NICE National Institute for Health and Care Excellence

Key therapeutic topics

Medicines optimisation: key therapeutic topics 2017 update

Draft for consultation: October 2016

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Multimorbidity and polypharmacy

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- Multimorbidity is associated with reduced quality of life, higher mortality, polypharmacy and high treatment burden, higher rates of adverse drug events, and much greater health services use (including unplanned or emergency care).
- Polypharmacy in people with multimorbidity is often driven by the introduction of multiple medicines intended to prevent future morbidity and mortality in specific health conditions. However, the absolute difference made by each additional medicine is likely to reduce when people are taking multiple preventative medicines. Resources and screening tools are available to help guide decision-making about the appropriateness of prescribing and stopping medicines (deprescribing).
- Develop and agree an action plan for multimorbidity and polypharmacy to inform local medicines optimisation strategic and operational plans.
- Support clinicians in developing an individualised, person-centred approach to reviewing people with multimorbidity and polypharmacy, in line with the NICE guideline on multimorbidity. This may be included in local education and support initiatives.

Evidence context

Multimorbidity

The NICE guideline on multimorbidity: clinical assessment and management explains that multimorbidity refers to the presence of 2 or more long-term health conditions, which can include:

- defined physical and mental health conditions such as diabetes or schizophrenia
- ongoing conditions such as learning disability
- symptom complexes such as frailty or chronic pain
- sensory impairment such as sight or hearing loss

- alcohol and substance misuse.

Measuring the prevalence of multimorbidity is not straightforward because it depends on which conditions are counted. However, all recent studies show that multimorbidity is common, becomes more common as people age, and is more common in people from less affluent areas. Whereas in older people multimorbidity is largely due to higher rates of physical health conditions, in younger people and people from less affluent areas, multimorbidity is often due to a combination of physical and mental health conditions (notably depression).

Multimorbidity is associated with reduced quality of life, higher mortality, polypharmacy and high treatment burden, higher rates of adverse drug events, and much greater health services use (including unplanned or emergency care). A particular issue for health services and healthcare professionals is that treatment regimens (including non-pharmacological treatments) can easily become very burdensome for people with multimorbidity, and care can become uncoordinated and fragmented.

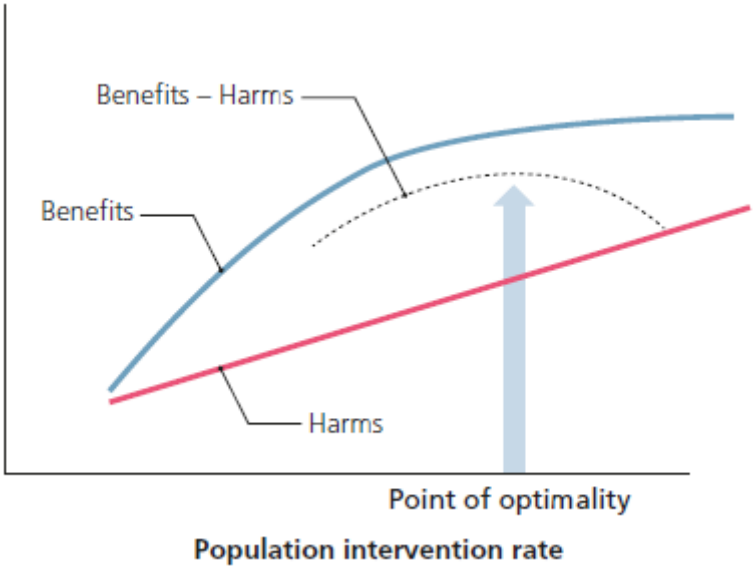
Polypharmacy

Data from NHS Digital show that between 2005 and 2015 there was a 50% increase in the total number of prescription items dispensed in the community in England, although the population grew by only 8%. This means that the average number of prescription items per head of population in England increased from 14 to 20 in that time. This is a simple average and should not be over-interpreted; some people have no or only a few prescriptions per year and others have many more than 20. The figures are also not adjusted for treatment duration per prescription. Nevertheless, they do suggest a general increase in prescribing rates.

Polypharmacy in people with multimorbidity is often driven by the introduction of multiple medicines intended to prevent future morbidity and mortality in specific health conditions. However, the evidence for recommendations in NICE guidance on single health conditions is regularly drawn from people without multimorbidity and taking fewer regular medicines. The absolute

difference made by each additional medicine is likely to reduce when a person is taking multiple preventative medicines; often referred to as the law of diminishing returns – see figure 1 below.

Figure 1. The relationship between benefits and harms when additional resources are invested (NHS Atlas of Variation in Healthcare 2015)



The King's Fund report (2013), All Wales Medicines Strategy Group (AWMSG) guidance (2014) and NHS Scotland guidance (2015) on polypharmacy recognise that not all polypharmacy is inappropriate. The King's Fund proposed a classification where treatment with multiple medicines may be either 'appropriate' or 'problematic':

Appropriate polypharmacy

Prescribing for a person for complex conditions or for multiple conditions in circumstances where medicines use has been optimised and where the medicines are prescribed according to best evidence.

Problematic polypharmacy

The prescribing of multiple medicines inappropriately, or where the intended benefit of the medicines are not realised.

Problematic polypharmacy may arise if medicines are used without a good evidence base for doing so, or if (taking into account the person's views and

preferences) the risk of harm from treatments is likely to outweigh the benefits, or where one or more of the following apply:

- the medicine combination is hazardous because of interactions
- the overall demands of medicine-taking, or 'pill burden', are unacceptable to the person
- these demands make it difficult to achieve clinically useful medicines adherence
- medicines are being prescribed to treat the side effects of other medicines, but alternative solutions are available to reduce the number of medicines prescribed.

Person-centred care

The NICE guideline on medicines optimisation recommends that all people are offered the opportunity to be involved in making decisions about their medicines.

As discussed in a BMJ article by McCartney et al. 2016, individual people may have values and preferences that are different from their healthcare professional(s) and from people who develop guideline recommendations. NICE guidelines should be understood as 'guidelines, not tramlines'; every guideline states clearly that although healthcare professionals are expected to take it fully into account when exercising their judgement, they should do so alongside the individual needs, preferences and values of their patients or service users. The application of the recommendations in NICE guidelines is not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient or their carer or guardian.

The NICE guideline on multimorbidity: clinical assessment and management recommends that clinicians think carefully about the risks and benefits of individual treatments recommended in guidance for single health conditions. This should be discussed with the person alongside their preferences for care and treatment.

The guideline also recommends the use of a tailored approach to care that takes account of multimorbidity for people of any age who are prescribed 15 or more regular medicines, and that this approach is considered for people of any age who:

- are prescribed 10 to 14 regular medicines
- are prescribed fewer than 10 regular medicines but are at particular risk of adverse events.

See the NICE guideline on multimorbidity for full details of the recommendations.

A tailored approach to care that takes account of multimorbidity involves personalised assessment and the development of an individualised management plan. The aim should be to improve quality of life by reducing treatment burden, adverse events, and unplanned or uncoordinated care. The approach takes account of the person's individual needs, preferences for treatments, health priorities and lifestyle. It aims to improve coordination of care across services, particularly if this has become fragmented. Medicines are likely to be just one aspect of a person's care and should not be considered in isolation.

Reviewing polypharmacy and deprescribing

The NICE guideline on medicines optimisation recognises that optimising a person's medicines can support the management of long-term health conditions, multimorbidity and polypharmacy. Deprescribing is the complex process needed to ensure the safe and effective withdrawal of inappropriate medicines (A patient centred approach to polypharmacy NHS Specialist Pharmacy Service 2015).

Resources have been developed to support healthcare professionals who are reviewing people with polypharmacy to help guide decision-making about the appropriateness of prescribing and deprescribing (see table 1). These resources include case examples and practical tools, such as the STOPP/START and NO TEARS tools. The NICE guideline on multimorbidity:

clinical assessment and management recommends that the use of a screening tool is considered (for example, the STOPP/START tool in older people) to identify medicine-related safety concerns and medicines the person might benefit from but is not currently taking.

Table 1. Polypharmacy resources

A patient centred approach to polypharmacy. NHS Specialist Pharmacy Service 2015
Polypharmacy guidance. NHS Scotland and the Scottish Government 2015
Polypharmacy: guidance for prescribing. All Wales Medicines Strategy Group 2014
Polypharmacy and medicines optimisation: making it safe and sound. The King's Fund 2013

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of a suitable comparator will be explored by the NHS England Medicines Optimisation Intelligence Group[1].

Update information

This is a new topic for the 2016/17 update of Medicines optimisation: key therapeutic topics.

[1] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority

Psychotropic medicines in people with learning disabilities whose behaviour challenges

Options for local implementation

- There is evidence of widespread prescribing of psychotropic medicines (antipsychotics, antidepressants and hypnotics) for people with learning disabilities, many of whom do not have potentially relevant licensed indications recorded for the psychotropic medicines they are prescribed. The use of psychotropic medicines to manage challenging behaviour in people with learning disabilities is off-label.
- People with learning disabilities may benefit from referral to a learning disability team for specialist review to minimise the use of psychotropic medicines.
- Review and, if appropriate, optimise prescribing and local policies relating to the treatment of challenging behaviour in people with learning disabilities to ensure these are in line with the NICE guidance on challenging behaviour and learning disabilities.

Evidence context

Background

The NICE guideline on challenging behaviour and learning disabilities explains that a learning disability is defined by 3 core criteria: lower intellectual ability (usually an IQ of less than 70), significant impairment of social or adaptive functioning, and onset in childhood. The guidance notes that the amount of everyday support a person with a learning disability needs will depend mostly on the severity of the disability. It advises that it is important to treat each person as an individual, with specific strengths and abilities as well as needs, and that a broad and detailed assessment may be needed.

The NICE guideline states that it is relatively common for people with a learning disability to develop behaviours that challenge, and more common in people with more severe disability. This behaviour can include aggression, self-injury, stereotypic behaviour, withdrawal, and disruptive or destructive behaviour. It can also include violence, arson or sexual abuse, and may bring the person into contact with the criminal justice system. Approximately 5-15% of people with learning disabilities in educational, health or social care services have behaviour that challenges, with higher rates in teenagers and people in their early 20s, and in particular settings. The behaviour may serve a purpose for the person such as creating sensory stimulation, getting help or avoiding demands. Some care environments increase the likelihood of behaviour that challenges. Multiple factors are likely to underlie the behaviour and thorough assessments of the person, their environment and any biological predisposition, together with a functional assessment, are needed to identify these. Interventions depend on the specific triggers for each person and may need to be delivered at multiple levels (including the environmental level). The aim should always be to improve the person's overall quality of life.

The full NICE guideline states that many types of psychotropic medicines have been used to manage behaviour that challenges, including antipsychotics, antidepressants, mood stabilisers and sedatives. Medicines are mostly used to reduce excitation and aggression, despite the limited evidence for efficacy in people with learning disability. Antipsychotics are the most frequently used class of psychotropic medicine, prescribed for as many as two-thirds of people with learning disability who are receiving any type of psychotropic medicine. The use of most psychotropic medicines to manage challenging behaviour in people with learning disabilities is off-label. The exception to this is risperidone which is licensed for the short-term symptomatic treatment of persistent aggression in conduct disorder in children (aged 5 years or more) and adolescents with learning disability who meet specific criteria. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using these medicines outside their authorised indications.

NICE guidance

The NICE guideline on challenging behaviour and learning disabilities, gives recommendations on the care of people with learning disabilities whose behaviour changes, including the use of medicines. The NICE quality standard on learning disabilities describes a concise set of prioritised statements designed to drive measurable quality improvements within these areas. A NICE pathway on challenging behaviour and learning disabilities brings together all related NICE guidance and associated products on this topic in a set of interactive topic-based diagrams.

The NICE guideline recommends considering medicines, or optimising existing medicines, for coexisting mental or physical health problems identified as a factor in the development and maintenance of behaviour that challenges. The guidance recommends considering antipsychotic medicines to manage behaviour that challenges only if:

- psychological or other interventions alone do not produce change within an agreed time or
- treatment for any coexisting mental or physical health problem has not led to a reduction in the behaviour or
- the risk to the person or others is very severe (for example, because of violence, aggression or self-injury).

Antipsychotic medicine should be offered only in combination with psychological or other interventions. Medicine choice should take into account the person's preference (or that of their family member or carer, if appropriate), side effects, response to previous antipsychotic medicine and interactions with other medicine.

The NICE guideline recommends that antipsychotic medicine should initially be prescribed and monitored by a specialist (an adult or child psychiatrist or a neurodevelopmental paediatrician). The specialist is responsible for identifying the target behaviour and monitoring the effectiveness of treatment, including the frequency and severity of the behaviour and its impact on functioning. Prescribers should prescribe only a single antipsychotic, start with a low dose

and use the minimum effective dose needed. The effectiveness and any side effects of the medicine should be reviewed after 3–4 weeks and it should be stopped if there is no response at 6 weeks. When required 'PRN' medicine should be prescribed for as short a time as possible and the specialist should ensure that its use is recorded and reviewed.

The NICE guideline highlights the importance of appropriate documentation when starting an antipsychotic, including a rationale for the medicine (which should be explained to the person with learning disability and everyone involved in their care), how long the medicine should be taken for and how the treatment should be reviewed and stopped. If there is a positive response to an antipsychotic medicine the extent of the response should be recorded, including how the behaviour has changed and any side effects or adverse events. A full multidisciplinary review should be conducted after 3 months and then at least every 6 months covering all prescribed medicines (including effectiveness, side effects and plans for stopping). Prescribers should only continue medicines that have proven benefit. When prescribing is transferred to primary or community care, or between services, the specialist should give clear guidance to the practitioner responsible for continued prescribing about the behaviours to target, monitoring of beneficial and side effects, taking the lowest effective dose, how long the medicine should be taken for and plans for stopping it.

The NICE guideline on mental health problems in people with learning disabilities makes recommendations for people with learning disabilities who are taking antipsychotic medicines and not experiencing psychotic symptoms. The guideline recommends the prescriber should:

- consider reducing or discontinuing long-term prescriptions of antipsychotic medicines,
- review the person's condition after reducing or discontinuing a prescription,
- consider referral to a psychiatrist experienced in working with people with learning disabilities and mental health problems, and

- annually document the reasons for continuing the prescription if it is not reduced or discontinued.

National reports

Three pieces of work have been commissioned following the Department of Health publication Transforming care: a national response to Winterbourne View hospital. These covered prescribing of psychotropic medicines for people with learning disabilities by GPs, a pilot improvement project that examined medicines practices and related matters, and medication prescribed for people with learning disabilities detained under the Mental Health Act (1983).

Prescribing of psychotropic medicines by GPs to people with learning disabilities

The largest natural sub-group of people with learning disabilities is those people who are currently not in hospital and who, for the most part, may be assumed to be receiving most or all of their medicines from their GP. Public Health England commissioned a study to examine prescribing of psychotropic medicines for this group of people. The analysis used GP records from the Clinical Practice Research Datalink primary care database (CPRD GOLD) and mainly focused on 5 classes of medicines: hypnotics, anxiolytics, antipsychotics, antidepressants and antiepileptic medicines.

The report, Prescribing of psychotropic drugs to people with learning disabilities and/or autism by general practitioners in England found widespread prescribing of psychotropic medicines, including prescription of multiple medicines from the same and different classes. With the exception of antiepileptic medicines, a high proportion of people had no potentially relevant licensed indications recorded for the psychotropic medicines they were prescribed.

The report found that adults with learning disabilities were exposed to 1 or more of the study medicines on 41% of person-days. Antipsychotics were being prescribed on 17% of person-days, medicines used in mania and hypomania on 7% of person-days, antidepressants on 17% of person-days,

anxiolytics on 4% of person-days and antiepileptic medicines on 23% of person-days. For most classes of medicine the exposure rates increased through adult life. A large proportion (90% or more) of the prescribing was not short term (prescriptions were followed by at least 1 repeat prescription).

Nearly one quarter (23%) of adults with learning disabilities receiving an antipsychotic received more than 1 medicine in this class. Only 6% were receiving doses of individual medicines above the recommended maximum, but the analysis did not consider additive dose effects in people prescribed more than 1 medicine in a BNF section or sub-section.

Among adults with learning disabilities a high proportion did not have potentially relevant indications recorded for the psychotropic medicines they were prescribed: 58% for antipsychotics, 32% for antidepressants, 56% for hypnotics and 46% for anxiolytics. The majority of people prescribed an antiepileptic drug (91%) had a relevant indication recorded. The authors estimated that between 30,000 and 35,000 adults with a learning disability in England (approximately 1 in 6) are taking an antipsychotic, an antidepressant or both in the absence of the conditions for which these medicines are indicated.

NHS Improving Quality report

NHS Improving Quality published the Winterbourne medicines programme report, a report on a pilot improvement project which examined medicines practices and related matters in 6 sites across England that provide care for those with learning disabilities. Although many examples of good practice were found, there were also some common themes for improvement. The report made 6 key recommendations intended to maximise improvement outcomes:

- involve people with learning disabilities, their families and carers
- invest in quality improvement training and time-out
- undertake analysis to understand current practice and areas for improvement
- ensure services actively use a care pathway for behaviours that challenge

- employ multidisciplinary/ interdisciplinary approaches
- stop and check at every stage along the pathway of care.

Care Quality Commission report

The Care Quality Commission (CQC) has access to data on medicines prescribed to people with learning disabilities detained under the Mental Health Act (1983) and who require a second opinion for treatment with medicines for mental health, under the provisions of that Act. Second Opinion Appointed Doctors (SOADs) provide a statutory safeguard for such people. SOADs visit the person and explore the current and proposed treatment, certifying what is considered to be appropriate and reasonable in circumstances where the person cannot or does not consent to it, discussing it with team members and the person before reaching their conclusions. A treatment plan is submitted to the CQC when the Second Opinion request is made by the provider clinician. These plans include information on medicines and the reasons given by the doctor for the prescription, together with information provided about the person's diagnosis.

The CQC conducted a survey of this information which is available in the report Survey of medication for detained patients with a learning disability. The survey identified 945 requests representing 796 individual patients across a 10 month period; the mean age was 34 years and two-thirds were male. Over half of the medicines did not have a recorded diagnosis that matched the recognised indications for that medicine. Antipsychotics were the most commonly used class of medicine, prescribed in 91% of requests, of which 44% were prescribed more than 1 antipsychotic at a time. The CQC report notes that we do not know the extent to which medicine was prescribed as an attempt to manage behaviour as opposed to treat a mental disorder. If at least some of the prescribing was to control behaviour, this might be because staff either lacked the resources or skills to manage in other ways behaviour that they found challenging. In general there was limited rationale offered for the entirety of the treatment plan, particularly when polypharmacy and high doses were used. The SOAD made changes to the overall treatment plan in around one-quarter of cases, commonly by restricting the total dose or number of

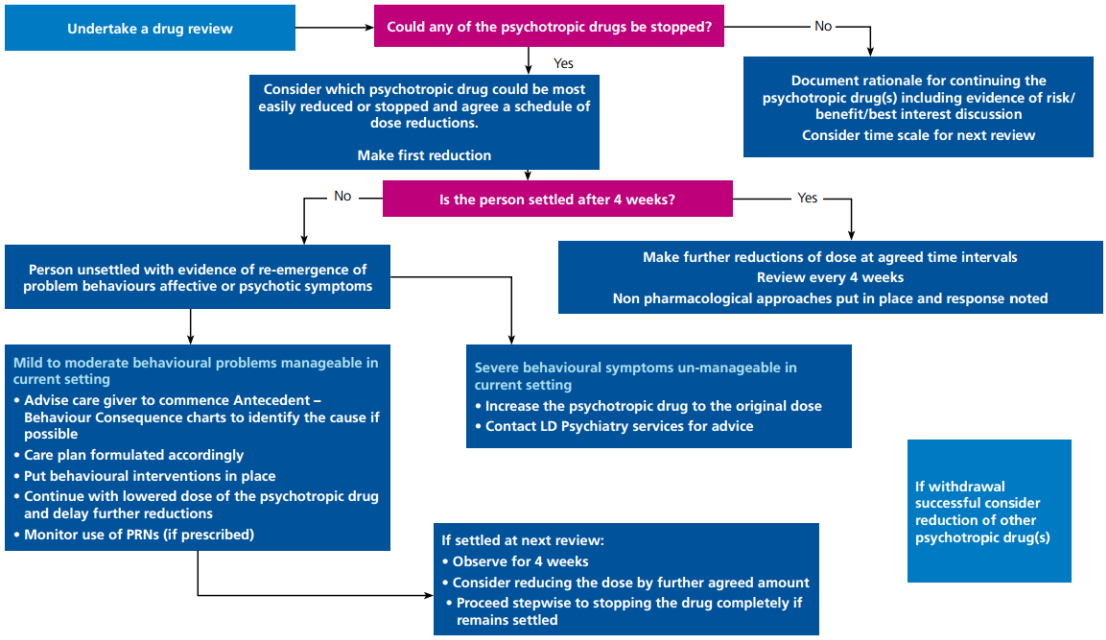
preparations permitted to be used. However, many certified treatment plans still permitted the administration of multiple psychotropic medicines and of high doses of antipsychotic medicines.

