Implementing key therapeutic topics: 2
Antipsychotics in dementia; statins and ezetimibe; and hypnotics

The QIPP medicines use and procurement workstream aims to ensure that value for money is further enhanced while quality of care is maintained or improved by optimising the use of medicines. This bulletin is the second of three that focus on several of the key prescribing topics outlined in the current version of the NPC document, Key therapeutic topics – Medicines management options for local implementation.

These bulletins summarise the evidence-base for the therapeutic topics reviewed, and contrast this with the prescribing data available for these topics. They aim to provide a focus for prescribers and prescribing managers on the ‘implementation gaps’ there may be in some localities between this evidence-base and prescribing, highlighting potential areas for local action.

Two earlier bulletins have discussed how people make decisions and how decision-making might be done better (MeReC Bulletin 22:1), and how the adoption of evidence into practice can be supported (MeReC Bulletin 22:2).

Topics included in this bulletin are:
- Antipsychotics in dementia
- Statins and ezetimibe
- Hypnotics

Topics included in the first bulletin in this series were NSAIDs; antibiotics; and inhaled corticosteroids in asthma.

The third bulletin will cover hypoglycaemic agents; long-acting insulin analogues; and self-monitoring of blood glucose in type 2 diabetes.

Useful resources
- Department of Health. Quality, Innovation, Productivity and Prevention (QIPP) webpage
- NHS Business Services Authority. QIPP prescribing comparators webpage
- NHS Business Services Authority. QIPP charts and data webpage
- NHS Business Services Authority. Prescribing Dispensing and Financial Management (with Prescribing Toolkit)
- NHS Business services Authority. ePACT.net
- National Prescribing Centre. Key therapeutic topics – medicines management options for local implementation
- NHS Evidence. QIPP collection webpage

All information was correct at the time of publication (February 2012)
Antipsychotics in dementia

What concerns are associated with prescribing antipsychotics for people with dementia?

The Banerjee report (November 2009) was an independent report commissioned by the Department of Health. It supports the need to follow NICE/SCIE guidelines with regard to behavioural and psychological symptoms of dementia. It recognised the limited benefits that have been demonstrated in clinical trials for antipsychotics when used to treat behavioural and psychological symptoms of dementia (BPSD). The report concluded that:

- Antipsychotics are in general over-prescribed for the treatment of behavioural and psychological symptoms of dementia.
- About 180,000 people with dementia are treated with antipsychotic medication in England per year.
- Of these, up to 36,000 may derive some benefit from treatment, but an additional 1,800 may die and an additional 1,620 suffer a cerebrovascular adverse event (around half of which may be severe) per year.
- If support was available to provide alternative methods of managing behavioural problems, prescribing of antipsychotics could be reduced by up to two-thirds in people with dementia.

Raising the quality of care for people with dementia and their carers is a major Government priority. In October 2011 the NHS Institute for Innovation and Improvement published an economic evaluation of alternatives to antipsychotic drugs for individuals living with dementia in England. It estimated that using behavioural interventions to treat individuals with dementia, rather than antipsychotic drugs, would cost an extra £27.6 million per year. However, health care savings would be nearly £70.4 million due to reduced incidence of stroke, falls, and medication savings. When these health care savings are combined with quality of life improvements, the net benefit of behavioural interventions was estimated at nearly £54.9 million per year.

How should people with BPSD be managed?

The NICE/SCIE clinical guideline on dementia advises that people with dementia who develop non-cognitive symptoms that cause them significant distress or who develop behaviour that challenges should be offered an assessment at an early opportunity to establish likely factors that may generate, aggravate or improve such behaviour. Individually tailored care plans that help carers and staff address the behaviour that challenges should be developed, recorded in the notes and reviewed regularly. The frequency of such review should be agreed by the carers and staff involved, and recorded.

Is there a place for the prescribing of antipsychotics for people with BPSD?

