As a medical student (long before evidence based medicine) I was led to believe that in this situation there was very little risk of addiction. But my faith in this comforting idea was shaken by my experience of being involved with the management of a mountaineer who had severe frostbite of the hands and feet in Nepal 40 years ago. When in hospital in Kathmandu the severe pain in his feet could only be controlled by opioids (pethidine). In discussions about the continued use of this drug I took a relaxed attitude because of the teaching I had received. The man later had to have both legs amputated below the knee. During this time he became thoroughly addicted to pethidine. The management of drug addiction was less developed in those days and he decided to come off "cold turkey." His experience in achieving this is graphically described in his book, No Place for Man. 1

From what we know of the effect of opioids in downregulating the opioid receptors it is hardly surprising that continued use of high doses of opioids even in opioid sensitive pain relief is likely to lead to addiction. The outcome, however, may well depend on the dose and route of administration. I agree with McQuay that we urgently need more hard data.

James S Milleedge  
Northwich Park Hospital, Harrow HA1 3UJ

1 McQuay H. Opioids in chronic non-malignant pain. BMJ 2001;322:1134-5. (12 May.)

Chronic pain should not be undertreated

Enrör—I am a patients’ advocate and literature researcher, not a physician. In internet community service work I have corresponded with hundreds of patients with chronic face pain. Many of these have diagnosed facial neuralgias or neuropathies. Many report that one or more doctors have refused to treat them with opioids, even on a trial basis. Some report having been accused of drug seeking behaviour simply for committing the offence of requesting treatment with drugs that they know from experience are effective for them. In the health insurance system in the United States the consequences of such a comment in a patient’s medical record can be horrendous.

I recognise that treatment with opioids is generally less effective for the categories of pain that I see than for the general population. But from long exposure to online discussions between patients themselves, I know that some people do get relief from individual opioids or "cocktails" tailored by a pain specialist. I am forced by this experience to condemn outright the refusal of many medical professionals to even try such measures, in the absence of other effective medical or surgical remedies. I heartily endorse research to assess factors related to patients and efficacy of drugs, as suggested by McQuay. 1

It is long past time to put to rest the myth that prescribed pain drugs create addiction problems on the street. This issue should be readily susceptible to simple retrospective studies. How many convicted drug offenders in the United States or United Kingdom have been prescribed opioids by a doctor? Surely these numbers are known or can readily be derived? Drug offenders tend to come from population cohorts that are among the least served by medical caregivers. In the United States, the evidence is strong that medical practice for pain management is about to undergo a popular revolution. What a shame that the process had to be forced by patients’ lawsuits, rather than proceeding from simple common sense and compassion on the part of professional caregivers. If you are one of those doctors who continue to withhold pain management measures from your patients, then I suggest that you need refresher training in current practice for pain management.

Richard A Lawhern  
Trigeminal Neuralgia Association (US), Sterling, VA 20165, USA  
lawhern@erols.com

Don’t forget methadone for chronic pain

Enrör—McQuay in his editorial says that the use of opioids for chronic non-malignant pain can be messy “but this need not be so.” The risks and benefits of opioids are well attested. The study of fentanyl patches versus long acting morphine is an imperfect comparison of one expensive opioid delivery system with another. 2 McQuay chose manufacturers’ recommendations over numerous clinical alternatives. Medical trials are often represented as a race with a clear winner. In this case, the winner happens to be the product of the company sponsoring the trial. McQuay’s question on treating pain responsive to opioids presumes that a patient has already tried opioids. We could instead ask whether doctors should deny opioids to a patient who seems to benefit from them? Withdrawing such drugs may be unwisely or even unethical.

Differences between various opioids are to be expected because their effects are individual and doses never exactly comparable. Since this trial was not blind, the claim of modest advantages for fentanyl is not scientifically robust, as McQuay points out. Some reported improvements may also stem from the novelty factor, with a patch delivery system. Transdermal patches have certain benefits, but they also have problems. Dose adjustments are not easy, disposal can be hazardous, and adhesion can be a problem, especially in countries where people usually bathe daily. The choice of drug for chronic pain should not ignore the safety profiles of traditional opioids such as oral methadone, morphine, or codeine. From its use in addiction, methadone has exemplary long term safety data. It is also taken once daily. Although it is a cheap drug and perhaps of less interest to drug companies, methadone can be highly effective for chronic pain.

Clinicians should always consider the safest and most effective drug initially, moving to other options if problems arise. Cost is also a factor, especially in conditions requiring long term pharmacotherapy. Any stigma from methadone or morphine quickly vanishes when these drugs are used appropriately. Fentanyl patches should probably not be used as first line treatment. Likewise, long acting morphine, which is expensive and generally administered twice daily, should probably be second line treatment to methadone. If methadone is found to be unsatisfactory, buprenorphine, oxycodeone, morphine (long or short acting), and fentanyl are all viable alternatives. Despite the best science, the use of such opioids is still often based on trial and error.

Andrew Byrne  
general practitioner  
Drug and Alcohol, Redfern, New South Wales, 2016, Australia

All makes a proportion of his income from treating addiction and pain management patients. No tobacco sponsorship. No cruel animal experiments in this practice.

1 McQuay H. Opioids in chronic non-malignant pain. BMJ 2001;322:1134-5. (12 May.)


Early growth and coronary heart disease in later life

Analysis was flawed

Enrör—Eriksson et al concluded that in Finnish men born 60 years ago “low weight gain during infancy is associated with increased risk of coronary heart disease,” yet they did not analyse infant weight gain. All their references to infant growth relate to size at 1 year (table 3). Had they applied the key regression models that we have described2 to separate the effects of weight at different ages on later outcome, they would have found that infant weight gain was unrelated to risk of coronary heart disease.