Reviewing, reducing or stopping psychotropic medicines in people with learning disabilities

In July 2015 NHS England pledged urgent action on over-medication of people with learning disabilities. The NHS England publication Stopping over-medication of people with learning disabilities provides support to begin the process of challenging the continued need for psychotropic medication in people with a learning disability.

The toolkit includes suggested steps to reduce inappropriate prescribing for GP practices, examples of good practice from NHS organisations and example case studies of psychotropic medicine reduction. The publication also includes an algorithm for the review, reduction or stopping of psychotropic medicines in people with a learning disability (see figure 1 below).

Figure 1. Algorithm for the review, reduction or stopping of psychotropic drugs in people with a learning disability (Stopping over-medication of people with learning disabilities)



A summary of Medicine advice for patients is available on the NHS England website, including guidance for patients, families and cares, a list of useful telephone numbers and a set of frequently asked questions.

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of a suitable comparator will be explored by the NHS England Medicines Optimisation Intelligence Group[2].

Update information

This is a new topic for the 2016/17 update of Medicines optimisation: key therapeutic topics.

[2] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority

Medicines optimisation in long-term pain: high-risk medicines

Options for local implementation

- Ensure people with long-term pain receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options.
- Assess risk and address harms of high-risk medicines such as opioids, gabapentin and pregabalin.
- Review and, if appropriate, optimise prescribing of opioids, gabapentin or pregabalin to ensure that it is in line with national guidance.

Evidence context

Managing long-term pain

There are a number of guidelines and resources that aim to improve communication between clinicians and patients around managing long-term pain, improving the safety and effectiveness of treatment for pain, and reducing the risks associated with high-risk medicines, such as opioids, pregabalin and gabapentin. It is important that patients receive appropriate treatment for their pain with careful consideration of the benefits and risks of their treatment options.

The NICE guideline on medicines optimisation provides recommendations for the care of all people who are using medicines and also those who are receiving suboptimal benefit from medicines. The use of strong opioids in palliative care for adults is addressed by the NICE guideline on palliative care for adults: strong opioids for pain relief. The recommendations cover safe and effective prescribing of strong opioids for pain relief in adults with advanced and progressive disease. The guideline recommends healthcare professionals discuss concerns with the patient about addiction, tolerance, adverse effects and fears of it implying the final stages of life; give verbal and written information to patients or their carers on strong opioid treatment; and offer patients access to frequent review of pain control and side effects. Care

during the last 2 to 3 days of life is covered by the NICE guideline on care of the dying adult, and is outside the scope of this key therapeutic topic. The NICE guideline on controlled drugs provides recommendations on the systems, processes or interventions for the safe use and management of controlled drugs. This includes recommendations for prescribers to review prescriptions for controlled drugs, prescribe an appropriate quantity and take into consideration the total opioid load that is being prescribed.

For managing neuropathic pain, recommendations are given in the NICE guideline on the pharmacological management of neuropathic pain in adults in non-specialist settings (see below). The NICE guideline on low back pain and sciatica is ongoing (date of publication to be confirmed). This is an update of the NICE guideline on low back pain and is looking at key issues including pharmacological interventions in the management of non-specific low back pain and sciatica.

See the NICE Clinical Knowledge Summaries on mild to moderate pain, pain in palliative cancer care, osteoarthritis, low back pain (without radiculopathy), rheumatoid arthritis, sciatica, neuropathic pain, non-specific neck pain, cervical radiculopathy and ankylosing spondylitis. The NICE pathways on controlled drugs, opioids for pain relief in palliative care and neuropathic pain bring together all related NICE guidelines and associated products on pain in a set of interactive topic-based diagrams. The NICE quality standard on medicines optimisation describes concise sets of prioritised statements designed to drive measurable quality improvements within these areas.

The opioids aware resource, a Public Health England funded project, contains specific information relating to the clinical use of opioids for pain that aims to support prescribers and patients in making a fully informed decision to use, or not use opioids. The resource includes good practice in prescribing, legislation, improving patient safety and minimising harms, clinical assessment and management, opioid dependence, structured approach to opioid prescribing, and information for patients.

Opioid medicines in long-term pain

Opioid medicines are prescribed to treat moderate to severe pain, but repeated use can lead to dependence and tolerance. Opioid medicines are subject to special legislative controls because there is potential for them to be abused, diverted or cause possible harm.

As outlined in the Opioids aware resource, there has been a marked and progressive rise in prescribing of opioid medicines in the UK over the past decade and the trend to increased prescribing continues. This resource highlights that:

- There is little evidence that opioids are helpful for long-term pain.
- A small proportion of people may obtain good pain relief with opioids in the long term if the dose can be kept low and use is intermittent, but it is difficult to identify these people at the start of treatment.
- The risk of harm increases substantially at doses above an oral morphine equivalent of 120mg/day, but there is no increased benefit.
- Opioids should be discontinued if the person is still in pain despite using opioids, even if no other treatment is available.
- A detailed assessment of the emotional influences on the person's pain experience is essential for people with chronic pain who also have refractory and disabling symptoms, particularly if they are on high opioid doses.

The Opioids aware resource also contains key points on the clinical use of opioids for long-term pain. It highlights that people with long-term pain who do not achieve useful pain relief from opioids within 2 to 4 weeks are unlikely to gain benefit in the long term, and that people who may benefit from opioids in the long term will demonstrate a favourable response within 2 to 4 weeks.

Side effects are common with opioid medicines; most commonly nausea, vomiting, constipation, pruritus, dizziness, dry mouth and sedation. The Opioids aware resource highlights that people taking opioids should be counselled about the possible effects on driving and other skilled tasks when initiating or increasing an opioid dose, and be warned of possible enhanced

risks associated with concomitant use of other medicines and substances with sedative properties, including alcohol.

Since March 2015, it is an offence to drive with certain controlled drugs above specified limits in the blood. Prescription drugs covered by the offence include amphetamine (such as dexamphetamine or selegiline), clonazepam, diazepam, flunitrazepam, lorazepam, methadone, morphine or opioid-based drugs (such as codeine, tramadol or fentanyl), oxazepam and temazepam. This list doesn't include all benzodiazepines and opioids. However, all benzodiazepines and opioids can impair driving ability. See the July 2014 edition of Drug Safety Update and the Drugs and driving: the law government webpage for more details.

A checklist for initiating opioids is available in the Opioids aware resource for prescribers. This includes information on what to discuss with the person when considering opioid treatment, documentation, prescribing responsibly and arranging reviews. The resource also includes advice on long-term prescribing that covers choice of opioid, formulation, agreeing outcomes, review and documentation.

There have been several safety concerns highlighted at a national level about the use of strong analgesics such as opioids to manage long-term pain. The Office for National Statistics (ONS) bulletin Deaths Related to Drug Poisoning in England and Wales, 2015 reported:

- Of all deaths related to drug poisoning in 2015, 54% involved an opioid drug (excluding combination compounds such as co-codamol). This proportion has been relatively stable since 2007.
- Deaths involving heroin or morphine doubled from 579 in 2012 to 1,201 in 2015.
- Deaths involving tramadol fell for the first time, from 240 deaths in 2014 to 208 in 2015. In June 2014, tramadol was controlled under the Misuse of Drugs Act 1971 as a class C substance.

- The number of deaths involving codeine were 130 in 2013, 136 in 2014 and 128 in 2015.

In July 2008, the National Patient Safety Agency (NPSA), which is now part of NHS Improvement, issued a rapid response report about reducing dosing errors with opioid medicines. This followed incidents being reported to the National Reporting and Learning System (NRLS) concerning people receiving unsafe doses of opioid medicines, where a dose or formulation was incorrect based on their previous opioid dose. A review of medicines-related safety incidents involving controlled drugs reported to the NRLS over 7 years found the risk of death with controlled drug incidents was significantly greater than with medication incidents generally (odds ratio 1.48, 95% CI 1.02 to 2.17). Incidents involving overdose of controlled drugs accounted for 89 (70%) of the 128 incidents reporting death or severe harm. Five controlled drugs (morphine, diamorphine, fentanyl, midazolam and oxycodone) were responsible for 113 (88%) of these 128 incidents.

The Care Quality Commission controlled drugs annual report 2015 found that the top 5 controlled drugs prescribed in primary care (number of items) were tramadol, buprenorphine, morphine sulfate, methadone and oxycodone. The report compared 2015 prescribing data with 2014 prescribing data and found there were increases in the volume of items prescribed for: oxycodone (9.9%), morphine sulfate (7.0%), buprenorphine (5.2%), and fentanyl (1.9%). There was a decrease in volume of items prescribed for tramadol (4.6%) and methadone (1.4%) compared with 2014.

The MHRA has published Drug Safety Updates for a number of opioid medicines, which should be considered when prescribing opioids for long-term pain. In the July 2011 and September 2009 editions of Drug Safety Update, the MHRA reinforced the issues about addiction to codeine following tighter controls for sales of over-the-counter (OTC) medicines containing codeine or dihydrocodeine. The September 2008 edition of Drug Safety Update highlighted evidence of unintentional overdose of fentanyl following inappropriate prescribing of fentanyl patches, including prescribing in unlicensed indications and in opioid-naive patients.

The Care Quality Commission and the NHS England Patient Safety Team (patient safety sub-group) have developed checklists for healthcare professionals for the safer use of several opioids used in long-term pain. These followed patient safety incidents reported to the NRLS, and include checklists for the safer use of fentanyl and buprenorphine transdermal patches, oral oxycodone medicines and use of MS syringe drivers. The patient safety sub-group also produce patient safety newsletters to share patient-related controlled drugs incidences, learning and signpost to relevant guidance.

Non-opioid medicines in long-term pain

Other types of analgesics are also used to manage long-term pain, particularly neuropathic pain. For managing neuropathic pain, the NICE guideline on the pharmacological management of neuropathic pain in adults in non-specialist settings recommends offering a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia). Regular clinical reviews are recommended to assess and monitor the effectiveness of treatment so that treatment with medicines can be optimised.

Prescribers should note that amitriptyline does not currently have a UK marketing authorisation for this indication, duloxetine is licensed for diabetic peripheral neuropathic pain only, and gabapentin is licensed for peripheral neuropathic pain only, so use for other conditions would be an off-label use[3]. In addition, the Lyrica (Pfizer) brand of pregabalin has patent protection until July 2017 for its licensed indication of treatment of peripheral and central neuropathic pain.

The use of both gabapentin and pregabalin can lead to dependence and these medicines may be misused or diverted. Public Health England and NHS England have published advice for prescribers on the risk of misuse of

[3] The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

pregabalin and gabapentin. This advice stated that in 2014, the total use in primary care in England of both these medicines was 8.2 million prescriptions, which represented a 46% rise in the prescribing of gabapentin and a 53% rise in the prescribing of pregabalin since 2011. At this time there was also wide variation in prescribing across England, which may be partly but not fully explained by social and demographic differences between populations. Since 2014, there has been a further 18% rise in prescribing for pregabalin and a 15% rise for gabapentin (Prescription cost analysis England 2015). In 2016, PrescQIPP published a bulletin on pregabalin and gabapentin prescribing in neuropathic pain.

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of prescribing comparators to support this key therapeutic topic will be explored by the NHS England Medicines Optimisation Intelligence Group[4].

However, the NHS Business Services Authority produces 2 sets of reports for controlled drug monitoring:

- comparator charts available for the last 2 quarters' prescribing data
- analysis reports that can be accessed via the information services portal.

These reports monitor the prescribing of schedule 2 and 3 controlled drugs to enable controlled drug accountable officers to highlight potential causes for concern within the prescribing of controlled drugs through demonstrating variance in prescribing between organisations, and by identifying prescribers or organisations exhibiting unusual prescribing behaviour (NHS Business Services Authority Controlled Drug Monitoring).

Update information

This is a new topic for the 2016/17 update of Medicines optimisation: key therapeutic topics.

[4] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

Safer insulin prescribing

Options for local implementation

- Clinicians should ensure that people with diabetes who are receiving insulin therapy are given information about awareness and management of hypoglycaemia.
- People with diabetes who use insulin and who drive should be aware of the need to notify the Driver and Vehicle Licensing Agency (DVLA). Clinicians should refer to chapter 3 of the DVLA's Assessing fitness to drive – a guide for healthcare professionals for more information.
- Clinicians should be aware of 'sick-day' rules and should ensure that people with diabetes who are receiving insulin therapy are given appropriate information about these.
- Several new insulin products have been launched recently, including high-strength, fixed combination and biosimilar insulins. Clinicians should be aware of the differences between these products and ensure that people receive appropriate training on their correct use. People should be advised to only use insulin in the way they have been trained because using it any other way may result in a dangerous overdose or underdose.
- Adults who are using insulin therapy should receive a patient information booklet and an Insulin Passport.

Evidence context

This key therapeutic topic focuses on safety issues with insulin, rather than treatment recommendations. Recommendations on the choice of insulin are provided in the NICE guidelines on:

- type 1 diabetes in adults: diagnosis and management,
- type 2 diabetes in adults: management,
- diabetes (type 1 and type 2) in children and young people: diagnosis and management, and

- diabetes in pregnancy: management from preconception to the postnatal period.

Recommendations on continuous subcutaneous insulin infusion (CSII or insulin pump) therapy are provided in the NICE technology appraisal guidance: continuous subcutaneous insulin infusion for the treatment of diabetes mellitus.

Hypoglycaemia

Hypoglycaemia is an inevitable adverse effect of insulin therapy. It can range from mild which includes symptoms such as hunger, anxiety or irritability, palpitations, sweating, or tingling lips, to severe which can result in convulsions, loss of consciousness, and coma.

All the NICE guidelines on diabetes recommend that people receiving insulin therapy are provided with education and information about awareness and management of hypoglycaemia. NICE guidelines on type 1 diabetes in adults, type 1 and 2 diabetes in children and young people, and diabetes in pregnancy recommend that people receiving insulin therapy should always have available a fast-acting source of glucose for the management of hypoglycaemia. In cases of severe hypoglycaemia where a person has a reduced level of consciousness, intramuscular glucagon given by another person is recommended.

Driving

People with diabetes who are using insulin therapy must notify the Driver and Vehicle Licensing Agency (DVLA). In order for the DVLA to license a person with insulin-treated diabetes certain criteria must be met depending on whether they are seeking a group 1 (car and motorcycle) or group 2 (bus and lorry) licence. The presence of certain diabetes complications such as visual and renal complications may mean that a person needs to stop driving and notify the DVLA depending on the circumstances. People with impaired awareness of hypoglycaemia must not drive and must notify the DVLA. Monitoring of blood glucose is mandatory for drivers with insulin-treated

diabetes in line with recommendations in chapter 3 of the DVLA's Assessing fitness to drive – a guide for healthcare professionals.

'Sick-day' rules

The NICE guidelines on type 1 and 2 diabetes in children and young people, and type 1 diabetes in adults recommend that clear guidance ('sick‑day rules') should be given to all people with type 1 diabetes (and their family or carers where appropriate) to help them to manage their condition appropriately during periods of illness. In children and young people this individualised guidance should include information on monitoring blood glucose, monitoring and interpreting blood ketones, adjusting insulin regimens, food and fluid intake, and when and where to seek further advice and help. The NICE guideline on type 1 diabetes in adults recommends that 'sick-day' information should help adults with type 1 diabetes to adjust their insulin dose during periods of illness, and that ketone monitoring (blood or urine) to facilitate self‑management of an episode of hyperglycaemia should be considered. Diabetes UK provides information for people with diabetes on dealing with illness.

Continuous subcutaneous insulin infusion therapy

Continuous subcutaneous insulin infusion (insulin pump) therapy makes use of an external pump that delivers insulin continuously from a refillable storage reservoir by means of a subcutaneously placed cannula. The pump can be programmed to deliver a basal rate of insulin throughout the day, with higher infusion rates triggered by the push of a button at meal times. This may be a bolus or over a period of time. The pump can also deliver different basal rates of insulin at different times of the day and night. Several medical device alerts regarding safety issues with the use of insulin pumps have been issued. See the MHRA alerts and recalls for drugs and medical devices page for more information.

Insulin prescribing and administration

Several new insulin products have been launched recently and the European Medicines Agency has issued guidance on preventing medication errors with

high-strength insulins. This includes advice for healthcare professionals such as ensuring people are provided with adequate information about their insulin, prescribing insulin doses in units ensuring that the word 'units' is spelled out in lower case, only using high-strength insulin with the pre-filled pen it is supplied in, explaining the difference in appearance between different insulin preparations to people, and telling people to closely monitor their blood glucose levels when starting high-strength insulin and in the weeks afterwards.

In the April 2015 edition of Drug Safety Update the MHRA issued advice to health professionals to minimise the risk of medication errors with recently launched high-strength, fixed combination and biosimilar insulin products. Recommendations included that clinicians should consult the summary of product characteristics and any educational material relevant to insulin product, ensure that people read and understand the patient leaflet and any patient education material, and ensure that people receive appropriate training on the correct use of the product. People should also be advised to only use insulin in the way they have been trained because using it in any other way may result in a dangerous overdose or underdose.

In 2010, the National Patient Safety Agency (NPSA), which is now part of NHS Improvement, issued a rapid response report about the safer administration of insulin. The report highlighted that errors in the administration of insulin by clinical staff are common. In certain cases they may be severe and can cause death. Two common errors were identified: the inappropriate use of non-insulin (IV) syringes, which are marked in ml and not in insulin units, and the use of abbreviations such as 'U' or 'IU' for units (when abbreviations were added to the intended dose, the dose was misread). The report made several recommendations including suggesting that a training programme should be put in place for all healthcare staff (including medical staff) expected to prescribe, prepare and administer insulin.

In 2011, the NPSA issued a patient safety alert on the adult patient's passport to safer use of insulin. The alert discussed that errors involving using the wrong insulin product, omitted or delayed insulin dose, and wrong insulin dose

accounted for 60% of 16,600 insulin-related adverse drug events (including 6 deaths) reported in the UK between November 2003 and November 2009. The NPSA made recommendations to improve patient safety by empowering patients to take an active role in their treatment with insulin. A patient information booklet and a patient-held record (the Insulin Passport) was developed which documents the patient's current insulin products and enables a safety check for prescribing, dispensing and administration. It was recommended that all adults who are using insulin therapy should receive a copy of these. The April 2015 edition of Drug Safety Update reinforced this message, reminding healthcare professionals that all people starting treatment with a high-strength, fixed combination or biosimilar insulin product should be provided with a patient booklet and Insulin Passport (or safety card). The NPSA patient safety alert also recommended that when prescriptions of insulin are prescribed, dispensed or administered, healthcare professionals cross-reference available information to confirm the correct identity of insulin products, and that systems should be put in place enabling hospital inpatients to self-administer insulin (where feasible and safe), to reduce the harm associated with incorrectly timing insulin administration with food, and deaths and severe harm caused by errors.

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of a suitable comparator will be explored by the NHS England Medicines Optimisation Intelligence Group[5]. An MO KTT prescribing comparator on l**ong-acting insulin analogues** is available to support the key therapeutic topic on type 2 diabetes mellitus.

Update information

This is a new topic for the 2016/17 update of Medicines optimisation: key therapeutic topics.

[5] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority

Biosimilar medicines

Options for local implementation

- Biosimilar medicines have the potential to offer the NHS considerable cost savings and widen the access to innovative medicines.
- Develop and agree local policies to support the managed introduction of biosimilar medicines into care pathways safely and effectively as they become available, taking into account relevant regulatory advice, national guidance, patient factors and cost.
- Review and, if appropriate, optimise prescribing of medicines for which biosimilar medicines exist to ensure it is in line with these policies.
- Ensure all biological medicines, including biosimilar medicines, are prescribed by brand name so that products cannot be automatically substituted at the point of dispensing. The choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient.

