PAIN® 154 (2013) S77–S86

PAIN®

www.elsevier.com/locate/pain

Review

What works for whom? Determining the efficacy and harm of treatments for pain

R. Andrew Moore *

Pain Research and Nuffield Division of Anaesthetics, Nuffield Department of Clinical Neurology, University of Oxford, The Churchill, Oxford OX3 7LE, UK

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 6 August 2012
Received in revised form 2 January 2013
Accepted 12 March 2013

Keywords:
Biennial review of pain 2013
Pain
Treatment efficacy

ABSTRACT

There has been a tension between the needs of regulators and industry to demonstrate that interventions are effective and safe, and the needs of professionals to understand how well interventions will work for their patients, and patients to understand what might work for them as individuals. The custom has been to focus on statistical outcomes based on average results, but in-depth analysis based on outcomes obtained by individual patients demonstrates that few are average. Rather, a minority of patients achieve very large reductions in pain (responders), while the majority achieve little (nonresponders). Those who benefit in terms of pain also benefit in other areas, with improved sleep, fatigue, mood, function, quality of life, and ability to work. This changes how benefit and risk are seen; nonresponders should stop treatments that don't work and not, therefore, be exposed to risks, while responders have very large benefits to offset against rare but potentially serious harm. This alternative view, patient-centred and practice-orientated, has major implications for clinical practice, how and why we do clinical trials and how they are designed, how health economic evaluations are done, for decisions made by regulatory and other bodies, and for the theory and practice of evidence-based medicine.

1. Introduction

"*Managers and trialists may be happy for treatments to work on average; patients expect their doctors to do better than that*" [23].

Sir John Grimley Evans was an Oxford gerontologist who had a jaundiced view of evidence-based medicine, not because he thought it a bad idea, but rather he thought it a good idea badly applied. His particular concern was that statistical outputs from meta-analyses missed the patient and physician perspective, and he was concerned that his patients were almost never average. Other concerns were that guidelines based on average values would fossilise clinical practice and deny patients and physicians choice.

Those concerns are just as relevant today, but for pain trials there has been a change of perspective, away from the narrow statistical approach of judging average benefits and harms of treatment and towards the perspective of the individual patient. That might be simple to say, but to achieve that change has not been easy, involving as it does a different approach to expressing and analysing evidence. Moreover, changing perspective brings with it some very significant challenges to how we judge what works, and what works for whom, under what conditions.

These changes in perspective have been driven, in part, by analyses of large clinical trial data sets at the level of the individual patient. Such analyses, using high-quality clinical trials with large numbers of patients, make possible a range of novel – or at least different – approaches to data presentation. Any concentration on evidence from drugs like duloxetine, etoricoxib, or pregabalin reflects individual patient data being made available by the relevant pharmaceutical companies. Unfortunately, similar data are not available for all drugs, particularly those historically used for pain. The trials used in these analyses generally exclude the most challenging patients, so results could be regarded as best case, and perhaps with more relevance for primary care than for the more complicated scenarios seen in secondary or tertiary care.

2. Patient experience of pain

A powerful appreciation of the impact of pain, especially chronic pain, comes from how patients express the impact of pain on their lives, to the extent of desperation: "*Feel I want to give up. Ready to take the lot (pills). Not a life, just an existence,*" or "*Life is at a standstill and I feel it is finished. Sometimes I wonder if it is worth going on*" [67]. Behind the desperation is not just the pain, but the poor sleep, fatigue, depression, and the multitude of ways that pain interferes with the simple activities of everyday life [13].

The summary construct now in common use is "quality of life," with standard measures of life quality sampling in a number of

* Tel.: +44 1865 225674.
E-mail address: andrew.moore@ndcn.ox.ac.uk

0304-3959/$36.00
http://dx.doi.org/10.1016/j.pain.2013.03.024

dimensions (one of which is pain) to try to standardise suffering and misery, and less often, well-being and happiness. Studies of quality of life in chronic pain consistently demonstrate that pain is associated with lower quality of life, and that greater pain severity is highly correlated with lower quality of life (Fig. 1) [9,37,39,60,68]. An extensive systematic review of health utilities in neuropathic pain up to 2008 [15] demonstrated this, with severe neuropathic pain particularly having very low quality of life; publications since 2008 have confirmed these conclusions in neuropathic pain [2,22], back pain [80], and fibromyalgia [65].

Studies comparing quality-of-life scores of patients with chronic pain with population normative values for age and sex universally conclude that chronic pain is associated with a markedly lower quality of life. What's more, chronic painful conditions have at least as large a negative impact on quality of life as chronic medical conditions like cancer and cardiovascular or neuromuscular disorders (Fig. 2) [70]. Severe migraine is ranked in the highest disability class, alongside dementia and quadriplegia [45], and patients consider severe migraine pain as a health state worse than death [72].

Nor is the burden one that only patients have to bear. Society also loses, because of increased health care costs and reduced ability for paid employment or work in the home. Health care costs of chronic pain are consistently rated to be at least 2.6 times higher comparing chronic pain with no chronic pain [6,31,44], comparing moderate/severe back pain with mild pain [80], or comparing low- vs high-grade chronic pain [61]. An extensive systematic review has examined the consequences of chronic pain for the workplace [59] and found a substantial negative impact on work-related outcomes like employment status, sickness absence, and presenteeism (being at work but not functioning properly).

We can now also go further, and seriously consider the likelihood that chronic pain is also associated with reduced *quantity* of life. While there is still some uncertainty, the majority of studies have found an association between chronic pain and increased mortality, and this is particularly the case for patients with the most severe pain [69,76] or walking disability [56]. It is tempting to consider the low physical activity levels seen in many chronic pain patients as causative; low physical activity and sleep disturbance are associated with higher mortality, and physical activity is known to be a potent protective factor against cardiovascular events [33].

3. Patient expectations from treatment

Given the dire starting point of patients with pain, it is hardly surprising that when patients are asked about their expectations of treatment, their answer is unequivocal: a very large pain reduction. Over 80% of those with most severe pain associated with rheumatoid arthritis declared pain reduction as the preferred goal of treatment, above function or any other benefit [26]. Patients with chronic back pain or fibromyalgia judged a satisfactory outcome of treatment to be a pain intensity reduction of 50%–70%, with concomitant benefits in sleep, fatigue, function, and improvement in activities of daily living [58]. Their ideal was no worse than mild pain, as found in rheumatology using patient acceptable symptom state methods [16,77]. Patients with migraine want complete relief of pain, quickly, and without adverse events [41].

4. Can treatments meet expectations?

Historically, clinical trials have not been able to answer this question adequately, for the simple reason that results have typically been reported as average pain benefits over placebo. Based on a 100-mm visual analogue scale, drug treatments for chronic pain have recorded about 10-mm improvement over placebo. This has been used as an argument that drugs are not particularly effective [7], especially in comparison with physical interventions like transcutaneous electrical nerve stimulation, electroacupuncture, or laser therapy [8], despite the substantial discrepancy in quality and amount of evidence. While the report of an average change may be helpful if data have a normal (Gaussian) distribution, they will be irrelevant if the distribution is skewed or multimodal. Patients want to know whether they will obtain a benefit useful for them; that entails setting an agreed and valued minimum efficacy criterion. The standard of at least 50% pain intensity reduction is not only patient centred, but also defined by professionals as indicating "substantial" improvement [18]. Of course, a correlation between pain outcomes is to be expected, as between the magnitude of the difference between active and placebo in terms of average pain change, and in the percentage of patients meeting expectations (Fig. 3).

