EDITORIALS

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thebmj.com ● Research: Efficacy and safety of paracetamol for spinal pain and osteoarthritis (*BMJ* 2015;350:h1225)

Where are we now with paracetamol?

Important questions remain unanswered about the most widely used drug in the UK

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When a doctor recommends a new medicine there are questions that a patient would hope to have answered. Will the treatment work for my clinical problem? Are there side effects? How many tablets do I take? Paracetamol was introduced into UK medical practice in 1956. It is the most widely used and prescribed drug in the UK and is generally considered to be effective and safe in therapeutic doses. In recent years, however, studies have raised questions regarding its efficacy and safety.[1 2] Where are we with regard to the patient's three questions?

Paracetamol is recommended in guidelines produced by agencies such as the UK National Institute for Health and Care Excellence. It is an effective mild analgesic but may not work for all types of pain. Paracetamol is effective for postoperative dental pain.[3] For headache, it is superior to placebo but less effective than other analgesics.[4] For the common cold, the evidence is insufficient to draw conclusions.[5] Randomised trial data report that paracetamol is no more effective than placebo for back pain.[2] For hip and knee pain, meta-analysis suggests that paracetamol has a small benefit that may not be clinically relevant.[6] Further efficacy trials are needed, but, until these are available, paracetamol will remain a first line analgesic in part because of the belief that it is safe in therapeutic doses.

Prescribers should establish whether patients are getting symptom relief from paracetamol to avoid long term exposure without benefit

Hepatic effects

Paracetamol does not make people feel unwell but there are recurrent concerns about increased risk of major harm. Liver injury is a well established consequence of paracetamol overdose, and there are also concerns about therapeutic doses. Studies have shown that around 25-40% of healthy volunteers will develop a small and often transient increase in alanine transaminase activity, a biomarker for liver injury, after ingesting therapeutic doses for one to two weeks.[7] Among patients with osteoarthritis, those taking paracetamol are reported to be four times more likely than others to have a modest rise in alanine transaminase.[6] What does this mean in practice? Decades of clinical experience with paracetamol suggest that at therapeutic doses serious liver injury is unlikely. For example, among 673 patients admitted to a UK liver transplantation unit with paracetamol induced liver injury only four reported taking 4 g or less (although there were still four, which does not provide complete reassurance).[8] Furthermore, there were no reported cases of fulminant hepatic injury in a review of 30 865 patients taking therapeutic doses of paracetamol in clinical trials.[9]

May not work for all types of pain

Concerns about the cardiovascular safety of non-steroidal anti-inflammatories and cyclooxygenase-2 (COX 2) inhibitors may increase the use of paracetamol in patients with raised cardiovascular risk. However, some studies suggest that it has an adverse cardiovascular safety profile.[1 10] Paracetamol has been shown to inhibit COX 2, which has the potential to increase blood pressure and promote thrombosis. Given that paracetamol is widely used and hypertension is common it is surprising that this interaction is not more clearly defined. Human mechanistic studies are needed.[11] Nevertheless, a recent study of over 24 000 patients from the UK did not show any association between paracetamol and myocardial infarction or stroke.[12] While observational data such as these may be confounded, they provide some reassurance, and the study should be repeated across international datasets.

Pregnant women often take paracetamol because non-steroidal anti-inflammatories have been associated with adverse fetal outcomes. Recent data from rodents suggest that paracetamol for one week, at equivalent doses to those taken by humans, adversely affects testosterone production from fetal testes.[13] Although this finding may explain a reported increased risk of cryptorchidism in infants with more than two weeks' exposure in utero,[14] the increase was of marginal significance in other observational studies.[15 16] Furthermore, in the rodent model, a short course of paracetamol had no adverse effect. Current guidance advising pregnant women to take paracetamol at the lowest effective dose for the shortest time is appropriate pending further data.