Evidence context

The NHS England publication, What is a biosimilar medicine? states that a biosimilar medicine is a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the originator biological medicine in terms of quality, safety and efficacy. The continuing development of biological medicines, including biosimilar medicines, creates increased choice for patients and clinicians, increased commercial competition and enhanced value propositions for individual medicines. Biosimilar medicines have the potential to offer the NHS considerable cost savings and widen the access to innovative medicines.

NICE position statement on evaluating biosimilars

NICE's position statement on evaluating biosimilar medicines was published in January 2015. This states that biosimilars notified to the NICE topic

selection process for referral to the Technology Appraisal programme will usually be considered in the context of a Multiple Technology Appraisal, in parallel with their reference products in the indication under consideration. The Department of Health has confirmed that a technology appraisal remit referred to NICE enables NICE to decide to apply the same remit, and the resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market. In other circumstances, where it is considered a review of the evidence for a biosimilar medicine is necessary, NICE will consider producing an evidence summary: new medicine.

Licensing and comparability

Biosimilar medicines introduced into the UK market are authorised by the European Medicines Agency (EMA). The EMA has produced a document covering a series of questions and answers on biosimilar medicines. Biological medicines such as monoclonal antibodies, growth hormone and insulin are produced in or derived from living systems. The size and complexity of biological medicines, as well as the way they are produced, may result in a degree of natural variability in molecules of the same active substance, particularly in different batches of the medicine. The active substance of a biosimilar and its reference medicine is essentially the same biological substance but, just like the reference medicine, the biosimilar has a degree of natural variability. When approved, this variability and any differences between the biosimilar and its reference medicine will have been shown not to affect safety or effectiveness.

In the development of a biosimilar, there is no requirement to demonstrate clinical benefit to patients *per se* as this has been shown for the reference medicine. Instead, biosimilars undergo a comprehensive regulatory process which demands extensive comparability studies that demonstrate similarity to the reference medicine. The benefits and risks are then inferred from the similarity of the biosimilar medicine to the reference medicine in terms of quality, efficacy and safety. Biosimilar medicines are usually licensed for all the indications in the licence of the originator biological medicine, but this requires appropriate scientific justification on the basis of demonstrated or

extrapolated equivalence. They are generally used at the same dose and route of administration as the biological reference medicine and have the same contraindications and warnings in their summaries of product characteristics. However, the ongoing safety of any biosimilar or originator biological medicine is monitored separately (see below).

Any biological drug is likely to be modified several times during its production history and development, for example when there is a change in manufacturing process. After each such change, a similar comparability exercise that is carried out for a biosimilar is carried out to ensure that the new biological drug is similar to the old one. Therefore from a scientific and regulatory point of view, the active substance of the biosimilar could be viewed as just another version of the active substance of the originator. See the NHS publication Answers to commonly asked questions about biosimilar versions of infliximab and The NHS England publication, What is a biosimilar medicine? for more details.

Brand name prescribing and pharmacovigilance

In the UK, the MHRA recommends that all biological medicines, including biosimilar medicines, are prescribed by brand name (February 2008 edition of Drug Safety Update). Because biosimilar and reference biological medicines that have the same international non-proprietary name (INN) are not presumed to be identical in the same way as generic non-biological medicines, brand name prescribing ensures that the intended product is received by the patient. It ensures that products cannot be automatically substituted at the point of dispensing. The choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient.

Pharmacovigilance is important for biosimilar medicines and every biosimilar authorised by the EMA will have a risk management plan in place (details of which will be in the European Public Assessment Report). Based on similarity being demonstrated with the reference medicine, the biosimilar can also refer to the safety experience gained with the reference medicine. As with all new medicines, biosimilars have a 'black triangle' in the first years after approval

and any suspected adverse drug reactions should be reported through the Yellow Card Scheme (see the June 2009 edition of Drug Safety Update on the black triangle scheme for more information).

Patient registers are used to monitor for emerging safety and efficacy issues with biological medicines, and the MHRA supports the recording of brand names and batch numbers for traceability when reporting suspected adverse drug reactions (November 2012 edition of Drug Safety Update). The NHS Specialist Pharmacy Service has developed a validated tool to determine potential safety issues associated with new medicines, and these 'in-use product safety assessment reports' will be published for new biosimilar medicines as they become available. The in-use product safety assessment report for the infliximab biosimilars, Inflectra and Remsima, states that brand name prescribing is vital if products are to be identified appropriately at the points of dispensing and administration. As with all biological medicines, for each patient, a traceable record of the brand, batch number, and other vital details of the product used should be made. Reporting and monitoring of patients through clinical registries will enable collection of specific data on serious adverse events, and these mechanisms will act in addition to routine pharmacovigilance activities. Safe introduction and ongoing safe use of biosimilars requires practitioner, patient and manufacturer engagement with these processes. An in-use product safety assessment report for the etanercept biosimilar, Benepali has also been published.

Managing the introduction of biosimilar medicines

NHS England are undertaking a programme of work to improve clinician confidence and clarify understanding amongst decision makers, such as commissioners, clinicians, pharmacists and patients in their consideration of the appropriate use of biosimilar medicines. This includes the publication of What is a biosimilar medicine? and a collaborative work programme to improve education and understanding of both the theory and practical considerations related to biosimilar medicines. NHS England are working with NHS Clinical Commissioners, regional Medical Directors and Academic

Health Science Networks to maximise the opportunities of a more competitive biological medicines market for the benefit of patients.

The NICE adoption resource introducing biosimilar versions of infliximab: Inflectra and Remsima, was produced to help manage the introduction of biosimilar medicines into care pathways safely and effectively. NHS organisations shared their learning and experiences of introducing biosimilar medicines and these are presented as a series of examples of current practice. They are not presented as best practice but as real-life examples of how NHS sites have planned and managed the introduction of biosimilars. Local organisations will need to assess the applicability of the learning from the examples of current practice, taking into consideration the time, resources and costs of an implementation programme.

The NHS staff involved in the production of the NICE adoption resource reported that the use of biosimilars can reduce costs, allowing more treatment with new medicines, as long as the appropriate follow-up and monitoring systems are in place to manage risk and patient needs and expectations. Particular tips for managing the introduction of biosimilar medicines included:

- Identify clinical and pharmacy champions to take the lead in introducing biosimilars.
- Consult all stakeholders (including patients) to ensure confidence in using biosimilars.
- Provide information about the EMA licensing process for biosimilars, extrapolation and equivalence, and the manufacturing process (including intra-product manufacturing changes for both biological medicines and their biosimilars).
- Identify the potential cost-saving and re-investment opportunities and explore gain-share agreements.
- Seek formal approval at the local formulary committee once there is clinical consensus to include biosimilars on the formulary.
- Collect baseline data and agree metrics to be collected during and after the introduction of biosimilars.

- Submit data to national audits and registries.

In February 2016, the British Society of Gastroenterology published guidance on the use of biosimilar infliximab (Inflectra and Remsima) in inflammatory bowel disease. This recommends that there is sufficient evidence to recommend that patients who are in a stable clinical response or remission on Remicade therapy can be switched to Remsima or Inflectra at the same dose and dose interval. This should be done after discussion with individual patients, with explanation of the reason for switching (which is usually on the grounds of benefit to the overall service by reduction in costs of the drug and its administration).

An evidence summary: new medicine publication on the insulin glargine biosimilar, Abasaglar is also available.

Prescribing data

Biosimilar versions of epoetin, filgrastim and somatropin have been available for some time. As for all medicines, the safety of biosimilar medicines is continuously monitored after authorisation, and no particular safety concerns have arisen for these biosimilar medicines that have required regulatory action to be taken. Recently, biosimilar versions of infliximab (Inflectra, Remsima and Flixabi) etanercept (Benepali) and insulin glargine (Abasaglar) have been launched in the UK. Further biosimilar versions of adalimumab, bevacizumab, pegfilgrastim, rituximab and trastuzumab are expected to be available in the next few years.

Biosimilars have the potential to offer the NHS considerable cost savings, especially as biological medicines are often expensive and are often used to treat long-term conditions. The NHS England publication, What is a biosimilar medicine? states that biosimilar medicines are more challenging and expensive to develop than generic medicines. Whilst they cannot offer the same percentage price reductions as traditional generic medicines, nevertheless, there are significant savings associated with increased competition between biological medicines, including biosimilar medicines. Recent research has given clear evidence that the additional competition is

bringing value and opportunity to widen access for patients in some circumstances. However, this research also demonstrates that biosimilar medicine uptake across Europe to date shows very different patterns, depending on the class of biological medicine and the procurement measures in place. Costs for both biosimilar and originator biological medicines may vary locally depending on local contractual arrangements, and Regional Pharmacy Procurement Specialists will be able to provide more details.

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of prescribing comparators to support this key therapeutic topic is currently being explored by the NHS England Medicines Optimisation Intelligence Group[6].

The medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors, includes a prescribing metric on biosimilars. This is the proportional split of the use of the originator biological medicine and biosimilar versions of infliximab by volume. There is an intention to include other biosimilar medicines in the medicines optimisation dashboard as they become available. The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence as appropriate.

[6] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

Anticoagulants, including non-vitamin K antagonist oral anticoagulants (NOACs)

Options for local implementation

- NICE has issued technology appraisal guidance on the use of the 4 non-vitamin K antagonist oral anticoagulants (NOACs), apixaban, dabigatran etexilate, edoxaban and rivaroxaban, in several clinical settings. All 4 NOACs must be included in local formularies for use in line with this guidance, with no additional funding or formulary restrictions.
- All anticoagulants are associated with several patient safety hazards. In 2007, the National Patient Safety Agency (NPSA), which is now part of NHS Improvement, issued a patient safety alert about anticoagulants. Although the alert pre-dates the widespread use of NOACs the principles within it are still applicable to practice.
- Review and, if appropriate, optimise prescribing and local policies relating to anticoagulants and antiplatelets, including NOACs, to ensure these are in line with NICE guidance and the principles of the NPSA safety alert.
- Several factors are likely to affect the choice of anticoagulant for an individual person. NICE has produced a patient decision aid to support discussions about anticoagulant options for people with atrial fibrillation.

Evidence context

Place in therapy of non-vitamin K antagonist oral anticoagulants (NOACs)

The 4 non-vitamin K antagonist oral anticoagulants (NOACs) currently licensed in the UK are apixaban, dabigatran etexilate, edoxaban and rivaroxaban. NICE has issued technology appraisal guidance on the use of NOACs in several clinical settings. These are summarised in table 1.

Table 1: NICE technology appraisal guidance on NOACs

Indication	Apixaban	Dabigatran etexilate	Edoxaban	Rivaroxaban
Prevention of VTE after elective hip or knee replacement	Recommended as an option: TA245[a]	Recommended as an option: TA157[a]	Not licensed for this indication	Recommended as an option: TA170[a]
Treatment and secondary prevention of DVT and/or PE	Recommended as an option: TA341[a]	Recommended as an option: TA327[a]	Recommended as an option: TA354[a]	Recommended as an option: TA261[a] and TA287[a]
Prevention of stroke and systemic embolism in people with non-valvular AF	Recommended as an option in specified circumstances: TA275[a]	Recommended as an option in specified circumstances: TA249[a]	Recommended as an option in specified circumstances: TA355	Recommended as an option in specified circumstances: TA256[a]
Prevention of adverse outcomes after acute management of ACS with raised biomarkers	Not licensed for this indication	Not licensed for this indication	Not licensed for this indication	Recommended as an option in specified circumstances: TA335[a]

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; TA, technology appraisal; VTE, venous thromboembolism.

[a] See the technology appraisal for full details of NICE's recommendations.

The technology appraisal guidance summarised in table 1 should be read in the context of the relevant NICE guidelines, which set out the alternative treatments:

- Venous thromboembolism: reducing the risk for patients in hospital NICE guidance CG92 (which is being updated; publication expected January 2018).
- Venous thromboembolic diseases: diagnosis, management and thrombophilia testing NICE guidance CG144
- Atrial fibrillation: management NICE guidance CG180

- Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease NICE guidance CG172

The NICE pathways on venous thromboembolism, atrial fibrillation and myocardial infarction: secondary prevention bring together all related NICE guidance and associated products on the conditions in a set of interactive topic-based diagrams. NICE has also published quality standards on venous thromboembolism prevention and atrial fibrillation: treatment and management which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas. It should be noted that, consistent with the NICE guideline, quality statement 2 for atrial fibrillation states: 'Adults with atrial fibrillation are not prescribed aspirin as monotherapy for stroke prevention.'

In some instances, not all the NOACs recommended as options in later technology appraisals are mentioned in the relevant NICE guideline. This is because they were not licensed for the indication at the time the guideline was published. Nevertheless, they should be considered as equal options alongside the NOAC(s) mentioned. All 4 NOACs must be included in local formularies for use in line with NICE technology appraisal guidance, with no additional funding or formulary restrictions. Further information is available in the document 'Frequently asked questions about NICE compliance', published on the NICE website.

As with all its recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions and the person's values and preferences. This discussion should aim to help the person to reach a fully informed decision. NICE has produced a patient decision aid to support discussions about anticoagulant options for people with atrial fibrillation.

The absence of direct comparisons between different NOACs and differences in study populations, analyses and other factors in key studies raise difficulties when choosing among them for different indications. Several factors are likely to affect the choice for an individual. The discussion should therefore consider

all the possible options, including the advantages and disadvantages of each as appropriate to the individual person's clinical circumstances, needs, values and preferences.

The NICE guideline on MI: cardiac rehabilitation and prevention of further cardiovascular disease advises against using a NOAC in combination with dual antiplatelet therapy in people who have had an MI. It recommends considering using warfarin and discontinuing treatment with a NOAC in such people, unless there is a specific clinical indication to continue it. This relates to people who have an indication for anticoagulation, such as atrial fibrillation, which may or may not be related to their MI. The full guideline explains that the recommendation arises from the limited evidence for the use of NOACs in this context, and the likely increased risk of bleeding. This is a different scenario from that considered in the NICE technology appraisal guidance on rivaroxaban after acute coronary syndrome. The licensed dose of rivaroxaban for preventing adverse outcomes after acute coronary syndrome is 2.5 mg twice a day; this is lower than the licensed dose for other indications (10–20 mg once a day). The risk of bleeding is therefore also likely to be lower.

Safety issues with anticoagulants

In 2007, the National Patient Safety Agency (NPSA), which is now part of NHS Improvement, issued a patient safety alert about anticoagulants. This recommended that healthcare organisations in England and Wales should:

- Ensure staff are properly trained.
- Review and update written procedures and clinical protocols to ensure they reflect safe practice.
- Audit anticoagulant services using British Society of Haematology (BSH)/NPSA safety indicators as part of the annual medicines management audit programme.
- Ensure that patients prescribed anticoagulants receive appropriate information.
- Promote safe practice for prescribers and pharmacists to check that patients' blood clotting (International Normalised Ratio, INR) is monitored

regularly and that the INR level is safe before issuing or dispensing repeat prescriptions for oral anticoagulants.

- Promote safe practice for prescribers co-prescribing one or more clinically significant interacting medicines for patients already on oral anticoagulants: arrange for additional INR blood tests and inform the anticoagulant service that an interacting medicine has been prescribed.
- Ensure dental practitioners manage patients on anticoagulants according to evidence-based therapeutic guidelines.
- Amend local policies to standardise the range of anticoagulant products used, incorporating characteristics which promote safer use.
- Promote the use of written safe practice procedures for the administration of anticoagulants in social care settings.

The alert pre-dates the widespread use of NOACs (for which INR monitoring is not appropriate) but the principles within it are still applicable to practice. This key therapeutic topic highlights 3 important safety issues relating to the use of anticoagulants (although all components of the NPSA safety alert should be considered):

- Information and awareness
- Dosing and administration errors, including omitted or delayed doses or inappropriately continued prescribing
- Interactions (including concomitant use of additional anticoagulant or antiplatelet drugs), contraindications and warnings

Information and awareness

It is important that people prescribed anticoagulants, and the health and social care practitioners looking after them, have sufficient information to use these medicines safely and effectively. The type of information to be provided to patients is described in the NICE guideline on venous thromboembolic diseases:

- how to use anticoagulants
- duration of anticoagulation treatment

- possible side effects of anticoagulant treatment and what to do if these occur
- the effects of other medications, foods and alcohol on oral anticoagulation treatment
- monitoring their anticoagulant treatment
- how anticoagulants may affect their dental treatment
- taking anticoagulants if they are planning pregnancy or become pregnant
- how anticoagulants may affect activities such as sports and travel
- when and how to seek medical help.

It is also very important that health and social care practitioners are aware that NOACs are anticoagulants: reports to the National Reporting and Learning System (NRLS) suggest that unawareness and lack of recognition of generic and brand names may be a contributing factor to safety issues (personal communication, NHS Improvement, July 2016).

The patient-held yellow booklet 'Oral anticoagulant therapy: important information for patients' includes an alert card designed to be carried at all times by a person taking warfarin, as recommended in the NICE guideline on venous thromboembolic diseases. The card informs health and social care practitioners that the person is taking oral anticoagulants, and provides a contact telephone number. The booklet also contains general information about the safe use of warfarin and has space for a written record of the latest INR test results, dosage information and the next clinic appointment. People prescribed NOACs should be directed to the manufacturer's patient information leaflets and be advised to carry an alert card, and show it to all health and social care practitioners who care for them (including community pharmacists and optometrists as well as doctors, nurses, dentists and social care practitioners). The card might be one provided by the manufacturer and specific to that particular NOAC, or a generic card such as that produced by Northern England Strategic Clinical Networks or the Atrial Fibrillation Association.

Dosing and administration errors, including omitted or delayed doses or inappropriately continued prescribing

Several instances of patient harm have been reported to the NRLS that involved doses of NOACs being omitted or delayed (personal communication, NHS Improvement). High adherence to all anticoagulants is important, particularly for NOACs because their half-lives are much shorter than that of warfarin. The CKS summary on oral anticoagulation states that the anticoagulant effect of NOACs fades 12–24 hours after the last dose is taken. Omitting or delaying doses could therefore lead to a reduction in anticoagulant effect, resulting in thrombosis. Apixaban has twice-daily dosing for all indications whereas dabigatran etexilate and rivaroxaban have twice-daily dosing for some indications and once-daily dosing for others. Edoxaban has once-daily dosing for all indications (see summaries of product characteristics [SPCs] for details). It is important that patients and health and social care staff realise the importance of adherence, and that prescribers select the correct dose and dosing interval for the indication (taking into account any need for dose reduction, for example in people with renal impairment).

The risk of bleeding associated with surgery (including dental surgery) is increased if a person is taking an anticoagulant. As with warfarin, there are recommendations around whether NOACs need to be stopped before planned surgery, and at what interval beforehand (see SPCs for drug-specific recommendations). However, instances of patient harm have been reported to the NRLS that involved NOACs not being stopped before surgery, or not being restarted at an appropriate time after surgery (personal communication, NHS Improvement).

A specific reversal agent for dabigatran etexilate is available: idarucizumab. This is licensed for use in adults treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding (see the evidence summary: new medicine publication Reversal of the anticoagulant effect of dabigatran: idarucizumab). There are currently no other licensed

agents to reverse the anticoagulant effect of dabigatran etexilate (or any other NOAC).

Analysis of adverse incidents involving inappropriate continuation of NOACs or omitted or delayed dosing suggests that failure to recognise the NOAC as an anticoagulant may have been a contributing factor in some cases (personal communication, NHS Improvement).

Interactions (including concomitant use of additional anticoagulant or antiplatelet drugs), contraindications and warnings

Warfarin is well-known to have a large number of drug–drug and drug–food interactions. These include interactions with medicines available over the counter. For example, the June 2016 edition of Drug Safety Update reminded healthcare professionals of the potential for serious interactions between warfarin and miconazole, including miconazole gel. This highlights the need for awareness that the person is taking an anticoagulant. NOACs also have drug–drug interactions that healthcare professionals should be aware of (see SPCs for details).

Patients may be placed at increased risk of bleeding if multiple anticoagulants are prescribed, or anticoagulants are co-prescribed with other drugs that increase the risk of bleeding. Examples include antiplatelets and non-steroidal anti-inflammatory drugs. Analysis of adverse incidents reported to NRLS suggests that failure to recognise NOACs as anticoagulants may have been a contributing factor in some cases where there was inadvertent co-prescribing of a NOAC with an antiplatelet, heparin or warfarin (personal communication, NHS Improvement).

