

Numbers needed to heal, numbers needed to harm, numbers needed to kill: reflections on opioid therapy and the primary duty of medicine

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I sometimes think that, having been called to practice the healing arts, and in particular the noble art of medicine, I feel like part of a wandering tribe in the desert.

Nothing ever seems to stay the same. While the human body and mind is probably more or less now what it was a few thousand years ago (perhaps a bit fatter from too much cereal consumption and soda pop and resulting in a little more type 2 diabetes and cardiovascular disease – but that is another story), everything else to do with caring for the human condition changes at a frightening pace.

Models of disease process and inferred practice that were considered acceptable and routine a generation or two ago are now considered to be grossly misleading and dangerous. I could mention blood-letting to quench fevers, but a more telling story is the account of how it took many years for the medical profession to accept that the main cause of upper gastrointestinal ulceration was not too much acid but instead a bacterial infection. Between 1984 and 1989, two Australian scientists Warren and Marshall published five papers in highly reputed journals that conclusively showed that it was in fact a

bacterium *Helicobacter pylori* rather than stomach acid that was the cause of gastrointestinal ulceration. Despite this, the medical profession continued for many years to prescribe ineffective antacid drugs and drastic surgery.¹ At one point in 1988, frustrated at the deaf ears and unmoved hearts and minds, Marshall infected himself with the *H. pylori* bacterium and of course promptly developed gastritis. It took approximately another five to 10 years before the medical profession finally came round to believing that the best way to treat stomach ulcers was to provide an antibiotic cocktail. Finally in 2005, Warren and Marshall were awarded the Noble Prize for medicine.

Why did it take so long for people to change in the face of new evidence?

In one commentary on this subject, it is stated that people regarded as experts become used to doing something one way for decades; they do not like to admit that another way involving a paradigm shift might be better. The commentators decided to call the systemic reticence to accepting the obvious change the Warren and Marshall

syndrome.² From my point of view it seems not quite the appropriate catchphrase as Warren and Marshall were the ones who pushed the change rather than inhibited it.

I am also reminded that in 1900, Lord Kelvin – an undergraduate at Peterhouse, Cambridge – was infamously attributed as saying: *'There is nothing new to be discovered.... now; All that remains is more and more precise measurement.'*³ This was quoted just, of course, before Einstein published his theories of relativity in 1905 and 1916.⁴

But the concern is that we who regard ourselves as experts, naturally think we know most of what is important to know about a subject; we examine every new idea with a critical mind and hopefully with understanding to realise if something truly new has been discovered. We need to be able to distinguish the useless snake oil from the highly effective tincture of opium that may relieve the suffering of all mankind. However, it does mean on the flip side that we as experts are less likely to accept a novel but possibly true idea if it does not fit the paradigms we have grown up with. The concept that getting rid of a fever by blood-letting, or that



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Figure 1

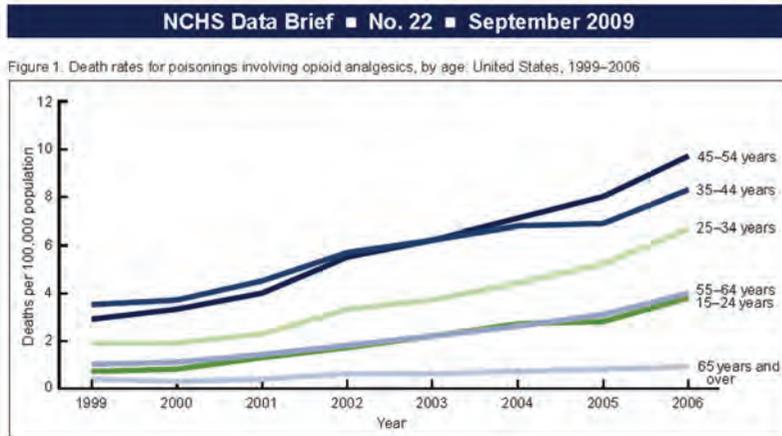
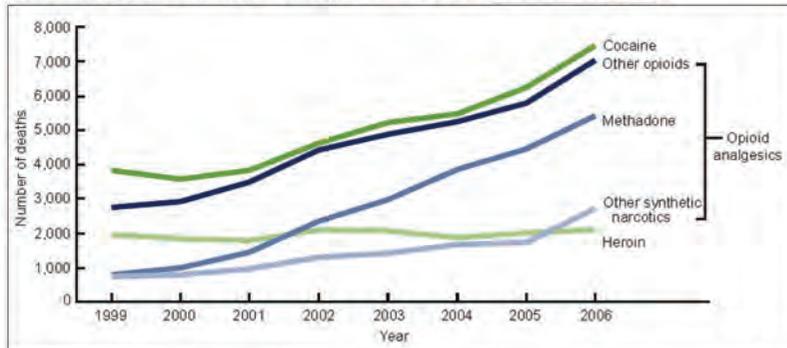


Figure 2

From 1999 through 2006, poisoning deaths involving methadone rose more rapidly than those involving other opioid analgesics, cocaine, or heroin.