Pharmacological interventions, including antipsychotics, have only a limited role in the management of non-cognitive symptoms of dementia. The NICE dementia quality standard states ‘the goal for the proportion of people with dementia and mild-to-moderate non-cognitive symptoms who are prescribed antipsychotic medication should be 0%’.

- NICE/Social Care Institute for Excellence (SCIE) clinical guideline states that people with dementia who develop non-cognitive symptoms or behaviour that challenges should be offered a pharmacological intervention in the first instance only if they are severely distressed or there is an immediate risk of harm to the person or others.
- Choose an antipsychotic after an individual risk–benefit analysis.
- Start on a low dose and then titrate upwards.
- Limit treatment time and review regularly (at least every 3 months or according to clinical need).
- For less severe distress and/or agitation, initially use a non-drug option.
- Do not use antipsychotic drugs for mild to moderate non-cognitive symptoms in:
  - Alzheimer’s disease, vascular dementia or mixed dementia, because of the risk of cerebrovascular events and death
  - Dementia with Levy bodies because of the risk of severe adverse reactions

Do prescribing data reflect the evidence?

Figure 1 compares the net ingredient cost (NIC) per 1000 patients of antipsychotics prescribed in the quarter to September 2011 in Primary Care Trusts (PCTs) in Northern England; Southern England is similar. It shows a three-fold variation among individual PCTs in this comparator. What cannot be seen from these data is the variation between practices within PCTs, which may also be considerable.

Figure 2 shows the trend in prescribing of antipsychotics in general practice in England from July 2006 to September 2011 (note the Banerjee report was published in November 2009). Total items for first generation antipsychotics have remained static, while those for second generation antipsychotics have steadily risen. It should be noted that prescribing data by indication is not available; these numbers reflect total antipsychotic prescribing for all indications.
These graphs show the variation between PCTs in spending, and trends in prescribing, for antipsychotic drugs.

Figure 1. Variation in spending on antipsychotics between Primary Care Trusts in Northern England (Quarter to September 2011)

- Second Generation Antipsychotics
- First Generation Antipsychotics

- NIC (£) per 1000 Patients
- Northern PCT median 1424.5
- National PCT median 1300.0

Figure 2. Trends in prescribing of antipsychotic drugs (BNF 4.2.1) in general practice in England. (July 2006 to September 2011)

- Second Generation Antipsychotics
- First Generation Antipsychotics

- BLEEDING
- Prescriptions

© Copyright NHSBSA 2011
So what?

The appropriateness of low dose antipsychotic prescribing for people with BPSD should be reviewed and, where appropriate, revised in accordance with NICE/SCIE guidance and the NICE Quality Standard on dementia.

Following the Banerjee report, the NHS Information Centre is performing a three stage audit of the level of antipsychotic prescribing within GP practices in England. The Alzheimer’s Society has also published guidance for the treatment and care of behavioural and psychological symptoms of dementia and a best practice guide for health and social care professionals to complement NICE guidance.

References

1. Banerjee S. The use of antipsychotic medication for people with dementia: Time for action. (see MeReC Rapid Review No. 847)
5. NHS Institute for Innovation and Improvement. An economic evaluation of alternatives to antipsychotic drugs for individuals living with dementia. October 2011
6. NICE. Dementia Quality Standard. June 2010
8. NHS Information Centre. The national dementia and antipsychotic prescribing audit (see audit schedule)
Statins and ezetimibe

NICE has issued several pieces of guidance relating to lipid modification in adults. These include the use of ezetimibe in TA132, which is referred to in the clinical guidelines on lipid management and type 2 diabetes and incorporated into the clinical guideline on familial hypercholesterolaemia (FH). A brief overview of the salient points is given below.

What does NICE recommend for lipid management?

The patient’s informed preferences should be taken into account, including the benefits and risks of initiating proposed treatment, or when considering a higher intensity statin.

