Do lipid-lowering drugs cause erectile dysfunction? A systematic review

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Background. Erectile dysfunction (ED) is common although under-reported by patients. Along with the better known causes of ED, drug-induced impotence needs to be considered as a cause of this symptom. Lipid-lowering drugs have been prescribed increasingly. Their relationship to ED is controversial.

Objectives. Our aim was to clarify the relationship between lipid-lowering therapy and ED. A secondary aim was to assess the value of the systematic review procedure in the area of adverse drug reactions.

Methods. A systematic review was carried out using computerized biomedical databases and Internet sources. Terms denoting ED were linked with terms referring to lipid-lowering drugs. Information was also sought from regulatory agencies.

Results. A significant literature was identified, much from obscure sources, which included case reports, review articles, and information from clinical trials and from regulatory agencies. Information from all of these sources identified fibrates as a source of ED. A substantial number of cases of ED associated with statin usage have been reported to regulatory agencies. Case reports and clinical trial evidence supported the suggestion that statins can also cause ED. Some information on possible mechanisms was obtained, but the mechanism remains uncertain.

Conclusions. The systematic review procedure was applied successfully to collect evidence suggesting that both statins and fibrates may cause ED. More numerous reports to regulatory agencies complemented more detailed information from case reports to provide a new perspective on a common area of prescribing.

Keywords. Adverse drug reactions, erectile dysfunction, fibrates, statins.

Introduction

Erectile dysfunction (erectile impotence, ED) is under-reported by patients. It may have a neuropathic, vascular, psychogenic or endocrine aetiology. Before initiating treatment, reversible causes needed to be considered, including drug-induced ED. One study surveyed 1180 men attending medical out-patients and found that 34% reported ED.1 Of those investigated, 25% were thought to be drug induced. Many of the drugs listed in textbooks as causing this adverse effect (e.g. reserpine, methyl-dopa, guanethidine) are little used now, but modern cardiovascular drugs are also candidates.

Thiazides and β-blockers are well known causes, but the situation with lipid-lowering drugs is less clear. Statins in particular have become widely used but are not generally accepted as a cause of ED. As part of a programme looking at the usefulness of the systematic review procedure in the area of adverse drug reactions, we undertook a literature search linking lipid-lowering therapy with ED. This technique has been little used in the area of adverse drug reactions.

Methods

The online literature search using Datastar (Dialog Corporation) was performed during March 1999. The term ‘impotence’ was used initially in the CROS™ database to detect the most relevant biomedical databases. As a result, the complete databases of Medline, Pharmline, Embase, Toxline, Pharmline, Iowa, International Pharmaceutical Abstracts and Biosis were examined. The two main themes of lipid-lowering drugs and impotence...
were linked together by entering the drug names (as used in the UK) and a mixture of MESH™ and Emtree™ thesauri terms together with free text. The same strategy was run in each of the above databases. Results from each were combined and duplicate entries removed. A total of 107 references were identified in this way, the majority (>70%) coming from Embase. Further details of the strategy are available from the authors. All available information (i.e. title, journal and abstract if available) was downloaded for each reference. Using these data, it was decided whether or not to obtain the full article from the local library. If there was the slightest suggestion of reference to a drug-induced reaction, the full reference was obtained. In addition, an Internet search was performed and regulatory agencies contacted for further information. All articles received were scanned for relevance. Other reports were identified using the references given by these authors.

Results

The articles obtained could be divided into four categories:

Case reports
Cases of ED were first reported after clofibrate.2,3 Those described by Schneider showed recovery after drug withdrawal and recurrence on rechallenge.2 Five reports identified seven cases of ED following gemfibrozil.4–8 Rechallenge confirmed the effect in two.5,6 Therapy with bezafibrate was without adverse effect in three of these patients, but clofibrate had a similar effect in one.4,5,8

ED in association with statins was first reported by Halkin et al. where both lovastatin and pravastatin separately caused ED in a 57-year-old man.9 Jackson reported five cases of ED with simvastatin at doses of 10 and 20 mg.10 Sexual function was restored within 1 week of stopping the drug. Two patients were rechallenged and impotence recurred. Alternative lipid-lowering therapies (fluvastatin or fenofibrate) did not cause this effect in these patients.

