptom, psychotic disorder, emotional disorder, emotional distress.

<table>
<thead>
<tr>
<th>Drug code</th>
<th>Event effect</th>
<th>Count</th>
<th>post.H0</th>
<th>FDR</th>
<th>FNR</th>
<th>Se</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerivastatin</td>
<td>Anxiety</td>
<td>2767</td>
<td>0</td>
<td>0.000</td>
<td>0.489</td>
<td>0.010</td>
<td>1</td>
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<tr>
<td>Rosuvastatin</td>
<td>Bipolar disorder</td>
<td>33</td>
<td>0.000</td>
<td>0.000</td>
<td>0.472</td>
<td>0.066</td>
<td>1</td>
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<tr>
<td>Rosuvastatin</td>
<td>Bipolar I disorder</td>
<td>5</td>
<td>0.066</td>
<td>0.014</td>
<td>0.444</td>
<td>0.169</td>
<td>0.998</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>Emotional disorder</td>
<td>53</td>
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<td>0.000</td>
<td>0.485</td>
<td>0.016</td>
<td>1</td>
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<tr>
<td>Atorvastatin</td>
<td>Emotional distress</td>
<td>337</td>
<td>0.007</td>
<td>0.001</td>
<td>0.464</td>
<td>0.096</td>
<td>1</td>
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<tr>
<td>Cerivastatin</td>
<td>Emotional distress</td>
<td>391</td>
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<td>0.000</td>
<td>0.488</td>
<td>0.002</td>
<td>1</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Psychiatric symptom</td>
<td>32</td>
<td>0.000</td>
<td>0.000</td>
<td>0.478</td>
<td>0.042</td>
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<tr>
<td>Lovastatin</td>
<td>Psychotic disorder</td>
<td>12</td>
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<td>0.466</td>
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</tr>
<tr>
<td>Simvastatin</td>
<td>Psychotic disorder</td>
<td>34</td>
<td>0.011</td>
<td>0.002</td>
<td>0.461</td>
<td>0.106</td>
<td>1</td>
</tr>
</tbody>
</table>

**Suicide not stated in SPCs:** complete suicide, suicide attempt, suicidal ideation, suicidal behavior.

<table>
<thead>
<tr>
<th>Drug code</th>
<th>Event effect</th>
<th>Count</th>
<th>post.H0</th>
<th>FDR</th>
<th>FNR</th>
<th>Se</th>
<th>Sp</th>
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</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Completed suicide</td>
<td>290</td>
<td>0.025</td>
<td>0.004</td>
<td>0.455</td>
<td>0.128</td>
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<tr>
<td>Lovastatin</td>
<td>Completed suicide</td>
<td>50</td>
<td>0.004</td>
<td>0.001</td>
<td>0.465</td>
<td>0.090</td>
<td>1</td>
</tr>
</tbody>
</table>
Drug code | Event effect | Count | post.H0 | FDR   | FNR   | Se   | Sp
---|---|---|---|---|---|---|---
Simvastatin | Completed suicide | 283 | 0.000 | 0.000 | 0.485 | 0.014 | 1
Simvastatin | Suicidal behavior | 6 | 0.093 | 0.022 | 0.437 | 0.191 | 0.996
Rosuvastatin | Suicidal ideation | 94 | 0.030 | 0.006 | 0.453 | 0.134 | 0.999
Simvastatin | Suicidal ideation | 91 | 0.063 | 0.014 | 0.444 | 0.166 | 0.998
Simvastatin | Suicide attempt | 97 | 0.000 | 0.000 | 0.483 | 0.022 | 1

D. Appendix 4. Detailed results of positive signals (FDR < 0.05; Specificity ≥ 0.99) of disorders referred in main manuscript related to statins reported as ADR in Vigiaccess™ database and analyzed by a contrasted approach of Bayesian confidence propagation neural network (BCPNN) extended to the multiple comparison setting for active ingredients groups

Interpretation of items: drug code: active ingredient reported; event effect: ADR reported; count: number of couples ‘active ingredient-ADR’ reported; expected count: couples ‘active ingredient-ADR’ expected; post.H0: posterior probability of null hypothesis; n11/E: ratio between the count observed and the count expected of the corresponding couple; drug margin: number of reports of a drug; event margin: number of reports of an event; FDR: false discovery rate; FNR: false negative rate; Se: Sensitivity(* ≥ 0.20); Sp: Specificity.

**Rhabdomyolysis.**

<table>
<thead>
<tr>
<th>Drug code</th>
<th>Event effect</th>
<th>Count</th>
<th>post.H0</th>
<th>FDR</th>
<th>FNR</th>
<th>Se</th>
<th>Sp</th>
</tr>
</thead>
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<td>Cerivastatin</td>
<td>Rhabdomyolysis</td>
<td>5219</td>
<td>0</td>
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<td>0.488</td>
<td>0.001</td>
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<td>4873</td>
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<td>0.487</td>
<td>0.004</td>
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</table>

**Transaminases increased.**

<table>
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<th>Event effect</th>
<th>Count</th>
<th>post.H0</th>
<th>FDR</th>
<th>FNR</th>
<th>Se</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>Transaminases increased</td>
<td>128</td>
<td>0.000</td>
<td>0.000</td>
<td>0.487</td>
<td>0.010</td>
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<td>Atorvastatin</td>
<td>Transaminases increased</td>
<td>787</td>
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<td>0.048</td>
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<td>Simvastatin</td>
<td>Transaminases increased</td>
<td>467</td>
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<td>0.000</td>
<td>0.474</td>
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**Myalgia.**

<table>
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<th>Count</th>
<th>post.H0</th>
<th>FDR</th>
<th>FNR</th>
<th>Se</th>
<th>Sp</th>
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<tr>
<td>Simvastatin</td>
<td>Myalgia</td>
<td>11,860</td>
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<td>0.487</td>
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<td>Myalgia</td>
<td>3209</td>
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**Myopathy.**

<table>
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<th>FDR</th>
<th>FNR</th>
<th>Se</th>
<th>Sp</th>
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<td>499</td>
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<td>0.487</td>
<td>0.006</td>
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<tr>
<td>Drug code</td>
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<td>Count</td>
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<td>FDR</td>
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<td>Se</td>
<td>Sp</td>
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<tr>
<td>-----------</td>
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<td>------</td>
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**Author details**

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