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This month in Eyes on Evidence

Patients' expectations of the benefits and harms of treatments and tests

A systematic review found that for many treatments and diagnostic or screening tests, the majority of people overestimated the likely benefits and underestimated the likely harms.

Nicotine replacement therapy for people trying to cut down cigarette use

A cross-sectional study in England found that at least half of people who used nicotine replacement therapy to reduce their cigarette consumption did not use the correct dosage. These people were less likely to cut down their cigarette use or be motivated to quit compared with people who used the products appropriately.

Life expectancy of people with cystic fibrosis

A US cohort study reported that mortality rate among people with cystic fibrosis decreased by 1.8% a year between 2000 and 2010, and estimated that children born and diagnosed with cystic fibrosis in 2010 would be likely to survive to approximately 56 years if this trend were to continue.

Intermittent versus continuous administration of proton pump inhibitors after treatment of bleeding ulcers

A meta-analysis found that the risk of re-bleeding following intermittent administration of proton pump inhibitors was similar to the risk with continuous administration of proton pump inhibitors in people who had undergone endoscopic treatment for bleeding ulcers.

Patients' expectations of the benefits and harms of treatments and tests



Overview: People are offered a wide range of interventions as part of their care: medicines; surgery or other treatments; and diagnostic or screening tests. The chances of benefiting from an intervention or being harmed by it are likely to be important when a person is deciding whether or not to have the intervention.

A person needs to weigh up how likely a treatment is to prevent an undesirable outcome or provide relief from unpleasant symptoms compared with the risk of adverse effects or complications. The implications for them if an outcome they hope to avoid were to happen should also be considered. For diagnostic and screening tests, a

person needs to consider the reliability of the results: given a positive or negative result, how likely it is that they truly do or do not have the condition being tested for, and the implications for them of that result. Patients may also need to consider if and how the results of a diagnostic test might change their treatment, and whether their outcome would be likely to improve.

Other questions are also important in a person's decision about their care, such as how unpleasant or inconvenient the intervention is. However, if someone overestimates or underestimates the benefits or harms of an intervention, they may come to a different decision from the one they would have made if they had had a better appreciation of these factors.

Current advice: The NICE guideline on [patient experience in adult NHS services](#) recommends giving people information, and the support they need to make use of it, to promote their active participation in care and self-management. This includes discussing the risks, benefits and consequences of the investigation or treatment options, clarifying what the person hopes these will achieve, and discussing any misconceptions with them.

The NICE Pathway on [patient experience in adult NHS services](#) brings together all related NICE guidance and associated products on this topic in a set of interactive topic-based diagrams.

New evidence: A systematic review has assessed the evidence from studies that quantitatively measured patient or public expectations of the benefit or harm of treatments, diagnostic tests or screening tests ([Hoffman et al. 2015](#)). The authors included data from 35 studies from 16 different countries (about half from the United States) involving 27,323 participants. Examples of the study topics included infliximab for inflammatory bowel disease, hormone replacement therapy (HRT), statin therapy, cataract surgery, cardiopulmonary resuscitation, mammography, prostate-specific antigen testing, bowel cancer screening and scans for fetal abnormalities.

For 34 treatment, diagnostic test or screening test outcomes, quantitative data were available about overestimation of benefits by study participants compared with the primary study authors' estimates of the 'correct' answers. The likely benefits of 22 (65%) of these outcomes, such as the number of breast cancer deaths prevented by mammography, were overestimated by the majority (50% or more) of study participants. The majority of participants correctly estimated the likely benefits for 2 outcomes (improved vision after cataract surgery and accuracy of cervical smear tests) and underestimated the benefits for 1 outcome (improved lower back pain after back surgery). There was not a majority overestimation or underestimation for the remaining 9 outcomes.

For 17 other beneficial outcomes, the authors of the systematic review could not calculate the proportion of participants who overestimated or underestimated benefit. However, for 15 (88%) of these outcomes, the primary study authors concluded that participants had overestimated benefits.

