Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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Important information is provided this month regarding **atomoxetine** for the treatment of attention-deficit/hyperactivity disorder. A review of clinical trial data has shown that atomoxetine can cause clinically important increases in blood pressure or heart rate, or both, in a small proportion of patients. This medicine should not be used in patients with severe cardiovascular or cerebrovascular disorders. Our advice in this issue covers the need for thorough pretreatment screening and regular ongoing monitoring of cardiovascular and cerebrovascular status (see article A1).

Statins are important and widely prescribed drugs for lipid control and cardiovascular prophylaxis, with usage continuing to increase. In 2010, a clinical trial meta-analysis reported that statin therapy was associated with a slightly increased risk of new onset diabetes. Statin use may produce a level of hyperglycaemia in some patients where formal diabetes care is appropriate. The risk appears to be mainly in patients already at increased risk of developing diabetes. However, the overall benefits of statins strongly outweigh any risks, including in those at risk of developing diabetes or those with pre-existing diabetes (see article A2).

With best wishes for the year ahead.

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Drug safety advice

A1 Atomoxetine (Strattera▼): increases in blood pressure and heart rate—new contraindications, warnings, and advice for monitoring

Atomoxetine causes clinically important increases in blood pressure or heart rate, or both, in a small proportion of patients. Atomoxetine should not be used in patients with severe cardiovascular or cerebrovascular disorders. Thorough pretreatment screening and regular monitoring of cardiovascular status is recommended. Specialist cardiac evaluation and advice should be sought if pretreatment findings suggest cardiac disease or history, or if symptoms suggesting cardiac disease are found during treatment

Atomoxetine (Strattera▼) is a selective noradrenaline reuptake inhibitor for treatment of attention-deficit/hyperactivity disorder (ADHD) diagnosed according to DSM-IV criteria or ICD-10 guidelines, as part of a comprehensive treatment regimen. Treatment must be initiated by a specialist in the treatment of ADHD.

New data for risk of blood pressure and heart rate increase

A recent review of clinical trial data in children and adults with ADHD showed mean increases in blood pressure and heart rate with atomoxetine to be as previously estimated (blood pressure: <5 mm Hg; pulse: <10 beats per minute).

However, approximately 6–12% of children and adults experienced clinically important changes in blood pressure (≥15–20 mm Hg) or heart rate (≥20 beats per minute), or both. Of these, 15–32% had sustained or progressive increases. Although there is no strong evidence from other data sources for an increased risk of adverse clinical cardiovascular or cerebrovascular outcomes, these increases in heart rate or blood pressure could have serious clinical implications for a small proportion of patients who take atomoxetine—especially when increases are sustained or progressive.

The contraindications, pretreatment screening, and ongoing cardiovascular risk monitoring recommendations for atomoxetine are now being strengthened so any potential risks can be minimised or avoided.

Key updated safety advice for healthcare professionals:

Contraindications—atomoxetine should not be used in patients with:

- Severe cardiovascular or cerebrovascular disorders in which clinical deterioration would be expected with increases in blood pressure or heart rate that could be clinically important (eg, 15–20 mm Hg in blood pressure or 20 beats per minute in heart rate). Examples of these severe cardiovascular or cerebrovascular disorders are included in the Summary of Product Characteristics, letter for healthcare professionals, physician's guide, and checklists

Pretreatment screening:

- Patients being considered for atomoxetine treatment need a careful history and physical examination to assess any presence of cardiac disease. They should be referred for specialist cardiac evaluation if initial findings suggest such history or presence of cardiac disease
- Before prescribing, the patient's cardiovascular status, including blood pressure and heart rate, should be measured and recorded appropriately
- Consider the balance of benefits and risks carefully when treating patients whose underlying medical conditions could be worsened by increased blood pressure and heart rate, such as those with hypertension, tachycardia, or cardiovascular or cerebrovascular disease not otherwise contraindicated

See http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON140590

Further information:

NICE guidance on attention-deficit/hyperactivity disorder: http://www.nice.org.uk/guidance/index.jsp?action=byId&o=12061

Guidelines from the European Network for Hyperkinetic Disorders (EUNETHYDIS): http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3012210/

BNF section 4.4 CNS stimulants and drugs used for attention-

deficit/hyperactivity disorder: http://bnf.org/bnf/bnf/62/128406.htm?q=strattera&t=search&ss=text&p=1

Ongoing monitoring:

- Cardiovascular status should be regularly monitored during treatment, with blood pressure and pulse recorded appropriately after every dose adjustment and at least every 6 months, to detect potentially clinically important increases
- Patients who develop symptoms that suggest heart disease during atomoxetine treatment should undergo a prompt specialist cardiac evaluation
- Patients with additional risk factors for cerebrovascular conditions (eg, history of certain cardiovascular diseases or concomitant use of medicines that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with atomoxetine

Yearly treatment review:

- Patients who take atomoxetine for extended periods (ie, >1 year) should have their treatment reviewed at least once a year by a specialist to determine whether continuation is needed

Additional tools for management of cardiovascular risks

See http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON140590

The licence holder for Strattera has developed a physician's guide to prescribing, and additional tools that should be used for cardiovascular screening and monitoring of patients.

Suspected adverse reactions to atomoxetine should be reported to us on a Yellow Card, available at www.mhra.gov.uk/yellowcard

Article citation: Drug Safety Update Jan 2012 vol 5, issue 6: A1.