Figure 2. Poisoning deaths involving opioid analgesics, cocaine, and heroin: United States, 1999–2006



NOTES: Drug categories are not mutually exclusive. Deaths involving more than one drug category shown in this figure are counted multiple times. Access data table for Figure 2 at http://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/Data_Briefs/db022/fig02.xls.

bacteria rather than stomach acid causes ulceration, can be particularly difficult to shift if the implicit message when we were taught implied that we were being told the absolute and incontrovertible truth.

It has come as quite a shock to many of us in pain medicine that a drug that we had all considered to be relatively safe, now has been shown to be a major cause of morbidity and mortality both for

the individual and society in general. Around 2004, we were just recovering from the COX-2 inhibitor story,^{5,6} thinking that initially these new type of drugs were going to mean that we could provide anti-inflammatory medication and analgesia to our patients without the nasty side effects of stomach erosion, kidney failure and so on, only to find that they dramatically increase the chances of heart attacks and strokes to the point

where the guidance from the medical authorities is now to virtually avoid using any COX-2 inhibitor and indeed to prescribe any nonsteroidal anti-inflammatory drug (NSAID) now in the smallest dose for the shortest period as they all share similar properties. Many of us switched to prescribing the seemingly safer opioids in view of the increasing dangers shown to be associated with anti-inflammatory medication.

However, there was another story that was unfolding, namely that there had also been a fairly aggressive increase in the use of opioids, particularly in the USA with a tenfold rise in opioid consumption in the last 20 years since 1992 and in particular, of the drug Oxycontin, which was aggressively marketed as the extended version of oxycodone on release in 1995. Between 1997 and 2002, the amount of oxycodone use quadrupled.⁷ But even at this time, clouds were looming over the 'safe opioid story', data were already emerging suggesting that the prescription of opioids was anything but benign. The National Centre for Health Statistics published a paper in 2009 reporting an increase in fatal poisonings in the USA between 1999 and 2006.⁸

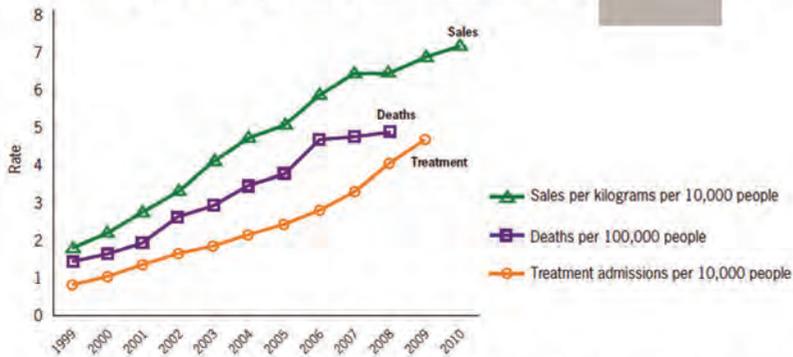
What was worrying was that the increasing death rate was particularly among younger people (see Figure 1). Overall the death rate tripled, particularly among young white males, and this particular study specifically highlighted methadone but also other opioids as a particular drug associated with these deaths.

It was known that states like, for example, Florida had very high death rates that were associated with inappropriate prescribing – three times the rate of prescription of opioids compared to Illinois. As one commentator put it, there was no evidence that the people in Florida suffered more chronic pain than the rest of the USA. Another comment was that enough prescription painkillers were

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Figure 3

Figure 3. Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)



SOURCES: National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009

diverted to people using them without prescriptions. More than three out of four people who misuse prescription painkillers used drugs prescribed to someone else.

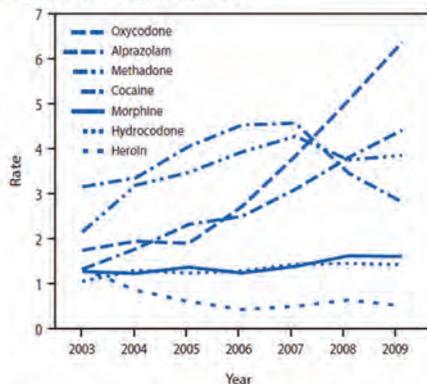
The Centre for Disease Control published a paper in July 2011¹⁰ stating that during 2003–09, death rates increased for all substances except cocaine and heroin. The death rate for prescription drugs increased by 84.2%, from 7.3 to 13.4 per 100,000 population. The greatest increase was observed in the death rate from oxycodone (264.6%), followed by alprazolam (233.8%) and methadone (79.2%). By 2009, the number of deaths involving prescription drugs was four times the number involving illicit drugs.

