Issue 86 – July 2016

This month in Eyes on Evidence

Eyes on Evidence: end of service
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A UK randomised controlled trial found that a group exercise programme had a lasting beneficial effect on physical activity levels in people aged 65 years or older living in the community, whereas a home exercise programme had no effect.

Evidence summaries from NICE's Medicines and Prescribing Programme
NICE has recently published summaries on:

- Chronic obstructive pulmonary disease: tiotropium/olodaterol (Spiolto Respimat)
- Reversal of the anticoagulant effect of dabigatran: idarucizumab
- Antibiotic stewardship interventions in hospitals: effect on clinical outcomes
- Text messaging to help medicines adherence
- Supporting adherence to medicines in people with long-term conditions: New Medicines Service community pharmacy scheme
- Urinary tract infection: antibiotic resistance in children in primary care

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Eyes on Evidence: end of service

NICE Evidence search Health and Social Care

The way in which NICE supports awareness of new evidence is changing. **After July 2016, NICE will no longer be providing the Eyes on Evidence awareness service.** This article explains the other routes by which busy professionals can keep up to date.

NICE produces the following types of evidence summaries that highlight new evidence and its context:

- Evidence summaries: unlicensed or off-label medicines

  Summaries of the best available evidence on selected unlicensed and off-label medicines, designed to meet demand for information to inform local NHS planning and decision-making.

- Evidence summaries: new medicines

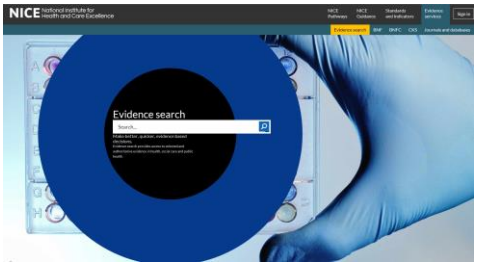
  Summaries of the best available evidence for selected new medicines, or for existing medicines with new indications, to inform local NHS planning and decision-making.

- Medicines evidence commentaries

  Summaries that contextualise and provide expert commentary on important new evidence, and highlight areas that could signal a change in clinical practice. These commentaries form part of

NICE's Medicines Awareness Weekly service.

You can sign up to the Medicines Awareness Weekly or to receive alerts on other medicines and prescribing related topics on the NICE website. In addition, NICE produces a number of email newsletters that you can sign up to on the NICE website.



You can also use NICE Evidence search and the Healthcare Databases Advanced Search (HDAS) to keep up to date with new evidence in your area.

To search for selected and authoritative evidence in health, management and commissioning, social care, and public health, please go to NICE Evidence search. Evidence search brings together high quality consolidated and synthesised evidence from hundreds of trusted sources – including NICE, the Cochrane Library and Public Health England – and selected new systematic reviews from PubMed. The service does not require a login or subscription.

After entering a search term, you can use the filters on the left hand side of the screen to limit the number of search results by 'Types of information' or by 'Areas of interest', to help you to find the information you need quickly. Using the 'Types of information' filter 'Evidence summaries' will show all previous Eyes on Evidence articles as well as other types of evidence summary.

You can also use NICE Evidence search to be notified of new evidence in your area by saving the results of a search as a bookmark in your browser. The search results will be updated with new evidence each time you return to this saved search results page.

You can use HDAS to search for primary research in 8 different databases, including CINAHL, EMBASE and MEDLINE. You can create an email alert to receive notification of when new research is published that relates to a specific search. You can create an alert by saving a search, and then choosing the 'create alert' option. Please note that an OpenAthens account is required to use HDAS.

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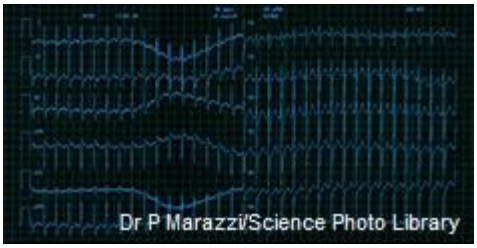
Modified Valsalva manoeuvre for supraventricular tachycardia

Overview:

- A UK randomised controlled trial assessed approaches to the Valsalva manoeuvre, a technique that involves exhaling forcefully against a closed airway (for example, by keeping the mouth closed and pinching the nose while trying to breathe out).
- Using a modified version of the Valsalva manoeuvre, where the patient was laid flat and raised their legs immediately after the move, was more effective than the standard manoeuvre at restoring normal heart rate in people who presented to emergency departments with supraventricular tachycardia.
- UK emergency departments should consider using the modified Valsalva manoeuvre as an effective, safe and easy-to-administer way to treat supraventricular tachycardia.



Background: Supraventricular tachycardia is a type of heart arrhythmia characterised by an abnormally fast heart rate of over 100 beats a minute (NHS Choices 2015).

Episodes of supraventricular tachycardia can sometimes be stopped using techniques that stimulate the vagus nerve. One example is the Valsalva manoeuvre, which involves exhaling forcefully against a closed airway; for example, by keeping the mouth closed and pinching the nose while trying to breathe out.

The Valsalva manoeuvre has been shown to restore normal heart rate in between 5% and 20% of people with supraventricular tachycardia (Appelboam et al. 2015).