Paracetamol has a relatively narrow therapeutic index, and it is important that patients understand the implications. Following review in 2012, UK guidance was issued that small therapeutic overdoses should be considered for treatment with the antidote acetylcysteine "as per clinician judgment." The UK position differs from international guidance (the United States and Australia use higher ingestion thresholds to trigger treatment[17 18]) and may need revisiting because a substantial increase in the number of patients admitted to hospital for treatment has been reported since the guidance changed.[19] A review could identify new measures to reduce the incidence of therapeutic overdose and reduce the number of low risk patients being unnecessarily treated with a time consuming antidote that commonly produces adverse reactions and results in substantial hospital bed occupancy.

The Medicine and Healthcare Products R egulatory Agency is reviewing all over the counter analgesia, which will hopefully go some way to answering patients' questions. For now, prescribers should establish whether patients are getting symptom relief from paracetamol to avoid long term exposure without benefit.

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Every hospital should follow every patient it treats, long enough to determine whether or not the treatment has been successful, and then . . . inquire, "If not, why not?" with a view to preventing similar failures in the future – Ernest Codman, 1869-1940

The death of death rates?

Using mortality as a quality indicator for hospitals

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A profession that was once responsible for balancing four humours is now obliged to juggle over 14 000 discrete conditions. Fumbles are inevitable. But to what extent are they avoidable?

The National Health Service is still dealing with the fallout from the Francis inquiry into failings at Mid-Staffordshire NHS Foundation Trust.[2] One of its first responses was to dispatch Bruce Keogh, the national medical director, to investigate other places of concern—hospitals with persistently high mortality rates.[3] But was this the best way to identify rogues?

In a linked article, Hogan and colleagues measured the association between death rates reported by hospitals and the number of deaths they should have avoided.[4] A strong link would mean that comparative mortality data could serve as a system-wide smoke alarm, providing administrators with an efficient means of monitoring quality of care across the entire health service. Without a link, this alarm becomes a misleading source of false alerts, subjecting outliers to unnecessary suspicion, over-inspection, and reputational damage.[5] And far worse: hazardous hospitals lurking inside the funnel are assumed to be safe.

Hogan and colleagues report two main results, and the one follows from the other. Firstly, the proportion of hospital deaths judged by a panel of experts to be potentially avoidable was just 3.6%. Secondly, the association between standardised mortality rates and avoidable deaths was, unsurprisingly, non-significant within wide confidence intervals (regression coefficient 0.3, 95% confidence interval −0.2 to 0.7). The signal of avoidable death, it seems, is lost in the din of unavoidable noise. The research team concluded that the association was too weak for overall mortality rates to be an effective monitoring tool.

Weak signal

In apparent anticipation of Hogan and colleagues' null finding, the Keogh review established plans to construct a national indicator for avoidable inpatient death, based on externally audited case note reviews.[3] Unfortunately, the current study also revealed the fallibility of even the most carefully structured case review. Despite the provision of extensive training and support, experienced clinical reviewers often disagreed on what constituted an avoidable death and were influenced by a range of extraneous factors. Improving reliability—for example, by engaging multiple reviewers for each case, would further increase the costs of what is already likely to be an expensive undertaking.

Assuming this can be achieved, there are further problems. Given that 97% of patients survive their hospital stay, this study implies that the proportion of admissions resulting in an avoidable death is around a 10th of 1%. Even the most accurate indicator of avoidable death would barely scratch the surface of suboptimal care.

Flirting with Codman

How then to monitor and improve quality? Pioneer Ernest Codman's approach was to look beyond adverse outcomes: he took the radical and deeply unpopular step of publishing not only his patients' outcomes but also his judgments on whether the results could have been improved and the probable causes of failure to achieve "perfection."[6] A century on the medical profession is still not ready to fully embrace Codman, but it is at least prepared to flirt with him.