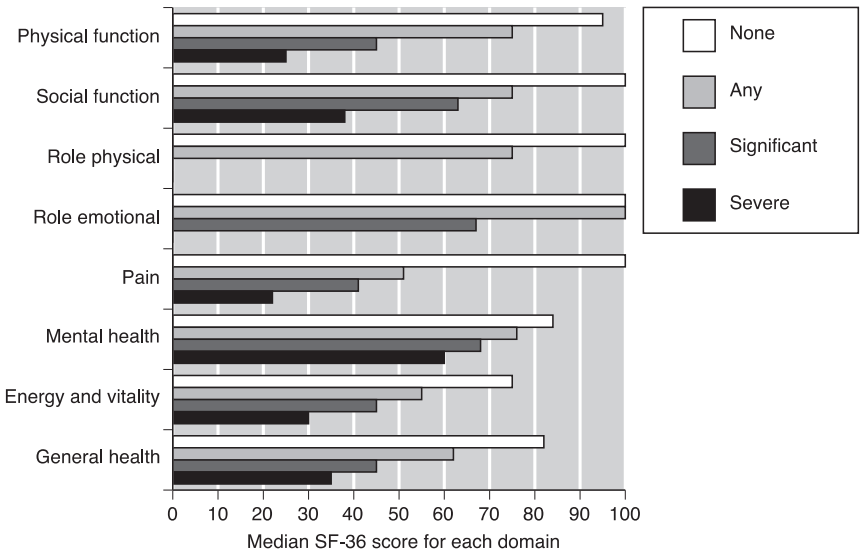

Fig. 1. Median Short Form-36 Health Survey (SF-36) score for each of the 8 domains, scored on a scale of 0–100, where higher scores represent better quality of life; results for no chronic pain, any chronic pain, significant chronic pain, and severe chronic pain (From [68]). Those with severe pain scored zero for role physical and role emotional.

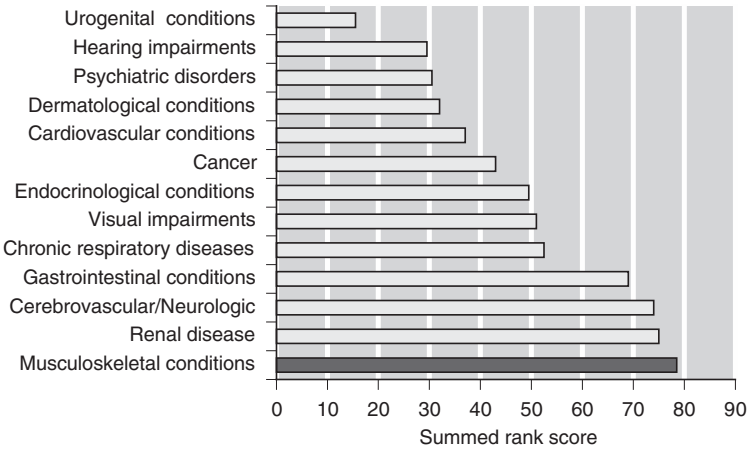

Fig. 2. Quality-of-life comparison for patients with chronic conditions living in the community, using Short Form-36 Health Survey (SF-36) or SF-24 quality of life scales (Data from [70]). A lower summed rank score is indicative of better functioning as assessed by SF-36 or SF-24.

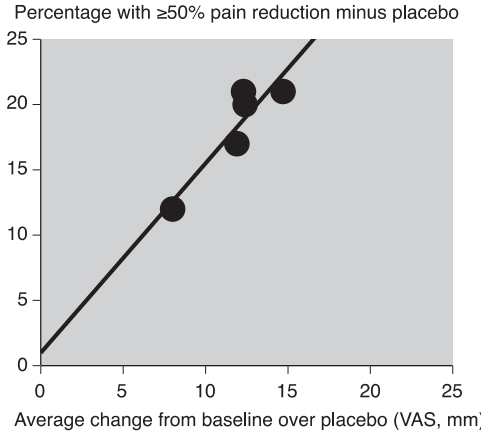

Fig. 3. Linear relationship ($r^2 = 0.84$) between treatment-specific (active minus placebo) average pain change from baseline and percentage of patients with at least 50% pain intensity reduction over baseline (Data from [51]; each symbol represents a different drug and/or dose).

4.1. Standards of evidence

Recent research has highlighted several important sources of potential bias in pain trials, all of which make interventions look more effective. Major biases include:

- Imputation method, or how to handle data when patients withdraw from a trial. Withdrawal rates in chronic pain studies can be as high as 60% for chronic low back pain [52], and are frequently around 30% in neuropathic pain or fibromyalgia [73]. The tendency has been to use last-observation-carried-forward when patients withdraw, as if pretending that they are in the trial and having pain relief even when they have discontinued the medicine and cannot therefore obtain pain relief from it. This has been shown to significantly overestimate treatment effects compared to a policy to regard all discontinuations as nonresponse, a sensible clinical practice perspective [53].
- Study duration in chronic pain can have dramatic effects on the apparent efficacy of treatments, even when discontinuation is regarded as nonresponse. For less effective therapy, especially short duration, particularly less than 6-8 weeks, can lead to overestimation of treatment effect [51,74].
- Study size can be a major issue. In chronic pain, studies with fewer than 100 patients per treatment arm show consistently larger treatment effects than those with 100 patients or more [57]. This is probably because size is a surrogate for other biases, but we have also known for some time that small size in individual studies or meta-analyses generates considerable uncertainty over the magnitude of the treatment effect [50].

So it is insufficient just to define a certain level of pain intensity reduction as an outcome for measurement. There has to be a sufficiency of data, long duration trials for chronic pain, and appropriate decisions on how to deal with dropouts. That is why the International Association for the Study of Pain Special Interest Group on systematic reviews, and the Cochrane Pain, Palliative, and Supportive Care Review Group have produced pain-specific guidelines for best practice in reporting trials and systematic reviews [49].

With these evidence standards, it is possible to evaluate the ability of drugs to meet patient expectations in acute pain, migraine, and chronic pain using data from meta-analyses, providing information that is unbiased, robust, and trustworthy. Results can be presented in a number of ways, including statistical outcomes like relative benefit, or number-needed-to-treat; for our purposes here we will use the percentage of patients achieving the expected level overall and after subtraction of placebo (drug-specific benefit). Selected results for acute pain and migraine are shown in Table 1, together with all the available data for chronic pain conditions. Selected examples of the bimodal (not normal) distribution that appears to be common in pain treatments are shown in Fig. 4.

4.2. Meeting expectations in acute pain

For single drug doses in acute postoperative pain, the outcome now commonly used to express benefit is that of at least 50% of the maximum possible pain relief over about 6 h. This has proven to be sensitive [54]. A Cochrane overview provides evidence on over 40 drug and dose combinations with trustworthy results, as well as highlighting many others with no data or where results are unreliable [48]. Standard doses of aspirin and paracetamol alone give good pain relief to fewer than 30% of patients, and the best performing are standard or high doses of nonsteroidal antiinflammatory drugs (NSAIDs), or combinations of paracetamol and opioids or NSAID (Table 1). But only 3 drugs or drug combinations provide relief in more than 50% after subtraction of the placebo response.

Those who do not achieve good levels of pain relief typically achieve little or no pain relief (Fig. 4).