Current advice: Guidance on peri-arrest arrhythmias from the Resuscitation Council (UK; NICE accredited) recommends that people with stable regular narrow-complex tachycardia should initially be treated with vagal manoeuvres, such as the Valsalva manoeuvre. A multilead electrocardiogram should be used during each manoeuvre.

In people with unstable regular narrow-complex tachycardia with adverse features caused by the arrhythmia (such as transient loss of consciousness), synchronised electrical cardioversion should be attempted. Vagal manoeuvres should be applied or adenosine administered, or both, while preparations are being made urgently for synchronised cardioversion.

The NICE Clinical Knowledge Summary on palpitations likewise recommends the Valsalva manoeuvre – for example, asking the person to blow into a syringe for 15 seconds while lying down (face up) – to stop an episode in people with persistent supraventricular tachycardia.

New evidence: Appelboam et al. (2015) undertook a randomised controlled trial to assess whether a modified version of the Valsalva manoeuvre was more effective than the standard Valsalva manoeuvre at restoring normal heart rate in people with supraventricular tachycardia (the REVERT trial).
People with suspected supraventricular tachycardia were recruited from the emergency departments of 10 hospitals in south west England.

Half of the participants were randomly assigned to the standard Valsalva manoeuvre (control group; n=216), which entailed lying semi-recumbent and performing the strain by forced expiration for 15 seconds. Participants assigned to the modified Valsalva manoeuvre (intervention group; n=217) likewise performed the same strain in a semi-recumbent position. This was immediately followed by lying flat and having their legs raised by a member of staff to 45° for 15 seconds. Participants were then returned to the semi-recumbent position for a further 45 seconds.

More people in the modified Valsalva manoeuvre group (43%) than people in the standard manoeuvre group (17%) achieved normal sinus rhythm at 1 minute after the manoeuvre. People in the modified Valsalva manoeuvre group were significantly more likely to achieve sinus rhythm than those in the standard manoeuvre group (odds ratio [OR]=3.7, 95% CI 2.3 to 5.8, p<0.0001).

People in the modified Valsalva manoeuvre group were less likely to need any further emergency treatment for supraventricular tachycardia (including adenosine) than those in the standard Valsalva manoeuvre group (OR=0.33, 95% CI 0.21 to 0.51, p<0·0001). The authors calculated that 3 people needed to undergo the modified Valsalva manoeuvre to avoid 1 case of further treatment.

Strengths of this study include that it recruited people presenting to English emergency departments, so is likely to be highly generalisable to other UK hospitals. In addition, the treating clinicians were existing treating staff who had been trained in the modified manoeuvre. Limitations include that treating doctors could not be masked to participants' treatment allocation.

Commentary by Professor Alasdair Gray, Professor of Emergency Medicine and Director of Emergency Medicine Research Group, Royal Infirmary of Edinburgh and University of Edinburgh:

"Patients with supraventricular tachycardia often present to UK emergency departments. Current guidelines (for example, from the Resuscitation Council [UK] and the European Society of Cardiology) recommend vagal manoeuvres, including Valsalva techniques, as first-line management for supraventricular tachycardia.

"The standard Valsalva technique has a 5–20% success of reverting supraventricular tachycardia to sinus rhythm. This low success rate means that many patients require adenosine, a short acting atrioventricular blocking agent. Although successful for most, adenosine requires intravenous cannulation and its use results in highly unpleasant although transient side effects.

"The REVERT trial compared a modified Valsalva manoeuvre with the standard Valsalva technique as first-line management for adults with supraventricular tachycardia presenting to UK emergency departments. The results of this robustly designed pragmatic trial are impressive. A total of 43% of people randomised to the modified technique reverted to sinus rhythm, compared with 17% in the standard Valsalva group. This is equivalent to an absolute risk reduction of 26 percentage points and a number needed to treat of 3. More than two thirds (69%) of people in the standard Valsalva arm required intravenous adenosine, compared with half (50%) of people in the modified Valsalva arm. There were no significant complications of the new technique.

"This trial will change practice in the acute management of supraventricular tachycardia. The modified Valsalva manoeuvre is safe, easy to administer after a simple education programme and cost neutral. It has the additional benefit of being simple to teach to patients and straightforward to deliver by prehospital care personnel, reducing the duration of symptoms and potentially preventing the patient's need to come to hospital."

Study sponsorship: National Institute for Health Research.

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Effects of calcium intake on bone mineral density and fracture risk

Overview:

- One systematic review and meta-analysis found that increasing dietary calcium or taking calcium supplements produced small increases in bone mineral density (BMD) in people aged more than 50 years, without much further improvement in BMD beyond 1 year.
- A second systematic review and meta-analysis in people aged over 50 years reported that increasing dietary calcium did not affect risk of fracture, whereas calcium supplements had small effects on total and vertebral fractures but not fractures at other sites.
- Calcium and vitamin D supplementation should not normally be used as the only treatment for osteoporosis but may still be appropriate in people receiving

pharmacological treatment for osteoporosis.