Recent innovations include aviation-style voluntary incident ("near miss") reporting,[7] structured risk assessment,[8] and the use of patient informants,[9] but the results have been underwhelming. This is not because the NHS lacks for either quality initiatives (clinician revalidation; Commissioning for Quality and Innovation; Quality, Innovation, Productivity and Prevention; the NHS Outcomes Framework; the Quality and Outcomes Framework; the patient safety improvement programme), quality oriented bodies (Care Quality Commission; Monitor; National Institute for Health and Care Excellence; National Quality Board; National Patient Safety Agency; NHS IQ), or other organisations with quality within their remit (clinical commissioning groups; health and wellbeing boards; Local Health Watch; the royal colleges). The costs and effectiveness of all this activity—with their potential for confusion, duplication, omission, and contradiction—are unknown, and the accretion of quality overseers suggests a desire to minimise regret rather than to maximise patient outcomes.

With this top-down hubbub, the best approach may be to follow Percival's advice and start at the bottom: unite "tenderness and steadiness"[10] by indoctrinating trainees in the medical professions with the principles of quality and compassion. Once these trainees emerge into practice there should be continuing and career-long support, with protected time for effective audit and reflection and properly aligned financial and reputational incentives. Clinicians, administrators, and policy makers also need to be statistically literate and able to distinguish common causes of variation from specifics using appropriate metrics. Rationalisation of candidate measures is required,[11] and the evidence is mounting that there may be no future for summary mortality rates. However carefully they are adjusted, these rates do not account for recording errors, variation in risk across hospitals, variation in performance within hospitals, and the availability of alternative places where patients can die.[12] Nor do they correlate with avoidable death.

Nevertheless, many within the NHS will find it difficult to accept that a tool that identified Mid-Staffordshire NHS Foundation Trust could fail to identify other sinners, and faith in funnel plots is likely to remain strong. Even apostates may find it difficult to let go in the absence of more cost effective alternatives. It will, after all, take a brave administrator to ignore an outlier.

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News: Services for neurological conditions are still poor, says National Audit Office (*BMJ* 2015;351:h3765)

Parts of this wonky, hub heavy wheel of neurology services have no spokes at all

Inadequate neurology services undermine patient care in the UK

Action is required to restore balance and ensure fair access

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"Neurology for the masses" announced *The BMJ*'s then editor, Richard Smith, in 1999.[1] Old stereotypes may associate neurology with rare syndromes and a fondness for diagnosis not treatment, he went on, but it is also a specialty of common illnesses such as epilepsy and Parkinson's disease. He might also have mentioned that neurological symptoms include some of the commonest complaints such as headache and fatigue. Sixteen years on and despite a doubling of consultants, a damning parliamentary report,[2] thrombolysis for stroke, and an awareness of increasing neurodegenerative disease, only people living in select areas, or able to travel, will encounter a neurologist.

The Neurological Alliance, a patients' organisation in England, reports that 31% of patients had to see their primary care doctor five or more times, and 40% waited more than 12 months with symptoms before seeing one.[3] The UK is the only developed nation with this problem. We have one neurologist per 90 000 people[4]; the European average is one per 15 000,[5] and in the United States concern has been expressed that one per 19 000 isn't enough.[6]

A scarce resource ought to be distributed fairly. Data emerging through the Neurology Intelligence Network show the poor match between need and provision of services.[7] London has the lowest prevalence of epilepsy and dementia yet the capital's residents have a 40% higher chance of being seen in a neurology outpatient clinic than people living elsewhere.[7] Even within London, access to specialists is poorly distributed and may not match patient need.

However, it is neurologists' involvement in acute care (or lack of it) that is most concerning. Neurological disorders are the third commonest cause of acute admission, behind disorders of the heart and lung.[8] However, of 145 UK district general hospitals surveyed by the Association of British Neurologists, only nine had dedicated neurology beds, 69 relied on a visiting neurology service, and seven had no service at all.[9] A quarter of acute admitting hospitals offered review by a neurologist on one in six days or fewer, and only 11% of patients admitted with a primary diagnosis of epilepsy were managed by a neurologist.[7] Neurologists are involved in thrombolysis for stroke in 90% of the 50 hospitals that have adjacent neurology centres and 14% of the 145 hospitals that don't.

