

Implementing key therapeutic topics: 1 NSAIDs; antibiotics; and inhaled corticosteroids in asthma

The QIPP agenda aims to ensure that value for money is further enhanced while quality is maintained or improved. This bulletin is the first 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:

- Non-steroidal anti-inflammatory drugs
- Antibiotic prescribing — especially quinolones and cephalosporins
- High dose inhaled corticosteroids in asthma

Topics to be included in the second bulletin are antipsychotics in dementia; statins and ezetimibe; and hypnotics. 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

National Prescribing Centre. Making Decisions Better. MeReC Bulletin Vol. 22, No. 1. August 2011

National Prescribing Centre. Supporting adoption of evidence into practice. MeReC Bulletin Vol. 22, No. 2. December 2011

All information was correct
at the time of publication
(January 2012)

Non-steroidal anti-inflammatory drugs

What are the risks of non-steroidal anti-inflammatory drugs (NSAIDs)?

- All NSAIDs are associated with **gastrointestinal (GI), cardiovascular (CV) and renal** side effects.
- **Paracetamol** (and/or topical NSAIDs) is recommended ahead of oral NSAIDs in the NICE osteoarthritis guideline¹. If NSAIDs are required, they should be prescribed at the **lowest effective dose** for the **shortest period of time** necessary to control symptoms².
- Following a European Medicines Agency review of **etoricoxib**▼, the MHRA recommends³ that:
 - patients whose blood pressure is persistently above 140/90 mmHg and inadequately controlled must not receive etoricoxib
 - high blood pressure should be controlled before starting treatment with etoricoxib, and should be monitored for two weeks after the start of treatment and regularly thereafter.

Co-prescribe NSAIDs with a PPI

How can the GI risks of NSAIDs be reduced?

- NICE guidance states that a **proton-pump inhibitor (PPI)** should routinely be co-prescribed with an NSAID (including coxibs) for anyone with osteoarthritis¹ or rheumatoid arthritis⁴, and anyone 45 years of age and older with chronic low back pain⁵, choosing the PPI with the lowest acquisition cost.
 - A hospital-based case control study showed a marked increase in risk of upper GI ulcer bleeding with NSAIDs overall, but use of a PPI attenuated the risk. **There was no increased GI risk of NSAIDs plus a PPI over non-use of an NSAID**⁶.
 - There is no good evidence to suggest that when NSAIDs are given with a PPI there are any differences between NSAIDs in terms of GI risk.

Use low-dose ibuprofen or naproxen in preference to other NSAIDs

How can the CV risks of NSAIDs be reduced?

- If an NSAID is required, **low-dose ibuprofen** (1200 mg/day or less) or **naproxen** 1000 mg/day or less would appear more appropriate than other NSAIDs for patients in whom CV risk is a significant consideration in decision making².
- **Coxibs** (celecoxib and etoricoxib) are associated with an increased thrombotic risk⁷.
- **Diclofenac** 150 mg/day has a similar excess thrombotic risk to etoricoxib and possibly other coxibs⁷.

- A meta-analysis of observational studies has confirmed an increased risk of CV events with diclofenac (even at comparatively low doses of 100 mg/day or less). A high CV risk was also seen with etoricoxib and etodolac. With regard to ibuprofen, the meta-analysis underlined the need to use lower doses (1200 mg/day or less) to avoid increasing the risk of CV events. The risk of CV events with naproxen was low or absent at higher as well as lower doses⁸. The European Medicines Agency has recently started a new review of the CV risks of NSAIDs⁹.

How can the renal risks of NSAIDs be reduced?

- Patients at risk of renal impairment or renal failure (particularly the elderly) should avoid NSAIDs if possible¹⁰. If NSAID treatment is absolutely necessary, the lowest effective dose for the shortest possible duration should be used and renal function should be carefully monitored¹⁰.

What do the prescribing data look like?