Conversely, the majority of study participants underestimated likely harms for 10 (67%) of the 15 outcomes for which data about underestimation of harms were available (for example, the risk of death or adverse events with infliximab). The likely harms were correctly estimated by the majority of people for

2 outcomes (the proportion of people who need glasses after cataract surgery and the risk of miscarriage from amniocentesis) and overestimated for 1 intervention (the risk of breast cancer with HRT).

Strengths of this systematic review include the diversity of interventions studied and countries included. However, this diversity made it difficult for the authors to compare individual studies. Some studies had small or selective samples. There is likely to have been variation in methods of assessing participants' expectations (which were largely untested), criteria for deciding whether an expectation was an underestimate or overestimate (such as how close a participant had to be to the 'correct' answer), and participants' backgrounds.

Commentary: "The authors claim that this is the first systematic review to pull together evidence on patient and public expectations of the benefits and harms of medical interventions, and I believe they are right. They have usefully focused attention on an issue of major importance – the public are over-optimistic about the benefits of treatment, screening and diagnostic tests. We will have no hope of ensuring that medical care delivers best value until people have a more balanced understanding of its limitations.

"The over-optimism probably derives from various sources, including difficulties in accessing reliable information, commercial influences, media distortions, advice from over-optimistic clinicians and a general tendency to want good news rather than bad. These influences lead to distortions in medical decision-making, making patients unaware of the risks and trade-offs involved and seriously undermining the principle of informed consent.

"One way to deal with the problem is to ensure that people receive clear, unbiased, evidence-based information at the point of decision-making. A Cochrane review by [Stacey et al. \(2014\)](#) found that use of patient decision aids led to significant improvements in people's understanding of their options and more informed decisions. There is plenty of evidence that patients want this type of information, but many don't receive it. Demand for ineffective or unproven treatments will continue to rise unless we make a more concerted effort to help people make informed decisions." – **Dr Angela Coulter, Senior Research Scientist, Nuffield Department of Population Health, University of Oxford**

Study sponsorship: This study did not receive specific funding.

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Nicotine replacement therapy for people trying to cut down cigarette use

Overview: Nicotine-containing products do not contain tobacco, so deliver nicotine without the harmful toxins found in tobacco ([NICE 2013](#)). Some nicotine-containing products, such as nicotine replacement therapy (NRT), are licenced and regulated by the Medicines and Healthcare Products Regulatory Agency, whereas others, such as electronic cigarettes, are not yet fully licenced. NRT products licensed for use for smoking reduction include transdermal patches, gum, inhalation cartridges, sublingual tablets and a nasal spray.

Clinical trials have shown that NRT can help people who may not be ready to stop smoking to reduce the number of cigarettes they smoke ([Moore et al. 2009](#)). However, 'real world' population studies often report that NRT has only a small effect on cigarette consumption ([Beard et al. 2013](#)). One possible reason for this discrepancy could be that smokers



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use too little NRT and for too short a period. Another possibility is that smokers are not using combinations of NRT products, which appear to be more effective than the use of a single product ([Stead et al. 2012](#)).

Current advice: The NICE guideline on [tobacco: harm-reduction approaches to smoking](#) recommends licensed nicotine-containing products as an option for smoking reduction and temporary abstinence from smoking.

People who smoke should be reassured that licensed nicotine-containing products are a safe and effective way of reducing the amount they smoke. These products can be used as a complete or partial substitute for tobacco, either in the short or long term.

People who smoke should receive an explanation of how to use licensed nicotine-containing products correctly. This includes ensuring people know how to achieve a sufficiently high dose to control cravings, prevent compensatory smoking and achieve their goals on stopping or reducing the amount they smoke. People who smoke should also be advised that they can use one product on its own or a combination of different products.

The NICE Pathway on [smoking: tobacco harm-reduction approaches](#) brings together all related NICE guidance and associated products on the area in a set of interactive topic-based diagrams.

