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ANALYSIS

Expect analgesic failure; pursue analgesic success

Most analgesic drugs work well but in only a small percentage of people. **Andrew Moore and colleagues** argue that we need to move away from a focus on average response and seek out what works for each patient

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A 2003 newspaper article caused considerable grief for the pharmaceutical industry. Entitled, "Our drugs do not work on most patients,"[1] it claimed that most drugs worked in only 30-50% of people. While that surprised journalists and the public, it was not news to professionals, including the then editor of the *BMJ*.[2]

Individual patient responses vary greatly, as a clinical trial of pregabalin in fibromyalgia shows (fig 1⇓). Pain relief is not normally distributed but usually bimodal, being either very good (above 50%) or poor (below 15%).[3-5] Using averages is unhelpful and misleading, because "average" pain relief is actually experienced by few (if any) patients, and it tells us nothing about how many patients will experience clinically useful pain relief. Research is therefore moving to responder analyses—reporting the proportion of patients achieving outcomes that patients consider worthwhile.

In this article we examine rates of success and failure of drugs used in treating pain. We suggest a radical rethink of achievable analgesic effects, and explore how anticipating and recognising analgesic failure will help improve the management of pain. This approach is relevant to all painful conditions, but here we use examples from acute postoperative pain, headache, and chronic musculoskeletal and neuropathic pain.

Measuring effectiveness

Patients want large reductions in pain intensity (typically at least 50%, ideally no worse than mild pain[6]), with relief from associated problems such as sleep disturbance and depression but without common adverse events interfering with treatment. Those who get better (responders) do well: recent individual patient analyses for chronic pain interventions have shown that people who respond experience improvements in fatigue, depression, and sleep interference,[7-9] and general measures of function and quality of life,[8 9] including ability to work.[10]

Non-responders have none of these benefits. This message is easy to communicate.

An important feature of responder analysis, reflecting clinical practice, is that everyone who withdraws from a trial for any reason is unequivocally a non-responder: if you don't take the tablet you don't get pain relief. This eliminates the need to assign efficacy results to people no longer in trials and eliminates the considerable bias inherent in the statistical practice of imputing missing data.[11] Imputation methods may be justified in establishing whether interventions have analgesic effects but not when determining clinical effectiveness.

We propose that the scientific assessment of analgesia and the clinical practice of analgesic delivery could be simplified into three guiding principles: measure pain in individual patients, expect analgesic drugs to fail to provide a good response in most patients, and prepare for the next step when failure occurs.

Defining and calculating failure for pain drugs

The table⇓ shows drug specific success and failure rates for postoperative pain, migraine, and chronic musculoskeletal and neuropathic conditions. Data came predominantly from Cochrane reviews or overviews, or individual patient data meta-analyses using sensitive trials in patients with initial pain of moderate or severe intensity. The reviews were done to the highest current standards,[12] avoiding known risks of bias, and with sufficient data to minimise random chance effects.[13] All reviews used a responder definition of at least 50% pain relief or its equivalent. When possible we did not use trials that had imputed data by carrying the last observation forward, but for painful diabetic neuropathy and postherpetic neuralgia, these were the only data available for most drugs.

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The size of response rates with placebo depends on the outcome (lower placebo rates with tougher outcomes), duration (in chronic pain trials), and pain condition studied. We therefore calculated the maximum possible success as 100%−placebo response and drug specific success as active response−placebo response. The success rate was calculated as a percentage of maximum possible response.

Confronting failure

Drug specific success rates were above 50% for only four drugs in acute postoperative pain (paracetamol 500 mg+ibuprofen 200 mg; paracetamol 1000 mg+oxycodone 10 mg; etoricoxib 120 mg; ibuprofen 400 mg+codeine 26-60 mg) and one in migraine (zolmitriptan 10 mg). For all other drugs and in all other conditions, fewer than half of patients achieved at least a 50% reduction in pain intensity. In acute postoperative pain, the failure rate was 66% with paracetamol 1000 mg and 53% for both ibuprofen 400 mg and diclofenac 50 mg. In migraine, failure rates were 55-71% for most interventions. Failure rates for non-steroidal anti-inflammatory drugs were 58-72% in ankylosing spondylitis, ≥70% in osteoarthritis, and ≥80% in chronic low back pain. For neuropathic conditions, antidepressants and antiepileptics had failure rates of ≥70% in painful diabetic neuropathy and postherpetic neuralgia, and ≥87% in fibromyalgia. Data for opioids in chronic non-cancer pain were available only for tapentadol and oxycodone in a combined analysis of osteoarthritis and chronic low back pain trials; tapentadol had a failure rate of 90% and oxycodone had a failure rate of 100%, consistent with what is seen with other analyses for conventional strong opioids.[11]

Reflecting on failure

The magnitude of the failure to achieve good pain relief, especially over the longer term in chronic pain, is sobering. The high failure rates are a consequence of using patient centred definitions of benefit combining high level of pain relief with tolerable adverse events, using higher standards of evidence, and avoiding major imputation bias. These higher standards are backed by considerable evidence supporting their validity.