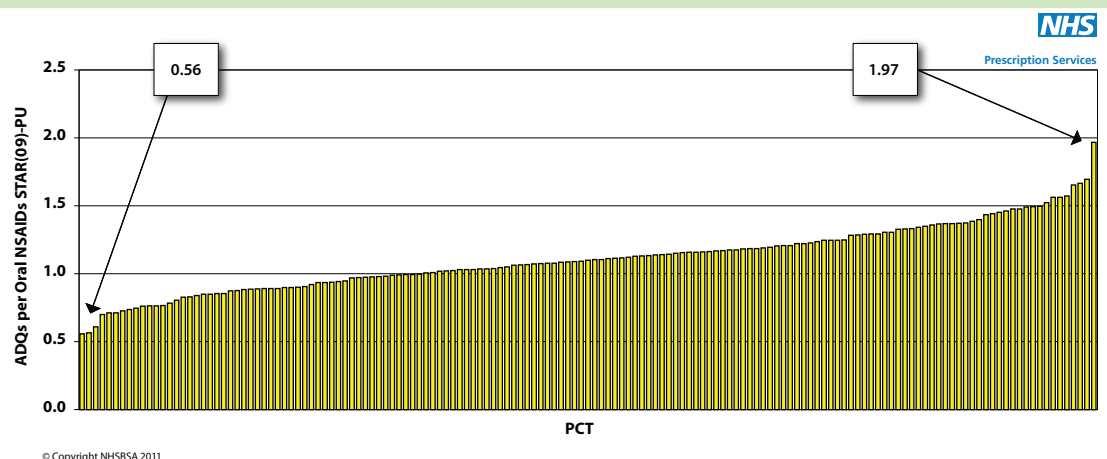
There are two QIPP comparators for NSAIDs¹¹. The first indicates the total quantity of NSAIDs that are being prescribed, expressed as average daily quantities (ADQ) per STAR-PU (specific therapeutic group age-sex related prescribing unit). **Figure 1** (page 3) shows there is more than a **three-fold 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.

The second QIPP comparator for NSAIDs indicates the number of prescription items for ibuprofen and naproxen as a percentage of the total number of prescription items for all NSAIDs. **Figure 2** (page 3) shows the wide variation there is among individual PCTs in this comparator, with a value of 32% for ibuprofen and naproxen prescribing at the lowest end to 73% at the highest end.

So what?

The appropriateness of NSAID prescribing should be reviewed widely and on a routine basis. This is especially the case for people at high risk of both GI and CV morbidity and mortality (e.g. older patients). If NSAIDs are required, steps should be taken as outlined above to reduce their GI, CV and renal risks. As a result, most prescribing of NSAIDs should be for low dose ibuprofen and naproxen.

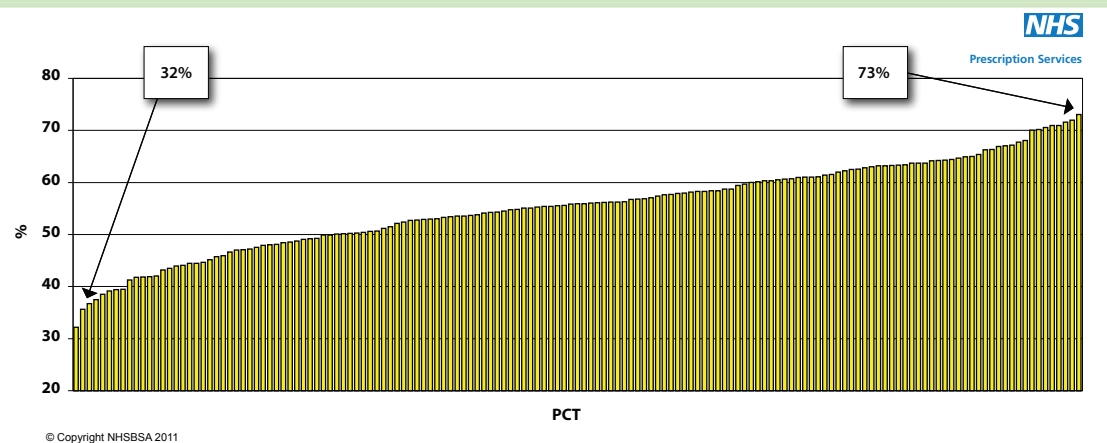
Figure 1. QIPP comparator: NSAIDs: ADQ/STAR-PU by PCT (Quarter to September 2011)¹¹



Number of ADQs per STAR-PU for all NSAIDs (BNF section 10.1.1). Values to the left indicate lower prescribing volumes of NSAIDs. Lowest value 0.56. Highest value 1.97.

These graphs show the variation between PCTs in the NSAID QIPP comparators

Figure 2. QIPP comparator: NSAIDs: ibuprofen & naproxen % items by PCT (Quarter to September 2011)¹¹



Number of prescription items for ibuprofen and naproxen as a percentage of the total number of prescription items for all NSAIDs. Values to the right indicate a higher percentage of ibuprofen and naproxen prescribing. Lowest value 32%. Highest value 73%.

