



Prescribing Points

A NEWSLETTER FOR ALL HEALTH CARE PROFESSIONALS IN OXFORDSHIRE, WRITTEN BY THE MEDICINES MANAGEMENT TEAM, OXFORDSHIRE PCT, JUBILEE HOUSE, OXFORD BUSINESS PARK SOUTH, OXFORD, OX4 2LH.

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Sibutramine cardiovascular concerns

The **European Medicines Agency** (EMA) has announced that they will be conducting a safety review for sibutramine (*Reductil*[®]) after cardiovascular safety concerns were raised.

The Sibutramine Cardiovascular OUTcomes (SCOUT) trial was designed to determine whether weight management in cardiovascular high-risk overweight and obese patients can impact upon cardiovascular endpoints. The study involved approx 9000 patients in 16 countries, who were treated with a novel lifestyle intervention programme and randomized in a double-blind fashion to receive either sibutramine or placebo.

The EMA are reviewing findings from this trial which could indicate an **increased risk of serious cardiovascular events**, such as stroke or heart attack. In the meantime clinicians and patients are reminded to use sibutramine containing medicines with **caution**, and only in accordance with the currently approved product information. It is noted that in the majority of patients recruited to the SCOUT study, sibutramine would have been contraindicated.

Clinicians should refer to the [Summary of Product Characteristics](#) and be aware of the following:

- Sibutramine is **contraindicated** in patients with a **history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or TIA)**
- All patients taking sibutramine should be **regularly monitored** for **increases in blood pressure and heart rate**
- Patients who do **not** lose at least **5% of their body weight within 3 months** should **stop treatment**
- The **maximum** treatment duration should **not exceed one year**

Action: Clinicians should be **aware** of this review and use **sibutramine cautiously** until it is completed. **Preferential use of orlistat**, for the time being at least, would seem sensible.

FDA requests new safety studies on exenatide (Byetta®)

The British National Formulary¹ reports that pancreatitis (sometimes fatal), including haemorrhagic or necrotising pancreatitis has been reported rarely as a side-effect of exenatide. According to a Reuters report, the US FDA has requested additional safety studies to ensure the benefits of exenatide (Byetta®) outweigh the risk of inflammation of the pancreas and acute renal failure. A letter posted on the Agency's website notes that it has 'determined that post-marketing requirements are needed to assess the risk of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotizing pancreatitis, and the risk of thyroid neoplasms'.

Action: Patients and their carers should be told how to recognise signs or symptoms of pancreatitis and advised to seek prompt medical attention if symptoms such as abdominal pain, nausea and vomiting develop. Exenatide should be discontinued permanently if pancreatitis is diagnosed.

¹ British National Formulary 58 September 2009

Researchers stand by diuretics as first line treatment for hypertension ¹

Researchers who have completed a 10 year follow up of the ALLHAT study say that they stand by their original conclusion that diuretics are as effective as other, more expensive options for treating hypertension and should be used as the first line treatment.

In the original double blind trial 42 000 participants were randomised to initial treatment with one of four classes of drug then in use: the α -adrenoceptor blocker doxazosin, the angiotensin converting enzyme (ACE) inhibitor lisinopril, the calcium channel blocker amlodipine, and the thiazide diuretic chlortalidone.

The doxazosin arm was stopped after three years because of poor results in comparison with the diuretic (concerns around increased risk of heart failure). The remaining three drugs emerged as equivalent with respect to the primary outcome of fatal coronary disease or non-fatal myocardial infarction. But chlortalidone was superior with respect to predefined secondary end points, including heart failure and stroke. The latest results were presented at the American Heart Association. The researchers used data from the trial for up to five years and gathered information from administrative databases, including the US national death index and those of the Centre for Medicare and Medicaid Services, to compile information on what had happened to patients 10 years after the original study.

The follow-up results again showed no differences among the drugs with respect to coronary heart disease. However, some of the differences in cardiovascular outcomes, such as stroke, seen during the original trial did not persist at 10 years. The only significant difference was a 34% higher risk of heart failure with amlodipine than with chlortalidone, which was evident in the original trial but did not increase in the follow-up.

Questions have been raised around the lack of information about post-trial blood pressure or medication use during the follow-up period, however it is generally accepted that the results provide reassurance that chlortalidone therapy does improve overall cardiovascular outcomes, even in patients who subsequently developed diabetes mellitus.