New evidence: [Beard et al. \(2015\)](#) used data from the [Smoking Toolkit Study](#) to assess how the amount and duration of NRT use in people trying to cut down on smoking affected cigarette consumption and motivation to quit. The Smoking Toolkit Study comprises monthly cross-sectional household surveys of randomly sampled smokers and recent ex-smokers in England. Participants are asked a number of questions in face-to-face interviews, including whether they are trying to cut down on cigarettes but not stop smoking and about their use of NRT products. Cigarette consumption and motivation to quit are also recorded.

This analysis used a sample of 2158 current smokers in the Smoking Toolkit Study who also used NRT. Almost half (47.8%) of participants used a single non-transdermal product (such as nicotine gum), a third (35.5%) used only a nicotine patch, and the remaining participants (16.7%) used more than one product.

People who were using more than one product (n=360) smoked significantly more cigarettes a day than those who used a single product (n=1798; mean 14.2 a day versus 12.5 a day; p=0.003). Use of multiple products had no significant effect on motivation to stop smoking in the next 3 months.

Among people who used non-transdermal products (n=1032), only a third (32.2%) used the products at least 4 times a day – the frequency expected to produce a significant clinical effect. People who used appropriate doses of non-transdermal products smoked significantly fewer cigarettes than people who were not using the products properly (11.9 cigarettes a day versus 12.8 a day; p=0.022), and were more likely to be motivated to quit (53.3% versus 35.3%; p<0.001).

Among people who used a nicotine patch (n=766), only half (54.4%) used it at least daily – the frequency expected to produce a significant clinical effect. People who used a patch daily smoked 1.3 fewer cigarettes a day than those who used a patch less frequently, although this difference was not significant (12.4 a day versus 13.7 a day; p=0.059). Daily users were significantly more likely to report that they were motivated to stop smoking (59.5% versus 31.8%; p<0.001).

Limitations of this study include that it cannot determine a direct effect of NRT on cigarette consumption and motivation to quit because of its cross-sectional nature. In addition, cigarette consumption was measured by self-report, and no biological measures of nicotine consumption were used.

Commentary: “In England, approximately £2.7 billion a year is spent in healthcare costs on treating tobacco-related illness, but less than £150 million is spent annually on treating tobacco dependence ([Department of Health 2010](#)).

“Basic quit smoking training follows established NICE guidance in being explicit about the importance of therapeutic dosing of NRT, whether someone is embarking on a quit or cut-down attempt. This new research demonstrates that translating good clinical trial evidence into correct care is a challenge. Underuse may be through fear of adverse events and price ([Silla et al. 2014](#)). We must do better to provide tobacco smokers who are ready to change with accessible and well-trained health workers and with low cost pharmacotherapy.

“The cross-sectional design of this study has its limitations, but the results suggested that people who used more than one NRT product were likely to smoke more and less likely to quit with time. In clinical practice we see people with high levels of addiction who continue to smoke heavily despite frightening and disabling daily breathlessness or loss of limbs. One could conclude that these individuals have a greater need for nicotine than people who are less addicted, and thus could be more likely to use multiple products but less likely to cut down on cigarette use. This possibility suggests a need to more clearly segment the population with tobacco addiction so that targeted quit smoking treatments can be commissioned depending on need and choice.

“What this study does tell us clearly is that there is widespread sub-therapeutic dosing for this population with a long-term condition. Health professionals must plan dosing when treating tobacco dependence with pharmacotherapy as seriously as they would plan dosing for any other chronic life-shortening condition. As a start, this would mean that health professionals working with smokers need to be trained and confident in having the right conversations, testing and interpreting biological measures of smoking tobacco, and prescribing quit smoking pharmacotherapy.” – **Dr Noel Baxter, GP lead, London clinical senate ‘Helping Smokers Quit’ programme**

Study sponsorship: The Smoking Toolkit Study is funded by Cancer Research UK, Pfizer, GlaxoSmithKline, Johnson & Johnson, and the Department of Health.