Table 1
Results from acute and chronic pain using current best evidence, predominantly from Cochrane reviews, to examine the therapeutic gain (active–placebo) for oral drug therapies except tanezumab, which is given intravenously, using an outcome equivalent to patient expectation being met.

Drug & dose (mg)	Percent with outcome		Drug-specific improvement
	Active	Placebo	(Active–Placebo)
Acute pain – single dose postoperative [w1]:[a] Outcome – at least 50% maximum pain relief over 6 h			
Paracetamol 500 + Ibuprofen 200	74	10	64
Paracetamol 1000 + Oxycodone 10	68	13	55
Etoricoxib 120	64	11	53
Paracetamol 1000 + Codeine 60	53	7	46
Diclofenac 50	57	19	38
Ibuprofen 400	54	14	40
Naproxen 500/550	52	15	37
Paracetamol 1000	46	18	28
Aspirin 1000	43	16	27
Acute migraine headache – single dose [w2–w5]: Outcome – pain free at 2 h			
Zolmitriptan 10	38	9	29
Sumatriptan 100 mg	32	11	21
Rizatriptan 2.5	30	10	20
Ibuprofen 400 mg	26	12	14
Aspirin 1000	24	11	13
Paracetamol 1000	19	10	9
Ankylosing spondylitis – 6 weeks of treatment [w8]: Outcome: At least 50% reduction in BASDI			
Etoricoxib 120	50	14	36
Etoricoxib 90	46	14	32
Naproxen 1000	38	14	24
Osteoarthritis – 12 weeks of treatment [6,w6,w7]: Outcome – at least 50% pain intensity reduction			
Tanezumab 10	51	31	20
Etoricoxib 60	44	23	21
Celecoxib 200	39	22	17
Naproxen 1000	44	23	21
Ibuprofen 2400	39	27	12
Duloxetine 60/100	40	30	10
Chronic low back pain – 12 weeks of treatment [5,w6]: Outcome – at least 50% pain intensity reduction			
Etoricoxib 60	47	35	12
Etoricoxib 90	47	35	12
Duloxetine 60/100	39	30	9
Osteoarthritis and chronic low back pain [w13]: Outcome – at least 50% pain intensity reduction			
Tapentadol 200–500	30	24	6
Oxycodone 40–100	21	24	−3
Painful diabetic neuropathy – 12 weeks of treatment [w9–w11]: Outcome – at least 50% pain intensity reduction			
Duloxetine 60/100	48	26	22
Pregabalin 600[b]	46	30	16
Gabapentin ⩾1200[b]	40	23	17
Lacosamide 400[b]	35	25	10
Pregabalin 300[b]	38	29	9
Postherpetic neuralgia – 12 weeks of treatment [w9,w10]: Outcome – at least 50% pain intensity reduction			
Pregabalin 600[b]	39	14	25
Pregabalin 300[b]	30	11	19
Gabapentin ⩾1200[b]	33	20	13
Fibromyalgia – 12 weeks of treatment [6,w12]: Outcome – at least 50% pain intensity reduction			
Duloxetine 60/100	28	17	11
Pregabalin 600	23	15	8
Pregabalin 450	21	15	6
Pregabalin 300	19	15	4

BASDI = Bath Ankylosing Spondylitis Disease Activity Index.
[a] For references, see Appendix A.
[b] Indicates last-observation-carried-forward imputation method used, otherwise baseline observation carried forward with withdrawal defined as nonresponse.

4.3. Meeting expectations in migraine

For single drug doses in acute migraine, the outcome judged most relevant by the International Headache Society (and patients) is that of being pain free 2 h after treatment. Only a small proportion of patients achieve this outcome with any of the available interventions, at best about 30% after subtraction of the placebo response, but for most interventions the proportion is 20% or below (Table 1).

About the same proportion can achieve the lesser level of benefit of having no pain or only mild pain after 2 h, but even this lesser outcome is not achieved by about half of patients with a migraine headache.

4.4. Meeting expectations in musculoskeletal pain

Trustworthy information for some drugs (mostly for NSAIDs) in longer duration studies is available for ankylosing spondylitis, osteoarthritis, and chronic low back pain (Table 1). All show that no individual drug meets patient expectation in more than a small minority of patients more than does placebo – 20%–30% after 6 weeks in ankylosing spondylitis, 10%–20% after 12 weeks in

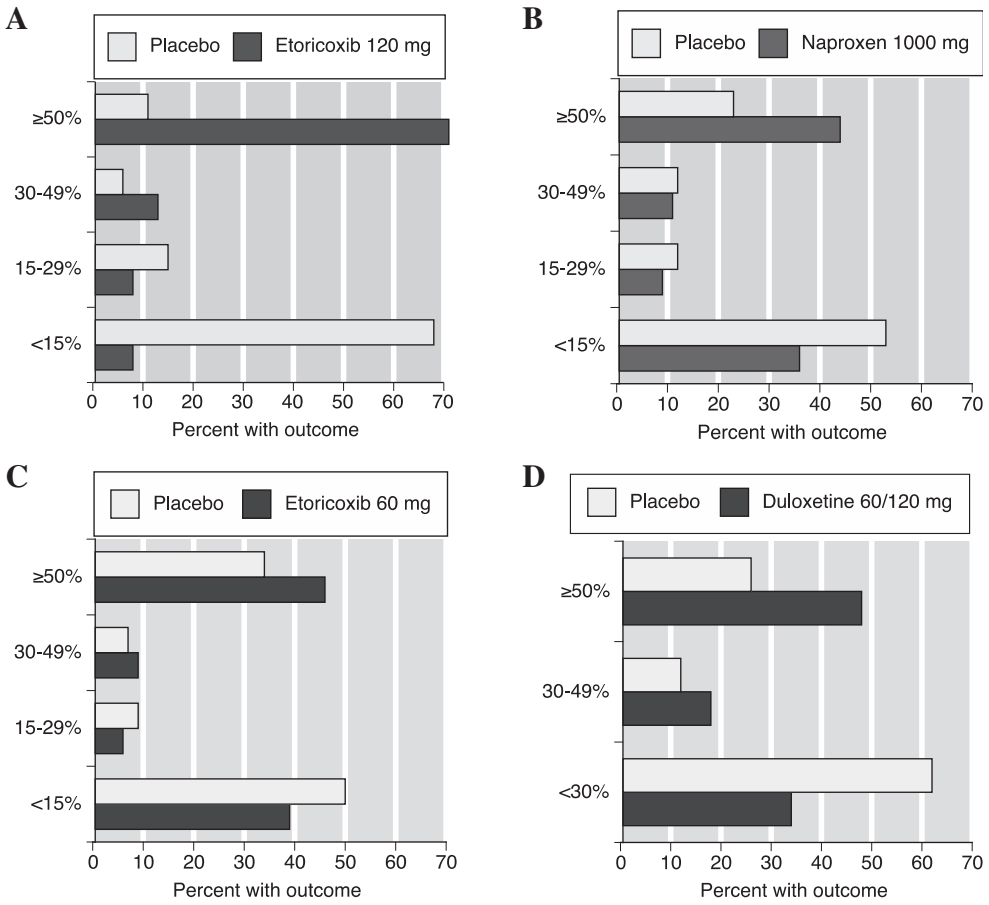

Fig. 4. Bimodal distribution of pain responses in acute postoperative pain and chronic pain (osteoarthritis, chronic low back pain, and painful diabetic neuropathy). (A) Acute postoperative pain. (B) Osteoarthritis. (C) Chronic low back pain. (D) Painful diabetic neuropathy.

osteoarthritis, and about 10% after 12 weeks in chronic low back pain.