Background: Bone density naturally decreases with age, causing osteoporosis and increasing the risk of fracture in some older people (NHS Choices 2015). Maintaining sufficient intake of calcium has been thought to reduce the risk of fracture in older people. US guidelines recommend that adults over the age of 50 years consume 1000–1200 mg of calcium a day (Institute of Medicine 2011).

Calcium intake can be increased through dietary sources, such as milk and cheese, supplements or both. However, calcium supplements have been associated with side effects such as heart attack (Bolland et al. 2010). As a result, some experts have questioned the risk:benefit ratio of calcium supplements in older people (Bauer 2013).

Current advice: NICE technology appraisal guidance recommends the bisphosphonates alendronate, etidronate and risedronate, as well as strontium ranelate and the selective oestrogen receptor modulator raloxifene, for the primary prevention of osteoporotic fragility fractures in certain postmenopausal women. NICE also recommends these drugs and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

The monoclonal antibody denosumab is recommended as an alternative treatment option in postmenopausal women at increased risk of fractures.

NICE does not make any recommendations on calcium intake to reduce fracture risk in older people.

The NICE pathway on osteoporosis brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: Two meta-analyses have assessed how increasing dietary calcium or using calcium supplements affected bone mineral density (BMD) and risk of fracture in people aged over 50 years.

The first meta-analysis by Tai et al. (2015) found 59 randomised controlled trials (RCTs) of calcium intake in people aged over 50 years that reported BMD as an outcome. Most trials looked at women who were living in the community.

In meta-analyses of the 15 trials that studied dietary sources of calcium (n=1533), increasing calcium intake improved BMD by 0.6–1.0% at the hip and in total body measurements at 1 year. At 2 years, BMD had increased by 0.7–1.8% at these sites and at the lumbar spine and femoral neck.

In meta-analyses of the 51 studies on calcium supplements (n=12,257), supplements increased BMD by 0.7–1.8% at all 5 skeletal sites assessed (lumbar spine, femoral neck, hip, forearm and total body) at 1 year, 2 years and more than 2.5 years.

In the second meta-analysis, Bolland et al. (2015) searched for RCTs and cohort studies on the effects of calcium intake on fracture in people aged over 50 years.

The authors identified 1 RCT (n=200) and 44 cohort studies (n=>60,000) on dietary sources of calcium. The single RCT found that increasing dietary calcium with milk powder did not significantly affect fracture risk. Among the cohort studies, no effect on fracture risk was found in 74% of analyses of dietary calcium, 89% of analyses of specifically milk intake and 85% of analyses of dairy intake.

A total of 26 RCTs (n=69,107) were found that assessed the effects of calcium supplements on fracture risk. Participants were mostly women aged 70 years or older.

Meta-analyses of these trials showed that calcium supplements reduced the risk of any fracture (relative risk [RR]=0.89, 95% confidence interval [CI] 0.81 to 0.96, p=0.004; 20 studies, n=58,573) and vertebral fracture (RR=0.86, 95% CI 0.74 to 1.00, p=0.04; 12 studies, n=48,967). However, no effect was seen on hip fracture (RR=0.95, 95% CI 0.76 to 1.18, p=0.63; 13 studies, n=56,648) or forearm fracture (RR=0.96, 95% CI 0.85 to 1.09; p=0.54; 8 studies, n=51,775).

Among 11 cohort studies of calcium supplements, 75% of the analyses reported no association or a negative association between supplements and fractures.

Commentary by Professor Peter Selby, Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust and Honorary Professor of Metabolic Bone Disease, University of Manchester:

"These 2 studies are the culmination of a series of publications by the same group in New Zealand. They have sought to demonstrate the limited utility of calcium intake in the prevention of osteoporotic fractures.

"The first paper (Tai et al. 2015) is a systematic review and meta-analysis that assessed the effect of calcium intake on BMD. This showed that increasing calcium intake – whether by dietary means or pharmacological supplementation – led to a modest increase in BMD of about 1%. This increase appeared to occur in the first year and then remained static.

"The second meta-analysis (Bolland et al. 2015) examined the effect of calcium intake on fracture incidence. This showed that increased calcium intake was associated with an 11% reduction in all fractures. However, the benefit varied between fractures sites, with a greater reduction in vertebral fracture and no significant reduction in hip or forearm fractures.

"The authors interpreted both these studies as being indicative of little or no benefit to the skeleton from increasing calcium intake. However, the changes in bone density are of a similar magnitude to some of the weaker agents licensed for the treatment of osteoporosis. Further, a reduction of 11% in all fractures and 14% in vertebral fractures, although not as large as seen with many other treatments for osteoporosis, cannot be dismissed as being of no clinical utility.

"Calcium supplementation is no longer widely used as a primary treatment for osteoporosis. However, it must be remembered that nearly all clinical trials of other osteoporosis treatments have used calcium and vitamin D supplementation as part of therapy. Therefore, the available evidence shows that these treatments for osteoporosis work only in the presence of adequate calcium and vitamin D intake. Accordingly, it is important that these two meta-analyses are not taken as suggesting that calcium and vitamin D supplementation is not indicated in people receiving pharmacological treatment for osteoporosis, especially where there is doubt regarding the basal calcium and vitamin D status of the patient."

Study sponsorship: Both studies were funded by the Health Research Council of New Zealand.