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Life expectancy of people with cystic fibrosis



Overview: Cystic fibrosis is a genetic condition in which the lungs and digestive system become clogged with thick sticky mucus ([NHS Choices 2014](#)). Symptoms usually start in early childhood and include persistent cough, recurring chest and lung infections, and poor weight gain.

People with cystic fibrosis have a reduced life expectancy relative to the general population. However, life expectancy among people with cystic fibrosis has improved over the past few decades as a result of advances in care. In 2013, the median predicted survival of people with cystic fibrosis in the UK was 36.6 years, up from 34.4 years in 2009 ([Cystic Fibrosis Trust 2013](#)). In the UK, adults with cystic fibrosis now outnumber children with this condition.

Current advice: The Cystic Fibrosis Trust's [Standards for the Clinical Care of Children and Adults with Cystic Fibrosis](#)

[Fibrosis in the UK](#) recommend that antibiotics are a key part of therapy for people with cystic fibrosis. Antibiotics should be used to manage all stages of airway infections – for prophylaxis, eradication of

infection, long-term treatment of chronic infection, and treatment of acute exacerbations. NICE recommends 2 types of dry powder inhaled antibiotic – [colistimethate sodium and tobramycin](#) – for treating pseudomonas lung infection in cystic fibrosis.

The standards also recommend lifelong chest physiotherapy with airway clearance techniques and nutritional support. Other treatment options for people with cystic fibrosis include medication with inhaled mucus-clearing treatments, such as nebulised rDNAase and nebulised hypertonic saline. NICE recommends the mucus-clearing treatment [mannitol dry powder for inhalation](#) as a possible treatment for some adults with cystic fibrosis.

NICE is currently preparing a clinical guideline on [cystic fibrosis](#), with an anticipated publication date of February 2017.

New evidence: A population-based cohort study in the USA by [MacKenzie et al. \(2014\)](#) has estimated mortality and predicted survival among people with cystic fibrosis. The study used data from people with a confirmed diagnosis of cystic fibrosis who were in the Cystic Fibrosis Foundation Patient Registry between 2000 and 2010. The registry tracks people with cystic fibrosis at 110 care centres, and as of 2010 included around 85% of all people with cystic fibrosis in the USA.

A total of 34,547 people were included in the registry between 2000 and 2010. Around 12% of those people were excluded from this analysis because of missing data, and 2% a year were lost to follow-up. Analyses were adjusted for gender, ethnicity, mutation of the F508del gene, presence of symptoms at diagnosis, and age at diagnosis.

The mortality rate among people with cystic fibrosis decreased by 1.8% a year between 2000 and 2010 (adjusted hazard ratio [HR]=0.982, 95% confidence interval [CI] 0.972 to 0.993), and by 17% for the whole 10-year period (HR=0.83, 95% CI 0.75 to 0.93). The adjusted risk of death was 19% lower (95% CI 13% to 24%) in males than females. Annual mortality was less than 0.5% until age 10 years, then increased steeply during adolescence and levelled out at age 25 years at 3–4% a year in females and 2–3% a year in males.

The analysis estimated that children born and diagnosed with cystic fibrosis in 2010 would survive to a median age of 39 years (95% CI 38 to 40 years), if age-specific mortality was assumed to remain indefinitely at 2010 levels. If mortality was assumed to decrease at the rate observed between 2000 and 2010, children born and diagnosed with cystic fibrosis in 2010 would be likely to survive to 56 years (95% CI 54 to 58 years).

Limitations of this analysis included that not all people with cystic fibrosis in the USA were recruited, and the projections apply only to people diagnosed in the first year of life and under the care of accredited cystic fibrosis centres. The authors add that some of the improvement in survival of people with cystic fibrosis may be related to diagnosis of more people with a milder phenotype as a result of widespread availability of genotype analysis.