Two further observations are important. The antidepressant duloxetine has an almost equivalent effect to that of NSAIDs in osteoarthritis and chronic low back pain (Table 1). But in the single example we have of traditional opioids, oxycodone meets patient expectations in no more patients than placebo in a mixed sample of osteoarthritis and back pain, while the newer opioid tapentadol meets expectations in 6% after subtraction of the placebo response. Other sources demonstrate that the evidence currently available on opioids shows that any effect observed is seen only because the 60% of patients who cannot use the drugs long term are used in the calculation [53].

Those who do not achieve good levels of pain relief typically achieve little or no pain relief, as for osteoarthritis and chronic low back pain (Fig. 4).

4.5. Meeting expectations in neuropathic pain and fibromyalgia

Trustworthy information for some drugs is available for some neuropathic pain conditions and for fibromyalgia, but for most neuropathic pain conditions the only information we have is potentially biased by the use of last-observation-carried-forward imputation (examples in Table 1). Despite this, no individual drug met patient expectation in more than a small minority of patients more than does placebo – after 12 weeks the proportion of patients whose expectations are met is on the order of 10%–20% more than with placebo in painful diabetic neuropathy, 13%–25% in postherpetic neuralgia, and 5%–10% for fibromyalgia. An example of 200 randomly selected patients from randomised trials of pregabalin in fibromyalgia who completed 12 weeks demonstrates the large disparity between individuals, and that some patients do very well both with placebo and pregabalin, but most do not (Fig. 5).

Those who do not achieve good levels of pain relief typically achieve little or no benefit, as for duloxetine in painful diabetic neuropathy (Fig. 4).

5. Benefits beyond pain

Recent studies have consistently demonstrated that patients who achieve good pain relief also obtain significant benefits in a range of other outcomes; a number of studies have been individual patient data analyses from randomised trials or meta-analyses involving over 6000 patients in migraine, fibromyalgia, neuropathic pain osteoarthritis, rheumatoid arthritis, chronic low back pain, and ankylosing spondylitis [1,4,5,14,17,29,38,55,66,75,78].

Benefits included increased activity of daily living, improved mood, less fatigue and better sleep, better functioning, greater ability to work, and an overall improvement in quality of life. Patients generally associate being very much improved on a patient global impression of change scale with having pain that is no worse than mild, and with having moderate or severe pain as not being improved (Fig. 6).

Fig. 7 shows the benefits for each of the Short Form-36 Health Survey quality-of-life domains for patients with and without expected benefits – at least 50% reduction in migraine frequency [14], or at least 50% pain intensity reduction in fibromyalgia [55]. The quality-of-life benefits are significant, with EQ-5D increases

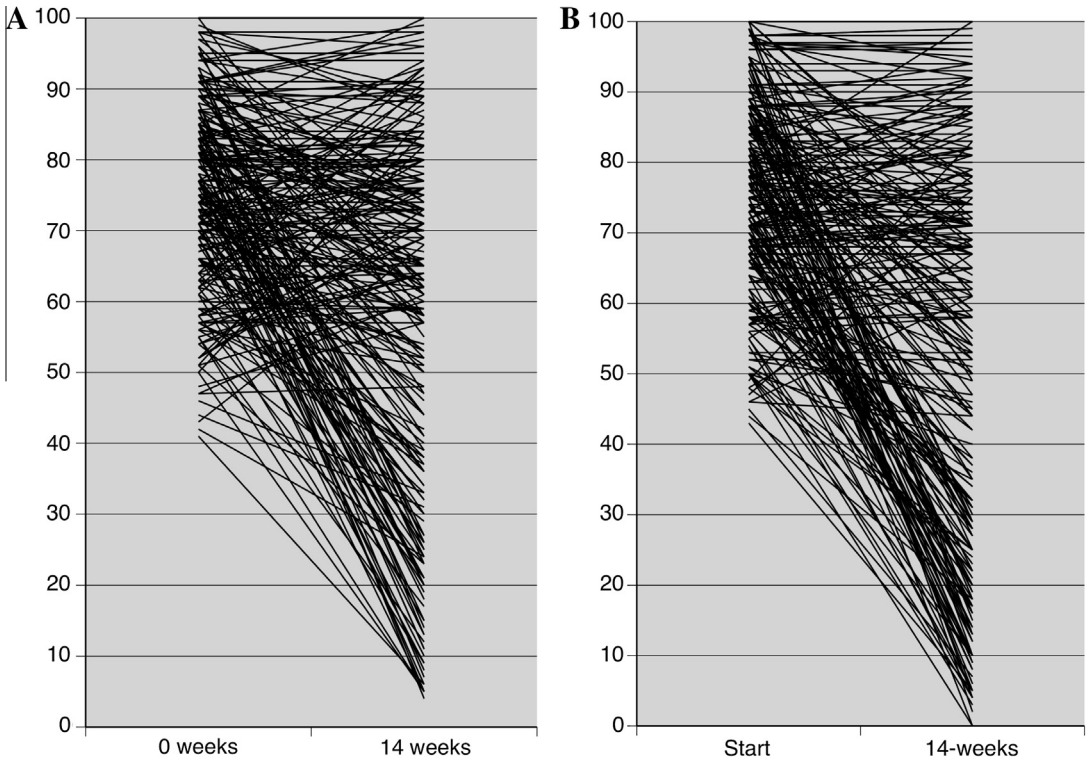

Fig. 5. Results from a random selection of patients with fibromyalgia treated with placebo (A) or 450 mg pregabalin (B) for 14 weeks and completing treatment, showing the individual visual analogue scale pain scores at the start and end of treatment.

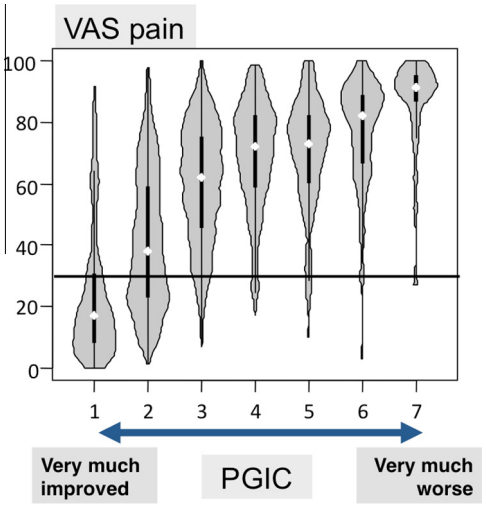

Fig. 6. Correlation between visual analogue scale (VAS) pain score at the end of 12–14 weeks of treatment with pregabalin or placebo in 1858 patients who completed the trials without withdrawal, and the patient global expression on change (PGIC) on a scale of 1 (very much improved) to 7 (very much worse). The width of the symbol represents the number of patients, the white circle the median, and the broad vertical line the interquartile range. The horizontal line at 30 mm represents a transition from mild to moderate pain.

over 1 year of 0.22 with successful tumour necrosis factor (TNF) antagonists in rheumatoid arthritis [24], 0.35 for ⩾50% pain intensity reduction in painful diabetic neuropathy [29], and a 1-year quality-adjusted life-year (QALY) gain of 0.11 for the same outcome in fibromyalgia [55]. In an analysis of tapentadol trials, patients who tolerated the treatment with tapentadol or oxycodone and completed the trial, and who were therefore likely to be those with good pain benefit, had EQ-5D average increments of 0.31 [30]. Good quality-of-life gains come with large percentage pain reductions, or from having a low pain state at the end of the trial, as with fibromyalgia (Fig. 8). These gains are larger than almost all those found over 6–12 months in quality-of-life survey of effective therapies across medicine, most of which were below 0.1 [62].