Care should be taken when considering prescribing any anticoagulant to a person with other conditions, procedures or concomitant treatments that may increase the risk of major bleeding. In the October 2013 edition of Drug Safety Update, the MHRA issued advice on the contraindications and warnings for the 3 NOACs licensed at the time (apixaban, dabigatran and rivaroxaban), and these have also been incorporated into the SPC for edoxaban. In addition to other warnings, the MHRA highlighted the need to pay attention to the

person's renal function. The BNF states that warfarin should be used with caution in people with mild to moderate renal impairment and, in people with severe renal impairment, INR monitoring should be conducted more frequently. Impaired renal function may be a contraindication to using a NOAC, or may require a dose reduction: see individual SPCs for more information. Note that the SPC for edoxaban states that, when edoxaban was used for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation, a trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared with well-managed warfarin. Therefore, edoxaban should be used in people with non-valvular atrial fibrillation and high creatinine clearance only after a careful evaluation of the individual thromboembolic and bleeding risk.

The NICE guideline on chronic kidney disease recommends that healthcare professionals should consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m^2 and non-valvular atrial fibrillation who have 1 or more specified risk factors for stroke. The full guideline explains that this recommendation is based on a pre-specified subgroup analysis of the ARISTOTLE study (Granger et al. 2011). This found that, compared with warfarin, apixaban reduced the rate of stroke, death, and major bleeding, and people with impaired kidney function (eGFR 25–50 ml/min/1.73 m^2) had the greatest reduction in major bleeding with apixaban compared with warfarin.

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of prescribing comparators to support this key therapeutic topic is currently being explored by the NHS England Medicines Optimisation Intelligence Group[7].

The medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors, does however include several

[7] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

cardiovascular and coronary heart disease metrics related to this key therapeutic topic. These include:

- Atrial fibrillation: access to audit tool, which is the number of downloads of the software that supports audit of patients prescribed anticoagulants for atrial fibrillation in relation to the number of practices within the CCG. Note: this can currently only measure practices who are engaged with the GRASP tool.
- Atrial fibrillation (AF004) % achieving upper threshold or above, which is the percentage of practices in a CCG that achieve upper threshold or above (70% or more inclusive of exceptions) for QOF indicator AF004.
- Atrial fibrillation (AF004) % underlying achievement, which is the number of patients with atrial fibrillation whose latest record of a CHADS2 score is greater than 1 who are currently treated with anticoagulation therapy.
- Oral anticoagulants % items, which is the proportion of prescription items for apixaban, dabigatran, edoxaban and rivaroxaban and the proportion of prescription items for warfarin as a percentage of the total number of prescription items for oral anticoagulants.

The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Apixaban, dabigatran, edoxaban and rivaroxaban are also included in the Innovation Scorecard, published by the NHS Digital. The Innovation Scorecard aims to improve transparency within the NHS of what treatments recommended by NICE are available within Trusts and CCGs and at National and Area Team level. It is intended to support monitoring of compliance with NICE Technology Appraisal recommendations and to assist the NHS in the identification of variation, which can be explained, challenged or acted upon. It is not intended to be used for performance management.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The topic has been broadened to include information on anticoagulants more generally, and the evidence context has been updated in the light of new guidance and important new evidence as appropriate.

Acute kidney injury (AKI): use of medicines in people with or at increased risk of AKI

Options for local implementation

- The NHS programme to improve the care of people at risk of, or with, acute kidney injury (AKI) is one of the Think Kidneys national programmes.
- Medicines optimisation is important to reduce the risk of AKI and mitigate its severity if it occurs. A Patient Safety Alert has been issued to further raise awareness of AKI, signposting healthcare professionals to the clinical resources available on the Think Kidneys website.
- Review and, if appropriate, optimise prescribing and local policies that relate to assessing the risk of AKI and preventing, identifying and managing it, to ensure these are in line with the NICE guideline on AKI.

Evidence context

Renal function is vulnerable to quite modest reductions in blood pressure or blood volume, including dehydration arising from diarrhoea or vomiting. The full NICE guideline on acute kidney injury (AKI) notes that it is a common problem among people admitted to hospital (occurring in 13–18% of such people), especially older people. AKI is a feature of many severe illnesses and patients are usually under the care of clinicians practicing in specialties other than nephrology. In addition, AKI is seen increasingly in primary care in the absence of any acute illness.

Many drugs can be harmful to the kidneys especially in people with AKI or at risk of it for non-pharmacological reasons. In addition, other drugs – such as those with a narrow therapeutic range and those that are cleared by the kidneys – may cause toxicity in the setting of AKI and acute illness, requiring additional monitoring, dose adjustment and measurement of drug levels (see below for more details).

The NICE guideline on acute kidney injury: prevention, detection and management gives guidance on the following areas:

- **Assessing the risk of AKI.** This includes investigating for AKI in people with acute illness who have predisposing risk factors, including recent use of drugs with nephrotoxic potential such as non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, renin-angiotensin system (RAS) drugs or diuretics, especially if the person is hypovolaemic. People with no clear acute component to their illness but certain other factors should also be investigated for AKI. People receiving iodinated contrast agents and people having surgery should have their risk of AKI assessed. The guideline notes that there is an increased risk of AKI if drugs with nephrotoxic potential are used in the perioperative period (in particular, NSAIDs after surgery).
- **Preventing AKI.** This includes following recommendations in the NICE guideline on acutely ill patients in hospital on using track and trigger systems (early warning scores) to identify adults who are at risk of AKI, and using similar systems for children and young people. The guideline recommends measures to reduce the risk of AKI in people receiving iodinated contrast agents who are at increased risk. It advises considering temporarily stopping RAS drugs in certain situations, and specifically advises health professionals to seek advice from a pharmacist about optimising medicines and drug dosing in all people with or at risk of AKI.
- **Detecting AKI and identifying its cause.** This includes monitoring serum creatinine in all people with or at risk of AKI.
- **Managing AKI.** The guideline makes specific recommendations about when loop diuretics may and may not be appropriate, and recommends against using low-dose dopamine to treat AKI.

- **Information and support for patients and carers**. This includes discussing the risk of developing AKI with people at higher risk, particularly the risk associated with conditions leading to dehydration (for example, diarrhoea and vomiting) and drugs with nephrotoxic potential (including over-the-counter NSAIDs).

See the guideline for full details of the recommendations. NICE has also published quality standards on AKI, which are concise sets of prioritised statements designed to drive measurable quality improvements within this area.

The NHS programme to improve the care of people at risk of, or with, AKI is one of the Think Kidneys national programmes. Think Kidneys also includes the Transforming Participation in Chronic Kidney Disease programme and the Kidney Quality Improvement Partnership. A Patient Safety Alert has been issued to further raise awareness of AKI, signposting healthcare professionals to publications and tools for different settings available on the Think Kidneys website. Among the tools are guidelines for medicines optimisation in people with AKI, which include a list of high risk medicines and appropriate related actions, and a checklist for medicines optimisation in people with AKI. There are also tools specifically addressing issues such as responding to AKI warning stage test results, drugs to be avoided or used with caution during an AKI episode and restarting drugs stopped during AKI.

The AKI section of the Think Kidneys website also includes educational resources aimed at different health and social care professional groups, such as the Centre for Pharmacy Postgraduate Education (CPPE) learning campaign on acute kidney injury, and information for the public

The Think Kidneys Programme Board issued an interim position statement on sick day guidance in July 2015, updated in November 2015. The update notes that Think Kidneys no longer wishes to use the term ‘sick day rules’ but prefers the term ‘sick day guidance’. This is because the former term may be unhelpful since it suggests a dogmatic approach to management instead of providing individualised advice. The interim position statement notes that

although there is strong professional consensus that advice on sick day guidance should be given, the evidence that provision of such advice reduces net harm is very weak. It is possible that there are potential harms associated with widespread provision of sick day rules or guidance, particularly when people have not been clinically assessed and where it is unclear at what level of ill health the medicine should be discontinued. The Programme Board recommends that health professionals should discuss the possible causes of AKI with patients and carers including the need to maintain fluid balance during episodes of acute illness. It advises that it is reasonable for clinicians to provide sick day guidance on temporary cessation of medicines to patients deemed at high risk of AKI based on an individual risk assessment. However, the Board considers that investment in a systematic approach to increase uptake of sick day guidance by patients should only be undertaken in the context of a formal evaluation.

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of prescribing comparators to support this topic is being explored by the NHS England Medicines Optimisation Intelligence Group[8].

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence as appropriate.

[8] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

Lipid-modifying drugs

Options for local implementation

- When a decision is made to prescribe a statin for primary or secondary prevention of cardiovascular disease, the NICE guideline on lipid modification recommends using a statin of high intensity and low acquisition cost. The NICE guideline on familial hypercholesterolemia (which is being updated; publication expected January 2017) gives recommendations for people with this condition.
- People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with the technology appraisal guidance: ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia.
- People with primary hypercholesterolaemia or mixed dyslipidaemia should be considered for treatment with the PCSK9 inhibitors alirocumab or evolocumab in line with the technology appraisal guidance: alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia and evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia.
- The NICE guideline on lipid modification recommends that bile acid sequestrants, nicotinic acid, fibrates and omega-3 fatty acid compounds should not generally be offered (see the guideline for details). It may be appropriate to use bile acid sequestrants, nicotinic acid or fibrates to treat familial hypercholesterolaemia in circumstances (see the NICE guideline on familial hypercholesterolemia).
- Review and, if appropriate, optimise prescribing of lipid-modifying drugs including statins, ezetimibe, bile acid sequestrants, fibrates, nicotinic acid, omega-3 fatty acid compounds and PCSK9 inhibitors to ensure it is in line with NICE guidance.

Evidence context

The NICE guideline on lipid modification makes recommendations on the care and treatment of people at risk of cardiovascular disease (CVD) and people who have had previous CVD. This includes people with chronic kidney disease (CKD), type 1 diabetes and type 2 diabetes.

People with familial hypercholesterolaemia are outside the scope of the NICE lipid modification guideline. There is a separate NICE guideline on the identification and management of familial hypercholesterolemia (which is being updated; publication expected January 2017). Recommendations on treating familial hypercholesterolaemia in adults are summarised in this key therapeutics topic: see the guideline for recommendations on treating the condition in children and young people

The technology appraisal guidance on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia was reviewed and updated in February 2016. Technology appraisal guidance was published in June 2016 on alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia and evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia.

NICE has also published quality standards on cardiovascular risk assessment and lipid modification, which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas.

Statins

The NICE guideline on lipid modification recommends that the decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy. NICE has produced a patient decision aid to help a person thinking about statins for primary

prevention of CVD weigh up the possible advantages and disadvantages of the different options.

For the purpose of the guideline, statins are grouped into 3 different intensity categories according to the percentage reduction in low-density lipoprotein cholesterol (LDL-C; see appendix A of the guideline for more information). High-intensity statins (more than 40% LDL-C reduction) are:

- atorvastatin 20–80 mg daily
- rosuvastatin 10–40 mg daily
- simvastatin 80 mg daily.

When a decision is made to prescribe a statin, the guideline recommends using a statin of high intensity and low acquisition cost.

Before offering statin treatment for **primary prevention** of CVD, NICE recommends discussing the benefits of lifestyle modification with the person and, if possible, optimising the management of all other modifiable CVD risk factors. The guideline recommends offering atorvastatin 20 mg daily for primary prevention to people who have a 10% or greater 10-year risk of developing CVD (estimated using the QRISK2 assessment tool), including those with type 2 diabetes and CKD. Among people with type 1 diabetes, primary prevention with statins may be considered in all adults and should be offered to adults who are older than 40 years, or who have had diabetes for more than 10 years, or who have established nephropathy, or who have other CVD risk factors. In adults with type 1 diabetes, treatment should be started with atorvastatin 20 mg daily.

NICE recommends that **secondary prevention** of CVD should usually start with atorvastatin 80 mg daily. However, in people with CKD the initial dose should be 20 mg daily, and in other people a dose lower than 80 mg daily should be used if there are potential drug interactions with existing therapy, a high risk of adverse effects or the person prefers a lower dose.

NICE recommends measuring total cholesterol, high-density lipoprotein cholesterol (HDL-C) and nonHDL-C in all people who have been started on

high-intensity statin treatment as above after 3 months of treatment, **aiming** for a greater than 40% reduction in nonHDL-C. If this reduction is not achieved, NICE recommends:

- discussing adherence and the timing of the dose
- optimising adherence to diet and lifestyle measures
- **considering** increasing the dose if the person started on less than atorvastatin 80 mg daily **and** they are judged to be at higher risk because of comorbidities, risk score or using clinical judgement (see the guideline for dose recommendations in people with CKD).

Many people will currently be taking a low-intensity statin or medium-intensity statin (such as simvastatin 40 mg daily). NICE recommends that healthcare professionals should discuss the likely benefits and potential risks of changing to a high-intensity statin with such people when they have a medication review, and agree with the person whether a change is needed.

The NICE guideline on the identification and management of **familial hypercholesterolemia** (which is being updated; publication expected January 2017) recommends statins as the initial treatment. In adults the dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

Rosuvastatin and high-dose simvastatin

The only high-intensity statin specifically named in the NICE guideline on lipid modification is atorvastatin 20–80 mg daily. Other possible high-intensity statins are rosuvastatin 10–40 mg daily and simvastatin 80 mg daily. In the May 2010 edition of Drug Safety Update, the MHRA advised that there is an increased risk of myopathy associated with simvastatin 80 mg daily, and that this dose should be considered only in people with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risk.

The NICE full guideline on lipid modification notes that the clinical outcomes of the only study that compared atorvastatin with rosuvastatin for prevention of CVD (SATURN, Nicholls et al. 2011) were inconclusive. The full guideline states 'Given the considerably higher cost of using rosuvastatin, it would need to be considerably more effective than atorvastatin for there to be a possibility that its use could be cost-effective. In the absence of trial evidence of greater effectiveness the guideline development group are therefore unable to recommend the use of rosuvastatin'.

Ezetimibe

The NICE guideline on lipid modification recommends that people with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with the NICE technology appraisal guidance: ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. This technology appraisal guidance makes explicit reference both to the NICE lipid modification guideline and also to the NICE guideline on familial hypercholesterolaemia (which is being updated; publication expected January 2017).

The technology appraisal guidance recommends ezetimibe monotherapy as an option for treating heterozygous-familial or non-familial hypercholesterolaemia in adults in 2 broad situations:

- As an alternative to a statin in people in whom statins are contraindicated or not tolerated; intolerance is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.
- In addition to **initial** statin therapy in people who have started statin treatment but whose serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration or because dose titration is limited by intolerance to the initial statin therapy (defined as above) **and** consideration is being given to changing from initial statin therapy to an alternative statin.

Appropriate control of cholesterol concentrations should be based on individual risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. Therefore, in the second of the situations above, in people with non-familial hypercholesterolaemia, adding ezetimibe to **atorvastatin** (the initial statin therapy recommended in the guideline) is an option if (and only if) a greater than 40% reduction in nonHDL-C is not achieved:

- despite optimising adherence and timing of the dose of atorvastatin and optimising adherence to diet and lifestyle measures, **and**
- increasing the dose of atorvastatin (if started at less than 80 mg daily) is not effective or not tolerated or the person has to decrease the dose because of tolerability problems (intolerance to statins is discussed below), **and**
- changing to a different statin is being considered.

The NICE guideline on familial hypercholesterolaemia gives recommendations on appropriate control of cholesterol concentrations in people with familial hypercholestrolaemia. Use of ezetimibe in people with homozygous familial hypercholesterolaemia was outside the scope of the NICE technology appraisal guidance. The NICE guideline on familial hypercholesterolaemia recommends that prescribing of drug therapy for adults with the homozygous form of this condition should be undertaken within a specialist centre.

The large, multicentre, randomised controlled trial (RCT) IMPROVE-IT (Cannon et al. 2015) was discussed in a NICE medicines evidence commentary, Acute coronary syndrome: ezetimibe added to simvastatin (IMPROVE-IT study). IMPROVE-IT found that adding ezetimibe to simvastatin 40 mg after acute coronary syndrome produced a greater reduction in risk of cardiovascular events than simvastatin 40–80 mg alone. However, the effect of the combination on this risk is that which would be predicted from the degree of lowering of LDL-C seen with a high-intensity statin such as atorvastatin 20–80 mg daily. The study provides no reason to depart from recommendations in the NICE lipid modification guideline.

Alirocumab and evolocumab

Alirocumab and evolocumab are lipid-modifying monoclonal antibodies (PCSK9 inhibitors) administered by subcutaneous injection. They are recommended for use in specified circumstances (more narrowly defined than their marketing authorisations) in NICE technology appraisal guidance: alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia and evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. The technology appraisals recommend them as options for these conditions, **only** if

- LDL-C concentrations are persistently above the thresholds specified (see table below) despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached or further titration is limited by intolerance (clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy).
- The dosage of evolocumab is 140 mg every 2 weeks (it is also licensed at a dosage of 420 mg once monthly; doses are clinically equivalent).
- The companies provide them with the discounts agreed in the patient access schemes.

Table: LDL-C concentrations above which alirocumab or evolocumab are recommended as options

	Without CVD	**With CVD**	
		High risk[a]	**Very high risk[b]**
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended	Only if LDL-C **persistently** >4.0 mmol/L	Only if LDL-C **persistently** >3.5 mmol/L
Primary heterozygous-familial hypercholesterolaemia	Only if LDL-C **persistently** >5.0 mmol/L	Only if LDL-C **persistently** >3.5 mmol/L	

[a] High risk means a history of any of the following: acute coronary syndrome, coronary or other arterial revascularisation, chronic heart disease, ischaemic stroke, peripheral arterial disease.

[b] Very high risk means recurrent CV events or CV events in more than 1 vascular bed (polyvascular disease).

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease, LDL-C, low-density lipoprotein cholesterol.

Evolocumab is also licensed for treating homozygous familial hypercholesterolaemia in adults and young people aged 12 years and over. This indication was outside the scope of the NICE technology appraisal.

The summaries of product characteristics for both alirocumab and evolocumab state that their effects on cardiovascular morbidity and mortality have not yet been determined. In ODYSSEY LONG TERM (Robinson et al. 2015), an RCT of alirocumab in 2341 people at high risk for cardiovascular events who had LDL-C levels of 1.8 mmol/L or more and were receiving treatment with statins at the maximum tolerated dose (with or without other lipid-lowering therapy), a post-hoc analysis of data at 78 weeks suggested a reduction in the risk of major cardiovascular events. However, this must be interpreted cautiously. A cardiovascular outcomes trial of alirocumab in people with a history of acute coronary syndrome in the past year, ODYSSEY OUTCOMES, is ongoing and is expected to complete in early 2018. A cardiovascular outcomes trial of evolocumab in people with CVD at high risk of recurrence, FOURIER, is expected to complete in late 2016.

Intolerance to statins

The NICE technology appraisal guidance on alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia states 'The committee heard from the clinical expert that although up to approximately 23% of people with primary hypercholesterolemia were currently reported to be intolerant to statins, the true rate was likely to be between 0.5% to 3.0% of the population because there were no clear diagnostic criteria for statin intolerance.' A large

observational study, which was discussed in a NICE medicines evidence commentary, Statins: many people who stop treatment due to side effects may be able to restart treatment, suggested that many people who have discontinued statins because of an adverse event, especially muscle pain, may be able to restart the same or a different statin.

The GAUSS-3 study which compared evolocumab with ezetimibe in people with muscle symptoms confirmed by statin re-challenge (Nissen et al, 2016) illustrated the difficulties of identifying people with true statin intolerance. This 2-stage RCT recruited 511 adults with uncontrolled LDL-C and a history of intolerance to 2 or more statins. In a double-blind crossover phase only 43% of participants experienced muscle-related adverse effects with atorvastatin 20 mg but not with placebo. More than a quarter (27%) of participants experienced them with placebo but not atorvastatin. This study suggests that careful selection is necessary to identify those people who are truly intolerant of statins and in whom treatment with non-statin alternatives is most appropriate.

The NICE guideline on lipid modification provides recommendations about monitoring for adverse effects of statins, and managing intolerance to statins. It advises that, if a person is not able to tolerate a high-intensity statin, the aim should be to treat with the maximum tolerated dose. NICE recommends telling the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins, the following strategies should be discussed with them:

- stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- reducing the dose within the same intensity group
- changing the statin to a lower intensity group.

