

LETTERS

RESPONSE

Andrew Moore and colleagues reply to Des Spence

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Spence's polemic on duloxetine loses power because most of what it is based on is wrong.¹ Making pronouncements in respected journals about good and bad medicine comes with the responsibility of knowing what you are talking about. Bad scholarship helps no one, especially those in pain; research in genetics, neurobiology, and psychology has contributed to huge advances in knowledge about the bio-psycho-social origins of pain.

Chronic pain is defined as pain of moderate or severe intensity that lasts for three months or more (think of a really bad headache lasting from Christmas to Easter). It affects one in five adults. Painful conditions are among the most prevalent conditions and are five of the top 11 in terms of years living with disability. Chronic pain destroys lives, has a huge negative impact on quality of life, is costly, reduces the ability to work or function inside the family, and may be associated with decreased life expectancy.

Here is a brief, non-comprehensive list of where Spence misses the point.

Women are not over-represented in trials. Chronic pain disproportionately affects women; their representation matches the epidemiology.

Pain is the most immediate of patient outcome measures, reported by patients themselves. Its subjectivity was recognised in the 1950s and dealt with. Different scales show excellent agreement, and patients in clinical trials record consistent pain levels over long periods, as in clinical practice.

Average benefits over placebo are in the order of 1 point on a 10 point rating score. But few patients are average; most have either little or great benefit. A responder is defined as someone with at least a 50% reduction in pain intensity maintained for

12 weeks, without intolerable adverse events that mean stopping treatment. Patients want this outcome, and it is accompanied by major improvements in sleep, function, and quality of life.

Cochrane reviews do not report effective non-drug alternatives. One of exercise in fibromyalgia involved only 223 patients in four small trials of barely adequate quality; another of psychological therapies found that effects are at best weak and that more research is urgently needed.²

Cochrane reviews endorse nothing.³ Several large good quality trials provide good evidence that duloxetine is effective in painful diabetic neuropathy and fibromyalgia. The effect size is not massive—a number needed to treat of five tells you that—but it is comparable to other treatments in neuropathic and other chronic pain, where treatment failure is expected more often than treatment success.⁴

We are not “steeped in conflicts of interest.” Some (but not all) make declarations of interest, not quite the same as conflicts. We are proud of this, when it means bringing otherwise unpublished information into the public domain, accessing data at the level of the individual patient to improve understanding of evidence and outcomes, and, importantly, demonstrating new sources of large potential bias. Our rule over 30 years is that we work only with organisations that agree an unrestricted right to publish the results, whatever they may be.

Spence omits the most important, valid, criticisms. These might include the bias against older treatments because authorities require trials fundable only by industry or government (which neither fund). Effective drugs like amitriptyline are understudied so have less evidence of efficacy to support their use. In addition, inappropriate imputation methods in statistical analysis

of results can mean that efficacy is sometimes hugely inflated⁵; this is not the case for duloxetine.⁶

Patients need options. Encouraging people to act against the evidence is the real “bad medicine.”

Competing interests: ML, RH, and PW wrote a Cochrane review on duloxetine. AM has received honorariums for consulting from Eli Lilly. AM, DA, and EK were authors of a *BMJ* article criticised by Spence. CE and AW declare no conflicts.

Full response at: www.bmj.com/content/348/bmj.g139/rr/685335.

- 1 Spence D. Bad medicine: the rise of duloxetine. *BMJ* 2014;348:g139. (17 January.)
- 2 Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* 2012;11:CD007407.
- 3 Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev* 2014;1:CD007115.
- 4 Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ* 2013;346:f2690.
- 5 Moore RA, Straube S, Eccleston C, Derry S, Aldington D, Wiffen P, et al. Estimate at your peril: imputation methods for patient withdrawal can bias efficacy outcomes in chronic pain trials using responder analyses. *Pain* 2012;153:265-8.
- 6 Moore RA, Cai N, Skljarevski V, Tölle TR. Duloxetine use in chronic painful conditions—individual patient data responder analysis. *Eur J Pain* 2014;18:67-75.

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