6. Impact on benefit vs harm calculations

What we have, then, is an expectation that there is a quite unequal distribution of benefit. For any single drug intervention (and probably most other types of intervention) we find that:

- Most patients will achieve levels of pain relief that are trivial, or obtain pain relief but be unable to continue with medication because of intolerable adverse events. They are likely to have no concomitant benefits in other areas and little or no increased quality of life.
- In a minority of patients, their expectations for pain relief are met. These patients have been defined as being able to continue with medication despite any common adverse events. They also obtain large benefit in a range of other areas, including sleep, mood, vitality, functioning, ability to work, and overall quality of life.

Since practically all interventions, drug or otherwise, come with some risk of a rare, serious, and probably irreversible adverse event, we can now put benefits and risks into perspective, with the important proviso that there is a stopping rule to prevent patients receiving ongoing treatment from a drug that does not benefit them. For the majority without a benefit, risk is irrelevant or minimal since they will have, or should, stop the intervention quickly. For a minority with a pain and other benefit that meets or surpasses expectations, overall risk is possibly less with treatment than without. The evidence is that almost all patients would run very high levels of risk of something extremely bad happening

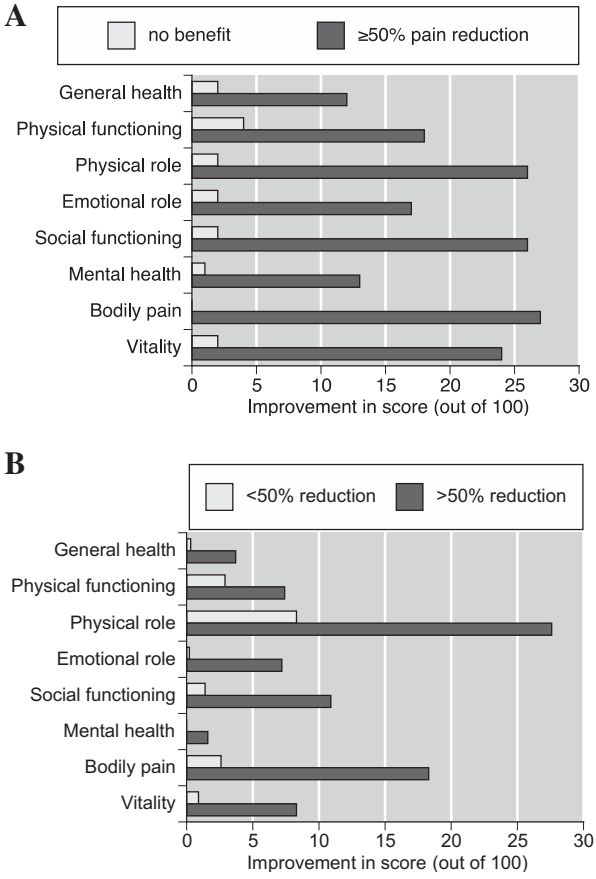

Fig. 7. Improvements in Short Form-36 Health Survey quality-of-life domain scores with effective treatment in (A) fibromyalgia and (B) reduction in migraine frequency (no benefit indicates <15% pain intensity reduction).

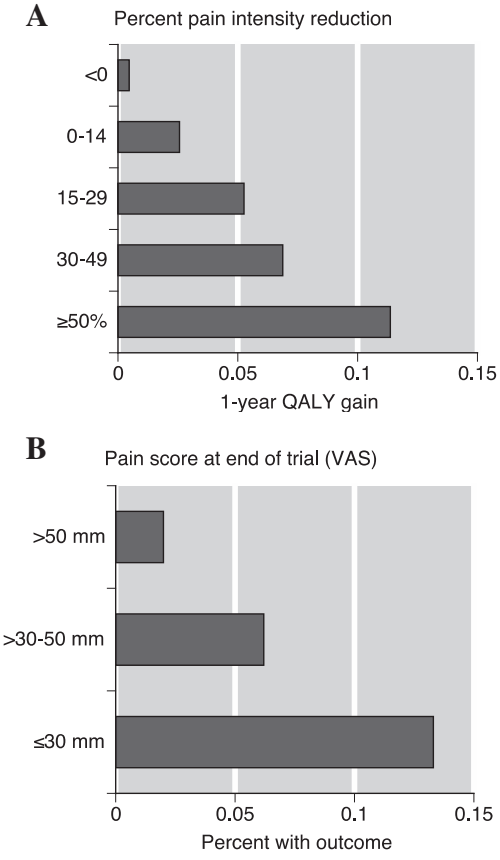

Fig. 8. Quality adjusted life-year gains over 1 year in fibromyalgia according to (A) pain intensity reduction or (B) end of trial pain score (Data from [55]).

(up to about 1 in 100 to 1 in 30) for high levels of benefit in chronic conditions [25,34,35], including chronic pain [63]. Rheumatoid arthritis may tell a different story, though this may be down to methodology [28].

This represents a considerable simplification, without the need of complex and irrelevant benefit-risk calculation based on average results from clinical trials, particularly because the average result will apply to almost no patients. There remains, though, a need to be aware of 2 potential pitfalls in the assessment of risk, numbers, and activity.

Rare but serious harm occurs infrequently in clinical trials, and even in large observational studies the number of events can be quite small, sometimes numbered in the tens, despite the number of patients from which those events derived being very much larger. Extrapolating from small numbers of events might be useful for summarizing available information and generating hypotheses for future research, but it does carry the danger that the result may be wrong, not only in magnitude, but also direction. There is a clear message from statistics that a minimum of 200 events is required to have a trustworthy result; as the number falls below 200, uncertainty about any result increases [19]. Much information about harm from analgesic interventions comes from studies or meta-analyses with fewer than 200 events. Early concerns about cardiovascular harm from NSAIDs based on relatively small numbers of events are being challenged by evidence of reduced all-cause and cardiovascular mortality with long-term use [21], including in studies with tens of thousands of events [43].

Being physically active is a major protective factor against heart disease, and can even be protective against the deleterious effects of obesity and smoking [33]. Severe pain [76] and walking disability [56,69] are associated with increased all-cause and cardiovascular mortality. It is tempting but premature to consider low activity levels as being causative, but low activity levels with chronic pain are likely to be implicated in the higher levels of serious harm that can occur in the chronic pain population. At least part of the improved all-cause mortality with successful treatment with TNF antagonists in rheumatoid arthritis [32], and with NSAIDs [3,21,43], may be due to increased activity with reduced pain. Yet activity levels are seldom considered as confounding factors in studies of harm, and this may have led to an overestimation of potential harm from pain therapies. The reality is that being in pain and inactive is probably more risky than having the pain adequately treated and being more active, though patients will have to make these decisions, with some help with understanding risk [46].

7. Broader implications

7.1. Qui bono?

Can we predict who will benefit from which treatment? At the present state of knowledge, the simple answer is that we cannot. We can say that there is enormous interindividual variation in the clinical pharmacology of analgesic drugs, for instance with NSAIDs [20], as well as many other complicating factors. We can also point to genetic predisposition to some rare but serious skin disorders that are more pronounced in some ethnic groups, as with carbamazepine in east and south Asians [11], which should preclude use in some populations. But there is no simple way of knowing who will benefit from which treatment, other than to try it.