Bile acid sequestrants, fibrates and nicotinic acid

The NICE guideline on lipid modification recommends that bile acid sequestrants (anion exchange resins) and nicotinic acid (niacin) should **not** be offered for primary or secondary prevention of CVD, alone or in combination

with a statin, including in people with CKD or type 1 or type 2 diabetes. The guideline recommends that fibrates should **not** be routinely offered for monotherapy for primary or secondary prevention of CVD including in people with CKD or type 1 or type 2 diabetes, and should **not** be recommended in combination with a statin in these indications.

The NICE guideline on familial hypercholesterolaemia recommends that adults with the condition who have intolerance or contraindications to statins or ezetimibe should be offered referral to a specialist with expertise in this condition for consideration for treatment with a bile acid sequestrant, a fibrate or nicotinic acid to reduce their LDL-C concentration. The decision to offer treatment with a bile acid sequestrant, a fibrate or nicotinic acid in **addition** to initial statin therapy should be taken by a specialist with expertise in familial hypercholesterolaemia. Healthcare professionals should exercise caution when adding a fibrate or nicotinic acid to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together.

Omega-3 fatty acid compounds

The NICE guideline on lipid modification recommends that people with or at high risk of CVD should be advised to consume at least 2 portions of fish per week, including a portion of oily fish. However, it advises that omega-3 fatty acid compounds should **not** be offered for primary or secondary prevention of CVD, alone or in combination with a statin, including in people with CKD or type 1 or type 2 diabetes. Moreover, the guideline recommends that healthcare professionals should tell people that there is no evidence that omega-3 fatty acid compounds help to prevent CVD.

The NICE guideline on familial hypercholesterolaemia also states that people with this condition should **not** routinely be recommended to take omega-3 fatty acid supplements. In addition, the NICE guideline on secondary prevention of myocardial infarction (MI) recommends that healthcare professionals should **not** offer or advise people who have had an MI to use omega-3 fatty acid capsules or omega-3 fatty acid supplemented foods to prevent another MI.

Prescribing data

The following medicines optimisation key therapeutic topic (MO KTT) prescribing comparator is available to support this topic[9]:

- **Other lipid modifying drugs: % items**: the number of prescription items for bile acid sequestrants, fibrates, nicotinic acid, omega-3 fatty acid compounds and 'other lipid modifying drugs' (BNF 2.12 sub-set) as a percentage of total prescription items for BNF 2.12.

The development of further prescribing comparators to support this key therapeutic topic is being explored by the NHS England Medicines Optimisation Intelligence Group[10].

Prescription Cost Analysis data of prescriptions dispensed in the community in England shows national statin and ezetimibe prescribing. In terms of costs, rosuvastatin 10–40 mg daily is between £220.22 and £358.54 per patient per year more costly than atorvastatin 20–80 mg daily at equivalent LDL-C-lowering doses. Adding ezetimibe 10 mg daily to a statin would cost an additional £342.03 per year (Drug Tariff September 2016).

Other lipid modifying drugs: % items

- Data for the quarter May to July 2016 show a 5.7 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 1.05% to 6.03%.
- Between the quarter October to December 2013 and the quarter May to July 2016 there was a 19.7% decrease in the comparator value for England (total prescribing) from 2.66% to 2.14%.

[9] The comparators and associated data presented here are based on the previous Key therapeutic topics publication (February 2016). Data provided by NHS Digital (October 2016; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

[10] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

- Over the same period there was a 31.3% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.73%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence as appropriate, including PCSK9 inhibitors.

Asthma: medicines optimisation priorities

Options for local implementation

- Review all people with asthma who have been prescribed more than 12 short-acting reliever inhalers in the previous 12 months.
- Inhaled corticosteroids (ICS) are the first-choice regular preventer therapy for adults and children with asthma, but the dose should be titrated to the lowest dose at which effective control of asthma is maintained to minimise side effects. Non-adherence to ICS is associated with increased risk of poor asthma control and should be continually monitored.
- Use of combination inhalers should be encouraged. Where long-acting beta agonists (LABAs) are prescribed for people with asthma, they should be prescribed with an ICS in a single combination inhaler. LABAs should not be used without ICS.
- The NICE quality standard for asthma states that people with asthma should receive a structured review at least annually and have a written personalised action plan. It is important to ensure that all people with asthma are treated optimally; this includes increasing and decreasing treatment appropriately by moving up and down the different treatment options.
- An assessment of inhaler technique to ensure effectiveness should be routinely undertaken and formally documented at annual review, and also checked by the pharmacist when a new device is dispensed.

Evidence context

The BTS/SIGN guideline on the management of asthma was updated in September 2016 and recommends that anyone prescribed more than 1 short-acting bronchodilator inhaler device a month should be identified and have their asthma assessed urgently, with measures taken to improve asthma control if this is poor. Good asthma control is associated with little or no need for a short-acting bronchodilator. Inhaled corticosteroids (ICS) are the recommended preventer drug for adults and children. These should be

introduced for people who have had an asthma attack in the last 2 years; are using inhaled short-acting beta-2 agonists 3 times a week or more; experience asthma symptoms 3 times a week or more; or are waking 1 night a week with their asthma symptoms. Long-acting beta agonists (LABAs) should only be started in people who are already on ICS, and the ICS should be continued. The MHRA also recommends that LABAs should not be used without also taking regular corticosteroids. When used alone, LABAs have been associated with a worsening (sometimes severe) of asthma in some patients. The NICE technology appraisal guidance on ICS for the treatment of chronic asthma in adults and children aged 12 years and over recommends a combination inhaler, within its marketing authorisation, as an option if treatment with an ICS and a LABA is considered appropriate.

The Royal College of Physicians' national review of asthma deaths (NRAD) looked into the circumstances surrounding deaths from asthma in the UK for a 12-month period from February 2012 to January 2013. Data were available for analysis on 195 people who were thought to have died from asthma during the review period. The NRAD had several key findings. For prescribing and medicines use it found evidence of:

- **Excessive prescribing of reliever medication**. From 189 people who were on short-acting relievers at the time of death, the number of prescriptions was known for 165, and 65 of these (39%) had been prescribed more than 12 short-acting reliever inhalers in the year before they died, while 6 (4%) had been prescribed more than 50 reliever inhalers. Those prescribed more than 12 reliever inhalers were likely to have had poorly controlled asthma.
- **Under-prescribing of preventer medication**. To comply with recommendations, most people would usually need at least 12 preventer prescriptions per year. From 168 people on preventer inhalers at the time of death, either as stand-alone or in combination, the number of prescriptions was known for 128, and 49 of these (38%) were known to have been issued with fewer than 4 and 103 (80%) issued with fewer than 12 preventer inhalers in the previous year.

- **Inappropriate prescribing of LABA bronchodilator inhalers**. From available data, 27 (14%) of those who died were prescribed a single-component LABA bronchodilator at the time of death. At least 5 (3%) people were on LABA monotherapy without ICS preventer treatment.

A further study conducted by Asthma UK also found evidence that inhaled LABAs are being prescribed without an ICS and short-acting reliever inhalers are being prescribed excessively in some people with asthma. (See the medicines evidence commentary asthma: new review of prescribing data highlights safety concerns).

The NRAD issued several recommendations. For prescribing and medicines use these include the following:

- All people with asthma who have been prescribed more than 12 short-acting reliever inhalers in the previous 12 months should be invited for urgent review of their asthma control, with the aim of improving their asthma through education and change of treatment if required.
- An assessment of inhaler technique to ensure effectiveness should be routinely undertaken and formally documented at annual review, and also checked by the pharmacist when a new device is dispensed.
- Non-adherence to preventer ICS is associated with increased risk of poor asthma control and should be continually monitored.
- Use of combination inhalers should be encouraged. Where LABAs are prescribed for people with asthma, they should be prescribed with an ICS in a single combination inhaler.

The BTS/SIGN guideline on the management of asthma recommends that inhalers should only be prescribed after people have received training in the use of the device and have demonstrated satisfactory technique. The person should have their ability to use the prescribed inhaler device (particularly for any change in device) assessed by a competent healthcare professional. The guideline recommends that, in primary care, people with asthma receive a proactive structured clinical review of their asthma regularly by a nurse or doctor with appropriate training in asthma management. Review should

incorporate a written action plan and should be conducted on at least an annual basis (although It is difficult to be prescriptive about the frequency of review as the need will vary with the severity of the disease). One of the components that the review should cover is reassessing inhaler technique. A systematic review found that around 30% of people using inhalers had 'poor' inhaler technique, and that no appreciable change in this has occurred over the last 40 years. (See the medicines evidence commentary inhaler use: has technique improved over time?)

The NICE quality standard for asthma also states that people with asthma should receive a structured review at least annually and that they should have a written personalised action plan. It recommends that they receive specific training and assessment in inhaler technique before starting any new inhaler treatment. These recommendations are in line with both the BTS/SIGN guideline on the management of asthma and the NRAD.

It is important to ensure that all people with asthma are treated optimally; this includes increasing and decreasing treatment appropriately by moving up and down the different treatment options. To minimise side effects from ICS in people with asthma, the BTS/SIGN guideline on the management of asthma recommends that the dose of ICS should be titrated to the lowest dose at which effective control of asthma is maintained. Doubling the dose of ICS at the time of an exacerbation is of unproven value and is no longer recommended. Prolonged use of high doses of ICS (as with the use of oral corticosteroids) carries a risk of systemic side effects, including adrenal suppression, growth retardation in children and young people, decreased bone mineral density, cataracts, glaucoma, and psychological or behavioural effects. (See the following links for more details: MHRA 2006; MHRA 2010; NICE Medicines Evidence Commentary March 2013; NICE Medicines Evidence Commentary November 2014)

The MHRA advises that corticosteroid treatment cards should be routinely provided for people (or their parents or carers) who need prolonged treatment with high doses of ICS (see the May 2006 edition of Current Problems in Pharmacovigilance for more information). The London Respiratory Network

has produced a corticosteroid card that is specifically tailored for people who are using high doses of ICS. The Committee on Safety of Medicines has issued warnings about the use of high-dose ICS, particularly in children and in relation to fluticasone propionate. The BTS/SIGN guideline recommends that children prescribed ICS should have their growth monitored annually (although isolated growth failure is not a reliable indicator of adrenal suppression).

The BTS/SIGN guideline on the management of asthma recommends that reductions in ICS dose should be slow because people deteriorate at different rates. Reductions should be considered every 3 months, decreasing the dose by approximately 25–50% each time. Data suggest that this is realistic and possible without compromising patient care (see Hawkins et al. 2003). For some children with milder asthma and a clear seasonal pattern to their symptoms, a more rapid dose reduction during their 'good' season is feasible. The guideline states that decreasing therapy (by moving down the different treatment options) once asthma is controlled is recommended, but often not implemented, leaving some people over-treated. The BTS/SIGN guideline also advises that regular review of patients as treatment is stepped down is important. When deciding which drug to decrease first and at what rate, the severity of asthma, the side effects of the treatment, time on current dose, the beneficial effect achieved, and the patient's preference should all be taken into account.

A Scottish retrospective database analysis, reported in the medicines evidence commentary asthma: study finds many people have a substantial increase in dose of inhaled corticosteroid when started on combination inhaler therapy, found that initiating combination ICS plus LABA therapy resulted in widespread increases in ICS dose. The average increase was about 50%, and was substantially greater among people previously on lower ICS doses. This raises questions around the awareness of ICS doses in different preparations, and suggests that an evaluation of the appropriateness of high-dose combination inhaler therapy in primary care is needed.

NICE guidelines on asthma: diagnosis and monitoring (publication date to be confirmed) and asthma management (which includes the pharmacological management of chronic asthma; expected publication June 2017) are currently underway. The NICE pathway on asthma brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of a suitable comparator will be explored by the NHS England Medicines Optimisation Intelligence Group[11]. However, there are several clinical and technical issues around the development of a meaningful comparator for this topic.

The medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors, does however include several respiratory metrics related to this key therapeutic topic. These include:

- Asthma (AST003) % achieving upper threshold or above, which is the percentage of practices in a CCG that achieve upper threshold or above (70% or more inclusive of exceptions) for QOF indicator AST003.
- Asthma (AST003) % underlying achievement, which is the percentage underlying achievement at CCG level for QOF indicator AST003 inclusive of exceptions.
- Emergency asthma admissions, which is the number of emergency attendances for asthma per 100 patients on the practice asthma disease register.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The scope has been broadened to include safety issues raised by the Royal College of Physicians' national review of asthma deaths

[11] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority

(NRAD) and the evidence context has been updated in the light of new guidance and important new evidence as appropriate.

Hypnotics

Options for local implementation

- The risks associated with hypnotics (including melatonin) such as falls, cognitive impairment, dependence and withdrawal symptoms, are well recognised. Hypnotics should be used only if insomnia is severe, using the lowest dose that controls symptoms for short periods of time.
- Review and, if appropriate, optimise prescribing of hypnotics to ensure that it is in line with national guidance.

Evidence context

Risks associated with the long-term use of benzodiazepine and 'Z drug' hypnotic drugs have been well recognised for many years. Recent data also suggests a similar safety concern with melatonin. These risks include falls, accidents, cognitive impairment, dependence and withdrawal symptoms, and an increased risk of dementia.

The prolonged-release melatonin preparation (Circadin) is licensed as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in people aged 55 years or over, for a maximum duration of 13 weeks treatment. The NICE Clinical Knowledge Summary on managing long-term insomnia recommends that if prolonged-release melatonin is prescribed that the initial duration of treatment should be 3 weeks. If there is a response to treatment, it can be continued for a further 10 weeks. An observational study discussed in a NICE medicines evidence commentary fracture risk associated with melatonin and other hypnotics has found that in people aged 45 years and over, receiving 3 or more melatonin prescriptions was associated with an increased risk of fracture compared with no use of any hypnotic drugs. Prescriptions for 'Z drugs' were also associated with an increased fracture risk.

An observational study discussed in an eyes on evidence commentary Benzodiazepines and the risk of dementia suggested that benzodiazepines

and ‘Z drugs’ (zaleplon, zolpidem and zopiclone) are associated with an increased risk of dementia. A case-control study discussed in a medicines evidence commentary Benzodiazepine use and risk of Alzheimer’s disease found that past benzodiazepine use was associated with an increased risk of Alzheimer’s disease. The study suggests that taking benzodiazepines for more than 3 months and the use of agents with longer half-lives strengthen the association, but potential biases in the study limit the conclusions that can be drawn.

Another observational study discussed in a medicines evidence commentary Psychotropic drugs and risk of motor vehicle accidents examined the relationship between exposure to psychotropic drugs and motor vehicle accidents and found that benzodiazepines and ‘Z drugs’ (and antidepressants) were associated with a significantly increased risk of motor vehicle accidents. In the May 2014 edition of Drug Safety Update, the MHRA warned about the risk of drowsiness and reduced driving ability the next day with zolpidem. Another study discussed in an eyes on evidence commentary Prescriptions for anxiolytics and hypnotics and risk of death found that people who were prescribed anxiolytic and hypnotic drugs had a significantly increased risk of death from any cause over a 7-year period.

As long ago as 1988, in the January issue of Current Problems in Pharmacovigilance, the Committee on Safety of Medicines advised that benzodiazepine hypnotics should be used only if insomnia is severe, disabling or causing the person extreme distress. The lowest dose that controls symptoms should be used, for a maximum of 4 weeks and intermittently if possible.

The NICE technology appraisal guidance on zaleplon, zolpidem and zopiclone recommends that 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, hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications. A meta-analysis discussed in an eyes on evidence commentary Small benefits of Z drugs over placebo for

insomnia found that ‘Z drugs’ reduce the time taken to fall asleep by 22 minutes compared with placebo but this may not be clinically significant. The NICE technology appraisal guidance states that there is no compelling evidence of a clinically useful difference between the ‘Z drugs’ and shorter-acting benzodiazepine hypnotics from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse. There is no evidence to suggest that if people do not respond to one of these hypnotic drugs, they are likely to respond to another.

The MHRA reinforced the issues about addiction to benzodiazepines in the July 2011 edition of Drug Safety Update. Various approaches to reducing hypnotic prescribing can achieve significant success. See the NICE Clinical Knowledge Summary on benzodiazepine and z-drug withdrawal for advice on assessing a person who is being prescribed long-term benzodiazepines or ‘Z drugs’, and on managing withdrawal of treatment.

An e-learning programme, Addiction, misuse and dependency: a focus on over-the-counter (OTC) and prescribed medicines, has been developed jointly by the Centre for Pharmacy Postgraduate Education (CPPE) and the Royal College of General Practitioners (RCGP). The programme aims to provide healthcare professionals with a better understanding of how to recognise people who may have an addiction to prescribed or over-the-counter medicines and how to approach and help them.

A new offence of driving with certain controlled drugs above specified limits in the blood came into force in March 2015. Prescription drugs covered by the new offence include amphetamine (e.g. dexamphetamine or selegiline), clonazepam, diazepam, flunitrazepam, lorazepam, methadone, morphine or opioid-based drugs (e.g. codeine, tramadol or fentanyl), oxazepam and temazepam. The above list doesn’t include all benzodiazepines and opioids. However, all benzodiazepines and opioids can impair driving ability. See the July 2014 edition of Drug Safety Update and the Drugs and driving: the law government webpage for more details.

Prescribing data

A medicines optimisation key therapeutic topic (MO KTT) prescribing comparator is available to support this topic – **Hypnotics ADQ/STAR PU (ADQ based):** Number of average daily quantities (ADQs) for benzodiazepines (indicated for use as hypnotics) and 'Z drugs' per Hypnotics (BNF 4.1.1 sub-set) ADQ based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU)[12].

- Data for the quarter May to July 2016 show a 4.1 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.11 to 0.46 ADQ/STAR-PU.
- Between the quarter July to September 2013 and the quarter May to July 2016 there was a 20.4% decrease in the comparator value for England (total prescribing) from 0.29 to 0.23 ADQ/STAR-PU.
- Over the same period there was a 23.8% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.05 ADQ/STAR-PU. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

Prescription Cost Analysis data of prescriptions dispensed in the community in England show that in 2015, nearly 600,000 items of melatonin were dispensed at a cost of nearly £29 million. These data relate to all melatonin preparations, including 'specials', for all indications.

The medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors, includes the prescribing comparator outlined above. The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being

[12] The comparator and associated data presented here are based on the previous Key therapeutic topics publication (February 2016). Data provided by NHS Digital (October 2016; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence as appropriate.

Low-dose antipsychotics in people with dementia

Options for local implementation

- The risks and limited benefits of using low-dose antipsychotics for treating dementia in people who exhibit challenging behaviours are well recognised.
- Review and, if appropriate, optimise prescribing of low-dose antipsychotics in people with dementia, in accordance with the NICE/Social Care Institute for Excellence (SCIE) guideline on dementia and the NICE quality standard on dementia.

Evidence context

The NICE/SCIE guideline on dementia (which is being updated, publication expected August 2017) gives recommendations on the care of people with all types of dementia. This includes managing behavioural and psychological symptoms of dementia. The NICE quality standards on dementia and supporting people to live well with dementia describe concise sets of prioritised statements designed to drive measurable quality improvements within these areas. A NICE pathway on dementia brings together all related NICE guidance and associated products on dementia in a set of interactive topic-based diagrams. See the NICE Clinical Knowledge Summary on dementia for a general overview of the condition.

The risks and limited benefits of using first (typical) and second (atypical) generation antipsychotic drugs for treating dementia in people who exhibit challenging behaviours are well recognised. They have been the subject of several previous reviews and MHRA warnings, collated in the May 2012 edition of Drug Safety Update.

The NICE/SCIE guideline on dementia recommends 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. The assessment should be comprehensive and include for example, the person's physical health, depression, undetected pain or discomfort, side effects of medication, psychosocial factors, physical environment factors, and the person's religious beliefs and spiritual and cultural identity. Individually tailored care plans that help carers and staff address the behaviour that challenges should be developed, recorded in the notes and reviewed regularly.

For people with all types and severities of dementia who have comorbid agitation, the NICE/SCIE guideline on dementia recommends that non-pharmacological approaches may be considered including aromatherapy, multisensory stimulation, therapeutic use of music or dancing, animal-assisted therapy, and massage.

The NICE/SCIE guideline on dementia advises against the use of any antipsychotics for non-cognitive symptoms or challenging behaviour of dementia unless the person is severely distressed or there is an immediate risk of harm to them or others. Any use of antipsychotics should include a full discussion with the person and carers about the possible benefits and risks of treatment. In the May 2012 edition of Drug Safety Update, the MHRA advised that no antipsychotic (with the exception of risperidone in some circumstances) is licensed in the UK for treating behavioural and psychological symptoms of dementia. However, antipsychotics are often prescribed off-label[13] for this purpose.

