Evidence-Based Pain Management: Building on the Foundations of Cochrane Systematic Reviews

We discuss the history and current status of evidence-based medicine for the prevention and treatment of acute and chronic pain as it has developed in the Cochrane Collaboration's Pain, Palliative and Supportive Care Review Group.

To date, the Pain, Palliative and Supportive Care Review Group has published 277 reviews and a further 11 reviews of systematic reviews summarizing the evidence for interventions. The Cochrane Library has readily available high-quality summaries of evidence of pharmacological interventions especially for postsurgical pain but also for chronic musculoskeletal and neuropathic pain. The library covers all forms of intervention, not only pharmacological.

The world of evidence-based medicine is changing: most historical trials have been entered into reviews, but the evidence is still not well disseminated and needs to be better translated into decision support. Evidence should be at the heart of policymaking. Much has been achieved in the past 21 years, but there are no grounds for complacency. (*Am J Public Health*. 2019;109:46–49. doi:10.2105/AJPH.2018.304745)

Dominic Aldington, MBBS, and Chris Eccleston, PhD

See also Carr et al., p. 17; and also the *AJPH* Pain Management section, pp. 30–72.

"You can't handle the truth."

—*Col. Jessup,* A Few Good Men *(Columbia Pictures, 1992)*

There is a short but active history of evidence-based pain medicine, and the Cochrane Library has more than 288 systematic reviews of primary randomized controlled trials. This is a foundation on which to build new, improved evidence syntheses that make the evidence more relevant and useful for clinical decision-making.

This commentary is about what we know, what we do not know, and how we plan to learn more about what can help people in pain. It is about our efforts to improve the science of pain management, even when the truth about the evidence and safety of our interventions is unwelcome and hard to handle. Our focus on evidence production and review is grounded on our work with the Cochrane Collaboration, now known simply as Cochrane (https://www.cochrane.org), which is an international collaboration of health care professionals and scientists with the overall purpose of providing evidence that is trusted, that informs decisions, and that ultimately leads to better health. The main activity of Cochrane is maintaining the Cochrane Database of Systematic Reviews (CDSR), which is accessed and searchable through the Cochrane Library (wyww.cochranelibrary.com). Cochrane has a central executive team and a senior editorial board, but its review production is managed through 52 specific review editing houses, organized into eight networks (https://www.cochrane.org/about-us/our-global-community/review-group-networks), and reviews are produced by authors who are largely science or health care professionals who volunteer to help. Cochrane has had 37 000 contributors from more than 130 countries.

Cochrane was the brainchild of Iain Chalmers and was named after Archie Cochrane (1909–1988). Cochrane had reflected during his time as a doctor in a World War II prisoner of war camp that much of medicine did not have sufficient evidence to justify its use. He is known for his monograph *Effectiveness and Efficiency: Random Reflections on Health Services*, published in 1972.[1] He suggested that because resources were limited, they should be used only to provide health care that was effective. He went on to suggest that the evidence from randomized controlled trials should be used because it was likely to be of the greatest reliability. In 1979 he wrote,

> It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials.[2(p9)]

The CDSR, established in 1995, is the basis for the library. In 1996 the Pain, Palliative and Supportive Care Cochrane Review Group was established, and it remains one of the 52 editing houses focusing specifically on acute and chronic pain, including headache and migraine, and on all aspects of palliative and supportive care. The Pain, Palliative and Supportive Care Review Group produces reviews across the age range, with reviews on pain at the start and end of life, with youths and with seniors. By January 2018, it had published 277 intervention reviews and eight protocols, together with 11 overview reviews and 1 overview protocol. The Pain, Palliative and Supportive Care Review Group also collaborates with the many other review groups with an interest in pain, including but not limited to Cochrane Neuromuscular Disease, Cochrane Oral Health, Cochrane Musculoskeletal, and Cochrane Neonatal.

Review production is, of course, only one part of the evidence discussion. From the

ABOUT THE AUTHORS

Dominic Aldington is with the Royal Hampshire County Hospital, Winchester, UK. Chris Eccleston is with the Centre for Pain Medicine Research, University of Bath, Bath, UK.

Correspondence should be sent to Dr Dominic Aldington, Consultant in Pain Medicine, Royal Hampshire County Hospital, Winchester SO22 5PY, United Kingdom (e-mail: daldington@me.com). *Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.*

This article was accepted August 22, 2018.

doi: 10.2105/AJPH.2018.304745

beginning, there has been a concern with the use of that evidence. David Sackett, for example, said as early as 1986,

> Evidence based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.[3(71–72)]

Although Cochrane avoids any clinical advice or guidance, and each review ends with a summary of uncertainty around any estimates of efficacy or safety, we are very interested in that evidence being used by stakeholders. Of course, different groups have different needs from "evidence." Public health practitioners will want an idea of average clinical response in a population, policymakers will want to know the financial costs weighed against the benefit, clinicians will want to know the probability of a response in an individual patient, and patients will often want to "try anything, doctor" albeit perhaps with only one eye on risks.

