

The seven-year rule for safer prescribing

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Worst Pills, Best Pills News
Washington DC, USA

Key words

adverse effects, drug
safety, fluoroquinolones,
sibutramine

Aust Prescr 2012;35:138-9

Public Citizen is a national research-based advocacy organisation in the USA. In 1999 our Health Research Group decided to advise against the use of any new prescription drug, except for truly 'breakthrough' drugs, for five years after approval by the Food and Drug Administration (FDA). Our decision was based on the impression that it was during this first post-approval period that a large proportion of drugs either required a new 'black box' warning or were actually withdrawn from the market for safety reasons.¹ This empirical observation was buttressed by the knowledge that the approval process for drugs is heavily tilted toward establishing evidence of benefit, but statistically underpowered to detect all but the most commonly occurring harms. Once the drug is approved, considerably larger numbers of people, including groups which were under-represented in the trials, become exposed to the drug. New adverse reactions and interactions with other drugs are then reported. As the information about harm begins to catch up with the information about benefits, a regulatory decision is frequently needed to either add a new black box warning or to withdraw the drug. The validity of this five-year rule, however, was challenged by the findings of a study published in 2002, based on the ultimate fate of the 548 new drugs approved in the USA between 1975 and 1999.²

The study examined how many of the new drugs were eventually the subject of a new black box warning or market withdrawal and when these actions occurred relative to the dates of approval. Our study found that by 25 years after approval, the estimated probability of either acquiring a new black box warning or market withdrawal was 20%. We also found that half

of these changes occurred within seven years of the drug's introduction. Of the 16 drug safety withdrawals studied, 94% had occurred within seven years.²

Our initial assumption, that five years was a safe enough time to wait after the approval of a non-breakthrough drug before considering its use, turned out to be inadequately conservative. We thus started using a seven-year rule (see Box). Our reasoning was that since one-half of all new safety actions, including almost all safety withdrawals, have occurred within seven years, these drugs should be in a DO NOT USE for seven years category. This change was reflected in the most recent edition of the book *Worst Pills, Best Pills*³ and in articles in our monthly publication *Worst Pills, Best Pills News*.

The Health Research Group's seven-year rule³

You should wait at least seven years from the date of release to take any new drug unless it is one of those rare 'breakthrough' drugs that offers you a documented therapeutic advantage over older proven drugs. New drugs are tested in a relatively small number of people before being released, and serious adverse effects or life-threatening drug interactions may not be detected until the new drug has been taken by hundreds of thousands of people. A number of new drugs have been withdrawn within their first seven years after release. Also, warnings about serious new adverse reactions have been added to the labelling of a number of drugs, or new drug interactions have been detected, usually within the first seven years after a drug's release.

The time intervals for bans or new black box warnings would be shorter if the FDA was not infrequently loath, even when faced with strong evidence, to remove unacceptably dangerous drugs from the market or to add new black box warnings in a timely manner. An example is the diet drug sibutramine, for which there was clear evidence of cardiovascular risk at the time of approval in 1997. We petitioned the FDA to ban it in 2002,⁴ but it was not removed from the US market until 2010 after further evidence of increased cardiovascular risk emerged. There was also an unwarranted delay in adding a black box warning for all fluoroquinolone antibiotics about the increased risk of tendinitis and tendon rupture. The warning did not occur until after we had petitioned the FDA and later sued the agency.⁵

From the Editor



With summer not too far away, it is an appropriate time (of year) for Jane Hanrahan to review sunscreens. Warmer weather also sees snakes on the move, so Ian Whyte and Nick Buckley report on changes to the way antivenom should be used.

The use of tests to measure bone turnover is the subject of Devika Thomas' article. At present, the tests are not for everyday practice.

Herpes zoster is being increasingly reported in general practice. Michael Wehrhahn and Dominic Dwyer discuss how to prevent it.

Prevention of relapse is also an important part of the management of bipolar disorder. Jon-Paul Khoo considers the current evidence for drug treatment.

In recent years drug regulatory agencies have required drug companies to prepare risk management plans, however these plans are predicated on known risks. The revelation of risks occurs, far too slowly, over time. Better postmarketing surveillance would need to involve more than 10% of adverse drug reactions being reported to the FDA. It would then be sooner rather than later that the required number of adverse reactions occurred to force a change in the product information or the withdrawal of the drug. Drugs which have been available for more than seven years have already gone through the tests of time

and the amount of information about their risks has expanded enormously from what was available when they were initially approved. The worst offenders have either been removed from the market or have important new information about harm that will aid prescribers and patients concerning safer use. As a result, for most patients using older drugs for their approved indications, the benefits will hopefully outweigh the risks. <

Conflict of interest: none declared

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Letters to the Editor

Safe prescribing of opioids for persistent non-cancer pain

Editor, - The article by Michael McDonough (Aust Prescr 2012;35:20-4) was well written and includes some good material. However, I consider many statements to be incorrect and dangerous such as:

- 'Every prescription for opioids is fraught with danger'
- 'Before prescribing long-term therapy, there should be a trial period of one month'. By that time many people are already dependent.
- 'If prescribing beyond 12 months a second opinion should be obtained'. This person is dependent.

Donald Beard
Surgeon
Norwood, SA

Michael McDonough, author of the article, comments:

While I find myself agreeing with many of the sentiments expressed in the letter, there is no evidence to support the broader generalisation that after a month or even 12 months many patients are already dependent. However, there is some evidence to support that at least some patients may

benefit from extended opioid therapy.¹ Dr Beard is referring to the state of physiological dependence rather than the dependence syndrome as described in DSM IV-TR² which is synonymous with the term addiction.

Most people who develop a form of physiological dependence to opioids in the context of medical treatment can be withdrawn from opioids without significant risk of developing persistent craving for opioids or chronic, relapsing and remitting opioid use disorder. Further, there are patients who may derive benefit from continued opioid therapy but within the caveats that both I and others have described.³

Having concern about opioid use is always appropriate. However, this concern should not, of itself, justify the absolute avoidance approach, especially in appropriately selected and monitored patients.

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