Commentary: “There have been remarkable improvements in clinical outcome for patients with cystic fibrosis over the past few decades. MacKenzie et al. (2014) used data from a large US patient registry to demonstrate a steadily decreasing mortality in cystic fibrosis. They estimated that if the improvements continue at the present rate, patients born in this current decade will survive to more than 50 years.

“These improvements in survival have been achieved through a multidisciplinary model of care at specialist centres, with stepwise introduction of new treatments. New therapies continue to emerge, including for the first time drugs that target the dysfunctional cystic fibrosis transmembrane conductance regulator protein and hence address the basic underlying cause of the disease.

“The number of adults in the UK with cystic fibrosis now exceeds that of children, and continues to rise. However, there needs to be sufficient capacity at specialist adult centres to accommodate the increase in patient numbers. The findings of this study highlight the urgent need to address the capacity issues at adult cystic fibrosis centres. It is important to adequately resource multidisciplinary clinical care and new effective therapies to ensure that the achievements in improved survival continue for the future

generations of people with cystic fibrosis." – **Dr Andrew M Jones, Consultant Physician and Honorary Reader, Manchester Adult Cystic Fibrosis Centre, University Hospitals South Manchester NHS Trust**

Study sponsorship: Cystic Fibrosis Foundation.

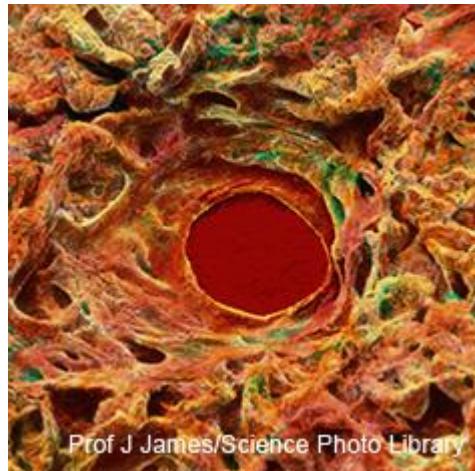
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Intermittent versus continuous administration of proton pump inhibitors after treatment of bleeding ulcers

Overview: Acute upper gastrointestinal bleeding is a common medical emergency and has a mortality rate of around 10% ([Button et al. 2010](#)). The most common cause of acute upper gastrointestinal bleeding is ulcers in the stomach or first part of the small intestine (known as peptic, gastric or duodenal ulcers), followed by dilated veins (varices) in the oesophagus or stomach ([Hearnshaw et al. 2011](#)).

People with bleeding ulcers (that is, non-variceal upper gastrointestinal bleeding) may be treated using endoscopic haemostasis techniques, such as cauterisation with thermal devices. However, around 8% of people who undergo treatment for bleeding ulcers experience subsequent re-bleeding, which considerably increases the risk of death ([Chiu et al. 2009](#)).



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To reduce the risk of further bleeding after endoscopic treatment, patients may receive an intravenous bolus of proton pump inhibitors (PPIs) followed by continuous infusion of PPIs for around 3 days ([Barkun et al. 2010](#)). An alternative approach for preventing re-bleeding after endoscopic treatment is to administer PPIs intermittently. This strategy could cost less, use fewer resources, decrease the total dose of PPIs used, and be easier to administer. However, the best dose and route of administration of PPIs after treatment in patients with bleeding ulcers is unclear.

Current advice: The NICE guideline on [acute upper gastrointestinal bleeding](#) recommends that one of the following approaches should be used for endoscopic treatment of non-variceal upper gastrointestinal bleeding:

- a mechanical method (for example, clips) with or without adrenaline
- thermal coagulation with adrenaline
- fibrin or thrombin with adrenaline.

Acid-suppression drugs (PPIs or H₂-receptor antagonists) should not be offered before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding.

PPIs should be offered to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy.