7.2. Clinical practice

The implication of a minority of patients benefiting from any one treatment, combined with an inability to predict which patient will benefit from what treatment is that having a choice of therapies to switch between is likely to be highly desirable. Regular measurement is essential to prevent ongoing treatment in the face of inadequately treated pain. There is limited evidence that switching drugs can work. About half of osteoarthritis patients with moderate or severe pain on treatment had a significant 30% pain intensity reduction when switched to another NSAID [40]. A comparison of amitriptyline with nortriptyline in a cross-over study in postherpetic neuralgia found that 5 of 31 participants had mild or no pain with amitriptyline but moderate to severe pain with nortriptyline, while 4 had good pain relief with nortriptyline but none with amitriptyline [79]. These examples suggest that 30%–50% of patients who get inadequate pain relief with one drug will get good relief, even with drugs closely related to those that previously failed.

The good news is that when pain relief comes, it comes quickly: onset is quite rapid, about 8 days with pregabalin in postherpetic neuralgia [71], and typically within 2–4 weeks in musculoskeletal pain with NSAIDs [51] and with pregabalin in fibromyalgia [74]; though possibly longer for antidepressants. This implies that switching need not be an overly delayed process to find a drug that works for an individual.

7.3. Clinical trials

The goal is to obtain good pain relief for the largest percentage of people in the shortest time and at the lowest cost for any particular pain condition. We have no idea about what might be best, but we do have a design for clinical effectiveness trials that could begin to answer these crucial clinical practice questions [47]. Resources for their design and conduct will, however, be hard to come by.

Low responder rates make it difficult to obtain sensitivity in classic parallel-group placebo-controlled trials. This has the potential to limit the flow of new and innovative drugs for pain treatment. One answer is to use enriched enrolment, randomised withdrawal trial designs [36,42]. These maintain sensitivity in the face of low rates of responders with high levels of benefit, and provide a clinical practice perspective on their use, as well as being useful for proof-of-concept early in drug development [27].

7.4. Health economic evaluation

Health economic evaluations typically depend on average results, and look for average resource use for average quality-of-life gain. The cost for a year of quality of life (QALY) gained is very different for the majority of patients (perhaps 80% who get little or no pain relief or quality-of-life gain) than for the 20% who get useful pain relief and quality-of-life gain. Cost per QALY is determined by dividing a finite cost by a QALY that is always <1. In nonresponders, where the QALY is very small or nonexistent, the cost per QALY is extremely large, and can approach infinity. In responders where QALY gains can be around 0.1–0.3, the cost per QALY is modest because the cost of drug treatment is modest. When average results are used for the whole group, results from nonresponders swamp modest cost per QALY for responders. The only important metric is the cost per QALY for responders, as nonresponders either will stop treatment or should stop treatment within a very short time.

7.5. Regulatory, guidelines, and formularies

There are clear challenges for regulatory authorities, which can differ markedly in their attitudes to pain therapies. For example, European authorities, in contrast to the US Food and Drug Administration (FDA), have so far rejected all applications for treatments for fibromyalgia (pregabalin, duloxetine, milnacipran) because their average treatment effect is judged small. Again, in contrast to the FDA, they have rejected duloxetine for musculoskeletal conditions because of low benefits for perceived risks. This is despite voluminous evidence that there is unlikely to be any treatment that is much better, and that those patients who do benefit have such major benefits that it is life changing. Vigilant monitoring of patients to stop therapy when it is not effective should be essential.

There are also clear challenges to organisations that judge cost-effectiveness, like the National Institute for Health and Care Excellence in the UK. These are wedded to older data interpretations, with guidelines that often limit choice, and are often made in the absence of any detailed knowledge about evidence in pain. The result tends to be formularies that limit access to only a few drugs, and where choice is based on cost-effectiveness models that rely too heavily on drug acquisition cost [10,12].

All of this poses huge challenges for pharmaceutical and medical device companies and the development of new therapies. It is improbable that any of them has a clear strategy or even any strategy to deal with the various pressures coherently.

7.6. Evidence-based medicine

The trouble with evidence-based medicine is that most of it is wrong, because it has slavishly adhered to methods and attitudes more suited to epidemiology (small numbers of events in large numbers of patients) than therapy (ideally large effects in much smaller number of patients); it focuses on population averages and interventions rather than the experience of individuals with pain. Evidence-based medicine was never about a blind adoption of rigid rules, but about developing flexible tools, better to combine evidence relevant to clinical practice with individual clinical expertise and patient preferences [64]. Fears that purchasers and managers would hijack evidence-based medicine to try to cut the costs of health care may have come true, but that still doesn't make it right, morally or economically.

The aim was that doctors practising evidence-based medicine would identify and apply the most efficacious interventions to maximise the quality and quantity of life for individual patients. The implementation of evidence standards developed by the International Association for the Study of Pain Systematic Review Special Interest Group and the Cochrane Collaboration Pain, Palliative, and Supportive Care Collaborative Review Group will give them tools to do that effectively.

8. Challenge

The implications of a patient-centred and practice-orientated evidence-based view of pain treatment are wide and significant. This will be uncomfortable for many of us, at least for a while. The danger is that because this view is uncomfortable we won't look at it; yet what is needed is more people looking at more data to test it to its limits. Time will tell, but the prospect is that the imperatives of the individual will vanquish a tyranny of averages; one trusts that Sir John would be pleased.

Conflict of interest statement

R.A.M. has received research grants, consulting, or lecture fees from pharmaceutical companies, including AstraZeneca, GlaxoSmithKline, Grünenthal, Menarini, Merck, Pfizer, and Reckitt Benkiser, for work involving analgesic drugs, but received no remuneration for work on this manuscript. Any research work is

done on the basis that results have to be published, and therefore R.A.M. declares no conflict of interest.

Acknowledgements

Many people have contributed to ideas and work encompassed in this paper. They include, but not exhaustively, Henry McQuay, Eija Kalso, David Sackett, Martin Tramer, Dawn Carroll, David Gavaghan, Jayne Rees, Sheena Derry, Sebastian Straube, Ceri Phillips, Dominic Aldington, Peter Cole, Phil Wiffen, and Chris Eccleston. Little would have been accomplished but for companies willing to provide or collaborate on individual patient data analyses, including Eli Lilly, Flynn Pharma, Grünenthal, MSD, Pfizer, and Reckitt-Benckiser. The Oxford Pain Relief Trust has provided institutional support for this work over many years.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2013.03.024.