A further example came from West Virginia when it was noted that there was a 550% increase in unintentional overdose opioid-related mortality between 1999 and 2004. While it seemed initially that the majority of the problem was due to diversion of opioid prescription to mainly young white males – two-thirds in fact, and this was often accompanied by doctor shopping¹¹ until a prescription was obtained – it also became clear that *about one-third of the mortality was actually in those patients who were prescribed the opioid in the first place*. Thus, this phenomenon of a massive rise in the marketing, sales and prescriptions of opioids was not just a problem of diversion that could be seen as a simple (mainly US) sociological problem, but also was the cause of unintended mortality among patients who were being prescribed opioids.

In a Canadian study, where opioids are prescribed on state funding without the financial incentives present in the USA, between 1997 and 2006, patients who were prescribed more than 200 mg of morphine a day were three times more likely to die as a consequence of the prescription.¹² Bonerht found the overall death rate to be in the order of 0.04%

Figure 4

FIGURE 4. Annual drug overdose death rates* for selected prescription and illicit drugs — Florida, 2003-2009



* Per 100,000 population. Based on U.S. Census resident population estimates. Available at <http://www.census.gov/popest/states/states.html>.

prescribed in 2010 to medicate every American adult around the clock for a month. In fact, in the same year, 2 million people reported using prescription painkillers non-medically for the first time – nearly 5,500 a day. Although most of these pills were prescribed for a medical purpose, many unfortunately ended up in the hands of people who misused or abused them. It was noted that most prescription painkillers were prescribed

by primary care and internal medicine doctors and dentists, not specialists. Roughly 20% of prescribers prescribe 80% of all prescription painkillers.⁹

The report also noted:

[A]lmost all prescription drugs involved in overdoses come from prescriptions originally. However, once they are prescribed and dispensed, prescription drugs were frequently

among those given an opioid prescription in a study funded by the Veterans Administration.¹³ The risk was in fact substantially higher with higher doses of morphine above 100 mg, being almost 10 times higher than if one was prescribed up to 20 mg per day; the risk was also substantially increased in those with a history of substance abuse and those on combined regular and *pro re nata* (PRN) prescription. Even accepting the lower overall risk of 0.04%, this worked out at one death in 2,500 patients.

The sharp eyed among you will notice that the figures above do not give any indication over what time frame the risk was present and in fact the authors worked out that the approximate average death rate per 1,000 chronic patient months was approximately one. That is, one patient would die every month for every 1,000 patients taking an opioid prescription. By any accounts this is an extraordinarily high death rate, even higher when one takes into account doses above 100 mg of morphine equivalent, substance abuse and the type of prescription.

This made me think about whether it was worth it. One could argue that if one person died but 999 every month 'thanked God for their doctor and their prescription' for the relief of their suffering, one could argue that providing a quality of life to 999 out of every 1,000 patients per month is not really that bad so long as everyone were aware of the risk. After all, lots of treatments in medicine are risky. The chances of dying on the road every year for each one of those is approximately 1 in 17,000; the chances of an over 75-year-old on an anti-inflammatory developing gastrointestinal haemorrhage is 1% per year according to Bandolier.¹⁴

However, what is the evidence that a prescription of opioids is effective for our patients in the first place? One of the studies above suggested that 3% of the American population was taking regular

opioid prescriptions. Presumably this is for severe pain... or is it? Is a complaint of pain a justifiable enough reason to give an opiate prescription? Would we have been negligent if we did not treat the pain and suffering of a fellow human being? It has been argued by Margaret Somerville, professor of law and medicine at McGill University, that the unreasonable failure to provide adequate pain relief constitutes negligence.¹⁵ Should we take patients at face value? If we did, we might be in trouble. In the Grampian Region of Scotland, one study put the incidence of self-reported pain as over 50%.¹⁶ On the face of it, other studies also support the very high incidence of self-reported musculoskeletal pain in the community, with a study from Europe giving rates of up to 50% or so for various pains, particularly with rising age.¹⁷ However, a further analysis in the same paper shows that while the incidence of general complaints of pain may be up to 40%–50% depending on age group studied, the prevalence of clinically significant pain is much lower at about between 3% and 15%.