The NICE Pathway on [upper gastrointestinal bleeding](#) brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence: [Sachar et al. \(2014\)](#) did a meta-analysis to compare intermittent PPI therapy with continuous PPI therapy for reducing ulcer re-bleeding after endoscopic therapy. The patient group was people who had a gastric or duodenal ulcer at high risk of bleeding (active bleeding, non-bleeding visible vessels or adherent clots) and had undergone successful endoscopic treatment. The intervention treatment was any regimen of intermittent doses of PPIs, and the comparator treatment was an 80 mg intravenous bolus dose of a PPI followed by continuous infusion of 8 mg of PPI an hour for 72 hours.

A total of 13 randomised trials and conference abstracts were eligible for the meta-analysis. The authors calculated 1-sided 95% confidence intervals (CIs) with per-protocol data to investigate how much higher the risk of re-bleeding was with intermittent PPIs compared with continuous PPIs. Intermittent PPIs would be considered non-inferior to continuous PPIs if the absolute difference in risk with intermittent PPIs was less than 3%.

Ten trials (n=1346) reported on the primary outcome of re-bleeding within 7 days of endoscopic treatment. The risk of re-bleeding within 7 days was slightly lower with intermittent PPIs than with continuous PPIs (risk ratio [RR]=0.72, upper boundary of 1-sided 95% CI 0.97). The absolute difference in risk with intermittent PPIs was -2.64% (upper boundary of 1-sided 95% CI -0.28%). This value fell below the predefined non-inferiority margin of 3% and suggested that intermittent PPIs were not inferior to continuous PPIs. When a standard superiority analysis was conducted on intention-to-treat data, intermittent PPIs were not associated with a significantly lower risk of re-bleeding within 7 days than continuous PPIs (RR=0.74, 95% CI 0.52 to 1.06).

Limitations of this evidence include the variation in the endoscopic treatment used in the included studies and the variation in the frequency, dose and route of administration of intermittent PPIs. Many of the included studies were at risk of bias relating to allocation concealment or blinding, or both.

Commentary: “The majority of peptic ulcer bleeds are self-limiting, because a fibrin blood clot plugs the hole in the eroded underlying artery and the bleeding ceases. Patients at greatest risk of continuing to bleed or re-bleed are treated endoscopically by injecting or spraying drugs, or by cauterising or placing clips onto the bleeding point. The stability of the blood clot that forms spontaneously or develops after endoscopic therapy is pH dependent, being less stable in an acid environment. This forms the rationale for giving acid-suppressing drugs, such as PPIs, to patients who present with upper gastrointestinal bleeding.

“The optimum regimen for PPI administration is unclear: the best specific PPI, route of administration (oral versus intravenous), composition (bolus versus continuous infusion), and duration of therapy are unknown. The analysis undertaken by Sachar et al. (2014) showed that intermittent PPI therapy (oral or intravenous) was similar to continuous infusion in patients who received endoscopic therapy for peptic ulcers at high risk of re-bleeding.

“This is a well conducted meta-analysis that shows no difference between groups in the accepted endpoints of uncontrolled bleeding, mortality or transfusion requirements. As the authors concede, however, the 13 included trials include a range of specific PPIs and doses, and a variety of endoscopic therapies. Eight studies were not blinded, and 2 were presented only in abstract form. Nevertheless, the conclusions are compelling, and no single trial is likely to be undertaken that will further clarify the issues.

“Should clinicians now accept that intermittent PPI therapy (given orally or by intravenous injection) should replace constant infusion of these drugs? PPIs have a relatively long physiological half-life, so there is therefore biological plausibility for such an approach. In addition, infusion pumps for continuous infusion are relatively costly (although this is a minor consideration in the overall cost of the bleeding event). The answer is that this approach should be considered, provided that the patient will reliably receive the PPI on time and at the correct dose. Whether (as implied in the literature) oral administration is as good as intravenous administration is in my view a moot point, because patients with gastrointestinal diseases are prone to vomiting. As such, there seems greater security in intravenous administration.” – **Dr Kelvin Palmer, Consultant Gastroenterologist, Western General Hospital, Edinburgh**

Study sponsorship: US National Institutes of Health.

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