Guidelines in the United States recommend diuretics as first line therapy for hypertension. European guidelines recommend any of five drug classes as first line. **Guidelines of the UK National Institute for Health and Clinical Excellence recommend a calcium channel blocker or thiazide-type diuretic for patients over 55 years old or for black people of any age. For those under 55 the initial NICE recommended therapy is an ACE inhibitor.**

Meta-analysis: Heart failure benefits of statins

A meta-analysis of placebo-controlled randomised trials featured in the American Journal of Cardiology has found that different statins have different effects on heart failure(HF).¹

The researchers searched for eligible studies that prospectively randomised patients with HF to statins or placebo. Primary end points were all-cause mortality, cardiovascular mortality, hospitalisation for worsening HF, adverse drug events, and changes in left ventricular ejection fraction (LVEF). Data was pooled using the random effects model with summary effect estimates (95% confidence intervals).

Ten studies (10,192 patients; mean age 69 years; 78% male) with follow-up from 3 to 47 months met the inclusion criteria. Three trials randomised patients to rosuvastatin (10- 40mg), one to simvastatin (5-10mg), and six to atorvastatin (10-40mg). The researchers found that overall statins did not affect all-cause (OR 0.89, 95% CI 0.72 to 1.10, $p = 0.27$, $I^2 = 50\%$) or cardiovascular mortality (OR 0.89, 0.71 to 1.13, $p = 0.35$, $I^2 = 65\%$) but did significantly decrease hospitalisation for worsening HF during follow-up (OR 0.67, 95% CI 0.50 to 0.90, $p = 0.008$, $I^2 = 64\%$). Patients randomised to statins had a significant 4.2% increase in LVEF at follow-up (95% CI 1.3 to 7.1, $p = 0.004$). Given the absolute risk ratio of 1.93%, 52 patients need to be treated for a weighted mean of 38 months to prevent 1 hospitalisation for worsening HF.

Post hoc analyses showed heterogeneity among different statins and demonstrated that randomisation to atorvastatin decreased all-cause mortality (OR 0.39, 95% CI 0.21 to 0.73, $p = 0.004$, $I^2 = 0\%$), decreased hospitalisation for worsening HF (OR 0.30, 95% CI 0.18 to 0.49, $p = 0.00001$, $I^2 = 0\%$) and randomisation to atorvastatin and simvastatin led to a significant improvement in LVEF (95% CI 3.3 to 7.8, $p = 0.00001$, $I^2 = 88\%$), **whereas these benefits were not observed in patients randomised to rosuvastatin.**

The authors concluded that their meta-analysis demonstrated that although statins don't reduce mortality, they are safe and improve LVEF and decrease hospitalisation for worsening HF.

¹*Am J Cardiol* 2009;104:1708-1716.

Oxfordshire Primary Care Trust and Oxfordshire & Buckinghamshire Mental Health NHS Foundation Trust

Good Practice Monitoring Guidelines for Severe Mental Illness patients

The following Oxfordshire PCT and Oxfordshire & Buckinghamshire Mental Health NHS Foundation Trust

guidelines provide information and guidance relating to the monitoring of patients diagnosed with Severe Mental Illness (SMI) – for example, Schizophrenia, Bipolar Disorder or treatment resistant depression. They have been developed on the principles of clinical safety, patient choice and social inclusion.

BACKGROUND

SMI patients have greater risks of diabetes & cardiovascular disease than the general population. Antipsychotics, especially atypical antipsychotics, may compound this through potential side effects of weight gain, dyslipidaemia, impaired glucose tolerance & diabetes. Adults of African-American, Asian or Hispanic race have higher cardiovascular and diabetes risk factors at lower BMIs and waist circumferences than western populations. Most weight gain occurs in the first few months of treatment. Some antipsychotics may cause hyperprolactinaemia, prolongation of the cardiac QT interval, muscular rigidity (raised CK levels) and neuroleptic malignant syndrome and monitoring may be necessary as clinically indicated.