- For people in whom statins are indicated, NICE recommends simvastatin 40 mg first line. The only people who should be considered for a statin other than simvastatin 40 mg or 80 mg are:
  - some people who have diabetes
  - some people who have acute coronary syndrome (ACS)
  - some people with the relatively rare familial lipid disorders
  - where simvastatin 40 mg or 80 mg is contraindicated or not tolerated
  - where there are potential drug interactions
- The only people who should be considered for ezetimibe are:
  - some people who have primary hypercholesterolaemia and in whom statins are contraindicated or not tolerated
  - some people with diabetes and primary hypercholesterolaemia, where intensifying cholesterol-lowering therapy is under consideration
  - some people with relatively rare familial lipid disorders

What does NICE advise about lipid targets?

Simvastatin 40 mg is the statin and dose of first choice for most people for primary or secondary prevention. There is no NHS lipid target for primary prevention patients, and higher intensity statins should not be used routinely. There is also no NHS lipid target for most secondary prevention patients.

- In most cases where NICE gives lipid levels, these are thresholds to prompt consideration for increasing the dose of simvastatin to 80 mg (or a drug of similar efficacy and acquisition cost), not targets patients are expected to achieve.
- Note that single lipid measurements may over or under-estimate true lipid levels by around 14%.

In what circumstances should we consider a statin other than simvastatin 40mg/day?

Where available evidence has shown additional or alternative action may be beneficial, NICE has given further specific advice on lipid management in certain circumstances or conditions. NICE has also published important guidance on involving patients in decisions about prescribed medicines and supporting adherence.

For primary hypercholesterolaemia (heterozygous-familial or non-familial)

Consider using a high intensity statin to reduce LDL by more than 50%. Ezetimibe may be co-administered with initial statin therapy when total cholesterol or LDL is not appropriately controlled, either after dose titration of initial statin therapy or because dose titration is limited by intolerance to the statin therapy and consideration is being given to changing from initial statin therapy to an alternative statin.

- Ezetimibe monotherapy is an option for adults with primary hypercholesterolaemia (at 20% or greater 10 year cardiovascular disease [CVD] risk) in whom statins are contraindicated or not tolerated.

For secondary prevention in people without ACS

Simvastatin 40 mg is the drug of first choice when offering to initiate treatment. If the patient’s total cholesterol is greater than 4 mmol/L and also their LDL is greater than 2 mmol/L then consider an increase to simvastatin 80 mg or a drug of similar efficacy and acquisition cost. If either level is less than this, no increase in dose is recommended.

For people with ACS

A higher intensity statin is advised. Simvastatin 80 mg and atorvastatin 80 mg are both considered cost-effective options. NICE does not specify a lipid target.

For type 2 diabetes

Simvastatin 40 mg is the drug of first choice when offering to initiate treatment. An increase to simvastatin 80 mg or a drug of similar efficacy and cost is advised if the patient’s total cholesterol is greater than 4 mmol/L and also their LDL is greater than 2 mmol/L. If either level is less than this, no increase in dose is recommended.

- In people with CVD or increased albumin excretion consider intensifying therapy (with a more effective statin or ezetimibe) to achieve a total cholesterol less than 4.0 mmol/L or LDL less than 2.0 mmol/L.

*In line with NICE Technology appraisal 132: ezetimibe for primary hypercholesterolaemia.

Do prescribing data reflect the evidence?

A QIPP comparator has been published for lipid modifying drugs. It indicates simvastatin and pravastatin
prescription items as a percentage of all statins, including formulations containing ezetimibe. Figure 3 shows there is wide variation in prescribing among individual PCTs for this comparator. What cannot be seen from these data is the variation between practices within PCTs, which may also be considerable.

Figure 3 shows the comparative annual costs of various statin and ezetimibe formulations. It demonstrates a 30 fold difference in price across the range of formulations shown.

Number of prescription items for simvastatin and pravastatin as a percentage of the total number of prescription items for all statins, including combination of simvastatin/ezetimibe and ezetimibe. Values to the right indicate a higher percentage of simvastatin and pravastatin prescribing. Lowest value 61%. Highest value 85%.

These graphs show the variation between PCTs in the Statin QIPP comparator, and comparative annual costs of various statin and ezetimibe formulations.
So what?