In September 2010, the Department of Health published Quality outcomes for people with dementia: building on the work of the national dementia strategy, which is an implementation plan for their guidance Living well with dementia: a national dementia strategy. These resources build on the NICE/SCIE guideline on dementia and include strategies to reduce inappropriate prescribing of antipsychotics. In the May 2012 edition of Drug Safety Update

[13] In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using a medicine outside its authorised indications. Informed consent should be obtained and documented.

the MHRA provides the following advice for health and social care professionals:

For prescribers considering using antipsychotics in people without a current prescription:

- Carefully consider, after a thorough clinical examination including an assessment for possible psychotic features (such as delusions and hallucinations), whether a prescription for an antipsychotic drug is appropriate.

For prescribers considering continuing antipsychotics in people with a current prescription:

- Identify and review people who have dementia and are on antipsychotics, with the purpose of understanding why antipsychotics have been prescribed.
- In consultation with the person, their family and carers, and clinical specialist colleagues such as those in psychiatry, establish: whether the continued use of antipsychotics is appropriate; whether it is safe to begin the process of discontinuing their use; and what access to alternative interventions is available.

A Cochrane review, which was discussed in the medicines evidence commentary Dementia: withdrawal of antipsychotic drugs in people with behavioural and neuropsychiatric symptoms, evaluated the effect of withdrawing treatment with antipsychotic drugs prescribed for behavioural and neuropsychiatric symptoms in people with dementia. It concluded that these can be withdrawn without detrimental effects on behaviour in many people. This review is consistent with the NICE/SCIE guideline on dementia.

A further medicines evidence commentary Alzheimer's disease: effect of citalopram on agitation discussed the efficacy and safety of off-label citalopram for treating agitation in people with Alzheimer's disease.

In March 2016 the Department of Health published the Challenge on dementia 2020: implementation plan, which sets out more than 50 specific commitments that aim to make England the world-leader in dementia care, research and awareness by 2020. The plan sets out priority actions across 4 themes: risk reduction; health and care; awareness and social action; and research. The Department of Health is working with SCIE to create a set of films demonstrating and promoting effective practice in person-centred care as the method for managing distress and challenging behaviours among people with dementia.

A separate key therapeutic topic is available on psychotropic medicines in people with learning disabilities whose behaviour challenges.

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic. The development of a suitable comparator is currently being explored by the NHS England Medicines Optimisation Intelligence Group[14]. The National dementia and antipsychotic prescribing audit from 2012 suggests that there has been an encouraging overall reduction in the proportion of people with dementia being prescribed antipsychotics in recent years. See the National Dementia and Antipsychotic Prescribing Audit website for more details.

Based on data from 46% of GP practices across England, the audit found that the number of people newly diagnosed each year with dementia increased by 68% in relative terms from 2006 to 2011. However, there was a decrease of 10.25 percentage points in the number of people with dementia receiving prescriptions for antipsychotic medication over that time (from 17.05% in 2006 to 6.80% of people in 2011, a 60% reduction in relative terms). The proportion of people receiving a prescription for an antipsychotic within a year of being diagnosed with dementia also decreased by 9.79 percentage points from 2006 to 2011 (from 14.25% to 4.46%, a 69% reduction in relative terms).

[14] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

Nevertheless, although reductions in prescribing rates were seen across all geographical areas of England, there was still considerable variation in the percentage of people diagnosed with dementia prescribed an antipsychotic.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence as appropriate.

Antimicrobial stewardship: prescribing antibiotics

Options for local implementation

- Antibiotic resistance poses a significant threat to public health, especially because antibiotics underpin routine medical practice.
- Review and, if appropriate, revise prescribing and local policies that relate to antimicrobial stewardship to ensure these are in line with the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. A guideline on antimicrobial stewardship: changing risk-related behaviours in the general population is in development.
- Review and, if appropriate, optimise current prescribing practice and use implementation techniques to ensure prescribing is in line with Public Health England (PHE) guidance on managing common infections, the Department of Health's guidance Start smart − then focus, local trust antimicrobial guidelines and the Antimicrobial Stewardship in Primary Care collaboration TARGET antibiotics toolkit.
- Review the following against local and national prescribing criteria:
    - total volume of antibiotic prescribing
    - prescribing of quinolones, cephalosporins, co-amoxiclav and other broad-spectrum antibiotics
    - prescribing of 3-day courses of trimethoprim, nitrofurantoin and pivmecillinam.

Evidence context

Antimicrobial resistance and stewardship

Antimicrobial resistance poses a significant threat to public health, especially because antibiotics underpin routine medical practice. The Chief Medical Officer's report on the threat of antimicrobial resistance and infectious diseases (2013) highlights that, while a new infectious disease has been

discovered nearly every year for the past 30 years, there have been very few new antibiotics developed. This is leaving the armoury nearly empty as diseases evolve and become resistant to existing drugs. The report highlights that looking after the current supply of antibiotics is equally as important as encouraging development of new drugs.

According to the English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2015), the rates of *Escherichia coli* and *Klebsiella pneumoniae* bloodstream infections increased by 15.6% and 20.8% respectively from 2010 to 2014, with associated increases in the numbers of people with antibiotic resistant infections. Nevertheless, for other bacteria where there have been targeted interventions to reduce the burden of infection or resistance, infection rates or proportions of infections where resistance is detected have declined. For example, through effective infection prevention and control within healthcare settings, meticillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections have reduced from 12% to 8% over the last 5 years.

As stated by the ESPAUR report (2015), good antimicrobial stewardship is a cornerstone for both effective treatment of infections and reduction of antimicrobial resistance. Antimicrobial stewardship programmes contain analysis of local antimicrobial resistance data to guide the development of evidence-based prescribing guidelines, educational resources to improve clinical practices to ensure antibiotics are prescribed appropriately, restrictive and persuasive interventions to use the appropriate antibiotics, and audit and feedback to clinical staff to improve patient care and outcomes against local and national prescribing criteria designed to drive quality improvements.

NICE has published a guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use and a guideline on antimicrobial stewardship: changing risk-related behaviours in the general population is in development. Public Health England (PHE) has published an antimicrobial resistance resource handbook, which collates national resources on antimicrobial resistance, antimicrobial stewardship and infection prevention and control. NHS England has also collated information on addressing

antimicrobial resistance. Resources include 2 national toolkits to support implementation of antimicrobial stewardship best practice: Treat antibiotics responsibly, guidance, education, tools (TARGET) for primary care and 'Start smart, then focus' for secondary care.

The ESPAUR report (2015) states that, in 2014, 60% of clinical commissioning groups (CCGs) and 87% of NHS acute trusts had reviewed the national antimicrobial stewardship toolkits for primary or secondary care; however, only 13% of CCGs and 46% of acute trusts had implemented an action plan to deliver antimicrobial stewardship activities.

Antibiotic prescribing

To help prevent the development of resistance it is important to only prescribe antibiotics when they are necessary, and not for self-limiting mild infections such as colds and most coughs, sinusitis, earache and sore throats. PHE guidance on managing common infections in primary care recommends that consideration should be given to a no, or back-up or delayed antibiotic strategy for acute self-limiting upper respiratory tract infections and mild urinary tract infections (UTIs). It also advises that people are given supporting information about antibiotic strategies, infection severity and usual duration.

The PHE guidance recommends that simple generic antibiotics should be used if possible when antibiotics are necessary. Broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved to treat resistant disease. They should generally be used only when narrow-spectrum antibiotics are ineffective because they increase the risk of MRSA, *Clostridium difficile* and resistant UTIs.

Addressing healthcare-associated *Clostridium difficile* infection remains a key issue on which NHS organisations have been mandated to implement national guidance. The Department of Health and Public Health England's report on *Clostridium difficile* infection: how to deal with the problem from 2008 recommends that trusts should develop restrictive antibiotic guidelines that use narrow-spectrum agents alone or in combination as appropriate. The report suggests that these guidelines should avoid recommending clindamycin

and second- and third-generation cephalosporins (especially in older people) and should recommend minimising the use of quinolones, carbapenems (for example, imipenem and meropenem) and prolonged courses of aminopenicillins (for example, ampicillin and amoxicillin). Broad-spectrum antibiotics should be used only when indicated by the person's clinical condition, and their use should be reviewed after the results of microbiological testing or based on the sensitivities of causative bacteria.

The Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) recommends the Start smart − then focus approach. This advises that, if immediate antibiotic treatment is necessary, the clinical diagnosis and continuing need for antibiotics should be reviewed within 48−72 hours. A study of Start smart − then focus, which was discussed in a NICE eyes on evidence article Implementation of antibiotic prescribing guidance, concluded that most hospital antibiotic policies in England 'start smart' by recommending broad-spectrum antibiotics for empirical therapy in severe infections. However fewer 'focus' by reviewing the ongoing need for antibiotics after a couple of days, as recommended.

A NICE evidence summary: medicines and prescribing briefing on Clostridium difficile infection: risk with broad-spectrum antibiotics outlines 3 meta-analyses on this infection. The first of these, Slimings and Riley (2014), concluded that cephalosporins and clindamycin are the antibiotics most strongly associated with hospital-associated *C. difficile* infection. Subgroup analyses showed that, although first-generation cephalosporins appear to carry a lower risk of *C. difficile* infection than second- or third-generation cephalosporins, there is no definitive evidence to prove this. Also, co-amoxiclav and piperacillin-tazobactam were associated with an increase in the risk of infection. The other 2 meta-analyses, Brown et al. (2013) and Deshpande et al. (2013), found that, for community-associated infection, the strongest association was seen with clindamycin, cephalosporins and quinolones. Trimethoprim and sulfonamides (co-trimoxazole) were associated with an increased risk of infection in all 3 meta-analyses but data were not reported for trimethoprim alone, which is most commonly used in England. The 3 meta-analyses have

many limitations and, because of those limitations and the observational nature of the studies, they cannot definitively establish a causal relationship between particular antibiotics and *C. difficile* infection. Changes in antibiotic prescribing practice, the frequent use of multiple antibiotics and other potential confounding factors make it difficult to determine the relative risk for individual antibiotics.

The ESPAUR report (2015) shows that, in general practice, use of quinolones decreased and use of cephalosporins and carbapenems remained unchanged, but use of penicillins plus an enzyme inhibitor (such as co-amoxiclav or piperacillin-tazobactam) increased between 2010 and 2014. In hospitals, the use of quinolones remained unchanged and use of penicillins plus an enzyme inhibitor, cephalosporins and carbapenems increased during the same period.

The *C. difficile* ribotyping network (CDRN) report (2013–2015), published by Public Health England, found that the strains of *C. difficile* identified and the antibiotics most frequently reported as being associated with *C. difficile* infections referred to the CDRN have changed markedly. In 2007/08, cephalosporins and quinolones were the most commonly cited antibiotics, but have since been superseded by co-amoxiclav and piperacillin-tazobactam. The report states that these data are likely to reflect real changes in prescribing of systemic antibiotics as one of the control measures for *C. difficile* infection.

These data should be interpreted with caution and should not be considered to indicate conclusively which antibiotics have the highest risks of *C. difficile* infection. Nevertheless, they show that antibiotic prescribing practice and the epidemiology of *C. difficile* infections are changing. The NICE evidence summary concludes that, without clear evidence showing that 1 particular antibiotic or class of antibiotic is ‘low-risk’, only general recommendations are possible and healthcare professionals should follow antibiotic guidelines that recommend that all broad-spectrum antibiotics are prescribed appropriately and with careful stewardship.

According to PHE guidance on managing common infections, cefalexin and other cephalosporins (cefixime, cefotaxime and ceftriaxone) should be used only in limited situations (for example, second-line in upper and lower UTI in children, and third-line in UTI in women who are pregnant). Clindamycin is recommended only for bacterial vaginosis (as a vaginal cream) and unresolving cellulitis, and is an option for dental abscess in limited circumstances.

The prescribing of quinolones (for example, ciprofloxacin and ofloxacin) in general practice is also a cause for concern. Resistance to quinolones has increased at a considerable rate (for example, quinolone-resistant *Neisseria gonorrhoeae*) and is usually high level, affecting all the quinolones (see Susceptibility testing of *N. gonorrhoeae* for details). PHE guidance on managing common infections recommends that quinolones are used as first-line treatment only for acute pyelonephritis, acute prostatitis, epididymitis and pelvic inflammatory disease. It states that they should be used in lower respiratory tract infections only when there is proven resistance to other antibiotics.

Although identifying the cephalosporin and quinolone classes as 'high-risk' may have been an important control measure in reducing the risk of *C. difficile* infection, an unintended consequence of this may have been a recent increase in clinically inappropriate prescribing of co-amoxiclav and other broad-spectrum antibiotics, such as piperacillin-tazobactam. These antibiotics have a very limited set of recommended clinical indications. According to the PHE guidance, in primary care, co-amoxiclav is recommended only for persistent acute rhinosinusitis, upper UTI in children, acute pyelonephritis, facial cellulitis, and the prophylaxis and treatment of infection after bites. It may be used second-line in acute exacerbations of chronic obstructive pulmonary disease if infection is resistant to first-line options, and is an option for dental abscess in limited circumstances. Piperacillin-tazobactam is an intravenous antibiotic and is not generally used in primary care.

According to the ESPAUR report (2015), with the reductions in cephalosporin and quinolone use in England in the last decade, co-amoxiclav and

piperacillin-tazobactam have become key agents in many hospital empiric antibiotic policies. They have a key role in treating hospital sepsis syndromes, particularly those related to intra-abdominal sepsis or sepsis without a defined source. The use of carbapenems is also almost exclusively within hospitals for suspected or confirmed multi-drug resistant Gram-negative infections, usually in intensive care, transplant or cancer units. However, resistance to carbapenems is increasing. Between 2013 and 2014, prescription of carbapenems and piperacillin-tazobactam rose by 4% and 7% respectively, with total increases between 2010 and 2014 of 36% and 55% respectively. The report states that it is important that acute NHS trusts prioritise antimicrobial stewardship and target clinical reviews by specialist infection doctors and pharmacists to patients prescribed broad-spectrum antibiotics to ensure that these continue to be the most appropriate agents, and that alternative antibiotics that can be used to preserve these 'last resort' antibiotics are considered.

Co-trimoxazole is not recommended in PHE guidance for primary care for any infections. However, the ESPAUR report (2015) states that use increased by 5% between 2011 and 2014. The British National Formulary advises that co-trimoxazole is associated with rare but serious side effects (for example, Stevens-Johnson syndrome, bone marrow depression and agranulocytosis) and states that it should only be considered for UTI and acute exacerbations of chronic bronchitis when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in acute otitis media in children when there is good reason to prefer it.

Three-day courses of antibiotics for uncomplicated urinary tract infection

According to PHE guidance, a 3-day course of antibiotics is sufficient for acute symptomatic UTI in most women with no fever or flank pain who are not pregnant. Nitrofurantoin is recommended first-line for people with a glomerular filtration rate (GFR) of over 45 ml/min because general resistance and community multi-resistant *E. coli* are increasing. If GFR is between 30 and

45 ml/min, nitrofurantoin should be used only if drug resistance is a problem and there is no alternative (see the September 2014 edition of Drug Safety Update for more information). Depending on local resistance patterns, or if GFR is less than 45 ml/min, trimethoprim or pivmecillinam are recommended as alternative first-line options. PHE recommends that risk factors for resistance should be considered and culture and sensitivity testing should be performed if first-line treatment for UTI fails. PHE has produced guidance for primary care on diagnosing UTI and understanding culture results.

More information on managing common infections can be found in the NICE Clinical knowledge summaries, the NICE guideline on respiratory tract infections, the NICE guideline on pneumonia and the NICE pathway on self-limiting respiratory tract infections – antibiotic prescribing. A NICE pathway on prevention and control of healthcare-associated infection brings information on this subject together.

NICE has also published quality standards on infection prevention and control and surgical site infection, which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas. The Department of Health webpage on antimicrobial resistance includes resources for healthcare professionals to help improve infection prevention and control practices and prescribing.

Prescribing data

In April 2016, NHS England launched a national programme to reduce inappropriate antibiotic prescribing. The payments form part of 2 schemes that reward excellence and quality improvement in the NHS: the 2016/17 Commissioning for Quality and Innovation (CQUIN) and the Quality Premium scheme.

The Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), which provides advice to the government on minimising the risk of healthcare associated infections, has agreed antimicrobial prescribing quality measures for primary and secondary care.

Three medicines optimisation key therapeutic topic (MO KTT) prescribing comparators are available to support this key therapeutic topic[15]. These are:

- **Antibacterial items/STAR-PU:** the number of prescription items for antibacterial drugs (BNF 5.1) per Oral antibacterials (BNF 5.1 sub-set) ITEM based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU).
- **Co-amoxiclav, cephalosporins & quinolones % items:** the number of prescription items for co-amoxiclav, cephalosporins and quinolones as a percentage of the total number of prescription items for selected antibacterial drugs (BNF 5.1).
- **3 day courses of antibiotics: ADQ/item:** the number of average daily quantities (ADQs) per item for trimethoprim 200 mg tablets, nitrofurantoin 50 mg tablets and capsules, nitrofurantoin 100 mg m/r capsules and pivmecillinam 200 mg tablets.

Antibacterial items/STAR-PU

- Data for 2015/16 (April 2015 to March 2016) show a 2.32 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.62 to 1.44 items/STAR-PU.
- Between the quarter January to March 2014 and the quarter January to March 2016 there was a 5.7% decrease in the comparator value for England (total prescribing) from 0.314 to 0.296 items/STAR-PU.
- Over the same period there was an 8.18% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.007 items/STAR-PU. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

[15] The comparator and associated data presented here are based on the previous Key therapeutic topics publication (February 2016). Data provided by NHS Digital (October 2016; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

Co-amoxiclav, cephalosporins & quinolones % items

- Data for 2015/16 (April 2015 to March 2016) show a 3.4 fold variation in prescribing rates at CCG level, from 4.07% to 14.02%.
- Between the quarter January to March 2014 and the quarter January to March 2016 there was a 19.9% decrease in the comparator value for England (total prescribing) from 10.6% to 8.5%.
- Over the same period there was a 32.9% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 2.41%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

3 day courses of antibiotics: ADQ/item

- Data for the quarter May to July 2016 show a 1.6 fold variation in prescribing rates at CCG level, from 4.91 to 7.75 ADQ/item.
- Between the quarter October to December 2013 and the quarter May to July 2016 there was a 5.3% decrease in the comparator value for England (total prescribing) from 6.15 to 5.82 ADQ/item.
- Over the same period there was a 10.9% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.11 ADQ/item. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

The medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors, includes the first 2 prescribing comparators outlined above. The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The focus has been changed to antimicrobial stewardship, and this topic now also includes key information from the 3-day courses of antibiotics for uncomplicated urinary tract infection topic. The evidence context has been updated in the light of new guidance and important new evidence as appropriate.

Non-steroidal anti-inflammatory drugs

Options for local implementation

- Review the appropriateness of non-steroidal anti-inflammatory drug (NSAID) prescribing widely and on a routine basis, especially in people who are at higher risk of gastrointestinal, renal and cardiovascular morbidity and mortality (for example, older people).
- If an NSAID is needed, use ibuprofen (1200 mg a day or less) or naproxen (1000 mg a day or less). Use the lowest effective dose and the shortest duration of treatment necessary to control symptoms.
- Co-prescribe a proton pump inhibitor with NSAIDs for people who have osteoarthritis, rheumatoid arthritis or for people over 45 years who have low back pain in accordance with NICE guidance.

Evidence context

There are long-standing and well-recognised gastrointestinal and renal safety concerns with all NSAIDs. There is also substantial evidence confirming an increased risk of cardiovascular events with many NSAIDs, including COX-2 inhibitors and some traditional NSAIDs such as diclofenac and high-dose ibuprofen. In the June 2015 edition of Drug Safety Update, the MHRA gave prescribing advice on the use of all NSAIDs. More information is also available in the NICE Clinical Knowledge Summary on NSAIDs: prescribing issues:

- The decision to prescribe an NSAID should be based on an assessment of a person's individual risk factors, including any history of cardiovascular and gastrointestinal illness.
- Naproxen (1000 mg a day or less) and low-dose ibuprofen (1200 mg a day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs.

- The lowest effective dose should be used for the shortest duration necessary to control symptoms. A person's need for symptomatic relief and response to treatment should be re-evaluated periodically.