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2. NPC. Cardiovascular and gastrointestinal safety of NSAIDs. MeReC Extra 30. November 2007
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4. NICE. Rheumatoid arthritis. The management of rheumatoid arthritis in adults. Clinical guideline 79. February 2009
5. NICE. Low back pain. Early management of persistent non-specific low back pain. Clinical guideline 88. May 2009.
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9. European Medicines Agency starts new review of cardiovascular risks of non-selective NSAIDs. EMA press release 21/10/11
10. MHRA. Non-steroidal anti-inflammatory drugs: reminder on renal failure and impairment. Drug Safety Update. May 2009
11. NHSBSA Prescription Services. QIPP Charts and Data

Antibiotic prescribing — especially quinolones and cephalosporins

What is appropriate antibiotic prescribing?

- Improving antibiotic prescribing is not about never prescribing antibiotics. It is about better targeting of antibiotics to those most at risk of having a complication from an infection and/or those most likely to have a bacterial cause for their symptoms. Targeting antibiotics aims to maximise their benefits and minimise their harms for individual patients, and minimise the development of antibiotic resistance on a population basis.
- There are encouraging trends with reductions in MRSA and *C. difficile* cases in recent years¹. However, there has been very little change in the rates of *E.coli* resistant to key antimicrobials (cephalosporins, quinolones and gentamicin) from 2005 to 2009².
- Antibiotic prescribing in primary care should be in line with local guidance based on Health Protection Agency (HPA) advice³ or NICE guidance (for respiratory tract infections)⁴.
- HPA guidance for the management of infection in primary care³, makes the following recommendations:
 - prescribe an antibiotic only when there is likely to be a **clear clinical benefit**
 - consider a **no, or delayed, antibiotic strategy** for acute self-limiting upper respiratory tract infections
 - **use simple generic antibiotics first** (such as amoxicillin) whenever possible
 - **avoid broad spectrum antibiotics** (such as co-amoxiclav, cephalosporins and quinolones e.g. ciprofloxacin) when narrow spectrum antibiotics remain effective, as they increase risk of *C. difficile*, MRSA and resistant urinary tract infections.
- NICE guidance for treating respiratory tract infections recommends three possible antibiotic prescribing strategies: **no antibiotic, delayed antibiotic** or **immediate antibiotic** prescribing⁴.
 - A **no antibiotic** or **delayed antibiotic** prescribing strategy should be agreed for patients with acute otitis media; acute sore throat/acute pharyngitis/acute tonsillitis; common cold; acute rhinosinusitis; acute cough/acute bronchitis.

Consider no or delayed antibiotics for acute self-limiting upper respiratory tract infections

Use simple antibiotics first whenever possible, e.g. amoxicillin not cephalosporins or ciprofloxacin

- Depending on clinical assessment of severity, patients in the following subgroups can also be considered for an immediate antibiotic prescribing strategy (in addition to no or delayed antibiotics): bilateral acute otitis media in children younger than 2 years; acute otitis media in children with otorrhoea; acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.
- An **immediate antibiotic** prescription and/or further appropriate investigation and management should only be offered to patients (both adults and children) in the following situations: if the patient is systemically very unwell; if the patient has symptoms and signs suggestive of serious illness and/or complications; if the patient is at high risk of serious complications because of pre-existing comorbidity; if the patient is older than 65 years with acute cough and two or more of the following criteria, or older than 80 years with acute cough and one or more of the following criteria: hospitalisation in previous year, type 1 or type 2 diabetes, history of congestive heart failure, current use of oral glucocorticoids. For these patients, the no antibiotic and the delayed antibiotic prescribing strategy should not be considered.

What do the prescribing data look like?