References

[1] Arnold LM, Wang F, Ahl J, Gaynor PJ, Wohlreich MM. Improvement in multiple dimensions of fatigue in patients with fibromyalgia treated with duloxetine: secondary analysis of a randomized, placebo-controlled trial. Arthritis Res Ther 2011;13:R86.
[2] Attal N, Lanteri-Minet M, Laurent B, Fermanian J, Bouhassira D. The specific disease burden of neuropathic pain: results of a French nationwide survey. PAIN® 2011;152:2836–43.
[3] Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. Ann Rheum Dis 2011;70:1921–5.
[4] Barthel HR, Peniston JH, Clark MB, Gold MS, Altman RD. Correlation of pain relief with physical function in hand osteoarthritis: randomized controlled trial post hoc analysis. Arthritis Res Ther 2010;12:R7.
[5] Bennett RM, Schein J, Kosinski MR, Hewitt DJ, Jordan DM, Rosenthal NR. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. Arthritis Rheum 2005;53:519–27.
[6] Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. J Pain 2004;5:143–9.
[7] Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomised placebo-controlled trials. Eur J Pain 2007;11:125–38.
[8] Bjordal JM, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. BMC Musculoskelet Disord 2007;8:51.
[9] Bouhassira D, Chassany O, Gaillat J, Hanslik T, Launay O, Mann C, Rabaud C, Rogeaux O, Strady C. Patient perspective on herpes zoster and its complications: an observational prospective study in patients aged over 50 years in general practice. PAIN® 2012;153:342–9.
[10] Chen LC, Ashcroft DM, Elliott RA. Do economic evaluations have a role in decision-making in Medicine Management Committees? A qualitative study. Pharm World Sci 2007;29:661–70.
[11] Chung WH, Hung SI, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin Drug Saf 2010;9:15–21.
[12] Cooke J, Walley T, Drumond MF. The use of health economics by hospital pharmacist decision makers – a survey of UK chief pharmacists. Pharm J 1997;259:779–81.
[13] Crichton B, Green M. GP and patient perspectives on treatment with non-steroidal anti-inflammatory drugs for the treatment of pain in osteoarthritis. Curr Med Res Opin 2002;18:92–6.
[14] Dahlöf C, Loder E, Diamond M, Rupnow M, Papadopoulos G, Mao L. The impact of migraine prevention on daily activities: a longitudinal and responder analysis from three topiramate placebo-controlled clinical trials. Health Qual Life Outcomes 2007;5:56.
[15] Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: a systematic review and meta-analysis of health utilities. PAIN® 2010;149:338–44.
[16] Dougados M. It's good to feel better but it's better to feel good. J Rheumatol 2005;32:1–2.
[17] Dworkin RH, Jensen MP, Gould E, Jones BA, Xiang Q, Galer BS, Gammaitoni AR. Treatment satisfaction in osteoarthritis and chronic low back pain: the role of pain, physical and emotional functioning, sleep, and adverse events. J Pain 2011;12:416–24.
[18] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.
[19] Flather MD, Farkouh ME, Pogue JM, Yusuf S. Strengths and limitations of meta-analysis: larger studies may be more reliable. Control Clin Trials 1997;18:568–79. discussion 661–6.
[20] Fries S, Grosser T, Price TS, Lawson JA, Kapoor S, DeMarco S, Pletcher MT, Wiltshire T, FitzGerald GA. Marked interindividual variability in the response to selective inhibitors of cyclooxygenase-2. Gastroenterology 2006;130:55–64.
[21] Goodson NJ, Brookhart AM, Symmons DP, Silman AJ, Solomon DH. Non-steroidal anti-inflammatory drug use does not appear to be associated with increased cardiovascular mortality in patients with inflammatory polyarthritis: results from a primary care based inception cohort of patients. Ann Rheum Dis 2009;68:367–72.
[22] Gormsen L, Rosenbergb R, Bach FW, Jensen TS. Depression, anxiety, health-related quality of life and pain in patients with chronic fibromyalgia and neuropathic pain. Eur J Pain 2010;14:127.e1–8.
[23] Grimley Evans J. Evidence-based or evidence-biased medicine? Age Ageing 1995;24:461–3.
[24] Gülfe A, Kristensen LE, Saxne T, Jacobsson LT, Petersson IF, Geborek P. Utility-based outcomes made easy: the number needed per quality-adjusted life year gained. An observational cohort study of tumor necrosis factor blockade in inflammatory arthritis from Southern Sweden. Arthritis Care Res (Hoboken) 2010;62:1399–406.
[25] Hauber AB, Johnson FR, Grotzinger KM, Ozdemir S. Patients' benefit-risk preferences for chronic idiopathic thrombocytopenic purpura therapies. Ann Pharmacother 2010;44:479–88.
[26] Heiberg T, Kvien TK. Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. Arthritis Rheum 2002;47:391–7.
[27] Hewitt DJ, Ho TW, Galer B, Backonja M, Markovitz P, Gammaitoni A, Michelson D, Bolognese J, Alon A, Rosenberg E, Herman G, Wang H. Impact of responder definition on the enriched enrollment randomized withdrawal trial design for establishing proof of concept in neuropathic pain. PAIN® 2011;152:514–21.
[28] Ho M, Lavery B, Pullar T. The risk of treatment. A study of rheumatoid arthritis patients' attitudes. Br J Rheumatol 1998;37:459–60.
[29] Hoffman DL, Sadosky A, Dukes EM, Alvir J. How do changes in pain severity levels correspond to changes in health status and function in patients with painful diabetic peripheral neuropathy? PAIN® 2010;149:194–201.
[30] Ikenberg R, Hertel N, Andrew Moore R, Obradovic M, Baxter G, Conway P, Liedgens H. Cost-effectiveness of tapentadol prolonged release compared with oxycodone controlled release in the UK in patients with severe non-malignant chronic pain who failed 1st line treatment with morphine. J Med Econ 2012;15:724–36.
[31] Ivanova JI, Birnbaum HG, Schiller M, Kantor E, Johnstone BM, Swindle RW. Real-world practice patterns, health-care utilization, and costs in patients with low back pain: the long road to guideline-concordant care. Spine J 2011;11:622–32.
[32] Jacobsson LT, Turesson C, Nilsson JA, Petersson IF, Lindqvist E, Saxne T, Geborek P. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:670–5.
[33] Johansson SE, Sundquist J. Change in lifestyle factors and their influence on health status and all-cause mortality. Int J Epidemiol 1999;28:1073–80.
[34] Johnson FR, Hauber AB, Ozdemir S, Lynd L. Quantifying women's stated benefit-risk trade-off preferences for IBS treatment outcomes. Value Health 2010;13:418–23.
[35] Johnson FR, Van Houtven G, Ozdemir S, Hass S, White J, Francis G, Miller DW, Phillips JT. Multiple sclerosis patients' benefit-risk preferences: serious adverse event risks versus treatment efficacy. J Neurol 2009;256:554–62.
[36] Katz N. Enriched enrollment randomized withdrawal trial designs of analgesics: focus on methodology. Clin J Pain 2009;25:797–807.
[37] Kerr S, Fairbrother G, Crawford M, Hogg M, Fairbrother D, Khor KE. Patient characteristics and quality of life among a sample of Australian chronic pain clinic attendees. Intern Med J 2004;34:403–9.
[38] Kosinski M, Janagap C, Gajria K, Schein J, Freedman J. Pain relief and pain-related sleep disturbance with extended-release tramadol in patients with osteoarthritis. Curr Med Res Opin 2007;23:1615–26.
[39] Langley P, Müller-Schwefe G, Nicolaou A, Liedgens H, Pergolizzi J, Varrassi G. The societal impact of pain in the European Union: health-related quality of life and healthcare resource utilization. J Med Econ 2010;13:571–81.
[40] Lin HY, Cheng TT, Wang JH, Lee CS, Chen MH, Lei V, Lac C, Gammaitoni AR, Smugar SS, Chen WJ. Etoricoxib improves pain, function and quality of life: results of a real-world effectiveness trial. Int J Rheum Dis 2010;13:144–50.
[41] Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? Headache 1999;39:S20–6.
[42] McQuay HJ, Derry S, Moore RA, Poulain P, Legout V. Enriched enrolment with randomised withdrawal (EERW): time for a new look at clinical trial design in chronic pain. PAIN® 2008;135:217–20.
[43] Mangoni AA, Woodman RJ, Gaganis P, Gilbert AL, Knights KM. Use of non-steroidal anti-inflammatory drugs and risk of incident myocardial infarction and heart failure, and all-cause mortality in the Australian veteran community. Br J Clin Pharmacol 2010;69:689–700.