GUIDANCE

1. When referring patients to Secondary care GPs should send a print out of the clinical summary including current treatment and latest blood tests and monitoring results.
2. Secondary care clinicians should include specific requests for the necessary monitoring in outpatient letters and results of these communicated to them on a regular basis to enable relevant care planning. Discharge summaries should include monitoring results and request follow up of abnormal results
3. Service users should be given a psychotropic monitoring record card to be completed and brought to appointments

BASELINE MONITORING	YEARLY MONITORING
<ul style="list-style-type: none"> BMI, Blood pressure & pulse Fasting lipids(random if not possible) including Triglycerides, HDL-C and Cholesterol ratio Fasting glucose(random if not possible) TFT, U+E, LFT, FBC <i>Drug specific monitoring as outlined in table below</i>	<ul style="list-style-type: none"> BMI, Blood pressure & pulse Fasting lipids(random if not possible) including Triglycerides, HDL-C and Cholesterol ratio Fasting glucose(random if not possible) Smoking and alcohol intake, Illicit drug use Check status of other annual health checks <i>Drug specific monitoring as outlined in table below</i>

Calculate Framingham cardiovascular risk score for patients > 40yrs or with raised BP or lipid profile

DRUG SPECIFIC MONITORING

(Treat abnormal results as per NICE guidance – refer to CMHT if risks outweigh benefits of treatment)

Drug/Drug group	Baseline	after 1 month	after 3 months	after 6months	6 monthly	Yearly	Repeat test
Antidepressants						U&E	
Typical antipsychotic Risperidone, Sulpiride	Prolactin		Prolactin				if symptoms
Amisulpiride	Prolactin ECG		Prolactin				if symptoms
Carbamazepine (CBZ)				LFT +FBC	U+E & CBZ-level		
Clozapine		BMI	BMI Fasting glucose, TG & cholesterol	BMI			
Haloperidol	Prolactin ECG		Prolactin				if symptoms
Lithium			Lithium level (and then every 3 months)		TFT, U+E, Lithium- level		Levels-5-7 days after dose ↑
Olanzapine		BMI	LFT,BMI, Fasting glucose, TG & cholesterol,	BMI			
Quetiapine				Fasting, TG & cholesterol,			
Valproate				BMI,LFT,FBC (incl ptt),			
Venlafaxine					BP		

Tacrolimus – importance of branded prescribing

Products & Administration: There are two tacrolimus products available; Prograf® and Advagraf®. There are also generic formulations available.

- Prograf® is an immediate-release formulation that is taken twice daily, once in the morning and once in the evening;
- Advagraf® is a prolonged-release formulation that is taken once daily in the morning

Safety issues: There have been several dispensing errors in the community, where by Advagraf® MR preparation has been dispensed instead of Prograf®, with patients taking the MR preparation twice a day. This has resulted in episodes of rejection in two patients nationally. It is therefore important to ensure branded prescribing of tacrolimus.

Action:

- Prograf® and Advagraf® are not interchangeable; switching between Prograf® and Advagraf® requires careful therapeutic monitoring.
- Substitution should be made only under the close supervision of a transplant specialist.
- To avoid confusion and the potential for patients receiving the wrong formulation, it is important that all tacrolimus prescriptions specify the brand (Prograf® or Advagraf®).

Prescriptions for seven days

Following a number of concerns from GPs and Community Pharmacies about the use of seven day prescriptions for monitored dosage systems, the LPC have requested the following guidance from Prescribing Points May 08 and January 09 be re-issued.

NHS Hampshire have also produced a useful 'question and answer' article on when 7 days may and may not be appropriate and with their permission this has been included below.

Weekly prescriptions allow the dispensing and issuing of a prescription including medicines dispensed into a MDS tray on a weekly basis. It should be noted that patients requiring a MDS with a prescription for 28 days, will be given 4 seven day trays at one dispensing. Seven day prescriptions therefore allow for weekly dispensing which means that adjustment to medications, dosage etc can easily be made.

Seven day prescriptions should therefore be used if

- ❖ flexibility is required to change the medication at short notice
- ❖ the patients' medicine needs are unstable and liable to change
- ❖ there may be a risk to the patient or others from having too much medicine in the home
- ❖ weekly provision of MDS is required

GPs may issue weekly prescriptions if they feel it is clinically appropriate for their patient.