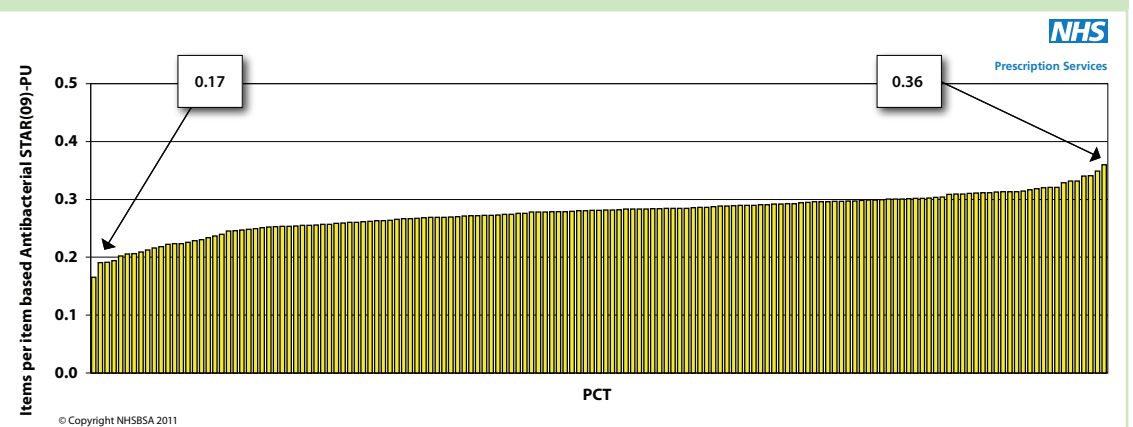
There are two prescribing comparators available to support the QIPP antibiotics topic⁵. The first indicates the total number of antibacterial items prescribed per STAR-PU. **Figure 3** (page 5) illustrates this comparator, showing the prescribing rate is twice as high in the PCT with the highest level of antibiotic prescribing than in the one with the lowest prescribing.

The second QIPP comparator shows the proportion of antibacterial prescriptions which are for cephalosporins or quinolones. **Figure 4** (page 5) shows the **six-fold variation** among PCTs in this comparator, from 2.3% to 13.7%.

So what?

The appropriateness of antibiotic prescribing, particularly for self-limiting upper respiratory tract infections, should be reviewed to ensure it is in line with HPA and NICE guidance. Antibiotics should only be prescribed when there is likely to be a clear clinical benefit.

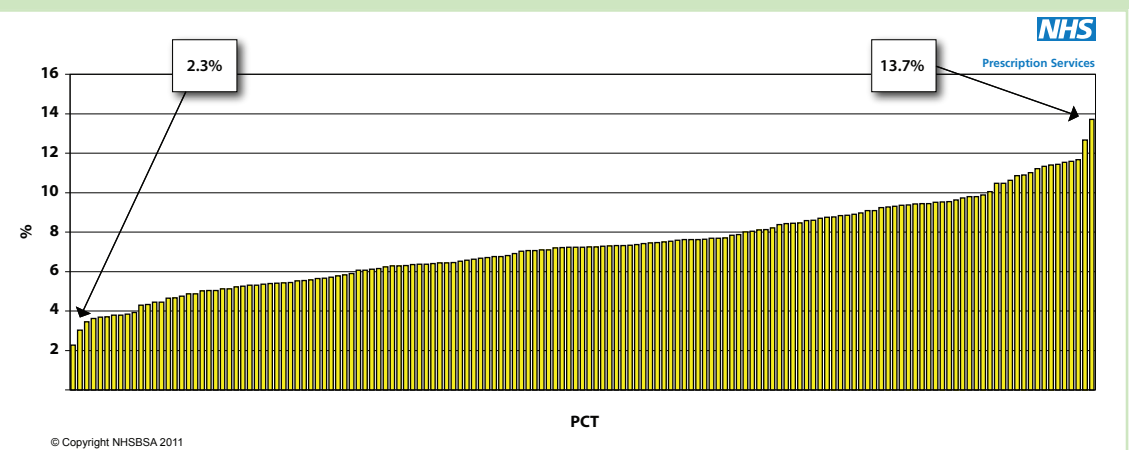
Figure 3. QIPP comparator: Antibacterial items/STAR-PU by PCT (Quarter to September 2011)⁵



Number of prescription items for antibacterial drugs (BNF 5.1) per STAR-PU. Values to the left indicate lower prescribing volumes of antibacterials. Lowest value 0.17. Highest value 0.36.

These graphs show the variation between PCTs in the antibiotic prescribing QIPP comparators

Figure 4. QIPP comparator: Cephalosporins & quinolones % items by PCT (Quarter to September 2011)⁵



Number of prescription items for cephalosporins and quinolones as a percentage of the total number of prescription items for selected antibacterial drugs (BNF 5.1). Lowest value 2.3%. Highest value 13.7%.