Review articles of lipid-lowering drugs and drug-induced impotence
Several reviews of the management of ED listed clofibrate as a cause11–14 and another listed gemfibrozil.15 The adverse drug reaction bulletin listed clofibrate and bezafibrate.16 In a substantial review of bezafibrate, impaired libido was noted to have been seen in a number of studies, but was rarely significant enough to require cessation of therapy.17 A review of clinical trial experience with fenofibrate reported that erectile impotence had been identified in ~1.3% of clinical trial patients with use of this drug.18 No reviews listed statins as a cause of ED. No systematic reviews have been reported previously.

Data from clinical trials
In the 4S study, a prospective randomized trial, 37 patients of 1814 on simvastatin developed ED, as did 28 of 1803 on placebo, a difference which was not significant. Thus the suggestion that statins cause ED has been challenged.19 ED was not reported in other major RCTs: the Helsinki Heart study (gemfibrozil), CARE or LIPID (both pravastatin).20–22

In a case–control study, Bruckert et al. investigated the prevalence of ED in 339 patients attending a lipid clinic compared with matched controls. Treatments with both fibrates [odds ratio (OR) 1.46] and statins (OR 1.51) were independent predictors of ED.23

Sexual dysfunction is prevalent in male patients with cardiovascular disease. Measurement of nocturnal penile tumescence (NPT) has been used to investigate drug effects. β-blockers and diuretics have been associated with decreased NPT in some studies whereas pravastatin and lovastatin appeared to have a beneficial effect. The authors of these studies admit methodological difficulties.24

Information from regulatory agencies
The Australian Adverse Drug Reaction Advisory Committee (ADRAc) reports 11 cases of ED due to clofibrate, six due to gemfibrozil and 42 cases of ED in association with simvastatin.25 The men affected by simvastatin ranged in age from 43 to 72 years (median 57) and the onset occurred from 48 hours to 27 months (median 6 weeks) after the drug was started. Simvastatin was the only drug implicated in 35 of the reports and, in four rechallenged, the symptom recurred. Of the 29 reports in which recovery was mentioned, 14 had recovered after discontinuing the drug whereas in the other 15 there had been no recovery at the time the report was submitted. ADRAc also lists 11 reports of gynaecomastia in association with simvastatin.26

In addition to the above letters and papers, we requested details of cases of ED on lipid-lowering therapy reported to the UK Committee on Safety of Medicines (Yellow Card Scheme). This identified a further 170 cases. Cases reported as ejaculatory disorder have been included, but abnormalities of seminal fluid or sperm production have not. Loss of libido or gynaecomastia was reported in a few cases. Two patients experienced ED with two hypolipaemic drugs (separately). Data from these reports to the CSM are given in Table 1.

Discussion

Although the numbers of cases of ED associated with lipid-lowering therapy reported to regulatory agencies is substantial, the information provided is sparse. Other factors that can cause ED are likely to be present in some patients, for example psychological influences in the post-myocardial infarction situation. Recovery after drug withdrawal is the best available confirmation of drug-induced
adverse effect from the data that are available. This was documented in many cases, including a majority of the cases of ED due to both fibrates and statins reported to the CSM. Recurrence on rechallenge was documented in a few (although blinded rechallenge was not used). Applying criteria suggested by Sackett and colleagues, the relationship between this adverse drug effect and both fibrates and statins would be classed as probably causal.

ED has not been reported in the major randomized double blind trials of lipid-lowering therapy, and on this basis the causative link has been disputed. However, large trials of both fibrates and statins failed to find this adverse effect despite the fact that evidence from other sources for ED, following fibrate therapy at least, is strong. Although RCTs are generally a good source of information on adverse drug effects, ED is well known to be under-reported by patients. It was not asked about specifically in these trials, and without specific inquiry we feel it is likely that no reliable picture will emerge in the case of this particular adverse effect. On the basis of the large number of reports to the CSM and the other evidence cited above, we believe that all of the commonly used statins and fibrates may cause ED.