Prescribing of ezetimibe and high-cost statins should be reviewed and, where appropriate, revised to ensure it is in line with NICE guidance.

Simvastatin and pravastatin both have considerably lower acquisition costs than other lipid modifying drugs of similar lipid-lowering effect9. It should be noted that while the patent on atorvastatin will expire on May 2012, the initial generic price and the pace at which this may fall remain unclear. Also, use of ezetimibe has increased to over 500,000 items per quarter10; practitioners need to be mindful that their prescribing is in keeping with NICE guidance11.

- There is no good evidence to suggest that any one statin is better tolerated than another at equivalent lipid-lowering doses on a population level12.
- Clinical trials have failed to prove any benefits for ezetimibe, either alone or in combination with a statin, in patient-oriented outcomes compared with active comparators12.
- There is no evidence that reducing the dose of a statin and adding ezetimibe improves tolerability12.
- PCTs with a high proportion of prescribing statins with a low acquisition cost are just as successful at meeting QOF targets as those that use more costly alternates13.

References

1. NICE. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. Technology appraisal 132, November 2007
3. NICE. Type 2 Diabetes. Clinical guideline 87. May 2009
8. NHSBSA Prescription Services. QIPP Charts and Data
9. NHSBSA. Drug Tariff February 2012
10. NHSBSA Prescription Services. Cardiovascular Charts and Data
11. Money, money, money. DTB 2010; 48 (7) (see MeReC Rapid Review No. 1722)
Hypnotics

What is the guidance on prescribing of hypnotics?

Providing advice on appropriate routines to encourage good sleep (i.e. sleep hygiene) is fundamental to the overall management strategy for insomnia. Benzodiazepines can provide limited relief from insomnia in the short term, but there is little evidence to support their efficacy during longer-term use. In 1988 the Committee on Safety of Medicines (CSM) raised concerns about adverse events including the risk of dependence and advised:

- A benzodiazepine should be prescribed only if insomnia is severe, disabling or subjecting the patient to extreme distress.
- The lowest dose which can control symptoms should be used. It should not be continued beyond four weeks.
- Long-term chronic use is not recommended.
- Treatment should always be tapered off gradually.
- When a benzodiazepine is used as a hypnotic, treatment should, if possible, be intermittent.

‘Z-drugs’ (zaleplon, zolpidem, zopiclone) are non-benzodiazepine hypnotics but they act on the benzodiazepine receptor and there is a lack of compelling evidence to distinguish between the ‘Z-drugs’ or the shorter-acting benzodiazepine hypnotics. Hypnotics are not licenced for long-term use; treatment should be limited to four weeks with zopiclone and zolpidem, or two weeks for zaleplon.

The NICE technology appraisal for the use of ‘Z-drugs’ in insomnia states:

- When, after due consideration of the use of non pharmacological measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, it should be prescribed for short periods of time only in strict accordance with their licensed indications.
- Because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepines, the drug regimen of lowest purchase cost should be prescribed.
- A switch from one hypnotic drug to another should only occur if a patient experiences an adverse reaction directly related to the specific agent. This is the only circumstance in which prescribing a drug of higher acquisition cost is recommended.
- Patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others.

What are the issues with hypnotics?

A large meta-analysis of randomised controlled trials found out of every 13 people over the age of 60 taking a hypnotic for at least five consecutive nights, on average:

- Only one person will find their sleep improves, who would not have improved had they all been taking placebo. Note that this ‘improvement’ was an average of 25 minutes longer sleep and one less night-time awakening every other night. The hypnotic made no difference to the sleep pattern of the other 12 people. Their sleep would improve, or not improve, just as if they had taken placebo.
- Two people will have an adverse event (e.g. hangover drowsiness, confusion, psychomotor effects), who would not have done had they all been taking a placebo. The hypnotic made no difference to the remaining 11 people. They would, or would not have an adverse event, just as if they had taken placebo.

