# Beware of how side effects are masked

Not all healthcare professionals are as informed about side effects as they could be. At a conference on adverse psychiatric reactions the underlying message was that greater awareness, in both healthcare professionals and patients, about drug side effects is needed. **Lin-Nam Wang** reports

Clinical trials can be rigged to make a drug look good in terms of efficacy but also to mask side effects or exaggerate the side effects of a competing drug, said Ben Goldacre, author of *The Guardian*'s "Bad science" column. For instance, in a comparison of two drugs, a competing drug may be administered in such a way that it is more likely to give side effects than the trial drug, for example, giving a drug intravenously instead of orally or increasing the dose of the competing drug rapidly and the test drug slowly.

Practices used to hide side effects or to distort the picture include giving the competitor drug at unusually high doses. This ensures that the test drug will have fewer side effects than its comparator. Another "trick" is to be careful how side effects are asked about. For example, reports of sexual side effects with selective serotonin reuptake inhibitors have varied from 2 per cent to 73 per cent, depending on how people are questioned, Dr Goldacre explained.

Then there is the issue of whom drugs are studied in, he added. Drugs tend to be studied in "clean cases" (eg, young healthy people with one medical problem) but prescribing is mainly to older people, who are more likely to experience side effects.

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**Ben Goldacre: ways to bury bad data**

Ignoring drop outs from trials and truncating the trial duration (because side effects have started to emerge) are other ways of manipulating results. It is important that people register trials before they are started to say exactly what they are going to do, but getting people to do this is "phenomenally difficult", he said.

Other ways to "bury bad data" include:

- Not to show it on a graph
- Not to publish it
- Burying it in more data or only mentioning it quietly
- Burying initial bad results in later good results and pretending it is a multicentre trial
- Publishing in an obscure journal so that most people are likely to only read the abstract

However, Dr Goldacre acknowledged that it is not always a case of black and white mendacity. Leaving results languishing in a drawer because of other work commitments or because the drug gets dropped can also mean that side effects are not known about until there have been fatalities.

# Adverse effects of drugs used in anaesthesia

There have been significant developments in identifying adverse reactions to anaesthetics, Anita Holdcroft, emeritus professor of anaesthesia, Imperial College London, reported. The availability of online information on adverse events has also improved, with the Royal College of Anaesthetists developing a series of patient information leaflets. For example, "Confusion after surgery" gives information about the frequency of postoperative cognitive dysfunction (POCD), possible causes and how patients can avoid it. Symptoms of POCD vary, but include loss of memory, difficulty in concentrating, reversal of day and night sleep patterns, emotional changes (eg, anxiety), behavioural changes (eg, aggression) paranoia and hallucinations. (The leaflet is available at www.rcoa.ac.uk.)

The fact that the Medicines and Healthcare products Regulatory Agency (MHRA) now allows patients to report on yellow cards is another step forward. Moreover, the MHRA has made additional data available to Dr Holdcroft's research team, which means that is has been able to produce analyses of hazard signs for pain-relieving drugs used during anaesthesia. It has been shown that fentanyl and nalbuphine have particular hazards for psychiatric adverse drug reports, she said. However, limitations in data collected on yellow cards mean that further research is needed to verify these signals, she added.

Another limitation in the identification of the causal agent of a psychiatric side effect is the variety of drugs given during anaesthesia. These include prophylactic antibiotics and Dr Holdcroft drew attention to case reports of acute psychosis caused by antibacterials.

# Are changes to prescriber education needed?

"Education is clearly a very important aspect of [prescribing and preventing adverse drug reactions]," said Simon Maxwell, senior lecturer in clinical pharmacology, University of Edinburgh. Dr Maxwell described the prescribing activity of a British doctor as 30 to 40 prescriptions a day when first qualified, and dropping as the doctor becomes senior and hands the activity to juniors.

Challenges in the field of prescribing are more drugs, more patients (especially vulnerable ones — older patients are more prone to neuropsychiatric effects) and more complicated drug regimens, he said. "So it's not surprising that if you look into the literature, it's not difficult to find studies showing drug errors," he added. Drugs do not respect system boundaries. For example, an expert in cardiology may be keen to tell students the benefits of a drug to the heart, but may not be so good at explaining its collateral effects, he said.

Dr Maxwell said that it is difficult to say whether there is any reason for concern about prescribing education but recommended that there should be an assessment built into the final examination structure and that doctors are signed off as competent. He noted the action of the medical director of an NHS Trust in the north of England in 2006, who withdrew the prescribing rights of all new doctors until they had been retrained.

Dr Maxwell also acknowledged that clinical pharmacists probably prevent a number of prescribing problems.

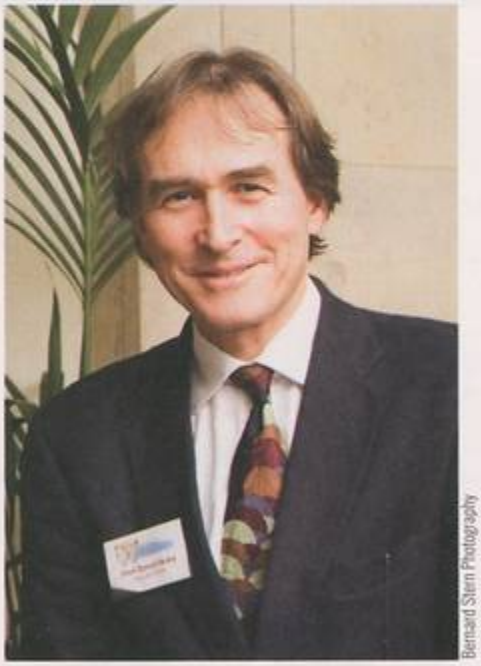
The annual conference of **Adverse Psychiatric Reactions Information Link (APRIL)** took place in London on 6 November. APRIL is a charity founded by Millie Kieve, who believes that the death of her daughter was caused by psychiatric adverse drug reactions