WHAT DO WE KNOW?

Although often ridiculed for it, the US Secretary of Defense Donald Rumsfeld drew a now famous distinction between what is known and what is unknown, splitting this latter case into known unknowns and unknown unknowns. He was attempting to draw attention to how far we can plan for the unknowable and thus mitigate risk. When it comes to attempting to take away people's pain, what do we know?

We know that pain is ultimately a private mental event, as is any perception, emotion, or cognition. We know that this private and subjective experience is also social, expressed, and so experienced in a common language, in behaviors subject to common rules, and in a form evolved over time to promote the protection of self and others. We know that untreated pain is a major personal, financial, social, and familial burden—a burden often underestimated because pain functions to silence and remove the sufferer from view. And we know that pain not associated with a progressive disease, such as cancer, can often persist past a presumed healing time and can become a condition in and of itself. Such persistent pain is not only a symptom of another disease but a disease in its own right. Finally, we know that pain is difficult to treat. But that is not for want of trying. There is a large number of possible interventions: pharmacological, surgical, psychological, and rehabilitative.

From both a clinical and an evidence synthesis perspective, it is sensible to consider interventions for acute pain and chronic pain separately. Intuitively, acute postoperative pain should give us the clearest evidence because it is relatively easy to model and because wider psychosocial influences on results should be less significant than pain in other settings—acute prehospital pains will vary with settings, and chronic pains are probably the most variable of all.

We also know the type of trial design that is likely to give the most reliable results.[4] A search of the CDSR for the term "acute pain" shows 97 systematic reviews covering topics from psychological interventions for acute pain after open heart surgery to breastfeeding for procedural pain in infants to diclofenac for acute postoperative pain in adults. However, looking a little more deeply, two clear facts seem to emerge. The first is that very few of the systematic reviews of interventions for acute pain can be said to show clinically significant differences at a meaningful level: typically, a 1-point change on a 10-point scale. This is slightly frustrating, as clinicians expect a clinically significant response in acute pain to be one that reduces pain to 50% or less of the maximum, or at least a 30% reduction from baseline. For example, research on the use of peripheral nerve blocks after major knee surgery in 2014 suggested the nerve blocks reduce pain in the first 72 hours, but the researchers commented that "more trials are needed to demonstrate significant difference when comparing nerve blocks with other ways of reducing pain."[5]

The second fact is that in the pooled analysis, a review of systematic reviews in which up to 50 000 patients' responses were analyzed, the very best responses in the field of pain management provide a number needed to treat of only slightly less than two.[6] Thus, only slightly more than 50% of patients randomized to treatment or alternative achieve at least 50% pain reduction after four to six hours who would not have done so with placebo. Again, at one level that does not sound very impressive and can certainly cause consternation when presented to professional colleagues who want to help. However, this is what the data show; the drugs are no less efficacious than they were before we looked at the data. It may be an uncomfortable truth that we have to handle. Of patient-controlled opioid analgesia for postoperative pain compared with "conventional" opioid analgesia, a 2015 review suggested that the evidence was of low to moderate quality that the patient-controlled opioid analgesia reduced pain about 10% but may lead to an increased opioid dose and, unsurprisingly, increased nausea.[7] This is an interesting finding because many in-hospital pain services are funded only because of the use of devices such as patient-controlled opioid analgesia and epidural pumps.

And what of chronic pains, which include those with the greatest societal impact in terms of illness burden, suffering, and cost? Considering the evidence base for acute pain interventions, it is not surprising that the same poverty of evidence exists for chronic pain interventions. The CDSR records 91 reviews of chronic noncancer pain. Although most of the reviews look at pharmacological interventions for neuropathic pain, also included are persistent pain in torture survivors, acupuncture patients, and those who have experienced interventions for reducing opioid use for chronic noncancer pain. Looking at some of these reviews in detail, it appears that there is no evidence to support the use of high dose (200 mg or more morphine equivalent daily) opioids in chronic noncancer pain.[8] The review of acupuncture for neuropathic pain concludes that because of the limited data there is insufficient evidence to reduce uncertainty.[9] A review of gabapentin in neuropathic pain suggested that after shingles, three in 10 people had their pain reduced by 50% with gabapentin (1200 mg daily or more), whereas two in 10 had the same response with placebo.[10]