A2 Statins: risk of hyperglycaemia and diabetes

Statin use may be associated with a level of hyperglycaemia in some patients where formal diabetes care is appropriate. The risk appears to be mainly in patients already at increased risk of developing diabetes. However, the overall benefits of statins strongly outweigh any risks, including in those at risk of developing diabetes or those with pre-existing diabetes

Statins are one of the most widely prescribed drug classes in Europe for lipid control and cardiovascular prophylaxis, and prescribing is continuing to grow. Between 2002 and 2008 in the UK, statin prevalence has doubled for those older than 40 year and quadrupled for those older than 80 years.

In 2010, a clinical trial meta-analysis reported that statin therapy overall was associated with a slightly increased risk of new onset diabetes (NOD).[1] Although a small risk (odds ratio 1.09 [95% CI 1.02–1.17]), given the extent of prescribing even a relatively small increase in the risk of NOD could potentially result in a significant number of additional cases of diabetes per year. Treatment of 255 (95% CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes.[1] However, the evidence suggests that risk depends markedly on individual risk factors.

1 Sattar N, et al. Lancet 2010; 375: 735–42.

Comparison of studies across the statin class is limited by numerous factors including differences in patient populations, duration of study, and dose of statin used. Furthermore, the endpoint used to diagnose diabetes varied in terms of frequency and time of analysis, and whether fasting blood glucose or, more rarely, HbA1c levels were measured. Importantly, a recent study[2] of the association between atorvastatin and NOD suggests that stratification of patients by risk factors may yield different conclusions to those drawn when considering the patient population as a whole.

2 Waters DD, et al. J Am Coll Cardiol 2011; 57: 1535–45.

There is sufficient evidence to support an association between statin use and NOD. However, the risk appears to be mainly in patients already at increased risk of developing diabetes. Raised fasting blood glucose at baseline is a key factor in determining this increased risk and may be sufficient to identify those at risk. Other risk factors include:

- history of hypertension
- raised triglycerides
- raised body mass index at baseline

There are limited data to support a further increased risk of diabetes with intensive high-dose atorvastatin or simvastatin therapy.[3] Given the important effect of patient characteristics on the risk of diabetes and the variability of the available studies, there are currently insufficient data to exclude any statin from the possibility of exacerbating the risk of NOD in a susceptible individual.

3 Preiss D, et al. JAMA 2011; 305: 2556–64.

Despite the increased risk of NOD in susceptible individuals, studies clearly show a benefit of statins in reducing major cardiovascular events.[3–5] The overall benefits of statins strongly outweigh any risks, including in those at risk of diabetes and those with diabetes at baseline. However, steps should be taken to ascertain patients who are at risk, to identify the onset of NOD, and to manage the condition appropriately. Patients at risk should be monitored both clinically and biochemically according to national guidelines.

4 The Cholesterol Treatment Trialists' Collaborators. Lancet 2005; 366: 1267–78.
5 The Cholesterol Treatment Trialists' Collaborators. Lancet 2008; 371: 117–25.

Advice for healthcare professionals:

- There is sufficient evidence to support an association between statin use and NOD
- The risk appears to be mainly in patients already at increased risk of developing diabetes
- Raised fasting blood glucose at baseline is a key risk factor. Other risk factors include: a history of hypertension; raised triglycerides; and raised body mass index at baseline
- Patients at risk should be monitored both clinically and biochemically according to national guidelines
- The level of risk of NOD may vary between statins. However, there is insufficient evidence to confirm or exclude an increased risk for any member of the statin class
- The reduced vascular risk from statin therapy outweighs the risk of diabetes, which is therefore not a reason for stopping statin treatment

Further information:

BNF section 2.12 Lipid-regulating drugs:
http://bnf.org/bnf/bnf/current/33422.htm?q=statins&t=search&ss=text&p=2#_hit

Article citation: Drug Safety Update Jan 2012 vol 5, issue 6: A2.

Articles continue…

Stop press

S1 Chlorhexidine: reminder of potential for hypersensitivity

Chlorhexidine is an antibacterial present in a wide range of topical and oromucosal antiseptic products, including over-the-counter mouthwashes. It can also be used in some indwelling catheters to prevent contamination.

Healthcare professionals are reminded that chlorhexidine is known to induce hypersensitivity, including generalised allergic reactions and anaphylactic shock. The prevalence of chlorhexidine hypersensitivity is unknown, but available literature suggests this is likely to be very rare. Products or medical devices containing chlorhexidine should not be administered to anyone with a possible history of an allergic reaction to chlorhexidine.

Article citation: Drug Safety Update Jan 2012 vol 5, issue 6: S1.

Other information from the MHRA

O1 Public consultation on new pharmacovigilance legislation: how to comment

We have launched a public consultation to seek views on the transposition into UK law of the EU Directive on pharmacovigilance, which makes substantial changes to existing pharmacovigilance requirements and comes in to effect in July 2012.

A key aim of the new legislation includes strengthening medicines safety transparency and communication to increase understanding and trust of healthcare professionals and patients in the safety of medicines, and improving penetration of key warnings.

Comments are invited by Feb 28, 2012.

Further information is available here:
http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON137667

Article citation: Drug Safety Update Jan 2012 vol 5, issue 6: O1.