When comparing ‘Z-drugs’ with benzodiazepines, the authors found no differences in outcomes between the two groups.

In a large observational study of Norwegian drivers aged 18 to 69 years, people prescribed zopiclone or zolpidem in the previous seven days had double the risk of road traffic accidents, compared with people not prescribed hypnotics.

- There were five to nine accidents per exposed 1000 person-years in groups treated with hypnotics, compared with two accidents per exposed 1000 person-years in the group not exposed to hypnotics.
- Standardised incidence ratio (SIR) of hypnotic use in previous seven days, compared with no use, was similar between zopiclone, zolpidem, and nitrazepam.

Another large observational study found an increased incidence of hip fracture associated with benzodiazepine use, after adjusting for confounders (e.g. age, gender, nursing home occupancy). A questionnaire study of patients in the UK who had been prescribed a hypnotic in the last six months gives some insight into what is happening in clinical practice. The high rate of repeat prescriptions and daily use points towards a high prevalence of dependence:

- Repeat prescriptions accounted for 92.1% of all hypnotics prescribed, with 67.4% taking daily medication.
- 42.3% of patients had not been advised regarding duration of treatment and of those who had received guidance 45.4% were advised to continue treatment longer than licensed recommendations.
- 87% of patients felt their insomnia had improved on medication, and 72.1% wanted to continue treatment.
- There were no advantages for ‘Z-drugs’ over benzodiazepines in either improved sleep or fewer adverse effects.
Prescribing was often contrary to both the NICE guidance\(^1\) and the product licences\(^4\).

**Do prescribing data reflect the evidence?**

The volume of prescribing of benzodiazepine and ‘Z-drugs’ in general practice in England has remained steady, and is not decreasing\(^9\). This is despite CSM advice\(^3\) and NICE guidance\(^1\) that recommends hypnotics should be used only in the management of severe insomnia interfering with normal daily life, for short periods of time.

There is a QIPP prescribing comparator for hypnotics\(^10\), which indicates the total volume of hypnotics that are being prescribed, expressed as average daily quantities (ADQ) per STAR-PU. **Figure 5** shows a **four-fold** variation among individual PCTs in this comparator. What cannot be seen from these data is the variation between practices within PCTs, which may also be considerable.

**Figure 6** compares the number of hypnotics prescribed in the quarter to September 2011 in general practice. It shows that over 100,000 items per quarter were issued for 50–56 tablets of ‘Z-drugs’, indicating that MHRA advice\(^3\) and NICE guidance\(^1\) to limit the prescribing of these drugs to two to four weeks is not being followed in many cases.

---

**Figure 5. QIPP comparator: Hypnotics: ADQ/STAR(09) PU (Quarter to September 2011)**\(^10\)

These graphs show the variation between PCTs in the hypnotics QIPP comparator, and the prescribing of hypnotics in general practice in England.

**Figure 6. Prescribing of hypnotics in general practice in England (Quarter to September 2011)**\(^9\)

Number of ADQs per STAR-PU for all hypnotics (BNF 4.1.1). Values to the left indicate lower prescribing volumes of hypnotics. Lowest value 0.55. Highest value 2.23.
So what?

Prescribing of hypnotics should be reviewed and, where appropriate, revised to ensure it is in line with national guidance.

The risks associated with long-term use of hypnotic drugs have been well recognised for many years, and the provision of advice on appropriate routines to encourage good sleep (i.e. sleep hygiene) is fundamental to the overall management strategy for insomnia. Treatment of insomnia with a hypnotic should only be considered if insomnia is severe, disabling or subjecting the patient to extreme distress, and long-term chronic use is not recommended.

### References

1. NICE. Technology appraisal 77. Zaleplon, zolpidem and zopiclone for the management of insomnia. April 2004 (date of last review August 2010)
2. Clinical Knowledge Summaries. Insomnia. Last revised July 2009
9. NHSBSA Prescription Services. Central Nervous System Charts and Data
10. NHSBSA Prescription Services. QIPP Charts and Data