In the May 2009 edition of Drug Safety Update, the MHRA reminded prescribers that NSAIDs may rarely precipitate renal failure and that people at risk of renal impairment or renal failure (particularly older people) should avoid NSAIDs if possible. The MHRA further advised that it is important to consider other concomitant disease states, conditions, or medicines that may precipitate reduced renal function when prescribing NSAIDs. For example, co-prescribing NSAIDs with renin-angiotensin system drugs may pose particular risks to renal function. This combination should be especially carefully considered and regularly monitored if continued. See the NICE medicines evidence commentary Risk of acute kidney injury with concurrent use of antihypertensives and NSAIDs for further information and the separate key therapeutic topic acute kidney injury (AKI): use of medicines in people with or at increased risk of AKI. Also see the key therapeutic topic on multimorbidity and polypharmacy for further information on reviewing polypharmacy and deprescribing.

There have been several European Medicines Agency (EMA) reviews and MHRA Drug Safety Updates concerning the cardiovascular safety of NSAIDs:

- In 2005, an EMA review on COX-2 inhibitors identified an increased risk of thrombotic events, such as heart attack and stroke, with these types of NSAIDs. In 2006, the EMA also concluded that a small increased risk of thrombotic events could not be excluded with non-selective NSAIDs, including diclofenac, particularly when they are used at high doses for long-term treatment.
- The July 2008 edition of Drug Safety Update advised that etoricoxib should not be prescribed to people whose blood pressure is persistently above 140/90 mmHg and inadequately controlled, following advice from an EMA review. The summary of product characteristics states that hypertension should be controlled before treatment with etoricoxib and special attention should be paid to blood pressure monitoring during treatment. Blood

pressure should be monitored within 2 weeks of starting etoricoxib treatment, and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

- Updated contraindications and prescribing advice for diclofenac were highlighted in the June 2013 edition of Drug Safety Update following publication of an EMA review. See the NICE medicines evidence commentary EMA review of cardiovascular risks of NSAIDs: higher risk with diclofenac compared with ibuprofen/naproxen confirmed and the NICE eyes on evidence article Non-steroidal anti-inflammatory drugs: new information and warnings about cardiovascular risk for more information on this issue. Further to these, the January 2015 edition of Drug Safety Update reported that oral diclofenac was no longer available without prescription.
- The January 2015 edition of Drug Safety Update also highlighted updated prescribing advice for aceclofenac, which is now contraindicated in people with certain cardiovascular diseases, in-line with diclofenac and COX-2 inhibitors.
- Following an EMA review, which confirmed that the cardiovascular risk of ibuprofen 2400 mg a day or more is similar to COX-2 inhibitors and diclofenac, the June 2015 edition of Drug Safety Update issued advice on prescribing and dispensing high-dose ibuprofen. The Drug Safety Update commented that it is uncertain whether ibuprofen doses between 1200 mg and 2400 mg per day are associated with an increased cardiovascular risk compared with not taking ibuprofen, because there are only limited data available.
- The June 2015 edition of Drug Safety Update also discussed the possible interaction between ibuprofen and low dose aspirin, noting that occasional ibuprofen use is unlikely to have a clinically meaningful effect on the benefits of low-dose aspirin. However, the possibility that long-term, daily use of ibuprofen might reduce the cardioprotective effects of low-dose aspirin cannot be excluded.

More information is available in the MHRA guidance on COX-2 selective inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs): Cardiovascular safety.

Further to this, a systematic review and meta-analysis of observational studies, which was outlined in a NICE medicines evidence commentary NSAIDs and risk of venous thromboembolism, found that there was a statistically significant increased risk of venous thromboembolism among users of NSAIDs compared to non-users of NSAIDs. However, the meta-analysis had a number of limitations and the results should be interpreted with caution.

A network meta-analysis on drug treatments for osteoarthritis which found no statistically significant benefit with lower doses of some NSAIDs and paracetamol on pain or physical functioning compared with placebo is reviewed in a NICE medicines evidence commentary. However, the results of this meta-analysis do not change the key messages discussed in this key therapeutics topic.

More information on the use of NSAIDs can be found in the NICE guidelines on osteoarthritis, rheumatoid arthritis (which is being updated, expected publication date August 2018) and low back pain (which is being updated, expected publication date to be confirmed). These guidelines include recommendations to co-prescribe a proton pump inhibitor with NSAIDs for people who have osteoarthritis, rheumatoid arthritis or for people over 45 years who have low back pain.

NICE has also published quality standards on osteoarthritis and rheumatoid arthritis, which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas. A NICE guideline on spondyloarthritis is also in development (expected publication date March 2017).

Prescribing data

Two medicines optimisation key therapeutic topic (MO KTT) prescribing comparators are available to support this topic[16]. These are:

- **NSAIDs: ADQ/STAR-PU:** the total number of average daily quantities (ADQs) per oral NSAIDs (BNF 10.1.1 sub-set) COST based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU).
- **NSAIDs: Ibuprofen & naproxen % items:** the total number of prescription items for ibuprofen and naproxen as a percentage of the total number of prescription items for all NSAIDs.

NSAIDs: ADQ/STAR-PU

- Data for the quarter May to July 2016 show a 3.8 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.61 to 2.36 ADQ/STAR-PU.
- Between the quarter July to September 2013 and the quarter May to July 2016 there was a 13.9% decrease in the comparator value for England (total prescribing) from 1.58 to 1.36 ADQ/STAR-PU.
- Over the same period there was a 12.1% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.11 ADQ/STAR-PU. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

NSAIDs: Ibuprofen & naproxen % items

- Data for the quarter May to July 2016 show a 1.3 fold variation in prescribing rates at CCG level, from 67.9% to 88.5%.

[16] The comparator and associated data presented here are based on the previous Key therapeutic topics publication (February 2016). Data provided by NHS Digital (October 2016; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority

- Between the quarter July to September 2013 and the quarter May to July 2016 there was an 11.6% increase in the comparator value for England (total prescribing) from 70.9% to 79.1%.
- Over the same period there was a 15.0% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 1.82%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

The prescribing of diclofenac has reduced in recent years. In the year from April 2015 to March 2016 diclofenac accounted for approximately 1.1 million prescription items (7.5% of all NSAID items) in primary care in England, but there is still variation in prescribing across localities.

The medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors, includes the NSAIDs: ibuprofen & naproxen % items prescribing comparator outlined above. The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence as appropriate.

Type 2 diabetes mellitus

Options for local implementation

- The NICE guideline on type 2 diabetes in adults: management recommends adopting an individualised approach to diabetes care. Involve people with type 2 diabetes in decisions about their individual glycated haemoglobin (HbA1c) target, and reassess their individual needs and circumstances at each review. Consider stopping any medicines that are not effective.
- Consider carefully, with an individualised approach, the benefits and risks of controlling blood glucose and the use of blood glucose lowering medicines. Review and, if appropriate, optimise prescribing to ensure that it is in line with NICE guidance taking into account the person's preferences, comorbidities, risks from polypharmacy, and their life expectancy and consequent chances of benefiting from long-term interventions.
- When choosing and reviewing medicines, take into account the person's individual clinical circumstances, preferences and needs; the medicines' efficacy (based on metabolic response), safety and tolerability; and the licensed indications or combinations available. Consider also the cost of medicines: the NICE guideline recommends choosing medicines with the lowest acquisition cost if 2 in the same class are appropriate.
- The NICE guideline recommends that self-monitoring of blood glucose levels for adults with type 2 diabetes should not routinely be offered. See the guideline for details on when self-monitoring is appropriate.

Evidence context

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance and insufficient pancreatic insulin production, resulting in high blood glucose levels. Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure and disturbed blood lipid levels, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications,

together with reduced quality of life and life expectancy. The NICE guideline on type 2 diabetes in adults: management recommends adopting an individualised approach to diabetes care, which takes into account personal preferences, comorbidities, risks from polypharmacy, and the ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. See also the key therapeutic topic on multimorbidity and polypharmacy for further information on reviewing polypharmacy and de-prescribing.

The guideline recommends that the person's needs and circumstances should be reassessed at each review and consideration given to stopping any medicines that are not effective. Controlling blood glucose levels requires a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. This key therapeutic topic focusses on blood glucose management; however, the NICE guideline also has recommendations on patient education, dietary advice, blood pressure management, antiplatelet therapy and management of complications. Recommendations on the management of blood lipids in people with type 2 diabetes are given in the NICE guideline on lipid modification. All these components should be given due consideration in the care of people with type 2 diabetes.

The NICE pathway on diabetes brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. NICE has also published quality standards on diabetes in adults, which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas. In September 2016, the Care Quality Commission published my diabetes, my care a community diabetes care review that considers how well care services work together to deliver high-quality diabetes care. The review makes a number of recommendations for how health and social care commissioners, providers and professionals could work together to improve diabetes care and prevention.

Target blood glucose levels

The NICE guideline on type 2 diabetes in adults: management recommends that people with type 2 diabetes should be involved in decisions about their

individual glycated haemoglobin (HbA1c) target and be supported to achieve and maintain this. For adults with type 2 diabetes that is managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, the guideline recommends supporting the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, the recommended aim is an HbA1c level of 53 mmol/mol (7.0%). If HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher, advice about diet, lifestyle and adherence to drug treatment should be reinforced, the person should be supported to aim for an HbA1c level of 53 mmol/mol (7.0%) and drug treatment should be intensified (taking into account principles of individualised care). When intensification of drug treatment is required the guideline recommends that additional treatments should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

The target HbA1c level can be relaxed on a case-by-case basis, with particular consideration for people who are older or frail, those with a reduced life expectancy, those for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, and those for whom intensive management would not be appropriate, such as people with significant comorbidities. The NICE patient decision aid for adults with type 2 diabetes can support the implementation of the guideline recommendations on the individualised agreement of HbA1c targets.

The Quality and Outcomes Framework (QOF) allocates points for achieving 3 levels of glucose control in people with type 2 diabetes: HbA1c of 75 mmol/mol (9%) or less, 64 mmol/mol (8%) or less and 59 mmol/mol (7.5%) or less.

What are the benefits and risks of controlling blood glucose?

The NICE guideline included a review question comparing intensive glycaemic control with conventional glycaemic control in people with type 2 diabetes (see the full NICE guideline for details). This used a Cochrane review (Hemmingsen et al. 2013 [CD008143]) as the primary source of evidence because it included all relevant randomised controlled trials (RCTs). The

Cochrane review included 28 RCTs in 34,912 people with type 2 diabetes; the NICE guideline excluded 8 RCTs in which intensive and conventional glycaemic control groups had significant baseline differences in adjunctive treatment for cardiovascular risk factors.

Compared with conventional control, the NICE guideline found that intensive glycaemic control did not statistically significantly reduce death from any cause (relative risk [RR] 0.98, 95% confidence interval [CI] 0.88 to 1.09; 16 RCTs, n=6504) or death from cardiovascular causes (RR 1.15, 95% CI 0.98 to 1.35; 14 RCTs, n=6356). No statistically significant effect of targeting intensive glycaemic control was found on the composite of macrovascular complications (RR 0.98, 95% CI 0.74 to 1.30; 8 RCTs, n=5334), non-fatal myocardial infarction (RR 0.92, 95% CI 0.78 to 1.09; 9 RCTs, n=5902), congestive heart failure (RR 0.82, 95% CI 0.62 to 1.08; 8 RCTs, n=5460), non-fatal stroke (RR 1.06, 95% CI 0.80 to 1.41; 8 RCTs, n=5488) or amputation of lower extremity (RR 0.73, 95% CI 0.42 to 1.25; 7 RCTs, n=5079).

Intensive glycaemic control did reduce the risk of the composite of microvascular complications (RR 0.75, 95% CI 0.61 to 0.92; 3 RCTs, n=4376), but no statistically significant reductions in risk were seen for the individual end points of nephropathy (RR 0.64, 95% CI 0.32 to 1.29; 7 RCTs, n=4754), progression to end-stage renal disease (RR 0.94, 95% CI 0.47 to 1.89; 4 RCTs, n=4803) or retinopathy (RR 0.79, 95% CI 0.56 to 1.11; 5 RCTs, n=4614).

Intensive glycaemic control increased the risk of severe hypoglycaemia (RR 2.23, 95% CI 1.22 to 4.08; 13 RCTs, n=5452) and mild hypoglycaemia (RR 1.85, 95% CI 1.53 to 2.25; 12 RCTs, n=6320). The guideline development group agreed overall that there was evidence to support the setting of target values, but considered it important to ensure that a person's risk of hypoglycaemia is evaluated when setting appropriate target levels.

Self-monitoring of blood glucose

The NICE guideline on type 2 diabetes in adults: management recommends that self-monitoring of blood glucose levels for adults with type 2 diabetes should not routinely be offered unless:

- the person is on insulin treatment or
- there is evidence of hypoglycaemic episodes or
- the person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery or
- the person is pregnant, or is planning to become pregnant (see the NICE guideline on diabetes in pregnancy for more information).

Healthcare professionals should also take the Driver and Vehicle Licensing Agency (DVLA) guidance Assessing fitness to drive guide into account when offering self-monitoring of blood glucose levels to people with type 2 diabetes and advise them about their own particular requirements.

The guideline development group discussed the evidence for self-monitoring of blood glucose and concluded that overall, while a statistically significant difference was observed in HbA1c levels in favour of self-monitoring, this was not clinically meaningful and was unlikely to be cost-effective. The reduction in HbA1c levels with self-monitoring was 2 mmol/mol (0.22%), which was less than 5 mmol/mol (0.5%), the agreed threshold for minimal important difference.

The guideline recommends considering short-term self-monitoring of blood glucose levels in adults with type 2 diabetes (and reviewing treatment as necessary) when starting treatment with oral or intravenous corticosteroids or to confirm suspected hypoglycaemia. It is also recommended for health professionals to be aware that adults with type 2 diabetes who have acute intercurrent illness are at risk of worsening hyperglycaemia, and reviewing treatment as necessary.

The guideline recommends that if adults with type 2 diabetes are self-monitoring their blood glucose levels this should be assessed in a structured

way at least annually, assessing various issues including the impact on the person's quality of life and the continued benefit of self-monitoring.

Blood glucose lowering therapy

The NICE guideline on type 2 diabetes in adults: management recommends that the choice of medicine for managing blood glucose levels should be made following a discussion with the individual person about the benefits and risks of drug treatment, and the options available. The guideline recommends an individualised approach to treatment choice taking into account the person's individual preferences and needs, and their individual clinical circumstances, for example, comorbidities and risks from polypharmacy. Choice should also take into account the medicine's efficacy (based on metabolic response), safety and tolerability; and the licensed indications or combinations available. Cost should be taken into account and the guideline recommends choosing medicines with the lowest acquisition cost if 2 in the same class are appropriate. The NICE patient decision aid for adults with type 2 diabetes can support the implementation of the guideline recommendations on the pharmacological management of blood glucose.

Efficacy

Although all blood glucose lowering medicines are effective (at a population level) in reducing HbA1c levels, clinical outcome data, particularly around cardiovascular outcomes, are limited. Improvements in surrogate markers (including HbA1c levels) do not automatically confer benefits on mortality or morbidity, and risks may only become apparent over time when medicines are used widely in a diverse population.

Metformin, sulfonylureas and insulin have outcome data from the UK Prospective Diabetes Study (UKPDS). In UKPDS 33 (UKPDS Group 1998), intensive glycaemic control with sulfonylureas or insulin compared with conventional control (median HbA1c after 10 years follow up: 53 mmol/mol [7.0%] compared with 63 mmol/mol [7.9%]) reduced the risk of microvascular complications, but not macrovascular disease. In UKPDS 34 (UKPDS Group 1998) in people who were overweight or obese, intensive glycaemic control

with metformin compared with conventional control (median HbA1c after 10.7 years follow up: 57 mmol/mol [7.4%] compared with 64 mmol/mol [8.0%]) reduced the risk of MI and death from any cause. Long-term follow-up of UKPDS (Holman et al. 2008) found a continued reduction in microvascular risk and emergent risk reductions for MI and death in the sulfonylurea-insulin group and a continued benefit for risk of MI and death in the metformin group.

Other blood glucose lowering medicines have not shown such cardiovascular benefits in people with type 2 diabetes. For example, in PROACTIVE (Dormandy et al. 2005), pioglitazone did not reduce the composite primary end point of death from any cause, non-fatal MI, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation in people with type 2 diabetes and pre-existing major macrovascular disease, but did increase the incidence of oedema, weight gain and heart failure. In SAVOR–TIMI 53 (Scirica et al. 2013), saxagliptin did not reduce the composite primary end point of cardiovascular death, MI, or ischemic stroke, but did increase the risk of admission to hospital because of heart failure in people with type 2 diabetes who had established cardiovascular disease, or were current smokers, or had dyslipidaemia or hypertension. (See the medicines evidence commentary Type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes.) In EXAMINE (White et al. 2013) alogliptin did not reduce the composite primary end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke in people with type 2 diabetes who had had a recent acute coronary syndrome. (See the medicines evidence commentary Type 2 diabetes: study finds no benefit from alogliptin on cardiovascular outcomes in people with a recent acute coronary syndrome). Similarly, in TECOS (Green et al. 2013) sitagliptin did not reduce the composite primary end point of death from cardiovascular causes, non-fatal MI, non-fatal stroke, or hospital admission for unstable angina in people with type 2 diabetes who had established cardiovascular disease.

More recently 2 outcome studies have shown cardiovascular benefits with blood glucose lowering medicines. In EMPA-REG OUTCOME (Zinman et al.

2015), adding the sodium glucose cotransporter 2 (SGLT-2) inhibitor empagliflozin to standard care in people with type 2 diabetes and established cardiovascular disease reduced the risk of cardiovascular outcomes. The composite end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke was reduced with a number needed to treat of 63 over 3 years (hazard ratio 0.86; 95% CI 0.74 to 0.99). However, this was driven by a reduction in the risk of cardiovascular death, not MI or stroke. See the medicines evidence commentary Type 2 diabetes: study finds empagliflozin reduces adverse cardiovascular outcomes, which discusses this study in more detail.

LEADER (Marso et al, 2016) assessed the cardiovascular effects of the glucagon-like-peptide-1 (GLP-1) mimetic liraglutide as an add-on to standard care in people with type 2 diabetes who had established cardiovascular disease or were at high risk of developing it. Liraglutide reduced the composite end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke with a number needed to treat of 66 over 3.5 years (hazard ratio 0.87; 95% CI 0.78 to 0.97). However, again this was driven by a reduction in the risk of cardiovascular death, not MI or stroke. See the medicines evidence commentary Type 2 diabetes: liraglutide reduces cardiovascular risk in people at high risk of having a cardiovascular event for more details. Another study with the GLP-1 mimetic lixisenatide in a people with recent acute coronary syndrome (ELIXA, Pfeffer et al. 2015), did not show a reduction in cardiovascular events.

The ORIGIN study found that, compared with standard care (non-insulin therapy), the early use of basal insulin glargine for a median of 6 years had no effect on cardiovascular outcomes in people with impaired fasting glucose, impaired glucose tolerance or early type 2 diabetes who also had cardiovascular risk factors. As perhaps expected, episodes of severe hypoglycaemia were more common in people receiving insulin glargine. The incidence of a first episode of severe hypoglycaemia was 1.00 per 100 patient-years with insulin glargine and 0.31 per 100 patient-years with standard care ($p<0.001$) (see the medicines evidence commentary Insulin

glargine: no effect on cardiovascular outcomes in early type 2 diabetes for details).

Because patient orientated outcomes are not reported in many studies of blood glucose lowering drugs, the guideline development group for the NICE guideline on type 2 diabetes agreed that change in HbA1c would be the main outcome measure to reflect glycaemic control and that a difference of 5 mmol/mol (0.5%) was clinically important.

Safety

The MHRA has highlighted several safety concerns with blood glucose lowering medicines and these are cross referenced in the NICE guideline on type 2 diabetes. For example, warnings about pioglitazone and risks of heart failure, bladder cancer and use in older people have been incorporated into the summaries of product characteristics, and the guideline recommends that pioglitazone should not be offered or continued in adults with heart failure, hepatic impairment, diabetic ketoacidosis, bladder cancer or uninvestigated macroscopic haematuria. The MHRA reported in the January 2011 edition of Drug Safety Update that cases of heart failure have been reported when pioglitazone was used in combination with insulin (especially in people with pre-existing risk factors for developing heart failure). If the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema; and pioglitazone discontinued if any deterioration in cardiac status occurs.