GLOW WELLNESS/ALAMY

Life at the hub

Why is neurology unlike other medical specialties that serve common illnesses? Despite the prevalence of neurological symptoms and conditions, neurology in the UK has always been physically and intellectually discrete from the general hospital and the community. Originating at one hospital in London, the specialty spread slowly to teaching hospitals in the capital and to regional centres. Few and far between, neurologists couldn't or wouldn't take on patients with common problems. Stroke, dementia, migraine, and epilepsy were typically managed in primary care or by other secondary care specialties.

The outpatient service changed dramatically in 1997 when waiting time targets were introduced. The regional centres had to respond quickly to overwhelming demand, and those central hubs of a "hub and spoke" service absorbed the bulk of newly appointed consultants. Some hubs now employ 20 or more neurology specialists while the spokes—the district general hospitals and community services—remain underserved; parts of this wonky, hub heavy wheel of provision have no spokes at all.

Why should local hospitals employ neurologists when they don't take part in the rota for acute medical admissions, may not manage stroke, and could be made redundant by advanced imaging? Neurologists would answer that neurological mismanagement is catastrophic for the patient and medicolegally expensive for the provider; generalists find diagnosis and management of neurological conditions difficult even with advanced imaging; neurological expertise often changes diagnoses and can reduce length of stay; neurological illness is often long term and disabling, and a locally based neurologist could improve care.[8] Nevertheless, more evidence that specialists improve outcomes cost effectively would be helpful. Patients might simply argue that they deserve to be treated locally by experts in their condition.[2]

Time for independent review

To provide a comprehensive and equitable service, the distribution of neurologists should be inverted, with more smaller centres located where need is greatest. The latest five year plan for the NHS states that "The future will see far more care delivered locally but with some services in specialist centres."[10] It is unfortunate for the two million people (nine million if stroke, dementia, migraine, fatigue syndromes, and traumatic brain injury are included) with a neurological condition, particularly those not living near a centre, that neurology has been deemed a specialised service.

The Future Hospital Commission[11] can promise "24/7 specialist care in hospital and in or close to the patient's home, particularly for those with long-term conditions" but as things stand this will not include specialist neurological care. The Shape of Training review proposes extra generalist training for specialists.[12] Neurologists taking part in the general medical rota, managing stroke, and providing outreach to the community might be more useful but do specialised commissioning and the professional bodies support that approach? If they do, there are unlikely to be enough neurologists to meet demand.

Professional oversight of the specialty followed by unsupervised market led growth has failed people with neurological symptoms and conditions. Specialised commissioning and the Future Hospital Commission are set to continue the trend. It is time for independent review to determine what neurologists should be doing, how many are needed, and where they should be based. The current situation is not working for patients and their families or for the wider medical community.

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The new study set out to define the risk of such bleeds when the two classes of drugs are combined, and the results give some cause for concern

Risk of intracranial haemorrhage linked to co-treatment with antidepressants and NSAIDs

Important implications for primary care doctors and patients with multimorbidity

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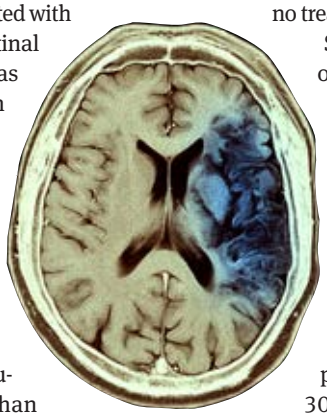
The linked paper by Shin and colleagues offers important new evidence about the relation between antidepressant drugs, non-steroidal anti-inflammatory drugs (NSAIDs), and intracranial haemorrhage.[1] Although NSAIDs and antidepressants are both associated with an increased risk of gastrointestinal bleeding, previous evidence has not shown clear links between intracranial haemorrhage and either type of drug when used alone.