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Bleeding risk with anticoagulants in atrial fibrillation or venous thromboembolism

Overview:

- A systematic review and meta-analysis found that, in people who had atrial fibrillation or venous thromboembolism, non-vitamin K antagonist oral anticoagulants (NOACs) reduced the risk of fatal bleeding by about half compared with warfarin.
- NICE has issued guidance on NOACs for atrial fibrillation and venous thromboembolism.
- Practitioners should be aware of the potential bleeding complications of all anticoagulants and their possible interactions with other drugs.

Background: NOACs are increasingly being used instead of warfarin for treating venous thromboembolism and preventing stroke or systemic embolism in people with non-valvular atrial fibrillation (Chai-Adisaksopha et al. 2015). The 4 NOACs currently licensed in the UK for these indications are apixaban, dabigatran etexilate, edoxaban and rivaroxaban.

Few direct comparisons between different NOACs are available, and key studies have differences in study populations, analyses and other factors. This makes it difficult to choose among NOACs for different indications.

Unlike warfarin, NOACs do not require routine anticoagulant monitoring (NICE 2015). However, bleeding is a common adverse effect of all anticoagulants (MHRA 2013).

Current advice: The NICE pathways on treating venous thromboembolism and atrial fibrillation bring together all related NICE guidance and associated products on these conditions in sets of interactive topic-based diagrams. In both pathways, a vitamin K antagonist (for example, warfarin) and the licensed NOACs are listed as anticoagulant treatment options.

Anticoagulation is standard treatment for venous thromboembolic diseases. In people with atrial fibrillation, the decision to use an anticoagulant should be based on the person's risk of stroke and bleeding.

The NICE guideline on atrial fibrillation recommends using the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation; people with atrial flutter; or those with a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm.

Anticoagulation with a NOAC or a vitamin K antagonist should be offered to people with atrial fibrillation who have a CHA_2DS_2-VASc score of 2 or above. Anticoagulation should be considered for men with a CHA_2DS_2-VASc score of 1, taking bleeding risk into account (the CHA_2DS_2-VASc score gives 1 point to all women).The options for anticoagulation should be discussed with the person and the choice based on their clinical features and preferences.

The MHRA has issued advice on contraindications to apixaban, dabigatran etexilate and rivaroxaban. Care should be taken when considering prescribing a NOAC to a person with other conditions, procedures or concomitant treatments that may increase the risk of major bleeding.

The recent NICE Medicines optimisation: key therapeutic topics gives a summary of the NICE technology

appraisal guidance on NOACs.

New evidence: A systematic review and meta-analysis of 13 randomised controlled trials (RCTs) by Chai-Adisaksopha et al. (2015) compared bleeding and mortality outcomes among people receiving NOACs or warfarin.

This analysis included studies on NOACs for long-term treatment of venous thromboembolism (8 RCTs) or prevention of secondary stroke or systemic embolism due to non-valvular atrial fibrillation (5 RCTs). It studied 102,843 adults who took warfarin (or heparin/low-molecular-weight heparin, followed by warfarin, titrated to a target international normalised ratio of 2.0 to 3.0) or a NOAC (apixaban [2 RCTs], dabigatran [4 RCTs], edoxaban [2 RCTs] or rivaroxaban [5 RCTs]). Follow-up ranged from 6 to 30 months.

The primary outcomes were the percentage of major bleeding events that were fatal and the incidence of fatal bleeding.

Death from major bleeding was reported in 12 studies. The percentage of major bleeding events that were fatal was higher for people taking warfarin (11.05%, 95% confidence interval [CI] 9.17 to 13.07%) than a NOAC (7.57%, 95% CI 6.53 to 8.68%).

The incidence of fatal bleeding was 0.32 per 100 patient–years (95% CI 0.27 to 0.37) with warfarin and half this (0.16 per 100 patient–years, 95% CI 0.12 to 0.20) with a NOAC. There was a statistically significant reduction in the risk of fatal bleeding with a NOAC compared with warfarin (relative risk=0.53, 95% CI 0.43 to 0.64%, p<0.001).

This study is limited by its inability to identify what proportion of people died from intracranial bleeding or to analyse the results for warfarin according to time spent in the therapeutic range. Just under half of the studies were considered to be at risk of bias, and study duration varied. Study participants were likely to be healthier, younger and more closely monitored than people in clinical practice, and these results may not apply to other indications for anticoagulation.

Commentary by Dr Amitava Banerjee, Senior Clinical Lecturer in Clinical Data Science and Honorary Consultant Cardiologist, University College London:

“Several meta-analyses have already considered NOACs versus warfarin in atrial fibrillation (Dogliotti et al. 2013, Liew et al. 2014) and venous thromboembolism separately (van der Hulle et al. 2014). Another analysis has included data for edoxaban (Hicks et al. 2016), which is the latest of the NOACs to undergo phase 3 trials. There have also been several network meta-analyses and indirect comparisons of NOACs and warfarin (Assiri et al. 2013, Sardar et al. 2013, Dogliotti et al. 2014, Tereshchenko et al. 2016).