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2. Health Protection Agency. Escherichia coli bacteraemia in England, Wales and Northern Ireland, 2006–2010. April 2011
3. Health Protection Agency, British Infection Association. Management of infection guidance for primary care for consultation & local adaptation. Antimicrobial Guidance. Last reviewed March to July 2010.
4. NICE. Respiratory tract infections – antibiotic prescribing. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. Clinical guideline 69. July 2008
5. NHSBSA Prescription Services. QIPP Charts and Data

High dose inhaled corticosteroids in asthma

High dose ICS should be considered as a therapeutic trial only at step 4 for adults and children aged 5–12 years

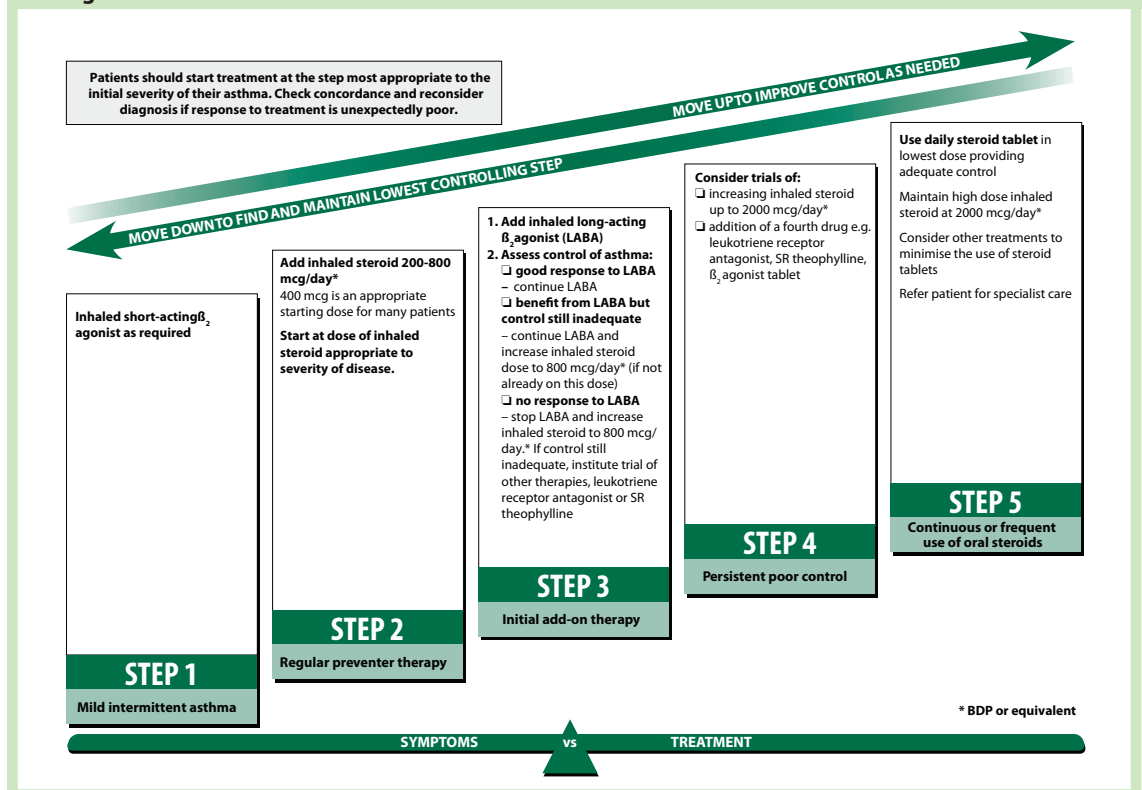
When are inhaled corticosteroids (ICS) recommended?

- There are safety issues relating to the use of **high** doses of ICS in asthma, but it is important to emphasise the benefits of ICS when used appropriately at standard doses.
 - The British guideline on the management of asthma¹ recommends **standard dose ICS (200–800 micrograms*/day in adults; 200–400 micrograms*/day in children ≤12 years)** as the first choice regular preventer drug for both adults and children at Step 2 (see **Figure 5** below of recommendations for adults).
 - **High dose ICS (800–2000 micrograms*/day in adults; 400–800 micrograms*/day in children aged 5–12 years)** should be considered as a therapeutic trial only at Step 4 of the British asthma guideline¹ (see **Figure 5** below of recommendations for adults).
 - Doubling the dose of ICS at the time of exacerbation is of unproven value and is no longer recommended¹.

What are the safety issues with high doses of ICS?