Length of prescription - Q and As

- **I would like my patient to receive their medicine on a weekly basis (for reasons of safety).**
In this situation it is necessary to prescribe weekly prescriptions. The quantity on a prescription should reflect the required frequency of dispensing.
- **A care home has asked the pharmacist to provide medicines in a MDS and the pharmacist is asking for weekly prescriptions to help cover the cost of the MDS.**
We can see no justification for practices to prescribe weekly prescriptions for patients in care homes unless the patient's clinical condition justified a weekly supply. GPs should not prescribe weekly prescriptions as a way of subsidising the cost of MDS and the pharmacist and home can enter into a private arrangement for the supply of medicines in a MDS.
- **A patient requires an MDS because of their disabilities should I write weekly prescriptions?**
The pharmacist is responsible for assessing a patient's needs and making appropriate and reasonable adjustments to their services so that the patient would not be prejudiced against. The supply of medicines in a MDS might be one of the possible adjustments (other examples might be large print labels or a medicines administration record sheet). Funding is included within the pharmacy contract to recognise the additional work and costs of this requirement and therefore weekly prescriptions would not be appropriate (unless clinically indicated).
- **A patient does not qualify for an MDS, should I write weekly prescriptions?**
If the pharmacist has assessed the patient and does not believe they are eligible under the DDA then the patient and pharmacy are free to enter into a private arrangement to provide the support requested. Weekly prescriptions would not be appropriate (unless clinically indicated)

PCT Commissioned MDS service

For the small number of patients where there is no local provision of MDS the PCT commissioned service may be used. In this case the practice should contact Continuing care on 01235 205480 who will

- Check that the patient has a carer administering their medicine
- Check that the local pharmacy is not able to take on additional patients
- Provide the Practice with details of the commissioned service
- Request that prescriptions are sent to the PCT commissioned service.

The PCT commissioned service will

- Receive a FP10 for an MDS patient from the GP
- Dispense and supply a sealed/labelled medicine compliance aid
- Arrange and provide delivery of the MDS to the patient/carer
- Supply with the MDS, an up to date administration record form and send a copy to the Continuing Care office
- Keep patient dispensing records
- Request from the practice regular prescriptions for dispensing

Potential for Error - Changes to Rifinah packaging

Although Rifinah is listed as red on the traffic lights (i.e. should **all** be hospital or specialist prescribed), we do have some prescribing in primary care. Therefore please note the following information which could result in prescribing, dispensing or administration errors;

The new label for Rifinah 300 tablets on the packaging and blister strip is for "Rifinah 150/300mg tablets".

The new label for Rifinah 150 tablets on the packaging and blister strip is for "Rifinah 100/150mg tablets".

Nowhere on the outer box or blister strip specifies these products by the more familiar names of "Rifinah 300" or "Rifinah 150".

Currently the packaging refers to these preparations by the names 'Rifinah 150/300mg tablets' and 'Rifinah 100/150mg tablets'. The latest edition of the BNF and the SPC both still use 'Rifinah 300' and 'Rifinah 150'.

Due to the similarities in name and easy confusion of tablet strength, it is important that prescribers, pharmacy staff and nurses are made aware of these changes. So far there has been no publicity from Sanofi-Aventis about this change.

NPSA Patient Safety Alert – Safer Lithium Therapy

The National Patient Safety Agency (NPSA) has published new guidance for the NHS and independent healthcare organisations to improve the safety of lithium therapy.

Over the last five years, the NPSA has received over 560 patient safety incidents relating to lithium use. The majority of these incidents resulted in no or low harm, but a key theme in these incidents was a lack of monitoring. Infrequent lithium monitoring and checking of key blood tests have been implemented in NHS litigations and patient death.

The alert calls on organisations to ensure that:

- Patients who are prescribed lithium are monitored in accordance with the National Institute for Clinical Excellence (NICE) guidelines. These stipulate that lithium blood levels should be assessed every three months and thyroid and renal tests should be undertaken every six months.

- There are reliable systems in place to make sure that the results of blood tests are communicated between laboratories and prescribers
- At the start of lithium therapy, and throughout their treatment, patients receive appropriate ongoing verbal and written information and a record book to track lithium blood levels and relevant clinical tests*
- Prescribers and pharmacists check that blood tests are being monitored regularly and that it is safe to issue a repeat prescription or dispense the prescribed lithium
- Systems are in place to identify and deal with medicines that might adversely interact with lithium therapy
- The NPSA has developed a patient information booklet, lithium alert card and record book for tracking blood tests

The recommendations should be implemented by 31st December 2010. All local health organisations will be involved and initial discussions will take place at the Area Prescribing Committee (APCO) meeting in January.