“Studies have suggested that NOACs are similar to warfarin in terms of bleeding outcomes in venous thromboembolism and superior to warfarin for major bleeding in atrial fibrillation. The majority of the difference between NOACs and warfarin is accounted for by reduced rates of intracranial haemorrhage.

“This meta-analysis (Chai-Adisaksopha et al. 2015) combines trial data across atrial fibrillation and venous thromboembolism to assess fatal bleeding and case fatality rate for major bleeding for NOACs and warfarin. It found that fatal bleeding was half as likely with NOACs as warfarin.

“The rationale or clinical relevance of combining data for atrial fibrillation and venous thromboembolism is concerning, because these two patient populations have differing baseline characteristics and different bleeding outcomes in existing meta-analyses (van der Hulle et al. 2014, Hicks et al. 2016).

“The study is limited by the bias of nearly half of the trial data (as noted by the authors), the

generalisability of trial populations, and unavailability of information about quality of warfarin control in the comparison arms of the trials. In addition, minor bleeding and non-fatal bleeding outcomes are not considered in this analysis. Included trials lasted for about 6 to 30 months. In practice, the majority of patients will be on lifelong anticoagulants, and we do not know the longer term outcomes.

“Since head-to-head trials of the NOACs are unlikely, observational data will be important in establishing differences between the outcomes of the individual NOACs in ‘real-world’ populations. Further studies in particular subgroups (for example, in people with renal impairment or aged more than 80 years) are necessary to understand the range of complications of NOACs.

“This study does not change clinical practice, where practitioners should prescribe a vitamin K antagonist (for example, warfarin) or a NOAC for people with atrial fibrillation or venous thromboembolism. However, people should be aware of the potential bleeding complications of all anticoagulants and their possible interactions with other drugs. MHRA advice on NOACs, which highlights that haemorrhage is a common adverse effect of all anticoagulants, should continue to be followed.”

Study sponsorship: None stated.

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Urgent referral for suspected cancer

Overview:

- A retrospective cohort study assessed the effect on mortality of the urgent referral pathway for cancer in England, which ensures that people are seen by a specialist service within 2 weeks if their GP suspects they have cancer.
- The study found that use of the urgent referral pathway by general practices was associated with lower mortality rates among their patients who were subsequently diagnosed with cancer.
- General practices should review the referral routes of their patients who have cancer and consider ways of optimising their selection of patients for referral.

Background: The time between first presentation of cancer symptoms in primary care and diagnosis can affect survival, with longer intervals associated with higher mortality (Tørring et al. 2013).

Since 2000, GPs in England have been expected to refer people with suspected cancer to be seen by a specialist within 2 weeks or less (Department of Health 2000). However, use of this urgent referral pathway varies among practices (Baughan et al. 2011), which could affect cancer survival rates.

Current advice: NICE guidance on suspected cancer recommends that healthcare professionals in primary care should refer people with symptoms and findings suggestive of cancer to a specialist service. Once the decision to refer has been made, the referral should be made within 1 working day.

How quickly someone is seen by a specialist service depends on their symptoms. People referred using a suspected cancer pathway referral should be seen within 2 weeks.

The NICE pathway on suspected cancer recognition and referral brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: A retrospective cohort study by Møller et al. (2015) assessed whether use of the urgent referral pathway for cancer in England was associated with cancer mortality rates.

Data on urgent referrals for suspected cancer and cancer diagnoses were collected from the National Cancer Waiting Times database. Data on survival were taken from the National Cancer Register.

These data were linked back to general practices using a database of all patients registered with a GP in England and Wales (the NHS Exeter database). Whether a practice's use of the urgent referral pathway was higher or lower than average was quantified using a ratio of the observed number of urgent referrals to the expected number of referrals (referral ratio).

The study cohort comprised 215,284 people diagnosed with cancer at 8049 general practices in England in 2009. A total of 91,620 of these people died during the 4-year follow-up period. Practices were divided into high, intermediate (reference) and low users of the urgent referral pathway on the basis of their referral ratio.

High use of the urgent ('two-week wait') referral pathway by a general practice (median referral ratio=1.39) was associated with lower mortality among its patients who had been diagnosed with cancer (hazard ratio [HR]=0.97, 95% confidence interval [CI] 0.96 to 0.99). Low use of the pathway (median referral ratio=0.68) was linked to higher risk of cancer mortality (HR=1.05, 95% CI 1.04 to 1.07).

The authors retrospectively assessed what proportion of diagnosed cancers had resulted from an urgent referral for suspected cancer by general practice (detection rate). Practices with a high detection rate (median=54%) had a lower mortality risk than average in people diagnosed with cancer (HR=0.96, 95% CI 0.95 to 0.98), whereas practices with a low detection rate (median=33%) had a higher mortality risk (HR=1.04, 95% CI 1.02 to 1.06).

The mortality risk in practices with the highest referral rates and detection rates was 47%, compared with 53% in those with the lowest rates.

The authors also considered what proportion of urgent referrals for suspected cancer resulted in a diagnosis of cancer (conversion rate). Conversion rates were a median of 17% among practices with the highest referral rates and 8% in those with the lowest rates. Conversion rate was not associated with mortality in people with cancer.