- Unpleasant local side effects, including oral candidiasis and dysphonia, can occur with ICS at standard doses, but are more common with higher doses².
- Potentially serious systemic side effects may be associated with ICS particularly at high doses¹ (above 800 micrograms*/day in adults and above 400 micrograms*/day in children).
 - Systemic side effects include adrenal suppression, growth failure, decrease in bone mineral density, cataracts and glaucoma, psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression (particularly in children), and diabetes mellitus³⁻⁶.
 - Marked adrenal suppression can occur with doses of ICS above 1,500 micrograms beclometasone dipropionate (BDP) or equivalent/day (750 micrograms fluticasone/day) in adults or 800 micrograms BDP or equivalent/day (400 micrograms fluticasone/day) in children, but considerable inter-patient variation occurs and

Figure 5. Summary of stepwise management of asthma in adults from the British guideline on the management of asthma¹



* beclometasone dipropionate (BDP) or equivalent.

In general, 400 micrograms BDP is equivalent to 400 micrograms budesonide or 200 micrograms fluticasone, but different CFC-free beclometasone inhalers do have different potencies (e.g. 400 micrograms Clenil Modulite[®] is equivalent to 200 to 300 micrograms Qvar[®]). See table 8b on page 37 of the British guideline on the management of asthma¹ for details.

adrenal suppression can occur with the use of lower doses in small numbers of patients^{1,5}.

- There is a dose response relationship with ICS and adrenal suppression⁵ (1000 micrograms/day of inhaled fluticasone has about the same effect on 8am serum cortisol levels as 10 mg/day of oral prednisolone).
- MHRA advice for **fluticasone**⁷ includes a warning that doses above 500 micrograms twice daily should be prescribed **only** for patients with severe asthma where additional clinical benefit is expected and demonstrated, initiated by a specialist in the management of asthma.
- MHRA advice about the risks of high dose ICS in **children**⁸ includes a warning that children not controlled on the maximum dose of ICS plus other therapies, should be referred to a paediatric asthma specialist (taking particular care with fluticasone).
- The British asthma guideline¹ recommends **children** prescribed ICS should have their growth monitored annually (although isolated growth failure is not a reliable indicator of adrenal suppression).
 - Adrenal insufficiency is a possibility in any child maintained on ICS presenting with shock or a decreased level of consciousness; serum biochemistry and blood glucose levels should be checked urgently¹.
- **Patients should be maintained at the lowest possible dose of ICS. Stepping down therapy** (including reducing the dose of ICS) once asthma is controlled is

recommended but is often not implemented, leaving some patients over-treated¹.

How should people on high doses of ICS be stepped down?

- Regular review of patients as they step down is important. Reductions in ICS dose should be slow as patients deteriorate at different rates. Reductions should be considered every three months, decreasing the dose by approximately 25 to 50% each time¹.
- A step down approach to ICS treatment can be achieved without compromising asthma control⁹.
- For some children with milder asthma and a clear seasonal pattern to their symptoms, a more rapid dose reduction during their 'good' season is feasible¹.

What do the prescribing data look like?