[44] Mehra M, Hill K, Nicholl D, Schadrack J. The burden of chronic low back pain with and without a neuropathic component: a healthcare resource use and cost analysis. J Med Econ 2012;15:245–52.
[45] Menken M, Munsat TL, Toole JF. The global burden of disease study: implications for neurology. Arch Neurol 2000;57:418–20.
[46] Moore RA, Derry S, McQuay HJ, Paling J. What do we know about communicating risk? A brief review and suggestion for contextualising serious, but rare, risk, and the example of cox-2 selective and non-selective NSAIDs. Arthritis Res Ther 2008;10:R20.
[47] Moore RA, Derry S, McQuay HJ, Straube S, Aldington D, Wiffen P, Bell RF, Kalso E. Rowbotham MC; ACTINPAIN writing group of the IASP Special Interest Group (SIG) on Systematic Reviews in Pain Relief. Clinical effectiveness: an approach to clinical trial design more relevant to clinical practice, acknowledging the importance of individual differences. PAIN® 2010;149:173–6.
[48] Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. Cochrane Database Syst Rev 2011:CD008659.
[49] Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, McQuay H, ACTINPAIN Writing Group of the IASP Special Interest Group on Systematic Reviews in Pain ReliefCochrane Pain, Palliative and Supportive Care Systematic Review Group Editors. "Evidence" in chronic pain – establishing best practice in the reporting of systematic reviews. PAIN® 2010;150:386–9.
[50] Moore RA, Gavaghan D, Tramèr MR, Collins SL, McQuay HJ. Size is everything – large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. PAIN® 1998;78:209–16.
[51] Moore RA, Moore OA, Derry S, Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. Ann Rheum Dis 2010;69:374–9.
[52] Moore RA, Straube S, Derry S, McQuay HJ. Chronic low back pain analgesic studies – a methodological minefield. PAIN® 2010;149:431–4.
[53] Moore RA, Straube S, Eccleston C, Derry S, Aldington D, Wiffen P, Bell RF, Hamunen K, Phillips C, McQuay H. 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.
[54] Moore RA, Straube S, Paine J, Derry S, McQuay HJ. Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. PAIN® 2011;152:982–9.
[55] Moore RA, Straube S, Paine J, Phillips CJ, Derry S, McQuay HJ. Fibromyalgia: moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. PAIN® 2010;149:360–4.
[56] Nüesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Jüni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ 2011;342:d1165.
[57] Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, Egger M, Jüni P. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. BMJ 2010;341:c3515.
[58] O'Brien EM, Staud RM, Hassinger AD, McCulloch RC, Craggs JG, Atchison JW, Price DD, Robinson ME. Patient-centered perspective on treatment outcomes in chronic pain. Pain Med 2010;11:6–15.
[59] Patel AS, Baker-Searle RD, Farquharson R, Carroll D, Moore A, Phillips CJ, Taylor RS, Barden J. The impact and burden of chronic pain (CP) in the workplace: a qualitative systematic review. Pain Pract 2012;12:578–89.
[60] Penny KI, Purves AM, Smith BH, Chambers WA, Smith WC. Relationship between the chronic pain grade and measures of physical, social and psychological well-being. PAIN® 1999;79:275–9.
[61] Raftery MN, Ryan P, Normand C, Murphy AW, de la Harpe D, McGuire BE. The economic cost of chronic noncancer pain in Ireland: results from the PRIME study, Part 2. J Pain 2012;13:139–45.
[62] Räsänen P, Roine E, Sintonen H, Semberg-Konttinen V, Ryynänen OP, Roine R. Use of quality-adjusted life years for the estimation of effectiveness of health care: a systematic literature review. Int J Technol Assess Health Care 2006;22:235–41.
[63] Richardson CG, Chalmers A, Llewellyn-Thomas HA, Klinkhoff A, Carswell A, Kopec JA. Pain relief in osteoarthritis: patients' willingness to risk medication-induced gastrointestinal, cardiovascular, and cerebrovascular complications. J Rheumatol 2007;34:1569–75.
[64] Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71–2.
[65] Schaefer C, Chandran A, Hufstader M, Baik R, McNett M, Goldenberg D, Gerwin R, Zlateva G. The comparative burden of mild, moderate and severe fibromyalgia: results from a cross-sectional survey in the United States. Health Qual Life Outcomes 2011;9:71.
[66] Schein JR, Kosinski MR, Janagap-Benson C, Gajria K, Lin P, Freedman JD. Functionality and health-status benefits associated with reduction of osteoarthritis pain. Curr Med Res Opin 2008;24:1255–65.
[67] Seers K, Friedli K. The patients' experiences of their chronic non-malignant pain. J Adv Nurs 1996;24:1160–8.
[68] Smith BH, Elliott AM, Chambers AC, Smith WC, Hannaford PC, Penny K. The impact of chronic pain in the community. Fam Pract 2001;18:292–9.
[69] Sokka T, Pincus T. Poor physical function, pain and limited exercise: risk factors for premature mortality in the range of smoking or hypertension, identified on a simple patient self-report questionnaire for usual care. BMJ Open 2011;1:e000070.
[70] Sprangers MA, de Regt EB, Andries F, van Agt HM, Bijl RV, de Boer JB, Foets M, Hoeymans N, Jacobs AE, Kempen GI, Miedema HS, Tijhuis MA, de Haes HC. Which chronic conditions are associated with better or poorer quality of life? J Clin Epidemiol 2000;53:895–907.
[71] Stacey BR, Barrett JA, Whalen E, Phillips KF, Rowbotham MC. Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. J Pain 2008;9:1006–17.
[72] Stafford MR, Hareendran A, Ng-Mak DS, Insinga RP, Xu R, Stull DE. EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of migraineurs. Health Qual Life Outcomes 2012;10:65.
[73] Straube S, Derry S, Moore RA, McQuay HJ. Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports. Rheumatology (Oxford) 2010;49:706–15.
[74] Straube S, Derry S, Moore RA, Paine J, McQuay HJ. Pregabalin in fibromyalgia – responder analysis from individual patient data. BMC Musculoskelet Disord 2010;11:150.
[75] Straube S, Moore RA, Paine J, Derry S, Phillips CJ, Hallier E, McQuay HJ. Interference with work in fibromyalgia: effect of treatment with pregabalin and relation to pain response. BMC Musculoskelet Disord 2011;12:125.
[76] Torrance N, Elliott AM, Lee AJ, Smith BH. Severe chronic pain is associated with increased 10 year mortality. A cohort record linkage study. Eur J Pain 2010;14:380–6.
[77] Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, Bombardier C, Felson D, Hochberg M, van der Heijde D, Dougados M. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005;64:34–7.
[78] van Seventer R, Serpell M, Bach FW, Morlion B, Zlateva G, Bushmakin AG, Cappelleri JC, Nimour M. Relationships between changes in pain severity and other patient-reported outcomes: an analysis in patients with posttraumatic peripheral neuropathic pain. Health Qual Life Outcomes 2011;9:17.
[79] Watson CP, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. Neurology 1998;51:1166–71.
[80] Wenig CM, Schmidt CO, Kohlmann T, Schweikert B. Costs of back pain in Germany. Eur J Pain 2009;13:280–6.