Strengths of this study include that it used complete national population data for England and controlled

for practice list size and patient population. Weaknesses include that individual practices often had small numbers of referrals and cancer cases, little information was available on stage of cancer, and that the analyses could not control for the time between cancer diagnosis and death.

Commentary by Professor Michael D Peake, Honorary Consultant and Professor of Respiratory Medicine, University of Leicester and Clinical Lead, National Cancer Registration and Analysis Service, Public Health England:

"This an important study because it is the first to show a mortality benefit of GPs using the urgent referral pathway for patients they suspect may have cancer.

"Showing such an effect at the level of 1 general practice is extremely difficult because of the small number of new cancers they diagnose in one year. But the authors of this study used high quality population-based data to show that practices that used the urgent referral pathway more often (that is, had a high referral rate) were associated with significantly lower risk of death among patients with cancer over the 4 years after diagnosis. In addition, for those patients in these practices who developed cancer, practices where higher proportion had reached secondary care via an urgent referral route (a high detection rate) had a lower risk of death.

"The authors estimated that had all practices behaved like those with the highest referral and detection rates, 2,400 fewer deaths would have been seen over the 4 year study period. Five years is the most commonly used follow-up period in international studies of cancer survival. However, it is highly unlikely that the results of this study would have been materially different had 5 year follow-up been possible. The estimated size of the mortality benefit seen in practices most likely to use the urgent referral route is of the same order of magnitude of the difference in cancer mortality rates between England and many other Western countries.

"The proportion of patients that practices referred via the urgent route who turned out to have cancer (the conversion rate) was not associated with a mortality benefit. Intuitively, this fits with the idea that practices with a high conversion rate would have a higher threshold for referral (that is, would tend to refer only patients with very firm, often more advanced, signs of cancer) and thus would be more likely to miss patients with earlier stage disease.

"It is difficult to assess the magnitude of the effect at the level of an individual general practice, let alone that of individual GPs. Nevertheless, this study suggests that practices should be regularly reviewing the referral routes and outcomes of their cancer patients and considering ways of optimising their selection of patients for referral for a specialist opinion."

Study sponsorship: Cancer Research UK and the National Institute for Health Research.

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Behavioural support with pharmacotherapy for smoking cessation

Overview:

- People who receive pharmacotherapy to help them stop smoking should also receive some form of behavioural support, such as counselling, but the relative efficacy of different types, frequency and duration of support is unclear.
- A Cochrane review reported that providing high intensity behavioural support to people receiving pharmacotherapy was 10% to 25% more effective at helping them to stop smoking than low intensity support.
- Practitioners assisting smokers to quit should be trained in behaviour change techniques that support the use of smoking cessation pharmacotherapy.

Background: People who are trying to stop smoking may be offered behavioural support to help them quit. Behavioural approaches range from minimal interventions, such as written self-help materials (Hartmann-Boyce et al. 2014), to more involved approaches like individual face-to-face counselling (Lancaster and Stead 2008). Another option to help people stop smoking is offering pharmacotherapy, such as nicotine replacement products, varenicline or buproprion.

Providing behavioural support and pharmacotherapy together increases the likelihood that someone will stop smoking (Stead and Lancaster 2012). The intensity of the behavioural support, in terms of type of support or number of sessions, may also affect the success of this combined approach.

Current advice: The NICE guideline on smoking: brief interventions and referrals recommends that healthcare professionals should advise everyone who smokes to stop and refer people who want to stop smoking to an intensive support service, such as NHS stop smoking services. People who are unwilling or unable to accept this referral should be offered pharmacotherapy and additional support.

NICE guidance on stop smoking services may offer behavioural counselling, group behaviour therapy, pharmacotherapies, self-help materials, telephone counselling or a combination of treatments. People offered pharmacotherapies (nicotine replacement therapy, varenicline or bupropion) should also be offered advice, encouragement and support to help them attempt to quit. Varenicline should normally be prescribed only as part of a programme of behavioural support.

NICE is currently developing new guidance on smoking cessation interventions and services.

The NICE pathway on smoking brings together all related NICE guidance and associated products on the area in a set of interactive topic-based diagrams.

New evidence: A Cochrane review by Stead et al. (2015) investigated how providing more intense behavioural support for people using pharmacotherapy affected their likelihood of quitting.

The authors identified randomised and quasi-randomised controlled trials of pharmacotherapy (such as nicotine replacement therapy, varenicline, bupropion and nortriptyline) in adults who smoked. Participants had to be offered some type of behavioural support, from minimal (such as written information) to multisession face-to-face or telephone counselling. Trials had to have an intervention arm where participants received more intensive behavioural support (in terms of number or length of sessions or type

of support) than those in the control arm.

The review included 47 studies with more than 18,000 participants, from mostly the US and Europe (1 UK study). The primary outcome was smoking cessation at the longest follow-up point. Most studies followed people up for 1 year, and the majority reported abstinence at a single point using biochemical verification of self-reported abstinence.

A pooled analysis of all 47 studies found that people who received high intensity behavioural support alongside pharmacotherapy were more likely to stop smoking than people who received lower intensity support and pharmacotherapy (risk ratio=1.17, 95% confidence interval 1.11 to 1.24, p<0.00001). In absolute terms, people who received high intensity behavioural support with pharmacotherapy were about 10% to 25% more likely to stop smoking than people who received variable intensity behavioural support with pharmacotherapy.