If success was defined as a reduction by 30% or more, five in 10 participants achieved this with gabapentin and three in 10 with placebo. Although side effects were more common with gabapentin, six in 10, an astounding five in 10 had them with placebo, and there was no difference in serious side effects. A systematic review of physiotherapy for pain

and disability in adults with complex regional pain syndrome failed to find any trials of appropriate quality, although physiotherapy maintains its role as the mainstay of treatment of this condition.[11] A systematic review of the use of botulinum toxin for myofascial pain syndrome concluded that there was "inconclusive" evidence to support its use and "more high-quality randomised controlled trials . . . need to be conducted."[12(p4)] And what of amitriptyline, which retains pole position in the lineup of pharmacological agents for the treatment of neuropathic pain in most guidelines? A systematic review stated, "There was no supportive unbiased evidence for a beneficial effect."[13(p4)] A review of opioids for pain associated with rheumatoid arthritis suggested there was "limited evidence" for the efficacy of weak opioids up to six weeks but no evidence beyond six weeks and no evidence for the use of strong opioids.[14]

One of the Holy Grail topics at the moment for pain is the prevention of chronic pain after surgery,[15] and a systematic review of pharmacotherapies suggested that better designed trials were needed and that there was no current evidence to support the use of a multitude of interventions.[16] And a review looking at psychological interventions for improving physical function, reducing pain, and reducing low mood in fibromyalgia suggested they may be effective but stated the "quality of the evidence is low."[17(p5)]

WHAT DON'T WE KNOW?

We do not yet know how to capture pain complexity as a multifaceted experience. Unidimensional scores, such as a zero to 10 pain rating, may not be telling us what we think they do. These are common in trials of pain treatments and in clinical practice to focus on the felt experience, and not on the consequences (behaviorally, relationally, or socially) of the pain. In some cases, altering the felt experience with relief or succor from pain may allow a return to prepain activity. In other cases, it may not. Perhaps this is why some societies are finding such difficulties with medication use, expecting responses that are unlikely to be achieved because the psychosocial components are ignored. Although we use the clumsy portmanteau neologism "biopsychosocial," our theories and practices remain largely unidimensional and biological. The greatest challenge will be to develop a common language of pain and a pain treatment that captures pain's complexity without sacrificing action.

We do not yet know how to tailor our evidence to the individual or even to subclasses of individuals. Most of our evidence is based on average effects for average patients. However, we know, as has been mentioned, that most patients are not average in their response to any intervention. So, when faced with an average number needed to treat, many providers reply with the question "Why bother if the medication is so unhelpful?" The answer, of course, is that some people will respond very well.[18] What is unknown often is how to predict who will respond well to a particular intervention. Clinically, it would be helpful to establish starting, stopping, and switching rules for any pain management plan. If a treatment is unlikely to provide the desired response, that knowledge will emerge quickly. Harm reduction and the opportunity for an analgesic response will be improved by timely review and change.

Unfortunately, the concept of an individual trial of medication is rarely done well in clinical practice. However, this statement brings into sharp relief another aspect of our known unknowns. Despite none of this information being in any way secret—it all sits happily in the public domain—we have not yet discovered a good way to disseminate this information to the wider health care community. The reasons for this are beyond the scope of this commentary, but we do know that the publication of more guidelines is unlikely to be the answer.[19] At a public health level, we encourage an approach to treatment provision on the basis of treatment pathways that consider the evidence but that also seek to reduce an individual's unnecessary exposure to ineffective interventions and a rapid assessment and switch to alternatives.

Finally, rarely discussed but critically important is the role of the comparator in trials that make up the evidence base. From the sham TENS (transcutaneous electrical nerve stimulation) machine to the waiting list control to the fake pill or injection, comparator (often placebo) responses in trials are often uncomfortably high. There are technical methodological reasons for this, including how researchers impute missing data, but they are also higher responses than in other fields of medicine. This has led to an interest in the potential therapeutic use of placebo. Properly framed, high placebo effects show that we should work harder to understand the psychosocial context of how pain is experienced and expressed.[20]

NEXT GENERATION EVIDENCE-BASED MEDICINE

What will be the future for evidence-based pain medicine? The answer to this has to go hand in hand with the requirements for medicine in the future. Innovations in both big (high-volume population) and small (high-volume individual) data may revolutionize the information we have to make personalized decisions. Cochrane itself is turning toward increased mining of individual patient data from the trials we have to greater decision support by translation of evidence into guidelines and to greater use of artificial intelligence in the updating and rapid production of evidence. Our focus is now more on prioritizing new reviews and updates, translating review outputs into practice, and developing new methodologies for the review of non–randomized controlled trial primary sources. We are also interested in developing methods of network meta-analysis that would allow an evaluation of indirect comparisons[21] in the use of novel trial design such as enriched enrolment,[22] in a more idiographic focus on individual change in complex interventions, and in outcomes in low-income countries.[23] This change in the medical evidence landscape will also likely change how we undertake both discovery and translational research.

