Tom Nolan's research reviews—1 December 2022

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Waiting for the next confidence interval

Many of the terms used in research papers seem ripe for being repurposed for clinical practice. For instance, the P value could be a measure of how likely a urine dipstick is to change a diagnosis for a patient with suspected urinary tract infection (usually <0.05). A confidence interval might be the part of the day, usually lasting about 20 minutes and never occurring after 11 am, when you feel that you’re doing a decent job. Crossing the futility boundary, instead of being the point at which they stop a trial early because the drug clearly doesn’t work, could be when you realise you’re not going to leave on time so there’s no point rushing.

Meanwhile, in a randomised controlled trial of pemafibrate versus placebo in over 10 000 patients with type 2 diabetes, high triglyceride levels, and low HDL cholesterol, an interim analysis found the “futility boundaries had been crossed” so the trial was ended early—and this is despite the primary endpoint being changed partway through the study—futility boundaries had been crossed “as high as 79% of those for drugs for LMICs—IUA (increase in unlicensed analgesia) succeeds in having a BIMB (big impact on medical behaviour).

IUA for OACGs

Unfamiliar abbreviations (UA) are a bugbear of mine—I’ve got a real bee in my bonnet (BIMB) about them. My BIMB got buzzing this week on reading a research letter about opioid analgesic and gabapentinoid co-prescribing. It included the UA for concurrent opioid analgesia and gabapentinoid episodes (OACG). That isn’t just an UA but also an illogical UA, or IUA, since the C is obviously in the wrong place. OACGs, defined as any overlap between opioid and gabapentinoid prescribing, have increased in the US, having occurred 1.9% of the time in 2016 but up to 7.6% in 2018. Let’s hope raising awareness of this IUA (increase in unlicensed analgesia) succeeds in having a BIMB (big impact on medical behaviour).


Transparency and generalisability in question

Recruiting people from low and middle income countries (LMIC) for clinical trials of new drugs whose findings are unlikely to be relevant for them (such as due to the high cost of the drug) is unethical and raises serious questions about the generalisability of the findings. Despite that, a new cross-sectional analysis of pivotal trials for 66 recently FDA-approved drugs for cancer, neurological disease, and cardiovascular disease between 2012 and 2019 found that most of the pivotal trials recruited from LMICS—as high as 79% of those for drugs for cardiovascular disease. Transparency was also an issue: from the 144 pivotal trials identified, country level involvement data were not available for 71 (55%) of them.


Bacterial causes of death

A systematic analysis in the Lancet reminds us how common death from infection (specifically bacterial infection) is. It estimates that in 2019 there were 13.7 million infection related deaths, with 7.7 million deaths from one of 33 bacteria included in the study. This was the second leading cause of death globally. The age standardised mortality rate from these bacteria varied according to location: four times higher for those living in sub-Saharan Africa than in high income regions, for example. The most deadly bacterium in the report is Staphylococcus aureus, the leading bacterial cause of death in 135 countries and in people over 15 years old.

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Morphine for breathlessness

Opioids are recommended in the palliative care setting as an option to consider for managing breathlessness. In patients with advanced COPD, who experience chronic breathlessness at rest or on minimal exertion, previous trials have suggested that low dose opioids might help some people’s symptoms. However, findings from a new randomised control trial of people with COPD and a modified MRC breathlessness scale score of 3 or 4 do not support use of low dose opioids in this group. It found that, compared with placebo, 8 mg or 16 mg of oral extended release morphine per day had no effect on worst breathlessness after a week.


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