# Yellow card system far from perfect

The yellow card system is not reaching enough people, said Nigel Meadows, coroner for the City of Manchester. He has investigated over 30,000 deaths, several hundred of which, particularly self-harm cases, have been linked to drugs. For example, you can weave a contribution from an SSRI antidepressant to a death within findings of fact even if you cannot not find a direct causal connection, he said. However, the standard of proof in suicide cases is high. Mr Meadows believes that, in the past two years he has had before him 25–30 deaths with some link to a drug but there has not been evidence or expert witnesses to pursue this. It is currently estimated that 150,000 deaths each year in England and Wales are wrongly certified by doctors. "If doctors . . . are not able to accurately estimate the [medical] cause of death of people they see, what chance do they have [with] potential adverse reactions," he asked.

Andrew Herxheimer, former editor of the *Drug and Therapeutics Bulletin*, commented that confidentiality presents a barrier to getting details of what has happened. One way of getting around this is for anyone reporting an adverse effect on a yellow card to be given the opportunity to say whether he or she would be willing to give further details if asked, he suggested.

# Put little weight on evidence showing that there are no risks



Bernard Stern Photography

**David Healy: healthcare professionals should hold meetings on side effects of medicines**

"We track the fate of parcels put in the post 100 times more accurately than we track the extent to which our medicines may be causing injuries," said David Healy, professor of psychiatry at Cardiff University.

He described the events leading to the association of suicidal behaviour with fluoxetine in adults being acknowledged and the difficulties patients faced because the scientific evidence of suicidal ideation was not made available.

Professor Healy said that if a patient reported the experience to his or her doctor, because the evidence said there was no association with increased suicidal behaviour, the doctor would be likely to treat the report as an anecdote: "their conclusion will go against your experience because [that] is consistent with scientific evidence."

Because the science pointed the other way, when a string of people presented such side effects to the US Food and Drug administration, action was not taken, he explained.

In addition, because there was published evidence indicating that the increased risk might be due to the condition itself rather than the treatment doctors would tell patients this.

Professor Healy went on to explain how significant data had been first concealed through the manipulation of figures. Furthermore, although trial results were published in the *BMJ*, which is read by 100,000 doctors, no one pointed out that there was an increased risk, he said.

His advice to prescribers is to trust the patient in front of them. "If they say they feel strange and abnormal, take note, even though the evidence says there is no link. . . . You should put little weight on evidence that says there are no risks," he said.

## Views from lay delegates and lay speakers

There was a strong presence of patients, carers and relatives at the conference. Views of lay delegates and lay speakers included that:

- Patients and carers should be made aware of the availability of genotype tests to indicate the suitability of antidepressant or antipsychotic drugs in order to get the drug right first time
- A person who has recently had an anaesthetic and is displaying signs of depression, confusion or irrational behaviour should be seen by a doctor straight away and should be carefully monitored
- To "come off" benzodiazepines, patients need to be fully armed with knowledge and supported
- The British National Formulary should have a list of drugs that cause psychiatric effects, just as it has a list of drugs that should not be used in renal impairment

## Meeting reports

**Timing and submission** *The Pharmaceutical Journal* welcomes submissions about meetings and conferences. Please contact the editorial department before sending in a report, ideally before the meeting takes place, to check that it is not already being covered and to discuss the length of the report. Photographs are also welcome, provided they are of publishable standard.

Reports should be sent in by e-mail. If the meeting is newsworthy, the report should be sent in by the Tuesday immediately after it takes place to ensure immediate publication. All reports should be sent within two weeks of the meeting to guarantee publication within a month of the meeting. Reports submitted later than this will not always be published in full in *The Journal*. It may be necessary to publish an abbreviated version in print and post the full report on *PJ Online* (www.pjonline.com).

**How to prepare a report** Readers need to be encouraged to read reports, so start the report with the most interesting item, not with details of what, where and when the meeting occurred.

Concentrate throughout the report on the most newsworthy contributions to a meeting, such as valuable information that has not already been publicised or strongly worded opinions voiced by influential speakers. Reports that repeat what readers already know or cover old issues will not be interesting. Write about what people actually said rather than what they talked about. Ask speakers for copies of their talks or notes. Do not submit reports that are just lists of speakers' topics; they are of no value to the reader. Instead of writing "Professor Plum gave a fascinating account of continuing professional development," readers will want to know exactly what Professor Plum said that was so fascinating.

Do not give every speaker an equal number of words. With the exception of keynote speakers if someone says nothing of interest, then do not report it, however well-known the person. If the keynote speaker says nothing of interest, consider how valuable a meeting report will be.

**Advice for photographers** *The Journal* is unlikely to publish more than two or three photographs from most meetings, so it is best to concentrate on the main speakers. The ideal time to take photographs is at the beginning of each address, while the speaker is still involved in introductions and is likely to be looking out at the audience rather than staring down into his or her notes. Take several shots of each speaker and always aim to be as close as possible to the podium, even if it means obstructing the view of the audience for a short time.