In conclusion, we know a lot. We have a wealth of evidence summarized and easily accessible, and that evidence is subject to regular updating. In most cases, the evidence directly addresses the efficacy and safety of interventions used for both acute and chronic pain. The evidence base also tells us what we do not

know: where the evidence is highly likely to be biased or is of low quality and where there is an absence of evidence. The greatest challenge now to evidence-based pain in general and Cochrane in particular remains one of relevance to everyday practice. A thoroughgoing skepticism of "eminence-based" medicine remains important, but this is a starting point for action, not its conclusion. We need to work harder to translate that evidence into action, from individual agents acting in the service of their patients to policymakers at local and national levels. Finally, we should remain mindful of the need for evidence-based medicine to evolve, expand, and address inequities in access to knowledge.[24] Access to evidence is how change begins. Much has been achieved in the past 21 years, but there are no grounds for complacency. AJPH

CONTRIBUTORS

Both authors decided on the contents of and wrote this commentary.

ACKNOWLEDGMENTS

Both D. Aldington and C. Eccleston have written and reviewed articles for the Cochrane Library. C. Eccleston is the coordinating editor for the Cochrane Pain, Palliative and Supportive Care Review Group.

CONFLICTS OF INTEREST

No conflicts of interest.

REFERENCES

1. Cochrane AL. *Effectiveness and Efficiency. Random Reflections on Health Services*. London, UK: Royal Society of Medicine; 2004.

2. Cochrane AL. 1931–1971: a critical review, with particular reference to the medical profession. In: Teeling-Smith G, Wells N, eds. *Medicines for the Year 2000*. London, UK: Office of Health Economics; 1979: 1–11.

3. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312(7023):71–72.

4. Moore RA, Eccleston C, Derry S, et al. "Evidence" in chronic pain—establishing best practice in the reporting of systematic reviews. *Pain*. 2010;150(3):386–389.

5. Xu J, Chen XM, Ma CK, Wang XR. Peripheral nerve blocks for postoperative pain after major knee surgery. *Cochrane Database Syst Rev*. 2014;(12):CD010937.

6. Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults—an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2015;(9):CD008659.

7. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database Syst Rev*. 2015;(6):CD003348.

8. Els C, Jackson TD, Hagtvedt R, et al. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017;(10):CD012299.

9. Ju ZY, Wang K, Cui HS, et al. Acupuncture for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;(12):CD012057.

10. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;(6):CD007938.

11. Smart KM, Wand BM, O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. *Cochrane Database Syst Rev*. 2016;(2):CD010853.

12. Soares A, Andriolo RB, Atallah ÁN, da Silva EM. Botulinum toxin for myofascial pain syndromes in adults. *Cochrane Database Syst Rev*. 2014;(7):CD007533.

13. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2015;(7):CD008242.

14. Whittle SL, Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. *Cochrane Database Syst Rev*. 2011;(11):CD003113.

15. Cohen SP, Raja SN. Prevention of chronic postsurgical pain: the ongoing search for the holy grail of anesthesiology. *Anesthesiology*. 2013;118(2):241–243.

16. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. *Cochrane Database Syst Rev*. 2013;(7):CD008307.

17. Bernardy K, Klose P, Busch AJ, Choy EHS, Häuser W. Cognitive behavioural therapies for fibromyalgia. *Cochrane Database Syst Rev*. 2013;(9):CD009796.

18. Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ*. 2013;346:f2690.

19. Moore RA, Derry S, Aldington D. From evidence-based medicine to guidelines and recommendations: a long and winding road. *Eur J Anaesthesiol*. 2011;28(11):753–755.

20. Klinger R, Kothe R, Schmitz J, Kamping S, Flor H. Placebo effects of a sham opioid solution. *Pain*. 2017;158(10):1893–1902.

21. Moore RA, Derry S, Wiffen PJ, et al. Estimating relative efficacy in acute postoperative pain: network meta-analysis is consistent with indirect comparison to placebo alone. *Pain*. 2018;159(11):2234–2244.

22. Moore RA, Wiffin PJ, Eccleston C, et al. Systematic review of enriched-enrolment randomised withdrawal trial designs in chronic pain: a new framework for design and reporting. *Pain*. 2015;156(8):1382–1395.

23. Eccleston C, Wells C, Morlion B, eds. *European Pain Management*. Oxford, UK: Oxford University Press; 2018.

24. Heneghan C, Mahtani KR, Goldacre B, Godlee F, Macdonald H, Jarvies D. Evidence based medicine manifesto for better healthcare. *Evid Based Med*. 2017;22(4):120–122.