Finnish men born 60 years ago “low weight gain during infancy is associated with increased risk of coronary heart disease,” yet they did not analyse infant weight gain. All their references to infant growth relate to size at 1 year (table 3). Had they applied the key regression models that we have described2 to separate the effects of weight at different ages on later outcome, they would have found that infant weight gain was unrelated to risk of coronary heart disease.

The hazard ratios for birth weight and weight at 1 year were similar and less than 1, showing that greater weight during infancy is protective. Weight gain is at 1 year less weight at birth, so if weight gain were protective it would appear as a protective effect of weight at 1 year and a relatively deleterious effect of weight at birth.3 But the two effects were equally protective, so weight gain in infancy (strictly, upwards centile crossing) is unrelated to later coronary heart disease.

The hazard ratios for weight at birth and at 1 year can be rearranged as hazard ratios for mean weight and weight gain. The hazard ratio for weight gain is equal approximately to the square root of the ratio of the ratios of the hazard ratios at 1 year and at birth—that is, $\sqrt{0.84/0.94} = 0.95$. This is similar to the birth-weight hazard ratio, which was not significant (95% confidence interval 0.83 to 1.06).

During childhood, increasing fitness was related to increased risk of coronary heart disease, particularly in those who were initially thin.4 This corresponds to our interaction model.5 The hazard ratio for the change in body mass index from age 1 to age 12 is obtainable from our combined
model. The hazard ratios for body mass index at ages 1 and 12 are 0.83 and 1.03 (table 4). On the assumption that they would be similar if fitted simultaneously, the square root of the ratio of hazard ratios gives the approximate hazard ratio for the change in body mass index, √1.03/0.83 = 1.11—not that different from 1.20.

So we agree that infant thinness and subsequent increasing fatness are synergistic risk factors for coronary heart disease, as others have shown.1 But for centile crossing to relate to coronary heart disease the hazard ratios for body size at the start and end of the period should differ significantly, and this is not the case in infancy. Routine use of our approach2 would have avoided this confusion.

J T Cole professor of medical statistics
Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London WC1N 1EH
tim.cole@ich.ucl.ac.uk

M Fewtrell MRC senior clinical scientist
A Lucas MRC clinical research professor
MRC Childhood Nutrition Research Centre, Institute of Child Health

References

Riluzole for motor neurone disease
Reply from chairman of appraisal committee at NICE

Editor—In commenting on the National Institute for Clinical Excellence’s guidance on riluzole Sandercoc et al show the difference between assessment and appraisal of evidence.1 One form of evidence used in an appraisal is a formal systematic review. The assessment report does not make recommendations on how the technology should be used in the NHS; that is the job of the institute’s appraisal committee. The committee also receives submissions from patient and professional organisations, which provide perspectives not captured by a formal review of published evidence.

The committee takes account of the clinical need of patients and the broad balance of benefits and costs of the technology. Its conclusions are subject to consultation and can be appealed against. This is all some distance on from the original assessment of the evidence.

Sandercoc et al suggest that a superficial reading of the guidance may not give an adequate understanding of the evidence base for riluzole. The institute’s guidance identifies what the committee considered to be important elements of the evidence. The full assessment report is made available on the institute’s website (www.nice.org.uk). Neither document, however, can fully convey the depth of the committee’s consideration of the evidence.

Sandercoc et al advise clinicians to prescribe in accordance with riluzole’s licence, say that patients offered the drug should be fully informed, and suggest further research. This is fully in accordance with the institute’s guidance.

In the same cluster of letters Wheatley and Gray accuse the institute of recommending a treatment “when there is no significant evidence of benefit.” Although the statistical measures of benefit may not be great (we acknowledge that the relative hazard reduction for tracheostomy free survival is 12% (that is, 1.00-0.88), not 17% as quoted in the guidance), the committee is required to consider what the reported measures of clinical effectiveness of the technology actually mean to people with the disease.

Wheatley and Gray say that the guidance is contrary to the conclusions of the Sandercoc et al report. We do not look to the authors of assessment reports for conclusions as, unlike the appraisal committee, they have neither access to the full evidence base nor the range of skills necessary to undertake an appraisal.

The institute’s guidance need not deter further research into this disease or its treatment. The guidance sets out a clear research agenda, which we would encourage the manufacturer and clinicians to pursue.

David Barnett chairman of appraisal committee National Institute for Clinical Excellence, London WC2N 5HR
david@nice.nice.org.uk

Any placebo controlled trial of riluzole would surely be unethical now

Editor—We are concerned about the opinions expressed by Sandercoc et al regarding the clinical efficacy of riluzole for the amyotrophic lateral sclerosis form of motor neurone disease and the appropriateness of the guidance issued by the National Institute for Clinical Excellence (NICE).2 Riluzole has been subject to regulatory scrutiny by the European Agency for the Evaluation of Medicinal Products and the Food and Drug Administration; an independent review by the Cochrane Collaboration3; and the review by the National Institute for Clinical Excellence. The health technology assessment report by Sandercoc et al formed only part of the evidence based assessment by the institute; evidence from a wide range of expert clinical, research, and patient based sources was also made available.

Of particular importance are the results of two large prospective, randomised, double blind placebo controlled trials of riluzole in amyotrophic lateral sclerosis.4 The study by Bensimon et al (n = 155) was stopped at 18 months because of a clear difference in favour of the active treatment arm.5 As a result, patients taking placebo were offered active treatment, which meant that the authors were unable to determine overall survival in comparison with survival with placebo. However, analysis of the study to 18 months showed that patients taking riluzole had a 28% better survival rate than those taking placebo (P = 0.014).

1 Correspondence. Riluzole for motor neurone disease. BMJ 2001;322:1305-6. (20 May.)