Use of responder analysis changes judgments of benefit and risk. With failure, patients without benefit should be exposed to no risk because the drug is stopped; only effective drugs should continue to be prescribed. With success, considerable benefits in terms of pain relief, sleep, fatigue, depression, function, and quality of life are balanced against rare risk of serious harm. Average benefits have no part in these discussions. The good news is that success is often achieved within the first two weeks or so of treatment or not at all,[14 15] and when achieved, tends to last.

Classic clinical trials, providing almost all our evidence in chronic pain, may underestimate efficacy. Fixed dose regimens may exacerbate adverse events and withdrawals, resulting in higher failure rates. An alternative approach is to allow patient directed titration to achieve adequate pain relief with tolerable adverse events; only those with treatment success are then randomised blindly between continuing therapy and placebo. Such trials, known as enriched enrolment randomised withdrawal trials, have lower failure rates. In fibromyalgia, titrating pregabalin to an effective dose resulted in good drug specific pain relief lasting six months in 15% of the original population of patients; the overall failure rate was only 85% compared with over 90% in classic trials.[16]

Drug therapy is rarely the only treatment used in chronic pain, but clinical trials designed for regulatory purposes force us into considering single interventions. Randomised withdrawal trials may reflect the real world more accurately and be a better test, but with only a single example this is speculation.

Pragmatic approach

The principles of treatment should be to measure pain, expect and recognise analgesic failure, and to react to it, pursuing analgesic success rather than blindly accepting failure. In any condition, the order in which analgesics should be tried is predicated on efficacy and safety, and adjusted for individual patient characteristics.

A pragmatic implication of high failure rates is that populations with pain need access to a broad range of drugs to have a better chance of success (box). The problem is the dearth of data to help devise starting, stopping, and switching rules. Currently, we have no good evidence from clinical trials that switching is successful in pain; we have a single study of limited methodological quality[17] and a suggestion of differences between closely related tricyclics.[18] Switching drugs works in other conditions, like depression, where randomised trials show that while drugs used individually benefited fewer than half of patients, the majority benefited when failure was followed by another drug.[19 20]

Guideline developers often restrict treatment options to one or two drugs (such as, the NICE neuropathic pain guideline[21]). They consider similar drugs to operate as a class, and so select one as the first or only option despite possibly important differences in pharmacokinetics or drug interactions. Less restrictive guidance, centred on patient-clinician interaction and a large dose of clinical wisdom as well as evidence, may do better; the NICE osteoarthritis guidance comes close.[22]

Regulatory authorities also need to recognise that failure is the norm. European regulators, unlike their US counterparts, have refused to license any drug in fibromyalgia because of inadequate average effect size, ignoring the fact that these drugs work well (≥50% reduction in pain intensity) in around 10% of patients with this difficult to treat condition. New drugs are unlikely to be much better. A change in regulatory attitude is overdue, would be sensible, and will benefit patients.

Clinical trial design

Chronic pain conditions are complex and associated with considerable comorbidity. Coupled with the intricacies of pain modulation, central nervous system changes, and genetic influences, high failure rates with single interventions are unsurprising. The new game in town is specificity of effect for specific targets, but with only a small percentage of patients benefiting. Randomised withdrawal designs seem promising,[23] but there are few good examples, and they are not always accepted or understood. New designs are also important for non-drug interventions that produce substantial benefits in few patients, including complementary therapies.

We need to determine how best to use the interventions we have to provide better care for more people at lower cost. Clinical effectiveness trials could be one way forward.[24] They should inform stopping and switching rules to underpin best practice; outlines of informative pragmatic designs are available, building on examples from other chronic diseases.[24]

Practical implications of high failure rates

- No single drug will treat successfully more than a minority of patients with a painful condition
- Successful pain relief is also likely to improve sleep, depression, fatigue, quality of life, function, and ability to work
- Experience (and some evidence) suggests that failure with one drug does not necessarily mean failure with others, even within a class
- We do not know the best order in which to use drugs, in terms of efficacy, harm, or cost
- Success or failure can be determined within 2-4 weeks, and success, when achieved, tends to be long lasting
- Because success rates are low, a wide range of drugs is needed to do the best for most patients, especially in complex chronic conditions

Conclusion

Embracing high failure rates is the first step to doing better with what we have. Pronouncing about the importance of failure is rare in science. We believe that pain medicine has now reached a degree of maturity where it can confront its failings. We propose a radical transformation in how we establish analgesic efficacy and harm. Clinically this means expecting analgesic failure, assessing pain, and understanding options for stopping and switching. For the drug industry, regulators, and researchers this means casting aside our slavish reliance on the average, and asking what works for whom in what circumstance, recognising that population improvements in overall effect will require access to numerous treatment options to achieve pain relief for the individual.

Contributors and sources: RAM is chairman of a special interest group on systematic reviews for the International Association of the Study of Pain and a Cochrane editor; SD is a Cochrane editor; CE is coordinating editor of the Pain, Palliative, and Supportive Care Cochrane Review Group; EK is professor of pain medicine at the University of Helsinki. RAM is the guarantor. All data used are from Cochrane or non-Cochrane reviews meeting the same rigorous standards, and where in a few cases evidence is not sufficiently rigorous this is highlighted.