Effect. It is far from clear that this effect accounts for reported cases of ED in patients on a variety of hypolipidaemic drugs. Gonadal hormone measurements from men with ED on lipid-lowering therapy do not seem to have been done except in one patient on simvastatin reported to the CSM where levels of testosterone and sex hormone-binding globulin were low. Statins as a class are known to undergo extensive first-pass extraction in the liver where their effect is to inhibit cholesterol synthesis. The major route of excretion is in the bile. With simvastatin, only 14% of drug/metabolites circulating in plasma is active in inhibiting cholesterol synthesis. With atorvastatin, the systemic availability of HMG-CoA reductase inhibitory activity is ~30%. Thus the potential to inhibit steroid hormone synthesis elsewhere is limited, although it does increase with increasing statin dose.

Although Halkin et al. suggested that ED is a class effect of statins, other reports suggest that switching to alternative lipid-lowering drugs of the same or a different class can resolve the problem (CSM data and reference 10). There are a number of mechanisms likely to cause ED in treated hypercholesterolaemic patients, including the direct effects of cardiac disease, the psychological sequelae of a cardiac diagnosis, peripheral vascular disease affecting the pudendal vessels, direct effects on the brain (lipid-soluble drugs in particular), multiple drugs and drug interactions, and effects on hormone synthesis. We feel there is sufficient evidence from the above case reports to recommend trying a different lipid-lowering drug, even of the same class, in such cases of ED.

### Table 1

Reports to the Committee on Safety of Medicines (Yellow Card Scheme) of cases of erectile dysfunction thought to be caused by lipid-lowering drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of cases reported</th>
<th>Age (years) median (range)</th>
<th>Outcome</th>
<th>No. of not recovered patients using another drug known to cause ED or with other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil</td>
<td>16</td>
<td>56 (38–69)</td>
<td>8</td>
<td>2: CABG surgery, nifedipine, spirolactone</td>
</tr>
<tr>
<td>Bezafibrate</td>
<td>39</td>
<td>56 (35–71)</td>
<td>24</td>
<td>3: nifedipine, atenolol, LVF, diabetes</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>7</td>
<td>56 (37–65)</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofibrate</td>
<td>18</td>
<td>51.5 (18–64)</td>
<td>9</td>
<td>3: nicardipine, atenolol, cimetidine</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>49</td>
<td>56 (25–76)</td>
<td>27</td>
<td>4: lisinopril, atenolol, diabetes</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10</td>
<td>59 (52–67)</td>
<td>6</td>
<td>1: bendrofluazide, gemfibrozil, methyl-dopa</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>3</td>
<td>58 (44–66)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>26</td>
<td>51 (41–69)</td>
<td>16</td>
<td>6: atenolol, lofepramine, ranitidine, azathioprine, bezafibrate</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>1</td>
<td>55</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>2</td>
<td>43</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Colestipol</td>
<td>1</td>
<td>38</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

The table describes total number of reports for each drug, whether erectile dysfunction had resolved at the time of reporting and, in those where it had not, the number in whom other possible explanations are given.
The systematic review procedure identified relevant articles from a variety of sources. Individual case reports provided the most detail whereas regulatory agencies produced the largest numbers. Reviews were a measure of what is accepted wisdom. It has not been accepted previously that statins might cause ED. The information compiled in this review challenges that assumption. The frequency of reports of ED with simvastatin may be due to its market domination rather than an increased risk with this particular drug. The frequency with which lipid-lowering drugs adversely affect sexual function is not clear and is an area for further study. The use of statins in particular in primary care has increased substantially in recent years such that cases of ED may be seen more often. Given the strong evidence we have of the benefit from lipid-lowering therapy, this report should not inhibit the use of these drugs in coronary prevention. Switching drugs may be beneficial. Such patients should be advised of the risk from discontinuing lipid-lowering therapy altogether.

Acknowledgements

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References