All the glucagon-like-peptide-1 (GLP-1)-based therapies, GLP-1 agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors (gliptins) have warnings in their summaries of product characteristics about a risk of developing acute pancreatitis. In the March 2009 edition of Drug Safety Update, the MHRA drew attention to reports of severe pancreatitis and renal failure associated with exenatide (Byetta), and in the September 2012 edition of Drug Safety Update, reports of acute pancreatitis associated with gliptins.

In the April 2016 edition of Drug Safety Update, the MHRA warned about the risk of diabetic ketoacidosis (DKA) with the SGLT-2 inhibitors canagliflozin,

dapagliflozin and empagliflozin. Serious and life-threatening cases of DKA have been reported in people taking SGLT-2 inhibitors and, in several cases, blood glucose levels were only moderately elevated, which is atypical for DKA. When treating people who are taking an SGLT-2 inhibitor the MHRA recommends testing for raised ketones in people with ketoacidosis symptoms, even if plasma glucose levels are near-normal. It advises informing people who are being treated with SGLT-2 inhibitors of the signs and symptoms of DKA and advising them to seek immediate medical advice if they develop any of these. SGLT-2 inhibitors should be discontinued immediately if DKA is suspected or diagnosed. Treatment with SGLT-2 inhibitors should also be interrupted in people who are hospitalised for major surgery or acute serious illnesses.

In the June 2016 edition of Drug Safety Update, the MHRA warned that a signal of increased lower limb amputation with the SGLT-2 inhibitor canagliflozin was being investigated. In the ongoing cardiovascular outcomes trial, CANVAS, the incidence of lower limb amputation (primarily of the toe) is higher in the canagliflozin groups compared with the placebo group.

One possible side effect of blood glucose lowering medicines is hypoglycaemia, and controlling blood glucose needs a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. The medicines evidence commentary Type 2 diabetes: increased risk of hypoglycaemia with combined use of dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas discusses a systematic review and meta-analysis which found that adding a DPP-4 inhibitor to a sulfonylurea increased the risk of hypoglycaemia by around 50%. Many of the summaries of product characteristics for blood glucose lowering medicines warn about the increased risk of hypoglycaemia when combining treatments, particularly with a sulfonylurea or insulin, and a lower dose of insulin or a sulfonylurea may be needed.

Blood glucose lowering therapy

This section outlines recommendations on blood glucose lowering therapy from the NICE guideline on type 2 diabetes in adults: management. See also

the algorithm for blood glucose lowering therapy in adults with type 2 diabetes at the end of this section.

Rescue therapy at any phase of treatment

If an adult with type 2 diabetes is symptomatically hyperglycaemic, the NICE guideline recommends considering insulin or a sulfonylurea, and reviewing treatment when blood glucose control has been achieved.

Initial drug treatment

The NICE guideline recommends offering standard-release metformin as the initial drug treatment for adults with type 2 diabetes (or considering a trial of modified-release metformin in people who have had gastrointestinal side effects with the standard-release preparation). If metformin is contraindicated (for example, in people with renal impairment) or not tolerated, the guideline recommends considering initial drug treatment with a DPP-4 inhibitor (gliptin) or pioglitazone or a sulfonylurea. The guideline also advises that repaglinide is both clinically effective and cost effective if metformin is contraindicated or not tolerated in adults with type 2 diabetes. However there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification. This subsequent constraint on intensification requires discussion with the individual.

If metformin is contraindicated or not tolerated, SGLT-2 inhibitors are an option in certain circumstances. NICE technology appraisal guidance on canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes recommends monotherapy with an SGLT-2 inhibitor as an option where metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

- a DPP‑4 inhibitor would otherwise be prescribed and
- a sulfonylurea or pioglitazone is not appropriate.

First intensification of drug treatment

In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed

threshold for intensification, the guideline recommends considering dual therapy with:

- metformin and a DPP-4 inhibitor (gliptin) or
- metformin and pioglitazone or
- metformin and a sulfonylurea or
- metformin and an SGLT-2 inhibitor in certain circumstances.

NICE guidance on treatment with metformin and an SGLT-2 inhibitor is given in NICE technology appraisal guidance on canagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in combination therapy for treating type 2 diabetes and empagliflozin in combination therapy for treating type 2 diabetes. The SGLT-2 inhibitors in dual therapy with metformin are recommended as options for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated or
- the person is at significant risk of hypoglycaemia or its consequences.

If metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA1c to below the person's individually agreed threshold for intensification, the guideline recommends considering dual therapy with:

- a DPP-4 inhibitor (gliptin) and pioglitazone or
- a DPP-4 inhibitor (gliptin) and a sulfonylurea or
- pioglitazone and a sulfonylurea.

The guideline development group considered that the overall quality of the evidence for first intensification was moderate to low, and the evidence was weighted towards metformin-based combinations. There was limited evidence for treatment intensification options for people for whom metformin is contraindicated or not tolerated. There was strong evidence from the health economic model showing that, when added to metformin, GLP-1 mimetics were not cost effective at first intensification and they were not recommended. The guideline development group noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second

intensification where GLP-1 mimetics would become an option in combination with metformin. GLP-1 mimetics were not considered at first intensification in people for whom metformin is contraindicated or not tolerated.

Second intensification of drug treatment

If dual therapy with oral drugs has not continued to control HbA1c to below the person's individually agreed threshold for intensification, the guideline recommends considering either triple therapy with oral drugs or starting insulin-based treatment. For triple therapy the following are recommended:

- metformin, a DPP-4 inhibitor (gliptin) and a sulfonylurea or
- metformin, pioglitazone and a sulfonylurea or
- metformin, pioglitazone or a sulfonylurea, and an SGLT-2 inhibitor in certain circumstances.

NICE technology appraisal guidance on canagliflozin and empagliflozin recommend these drugs as options in triple therapy as above. The NICE technology appraisal guidance on dapagliflozin states that dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended, except as part of a clinical trial. A partial update to this technology appraisal, dapagliflozin in triple therapy regimens for treating type 2 diabetes, is currently in development (publication expected January 2017).

If this triple therapy is not effective, not tolerated or contraindicated, the guideline recommends considering combination therapy with metformin, a sulfonylurea and a GLP-1 mimetic for adults with type 2 diabetes who:

- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or

- have a BMI lower than 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

GLP-1 mimetic therapy should be continued only when people have a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c **and** a weight loss of at least 3% of initial body weight in 6 months).

If metformin is contraindicated or not tolerated, and if dual therapy with 2 oral drugs has not continued to control HbA1c to below the person's individually agreed threshold for intensification, the guideline recommends considering insulin‑based treatment. GLP-1 mimetics were not considered here.

The guideline recommends that a GLP-1 mimetic in combination with insulin should be offered only with specialist care advice and ongoing support from a consultant-led multidisciplinary team.

The guideline development group considered that the overall quality of the evidence for second intensification was low.

Insulin-based treatments

The NICE guideline recommends that a structured programme employing active insulin dose titration should be used when insulin therapy is started in adults with type 2 diabetes. Metformin should be continued in people without contraindications or intolerance. The continued need for other blood glucose lowering therapies should be reviewed: use of an SGLT-2 inhibitor in combination with insulin with or without other blood glucose lowering drugs is recommended as an option in NICE technology appraisal guidance.

When insulin therapy is necessary, the guideline recommends that it should be started from a choice of a number of insulin types and regimens. NPH insulin injected once or twice daily according to need is the preferred option. The long-acting insulin analogues, insulin detemir or insulin glargine can be considered as an alternative in certain circumstances (see the guideline for full details), such as if:

- the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or
- the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or
- the person would otherwise need twice daily NPH insulin injections in combination with oral glucose lowering drugs.

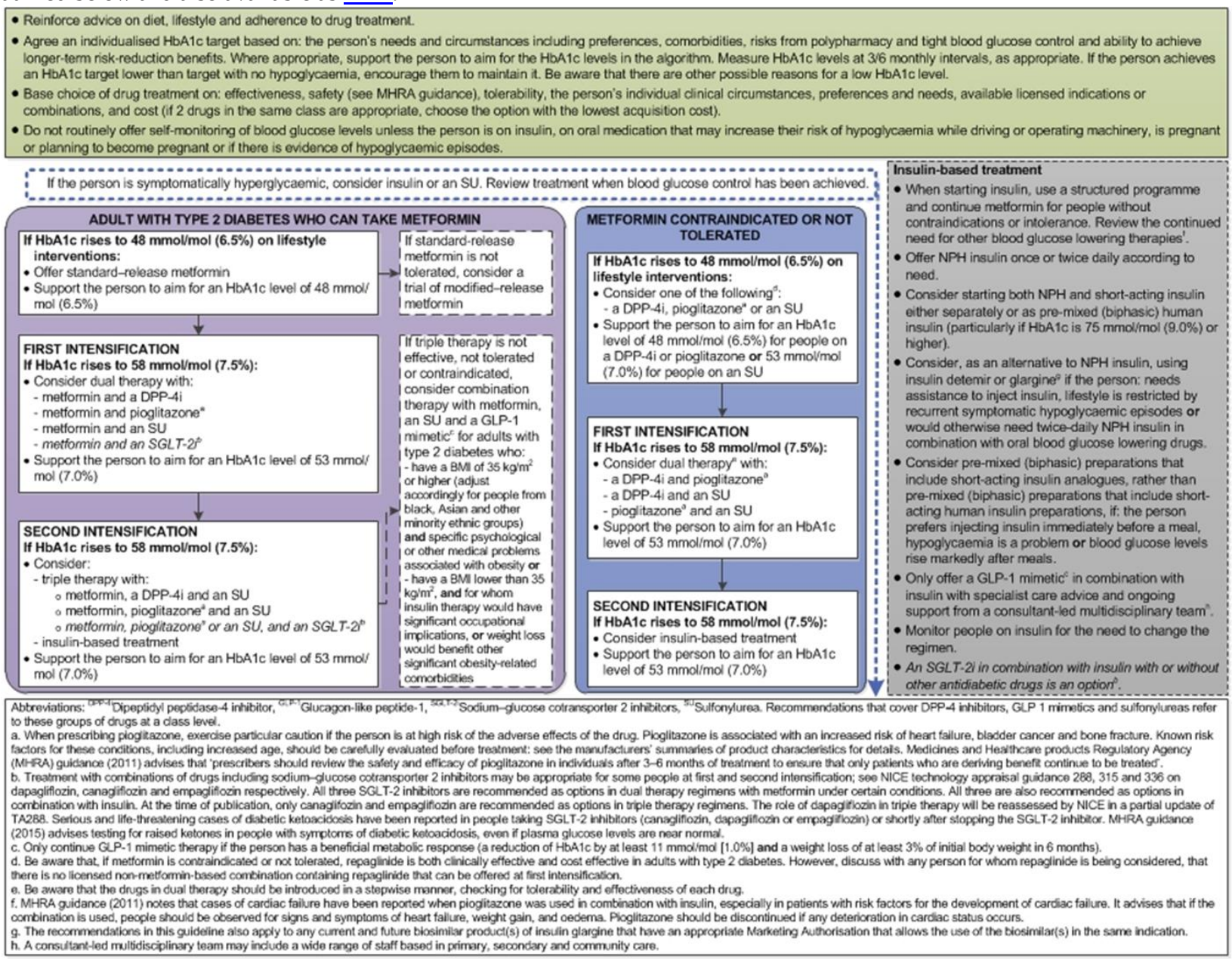
The recommendations for insulin glargine also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate marketing authorisation that allows the use of the biosimilar(s) in the same indication. For more information the insulin glargine biosimilar, Abasaglar see the evidence summary: new medicine publication diabetes mellitus type 1 and type 2: insulin glargine biosimilar (Abasaglar).

The guideline development group considered that there was strong evidence that insulin degludec was not cost-effective, and this long-acting insulin analogue was not recommended. Short-acting insulins and pre-mixed (biphasic) insulin preparations are also options in particular circumstances (see the guideline for details).

Several new insulin products have been launched recently and the European Medicines Agency issued a risk minimisation strategy for high-strength and fixed-combination insulin products in October 2015. In the April 2015 edition of Drug Safety Update the MHRA issued advice to health professionals to minimise the risk of medication errors with recently launched high strength, fixed combination and biosimilar insulin products. See the key therapeutic topic on safer insulin prescribing for more information.

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

This is outlined below and also available as PDF.



Prescribing data

The Health and Social Care Information Centre report Prescribing for diabetes in England: 2005/6 to 2015/16 found that in the financial year 2015/16 there were 49.7 million items prescribed for diabetes at a net ingredient cost of £956.7 million. This was a 5.3% (2.5 million) rise in the number of items and a 10.1% (£88.0 million) rise in the net ingredient cost from 2014/15. The prescribing of 'other antidiabetic drugs' (which includes the newer blood glucose-lowering drugs) has increased considerably in recent years. The number of items prescribed increased by 256% (5.0 million) from 2005/6 to 2015/16 with a growth in net ingredient cost of 243% (£193.2 million).

The net ingredient cost of all insulin therapy in primary care in 2015/16 was £343.7 million; a growth of 55.6% from 2005/6. In the financial year 2015/16, 1.4 million items of insulin glargine were prescribed at a cost of £80 million, 700,000 items of insulin detemir were prescribed at a cost of £44 million and 43,000 items of insulin degludec at a cost of £4.7 million. This compared with 600,000 items of NPH (isophane) insulin at a cost of £17.5 million.

A medicines optimisation key therapeutic topic (MO KTT) prescribing comparator is available to support this topic – **Long-acting insulin analogues:** the number of prescription items for long-acting human analogue insulins as a percentage of the total number of prescription items for all long-acting and intermediate acting insulins excluding biphasic insulins[17].

- Data for the quarter May to July 2016 show a 2.2 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 44.5% to 97.3%.
- Between the quarter July to September 2013 and the quarter May to July 2016 there was a 4.1% decrease in the comparator value for England (total prescribing) from 81.9% to 78.5%.
- Over the same period there was a 9.5% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 2.4%.

[17] The comparators and associated data presented here are based on the previous Key therapeutic topics publication (February 2016). Data provided by the NHS Digital (October 2016; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

The development of further prescribing comparators to support this key therapeutic topic is being explored by the NHS England Medicines Optimisation Intelligence Group[18].

The medicines optimisation dashboard, which brings together a range of medicines-related metrics from across sectors, includes 4 diabetes metrics related to this key therapeutic topic. These are:

- Antidiabetic drugs (BNF section 6.1.2), which is the proportion of prescription items for sulfonylureas (BNF 6.1.2.1), biguanides (BNF 6.1.2.2) and other antidiabetes drugs (BNF 6.1.2.3): DPP-4 inhibitors, GLP-1 mimetics, insulin release stimulators, intestinal alpha glucosidases inhibitors, SGLT-2 inhibitors and pioglitazone.
- Diabetes Mellitus (DM009) % achieving upper threshold or above, which is the percentage of practices in a CCG that achieve upper threshold or above (92% or more inclusive of exceptions) for QOF indicator DM009.
- Diabetes Mellitus (DM009) % underlying achievement, which is the percentage underlying achievement at CCG level for QOF indicator DM009 inclusive of exceptions.
- Emergency diabetes admissions, which is the number of emergency attendances for diabetes per 100 patients on the practice diabetes disease register.

The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

[18] For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence as appropriate.

Wound care products

Options for local implementation

- Review and, if appropriate, optimise prescribing of wound dressings to ensure that the least costly dressings that meet the required clinical performance characteristics are routinely chosen.
- Prescribe the minimum quantity of dressings sufficient to meet people's needs.
- Do not routinely choose antimicrobial (for example, silver, iodine or honey) dressings ahead of non-medicated dressings.

Evidence context

A large number of wound dressings are available with a wide range of physical performance characteristics (such as size, adhesion, conformability and fluid-handling properties) and costs, presenting a challenge for healthcare professionals who are managing wounds.

Although representing only 1 route by which dressings are procured within the NHS, the prescription costs of advanced wound dressings and antimicrobial dressings in primary care in England were over £110 million in the year to August 2015 (based on British National Formulary [BNF] volume 69 sections at presentation level; personal communication: NHS Business Services Authority 2015). There is considerable variation in the cost of dressings both between categories of dressings and within each category. For example, silver dressings accounted for about 9% of items supplied on prescription, but in view of their relatively high cost were associated with over 18% (£20.5 million) of the total cost of advanced wound dressings.

NICE has issued guidance on preventing and managing pressure ulcers and preventing and managing diabetic foot problems, and the Scottish Intercollegiate Guidelines Network (SIGN, accredited by NICE) has issued guidance on the management of chronic venous leg ulcers. Although these guidelines give important recommendations about wound care, they do not make recommendations on specific products.

Prescribers' ability to choose wound dressings on the basis of clinical evidence is hindered by the relative lack of robust clinical- or cost-effectiveness evidence, as highlighted in numerous systematic reviews (see the Cochrane reviews on wounds) and an Evidence summary: medicines and prescribing briefing on advanced wound dressings and antimicrobial dressings for managing common chronic wounds (including diabetic foot ulcers, pressure ulcers, venous leg ulcers and infected wounds), produced by the NICE Medicines and Prescribing Centre. For the purposes of the evidence summary, advanced dressings are those that provide the optimal environment for wound healing by simple physical or chemical means, typically by controlling moisture levels (for example, alginate, film, foam, hydrocolloid and hydrogel dressings).

The evidence summary concluded that there is little high-quality evidence from randomised controlled trials (RCTs), or systematic reviews of controlled clinical trials to support the use of advanced or antimicrobial dressings for chronic wounds. From the studies included in the evidence summary, there is some limited evidence that some advanced dressings are more clinically effective than simple conventional dressings for treating some wounds. For example, systematic reviews and meta-analyses found:

- hydrogel dressings were more effective than basic wound contact dressings for complete healing of diabetic foot ulcers (low-quality evidence), as were foam dressings (very low-quality evidence)
- hydrocolloid and polyurethane film dressings were more effective than gauze dressings in terms of the proportion of pressure ulcers completely healed (low-quality evidence).

However, many of the conventional dressings used as comparators are no longer routinely recommended for chronic wounds (for example, gauze dressings) and there is generally insufficient evidence to distinguish between different types of advanced dressings.

As well as being few in number, many of the RCTs have significant limitations and the evidence is generally of low quality. Overall, estimates of the effects of dressings are uncertain and not optimal in terms of informing clinical practice. Further good quality research is needed to improve confidence in the evidence, and would probably change the implications for practice.

Safety, efficacy and cost effectiveness are important factors to consider when choosing dressings. However, a decision on which dressing is most appropriate for a specific chronic wound also requires careful clinical assessment of the person's wound, their clinical condition, any comorbidities and their personal circumstances and preferences.

For local wound infections, the antimicrobial dressings section of the BNF advises that a topical antimicrobial dressing can be used to reduce the level of bacteria at the wound surface but that it will not eliminate a spreading infection. Antimicrobial dressings containing iodine or silver should be used **only** when clinical signs or symptoms of infection are present.

When a specific dressing cannot be adequately justified on clinical grounds, it would seem appropriate for NHS healthcare professionals to routinely choose the **least costly dressing** of the type that meets the required characteristics appropriate for the type of wound and its stage of healing (for example, size, adhesion, conformability and fluid handling properties). The frequency of dressing change needs to be carefully considered and should be appropriate for the wound and dressing type. Patients should be assessed regularly. Prescribing the minimum quantity of dressings necessary to meet a person's needs can avoid wastage and stockpiling.

In view of the many dressings available, the absence of good-quality evidence for national guidelines to base specific recommendations on, and recognising financial constraints, local formularies provide a means of rationalising the choice of dressings. The NICE guideline on developing and updating local formularies provides good practice recommendations for the systems and processes needed to ensure NHS organisations develop and update local formularies effectively and in accordance with statutory requirements. In line with these good practice recommendations, a Wounds UK best practice statement offers advice on developing a wound dressings formulary, regular update and audit, and provision of an ongoing educational programme to ensure that use of formulary wound dressings is optimised.

See the Evidence summary: medicines and prescribing briefing for more information on the best available evidence for advanced wound dressings and

antimicrobial dressings and recommendations from national guidance for managing common chronic wounds.

Prescribing data

There are currently no medicines optimisation key therapeutic topic (MO KTT) prescribing comparators for this topic.

Update information

This topic was retained for the 2016/17 update of Medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence as appropriate.

About these key therapeutic topics

This document summarises the evidence base on key therapeutic topics which have been identified to support Medicines optimisation. **It is not formal NICE guidance.**

For information about the process used to develop Key therapeutic topics, see the integrated process statement.

ISBN: 978-1-4731-0947-6