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Table

Table 1| Success and failure of drug treatment for acute and chronic painful conditions

Drug and dose (mg)	% with outcome		Maximum possible success (100–placebo)	Success (active–placebo)	Failure (maximum–active)	Treatment specific effects (% of maximum)	
	Active	Placebo				Success	Failure
Acute pain (single dose postoperative)[w1]; outcome: ≥50% maximum pain relief over 6 hours							
Paracetamol 500+ibuprofen 200	74	10	90	64	26	71	29
Paracetamol 1000+oxycodone 10	68	13	87	55	32	63	37
Etoricoxib 120	64	11	89	53	36	60	40
Ibuprofen 400+codeine 25.6-60	64	18	82	46	36	56	44
Paracetamol 1000+codeine 60	53	7	93	46	47	49	51
Diclofenac 50	57	19	81	38	43	47	53
Ibuprofen 400	54	14	86	40	46	47	53
Naproxen 500/550	52	15	85	37	48	44	56
Paracetamol 1000	46	18	82	28	54	34	66
Aspirin 1000	43	16	84	27	57	32	68
Acute migraine headache (single dose)[w2-w5]; outcome: no worse than mild pain at 2 hours							
Zolmitriptan 10	68	34	66	34	32	52	48
Rizatriptan 2.5	61	29	71	32	39	45	55
Ibuprofen 400	57	25	75	32	43	43	57
Sumatriptan 100	61	32	68	29	39	43	57
Paracetamol 1000	56	36	64	20	44	31	69
Aspirin 1000	52	32	68	20	48	29	71
Osteoarthritis (12 weeks' treatment)[6 w6-w8]; outcome: ≥50% pain intensity reduction							
Tanezumab 10	51	31	69	20	49	29	71
Etoricoxib 60	44	23	77	21	56	27	73
Naproxen 1000	44	23	77	21	56	27	73
Celecoxib 200	39	22	78	17	61	22	78
Topical diclofenac 1.5%	60	50	50	10	40	20	80
Ibuprofen 2400	39	27	73	12	61	16	84
Duloxetine 60/100	40	30	70	10	60	14	86
Ankylosing spondylitis (6 weeks' treatment)[w9]; ≥50% reduction in BASDI							
Etoricoxib 120	50	14	86	36	50	42	58
Etoricoxib 90	46	14	86	32	54	37	63
Naproxen 1000	38	14	86	24	62	28	72
Chronic low back pain (12 weeks' treatment)[5 w6]; outcome ≥50% pain intensity reduction							
Etoricoxib 60	47	35	65	12	53	18	82
Etoricoxib 90	47	35	65	12	53	18	82
Duloxetine 60/100	39	30	70	9	61	13	87
Painful diabetic neuropathy (12 weeks' treatment)[w10-w12]; outcome ≥50% pain intensity reduction							
Duloxetine 60/100	48	26	74	22	52	30	70
Pregabalin 600*	46	30	70	16	54	23	77
Gabapentin ≥1200*	40	23	77	17	60	22	78
Lacosamide 400*	35	25	75	10	65	13	87
Pregabalin 300*	38	29	71	9	62	13	87
Postherpetic neuralgia (12 weeks' treatment) [w10 w11 w13]; outcome ≥50% pain intensity reduction or PGIC							
Pregabalin 600*	39	14	86	25	61	29	71
Topical capsaicin 8%	39	25	75	14	61	19	81
Pregabalin 300*	30	11	89	19	70	21	79

(continued)

Drug and dose (mg)	% with outcome		Maximum possible success (100–placebo)	Success (active–placebo)	Failure (maximum–active)	Treatment specific effects (% of maximum)	
	Active	Placebo				Success	Failure
Gabapentin ≥1200*	33	20	80	13	67	16	84
Fibromyalgia (12 weeks' treatment[6 w14]; outcome ≥50% pain intensity reduction							
Duloxetine 60/100	28	17	83	11	72	13	87
Pregabalin 600	23	15	85	8	77	9	91
Pregabalin 450	21	15	85	6	79	7	93
Pregabalin 300	19	15	85	4	81	5	95
Osteoarthritis and chronic low back pain[w15]; outcome ≥50% pain intensity reduction							
Tapentadol 200-500	30.1	23.5	76.5	6.6	69.9	9	91
Oxycodone 40-100	20.8	23.5	76.5	-2.7	79.2	0	100

BASDI=Bath Ankylosing Spondylitis Disease Activity Index; PGIC=patient global impression of change.

*Used imputation by last observation carried forward.

Figure

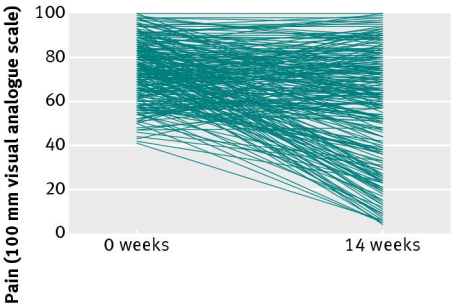

Fig 1 Individual changes in pain over 14 weeks of treatment with pregabalin 450 mg in 200 patients with fibromyalgia