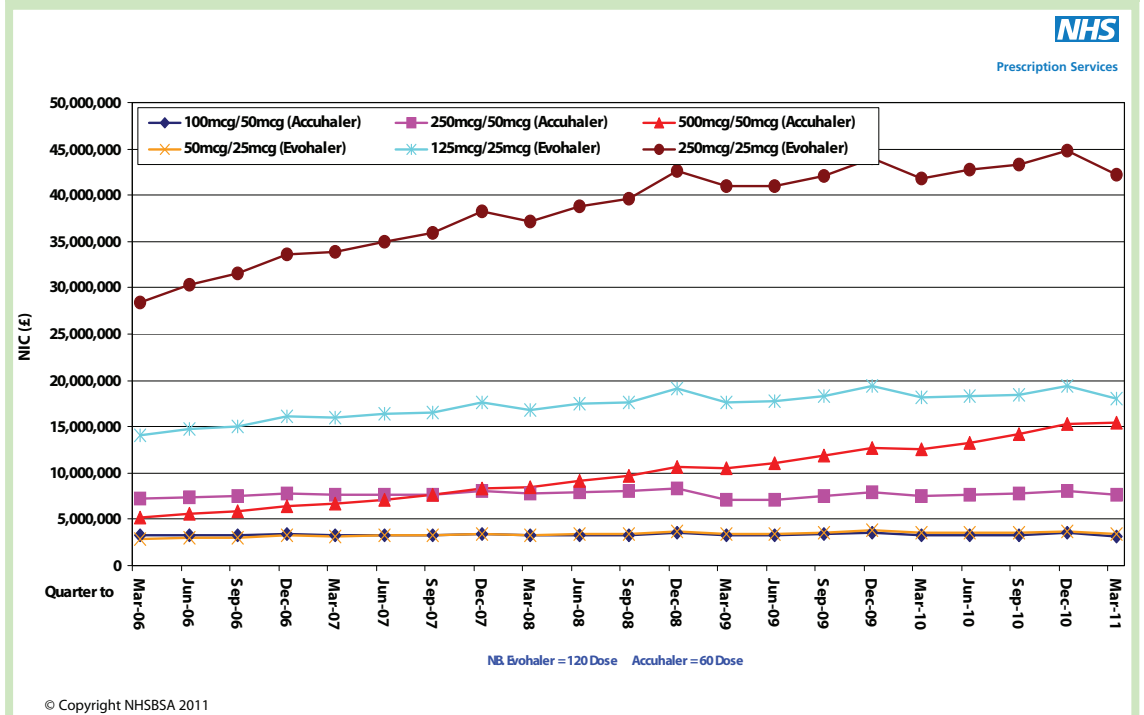
There are no prescribing comparators available to support this QIPP topic at the current time. From prescribing data alone, it is not possible to differentiate between the prescribing of ICS for asthma and for chronic obstructive pulmonary disease (COPD), nor to determine the daily doses prescribed or used by an individual with asthma.

With regard to the prescribing of **high dose ICS in children**, a UK observational study of GP prescribing conducted in July 2003 found that high-dose prescribing (>400 micrograms*/day) occurred in 5.6% of the under-5s and 10% of the 5 to 11 year olds¹⁰. Very high doses of ICS, exceeding 800 micrograms*/day were prescribed to 3.9% of the under-5s and to 4.9% of 5-11 year olds who were treated with ICS. Analysis of the ICS prescribed

Serious systemic side effects may be associated with ICS, particularly at high doses

Particular care is needed with the dose of fluticasone prescribed, and the use of high dose ICS in children

Figure 6: Trends in prescribing of Seretide® inhaler by strength in primary care in England¹²



Stepping patients down to lower strength inhalers reduces the risk of side effects and could bring cost savings

showed that although beclometasone was the most commonly used treatment overall, for those children prescribed more than 800 micrograms*/day, fluticasone predominated¹⁰. More recent UK primary care data from 2006/7 suggest that the use of high dose ICS in children has reduced, with high dose ICS (>400 micrograms*/day but <800 micrograms*/day) prescribed for 1.5% of the under-5s and 3.2% of the 5 to 14 year olds¹¹. Very high dose ICS (>800 micrograms*/day) were prescribed for 0.5% of the under 5s and 2.4% of those over 5 years age. However, such high doses were sometimes prescribed to children classified as having only intermittent or mild persistent asthma¹¹.

ICS continue to be a **high-cost** area of prescribing, with the spend on **combination inhalers** (ICS plus long-acting beta-2 agonist [LABA]) in particular continuing to rise. Of the combination inhalers, Seretide® is most frequently prescribed, with the Seretide 250 Evohaler® (the highest strength formulation within the Evohaler® range), being the most commonly prescribed product within this brand (see **Figure 6** on page 7)¹².

NICE recommends^{13,14} that, in asthma, the decision to use a combination inhaler or ICS and LABA in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence. If a combination device is chosen then the least costly device that is suitable for the individual is recommended^{13,14}. Combination inhalers may be more convenient and cheaper than individual inhalers, but they offer less flexibility for dose titration and stepping down, and may lead to over-treatment. Higher strength formulations typically attract higher acquisition costs within single or combination inhaler brands. Therefore, stepping patients down to lower strength inhalers could bring cost-savings in addition to reducing the risk of dose-related ICS side effects.

So what?

The use of ICS should be reviewed routinely in patients with asthma, stepping down the dose and use of ICS where it is clinically appropriate. Particular care should be taken with the dose of fluticasone prescribed, and the use of high dose ICS in children.

References

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The National Prescribing Centre (NPC) is responsible for helping the NHS to optimise its use of medicines. NPC is part of the National Institute for Health and Clinical Excellence (NICE), an independent organisation providing national guidance on promoting good health and preventing and treating ill health.