Limitations of this review include the variation in the intensity of behavioural support used in the included trials, and the degree to which the intensity of support differed between the intervention and control groups in each trial. In addition, two thirds of trials were at high or unclear risk of bias.

Commentary by Dr Andy McEwen, Executive Director, National Centre for Smoking Cessation and Training:

"This comprehensive review follows the rigorous methodology used by the Cochrane Tobacco Addiction Group to assess the effectiveness of behavioural support accompanying the use of stop smoking medications.

"The review confirms, and adds to, our knowledge about the importance of using behavioural support with smoking cessation medications. For example, we know that nicotine replacement therapy purchased over the counter without behavioural support is no more effective than quitting 'cold turkey' without any support (Kotz et al. 2014). However, nicotine replacement therapy is effective when accompanied by behavioural support provided by local stop smoking services.

"One of the limitations of this review lies not in the review itself, but in the lack of detail from the included studies as to what constitutes behavioural support, and furthermore what 'intensive support' looks like. A call has previously been made for more detailed reporting of the content and intensity of behaviour change interventions (Michie et al. 2009), which would assist us in further understanding these issues.

"A methodology has been developed to identify behaviour change techniques for smoking cessation (Michie et al. 2011), and we know which of these techniques have most evidence of effectiveness (West et al. 2010). As such, there is a strong case for future studies to describe the intensity of behavioural support, at least in part, in terms of the behaviour change techniques included in the intervention.

"Helping smokers to have a realistic expectation of what stop smoking medications can offer (that is, that they are not a 'magic bullet') is one example of an evidence-based behaviour change technique. Other approaches supported by the evidence include advising people on the methods of using the medication, dose and duration, and how to deal with side effects.

"This type of support is provided by local stop smoking services and this review underlines the important role that they play. A free online training course on behavioural support around stop smoking medications is available from the National Centre for Smoking Cessation and Training to support practitioners in helping smokers to quit."

Study sponsorship: National Institute for Health Research.

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Improving physical activity among older people in the community

Overview:

- A group exercise programme produced a lasting increase in physical activity compared with no exercise programme among people aged 65 years or older living in the community and recruited from UK general practices.
- A home exercise programme had no effect on physical activity in these people.
- Healthcare professionals should consider offering individualised group exercise programmes to older people.

Background: In England, less than half of women (42%) and half (51%) of men aged 65–74 years do the recommended amount of physical activity (Health and Social Care Information Centre 2013).

A number of interventions designed to increase physical activity in older people, such as information sheets sent by post or face-to-face counselling sessions, have been shown to be effective among older adults who live in the community (Chase 2015). The effectiveness of individual versus group interventions is less clear (Ashworth et al. 2005).

Current advice: The NICE guideline on physical activity: brief advice for adults in primary care recommends that adults who have been assessed as being inactive should be advised to do more physical activity, with the aim of achieving the levels recommended in UK physical activity guidelines.

The UK physical activity guidelines recommend that adults aged 65 years or older should aim to complete at least 150 minutes of moderate intensity activity a week. This should be done in bouts of 10 minutes or more; for example, 30 minutes of exercise on at least 5 days a week.

The NICE pathway on physical activity brings together all related NICE guidance and associated products on the area in a set of interactive topic-based diagrams. NICE also has guidance on mental wellbeing in over 65s: occupational therapy and physical activity interventions.

New evidence: A 3-arm cluster randomised controlled trial by Iliffe et al. (2015) compared 2 exercise programmes with no specified programme in older people who lived in the community.

People aged 65 years or older who were living in the community were identified from 43 general practices in London, Nottingham and Derby. A total of 20,507 people were sent an invitation to participate, of whom 1255 (6%) were recruited.

General practices were randomly assigned to 1 of 3 interventions, which patients in these practices

completed for 6 months:

- A home exercise programme (the Otago Exercise Programme), which comprised exercises at home 3 times a week and support from volunteer peer mentors.
- A group exercise programme (Falls Management Exercise – FaME), which comprised group exercise classes once a week run by trained postural stability instructors and exercises at home twice a week.
- No specified exercise programme.

The primary outcome was the proportion of participants who reported reaching 150 minutes or more of moderate-to-vigorous physical activity a week at 12 months after the intervention period.

A total of 761 (61%) participants remained in the trial at 12 months after the end of the intervention period, and 572 (46%) had sufficient data for analysis.
In the group exercise arm, the proportion of participants who reached or exceeded the target level of physical activity rose from 40% at baseline to 49% at 12 months. This difference was equivalent to around 15 minutes' extra moderate-to-vigorous physical activity a day. The proportion who reached the physical activity target increased from 41% to 43% in the home exercise arm and from 37.5% to 38% in the no exercise programme arm.

People in the group exercise arm were significantly more likely than those in the no exercise programme arm to reach the target level of physical activity (odds ratio [OR]=1.78, 95% confidence interval [CI] 1.11 to 2.87, p=0.02). There was no significant difference between the home exercise arm and the no exercise programme arm in the proportion reaching the target level of physical activity (OR=1.17, 95% CI 0.72 to 1.92, p=0.52).