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The new study, however, set out to define the risk of such bleeds when the two classes of drugs are combined, and the results give some cause for concern. In a retrospective population cohort study of more than four million people in Korea, the authors found that the combination of antidepressants and NSAIDs was associated with a substantially increased risk of intracranial haemorrhage, compared with antidepressant treatment alone.

Antidepressants are widely prescribed globally, and their use is increasing.[2-4] In England, almost 40 million antidepressant prescriptions were issued in 2012, compared with just under 15 million in 1998.[4] NSAIDs are also widely used, often without prescription and in non-pharmacy settings. In the United Kingdom, NSAIDs are in the top 20 medication items dispensed in primary care (15.1 million items in 2014).[6] The availability of over the counter analgesics is particularly important, as doctors often fail to consider the risks and potential interactions posed by non-prescribed drugs. Although NSAIDs bought over the counter are often taken for a short period only, Shin and colleagues' study reported elevated bleeding risk within 30 days of a new prescription. Most worryingly, conditions requiring NSAIDs and antidepressants commonly coexist; 65% of people with major depression also have chronic pain,[7] with both morbidities sharing common psychological risk factors and neurobiological processes.[8]

Although the new work is an important contribution to the literature, several unanswered questions remain. Firstly, the risks of intracranial bleeding associated with these drugs when used alone remains unclear, and previous studies examining this have been small. Insight into the risks of combined treatment compared with no treatment would be valuable.

Secondly, the long term risks of combined treatment remain unknown. Shin and colleagues examined bleeding risk within 30 days. This is very relevant to use of over the counter analgesics, but many patients are treated with antidepressants long term, as well as long term NSAIDs. According to Shin and colleagues' data, a patient's absolute risk in the first 30 days of combined treatment is around 0.05%, but the risk may be considerably higher in those treated for longer.

Thirdly, Shin and colleagues studied this problem in Korea, and the question of generalisability to other populations is important. Ethnic variations in the activity of various cytochrome P450 enzymes exist, so adverse events secondary to drug interactions may vary among different ethnic groups.[9]

Fourthly, the excess risk of intracranial haemorrhage associated with combining antidepressants and NSAIDs was markedly higher in men than in women, but the reason for this remains unknown. The added risk of co-treatment with other drugs such as anticoagulants is also unknown. Although warfarin was not found to increase risk any further, this finding may be subject to confounding by contraindication, as doctors may avoid prescribing warfarin to patients receiving concomitant NSAIDs owing to the potential for gastrointestinal bleeding.

Clinical implications

Guidelines are generally poor at informing therapeutic decisions in patients with multimorbidity, in whom polypharmacy is ubiquitous.[10] This makes evidence based decision making very difficult, as useful information such as number needed to treat and number needed to harm is often lacking. Even if such information was available, general practitioners and patients would still need to weigh up the harms and benefits of treatment within the broader clinical and social context of, for example, very elderly frail patients, those with complex multimorbidity or dementia compounded by depression and pain, and terminally ill patients. In such circumstances, knowing patients and their wishes well, and taking an empathic, person centred approach may be as important as having better guidelines and a better evidence base. High quality primary care depends on a combination of effective "technical care," effective "interpersonal" care, and the flexibility to tailor both of these to the individual patient's needs and wishes.

Shin and colleagues' findings may be especially relevant in areas of high socioeconomic deprivation, where the combination of mental and physical problems is very common. Such mental-physical multimorbidity is two or three times more prevalent in the poorest areas than in the most affluent.[11] Given the ongoing "inverse care law" still operating in primary care in deprived areas, the study suggests that general practitioners working in deprived areas will need to be extra vigilant when prescribing and discussing the risks with patients.[12]

These important new findings on the risks of intracranial haemorrhage associated with combined use of antidepressants and NSAIDs need to be understood within the broader context of multimorbidity, polypharmacy, and primary care systems. Further research is needed to extend the findings over longer time periods and to quantify risks in different populations.

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