More importantly, it is crucial to recognise that the perceived pain may be a symptom of another underlying diagnosis, or may certainly be exacerbated by it, in particular depression.¹⁸ Indeed, some authorities believe that many cases of fibromyalgia are generally a manifestation of depression.¹⁹ Failure to recognise that many factors may contribute to the final common presentation of pain is a profound mistake. The commonest error is to prescribe strong opioids in the presence of severe depression, distress and complaints of pain, often on an unrecognised background of past history of significant psychological problems including drug abuse²⁰ and alcohol problems in the vain hope that they will help generally. As one author put it: 'Opioids are being used to treat this undifferentiated state of mental and physical pain.'²¹

The presence of depression or anxiety has to be recognised in such patients and treated independently by pharmacological, psychological or other techniques.²² The largest studies of opioid treatment of chronic pain suggest that particularly in this distressed group of patients, improvements in either pain scores or quality of life are *not* achieved.²³ Becker et al. (in Denmark, with the world's highest rates of opioid prescription and consumption) suggest that those who go on to opioid therapy already had significant comorbidity and were already consuming *five* times the health care resources *prior* to the initiation of opioid therapy, and indeed already are more likely to have had pre-existing drug and alcohol problems.²⁴ Although interestingly, Eriksen and his co-authors reported that addiction rates in their study patients (again in Denmark) were comparable to the general population.²⁵

Yet it is clear that subgroups of (correctly chosen) patients can do well with opioids on a number of measures, including addiction rates of less than 1%^{26–30} and doctors with a little training can instinctively predict who are likely to do well.³¹ On balance, carefully chosen opioid prescriptions in carefully chosen patients are unlikely to cause long-term morbidity and mortality.³² However, we need to recognise that currently the patients who end up on opioids may have severe pre-existing risk factors such as anxiety, depression and addiction problems,³³ and quite simply, these patients need to be recognised and treatments planned more carefully for them.³⁴ These points have been highlighted by the British Pain Society in its opioid prescribing and other guidelines³⁵ and by Joan Hester in the *British Medical Journal*.³⁶

It is also becoming increasingly clear that not all opioids are the same: diversion of opioids from their intended recipients is less likely to take place with sustained release-patch formulation, particularly the newer opioid patch

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medications such as Butrans and Transtec (Buprenorphine patch) or Fentanyl patch (Durogesic patch); problematic addiction problems and dose escalation is less likely particularly with buprenorphine, which incidentally, is used to treat opioid addiction in some countries.³⁷⁻³⁹ However, it is clear that further research is required.⁴⁰

What are the alternatives to prescriptions of analgesics? Talking therapies? Pain management programmes? They are certainly unlikely to harm our patients, but are time intensive and expensive. One study looking at the efficacy of practice-based cognitive behavioural therapy found significant gains in only one out of four to seven patients.⁴¹ A recent view in the *Lancet* by Turk et al.⁴² makes very sobering reading as it states: *'psychological treatment as a whole results in modest benefits in improvement of pain and physical and emotional functioning. ...evidence for the long-term effects is inadequate, and evidence is somewhat contradictory for effects on vocationally relevant outcomes.'* In fact the article is not particularly positive about any pain

treatment including any pharmacological or interventional therapies, stating that very roughly: 'the best evidence for pain reduction averages roughly 30% in about half of treated patients, and these pain reductions do not always occur with concurrent improvement in function.'

Against this modest benefit of active pain therapy, the authors suggest that placebo-based responses range between 10% and 20%. The authors go on to state that this is hardly surprising in view of the complexity of chronic pain; in the absence of a cure we need to maximise pain relief so that patients are able to lead the highest quality of life possible. They also mention managing patient expectation, but even more importantly they go on to state that because of the complexity of pain, the individual tailoring of a treatment to an individual is paramount and this is where future research should lie. We all have patients who have responded dramatically to one particular type of treatment or another. The real issue is how not to do anybody else any harm in the process of selecting the one who benefits. In the absence of a large group affect for any type of pain treatment, individual selection of patients is paramount.

Primum non nocere

First, do no harm, and second, show a degree of humility not only as to the cause of what is troubling our patients, but how much we think we know about the treatment we are providing and how much good it will do. It is not that we get things wrong that is the problem, particularly when everybody else has made the same mistake, but it is a failure not to listen when evidence is there in front of us that we may have got things wrong and we continue to insist on keeping deaf ears, hard hearts and closed minds. If the wandering tribe of Israel had been a little more open perhaps they would not have had to wander around the desert for 40 years.

Conflict of interest

Part of this article was submitted electronically as a letter to the *British Medical Journal*. All mistakes, opinions expressed and misleading statements are entirely the responsibility of the author.

References are not included but can be obtained from the author by email.