Strengths of this study include its size, that it was based in the UK, and that it used a number of validated scales for participants to self-report physical activity levels. However, the study had a low response rate and a high number of drop outs, and it was not possible to blind participants and people delivering the programmes to treatment allocation.

Commentary by Rob Morris, Pathway lead Clinician for Older People, Nottingham University Hospitals NHS Trust:

"Sedentary behaviour is common and becomes more prevalent with aging. Around 40% of adults over 50 in England are insufficiently active to benefit their health (Health Survey for England 2012). Yet the advantages of increased physical activity extend across a range of health domains, reducing the prevalence of disability and improving functional capacity and quality of life. The key challenge in realising these desirable benefits is changing societal attitudes toward exercise in a sustainable way.

"Perhaps the most significant finding in this new study by Iliffe et al. (2015) is that the benefits of the exercise programmes in terms of moderate-to-vigorous physical activity appeared to be sustained beyond the initial intervention period.

"This study also adds to the debate regarding the differential effects of group- and home-based exercise. People who participated in group-based exercise were more likely to be physically active than those who did home-based exercise. Both approaches should be accessible for heterogeneous populations, but there are wider benefits associated with group-based schemes, such as greater participation and the reduction of social isolation. Although there is an inevitable cost in the provision of group-based programmes, there are also more elusive benefits in terms of opportunity costs, such as the demonstrated and sustained reduction in falls.

"The group exercise programme (FaME) and the home exercise programme (Otago Exercise

Programme) used in this research were both devised to reduce fall risk among older adults. Both programmes have been proven to be effective at reducing the incidence of falls (Skelton et al. 2005, Thomas et al. 2010). Falls are a symptom or herald of emerging frailty in older people, and many of the risk factors for falls relate to parameters modifiable through increased physical activity. Strength and balance training through systematic physical exercise is the most effective intervention in reducing falls amongst older adults (Gillespie et al. 2012).

"This study, as with other similar studies, had a low rate of uptake. Only 1 in 16 people invited responded positively, and further attrition halved the number available for final analysis.

"Whether exercise programmes are offered in an individualised way can influence uptake, in the same way that personalised 'brief interventions' have improved uptake of other lifestyle interventions such as reducing tobacco consumption. Trusted healthcare professionals and family doctors in particular can play a pivotal role in this respect."

Study sponsorship: National Institute for Health Research.

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Evidence summaries from NICE's Medicines and Prescribing Programme

Evidence summaries: new medicines form part of NICE's service to provide high quality medicines and prescribing information to the NHS and patients in England. The summaries are aimed at commissioners, budget holders and groups such as Area Prescribing Committees to help them make informed decisions and aid local planning on the introduction of key new medicines. Evidence summaries: new medicines do not constitute formal NICE guidance but are designed to support the managed introduction of selected new medicines or new indications for existing medicines not covered by NICE's Technology Appraisal programme.

NICE has recently published the following Evidence summary: new medicine:

- **Chronic obstructive pulmonary disease: tiotropium/olodaterol (Spiolto Respimat)**

  Spiolto Respimat inhalation solution is a maintenance bronchodilator treatment that contains tiotropium (a long-acting muscarinic antagonist [LAMA]) and olodaterol (a long-acting beta-2 agonist [LABA]). Two double-blind, randomised controlled trials have compared tiotropium/olodaterol with the individual mono-components tiotropium and olodaterol in people with chronic obstructive pulmonary disease.

- **Reversal of the anticoagulant effect of dabigatran: idarucizumab**

  Idarucizumab is the first agent to be licensed in the UK that reverses the anticoagulant effect of a non-vitamin K antagonist oral anticoagulant. An ongoing, phase III, uncontrolled, cohort study (RE-VERSE AD) has evaluated the effect of idarucizumab on the anticoagulant properties of dabigatran etexilate in adults who had either serious bleeding or required urgent surgery.

Medicines evidence commentaries form part of NICE's Medicines Awareness Service and help

contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. These commentaries are published in NICE's Medicines Awareness Weekly service and are available online in NICE Evidence search.

NICE has recently published the following Medicines evidence commentaries:

- **Antibiotic stewardship interventions in hospitals: effect on clinical outcomes**

  A systematic review and meta-analysis has looked at the effects of antimicrobial stewardship interventions on clinical outcomes, adverse events, cost and bacterial resistance in hospitals.

- **Text messaging to help medicines adherence**

  A meta-analysis of 16 randomised controlled trials has estimated the effect of mobile text messaging on medication adherence in middle-aged adults with chronic disease.

- **Supporting adherence to medicines in people with long-term conditions: New Medicines Service community pharmacy scheme**

  A pragmatic randomised controlled trial in 46 community pharmacies in England has evaluated the effectiveness of the New Medicines Service in improving medicines adherence.

- **Urinary tract infection: antibiotic resistance in children in primary care**

  A systematic review has investigated the prevalence of resistance to the most commonly prescribed antibiotics given to children for community-acquired urinary tract infection in primary care (ampicillin, co-amoxiclav, co-trimoxazole, trimethoprim, nitrofurantoin, ciprofloxacin, and ceftazidime [as a marker for cephalosporin resistance]).

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