Adverse drug reactions: prescribing’s twilight zone

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Published studies cannot be fully relied upon to provide all the information needed about adverse drug reactions (ADRs), so there is a pressing need to improve ADR reporting by healthcare professionals and patients. For many years, the Yellow Card Scheme has offered an early warning signal for ADRs, but the scheme still needs be more widely used, and to be fully integrated into clinical systems.

Prescribing means treading the fine line between efficacy and tolerability, whether it is aspirin’s association with gastrointestinal bleeding and Reye’s syndrome, warfarin’s notoriously narrow therapeutic window or a new medicine with a unique, poorly characterised mode of action. Unfortunately, however, prescribers often have an incomplete picture of adverse drug reactions (ADRs), even with well-established medicines. “We are plagued by having to make prescribing decisions, and choose drugs based on an incomplete picture of the benefit/harm profile,” remarks Yoon Loke, professor of medicine and pharmacology at the University of East Anglia.

Most phase 3 studies, for instance, enrol a selected group of patients, typically with fewer co-morbidities, on fewer concomitant medications, and less ill than many of those managed in routine clinical practice. In addition, phase 3 studies often enrol inadequate numbers of patients to detect rare ADRs.

In the UK, for example, the annual number of cases of Reye’s syndrome – a serious, often fatal swelling of the liver and brain – declined from 81 in 1983–84 to five in 1996–97.¹ The decline followed advice from the Committee on Safety of Medicines – the precursor of the Medicines and Healthcare products Regulatory Agency (MHRA) – to not prescribe aspirin to children. “The advice virtually eliminated cases of Reye’s syndrome,” notes Mitul Jadeja, special projects manager, Vigilance and Intelligence Research Group, Vigilance and Risk Management of Medicines

division of the MHRA. Detecting the increased risk of Reye’s syndrome in children taking aspirin would be impractical in a clinical study – the insight came from spontaneous reports to regulatory authorities, including the MHRA’s Yellow Card Scheme. Nevertheless, the scheme has faced criticism, most notably highlighting the pervasive under-reporting.

In addition, prescribers face a lag between the first hints of a side-effect in the clinic and the MHRA’s ability to separate the ADR from the background noise. In the meantime, prescribers rely on peer-reviewed papers to guide prescribing. However, new research suggests that about two-thirds of the ADR data seems to be missing from published papers. Moreover, the number and range of ADRs appears consistently higher in the unpublished than the published version of the same study.\(^2\) So, when it comes to tolerability, are clinicians prescribing in the dark?

**The Yellow Card Scheme**

The thalidomide tragedy ushered in a raft of regulations worldwide to improve the safety of medicines and to detect emerging problems. In the UK, for instance, the MHRA runs the Yellow Card Scheme.

“The Yellow Card Scheme is an early warning system to help identify important safety issues with medicines and other healthcare products to ensure they are acceptably safe for patients,” says Mr Jadeja.

Launched in 1964, the Yellow Card database now includes more than 800,000 suspected ADRs. During 2015, the MHRA received nearly 40,000 suspected ADR reports – the highest annual figure to date – comprising 59% received directly via the Yellow Card Scheme (see Figure 1) and 41% via the pharmaceutical industry to the MHRA. “Yellow Card reporting is increasing year on year, mainly due to recent awareness campaigns and continuing strategic efforts by the MHRA – such as making it easier for GPs and pharmacists to report suspected ADRs directly through their clinical IT systems,” says Mr Jadeja.

Over the years, this large database has helped identify numerous safety concerns. For instance, in April 2014, based partly on Yellow Card data, the MHRA warned that patients taking warfarin should limit or avoid drinking cranberry juice and that St John’s wort resulting in Cushing’s syndrome,” Mr Jadeja adds. “This led to a review and the addition of this interaction to product information.”

Yellow Cards can also help identify drug-drug and drug-diet interactions. Based on Yellow Card reports, the MHRA warned that patients taking warfarin should limit or avoid drinking cranberry juice and that St John’s wort could reduce the efficacy of concurrent hormonal contraceptives and implants.\(^3\)

Although the Yellow Card Scheme began with ADRs, the system now encompasses adverse incidents related to medical devices, including concerns about the performance of diagnostic assays and technologies. The Yellow Card Scheme also includes counterfeit and defective medicines (those that are not of an acceptable quality), and from May 2016, safety concerns associated with e-cigarettes. “The Yellow Card Scheme was expanded to also collect problems or incidents with medical devices, suspected counterfeits and defective medicines in November 2014,” Mr Jadeja notes. “In the following year, the numbers of reports received by MHRA for medical device incidents increased by 23% compared to the year before. We are now planning campaigns to promote reporting of problems with medical devices.”

The MHRA works “very closely” with other regulators, such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). “Safety signals identified from the Yellow Card Scheme are discussed at a European level through the Pharmacovigilance Risk Assessment Committee, which is chaired by the UK, to reach a consensus about any regulatory action necessary,” Mr Jadeja says. “The MHRA is also an active contributor to the WHO network of National Pharmacovigilance Centres, where we share our experience with our global partners.”

Based on these deliberations, the MHRA decides on any regulatory action, which might include: changes in the marketing authorisation; restrictions in use; reclassification; refinement of dose instructions; or introducing specific warnings in product information.

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**Figure 1.** Number of direct Yellow Card reports received by combined reporter qualifications in 2011–15. Source: MHRA. Adapted from the Human Medicines Regulations 2012 Advisory Bodies Annual Report 2015 data to include patient reporting data.
In some cases, drugs are pulled from the market. “Rimonabant was withdrawn from the market after evidence emerged, partly through the Yellow Card Scheme, that the risks of the antiobesity drug outweighed the benefits,” Mr Jadeja recounts.

The problem of under-reporting

Nevertheless, the Yellow Card Scheme and other spontaneous reporting systems have long faced criticisms including under-reporting, reports of known ADRs and falsely attributing causality. As we will see, sophisticated analyses help avoid spurious attributions. But according to Professor Loke, a world expert on adverse event reporting, “under-reporting remains a big problem”. Indeed, only about 10% of serious ADRs and 2 to 4% of nonserious reactions are reported to the Yellow Card Scheme. Yet the UK performs better than many other countries. Mr Jadeja points out that the UK accounts for the second largest proportion of reports in the WHO global database, after the USA.

“All spontaneous ADR reporting systems are associated with under-reporting,” Mr Jadeja confirms. “Reporting rates are likely to be influenced by the seriousness of reactions, their ease of recognition, including the extent of use of a particular drug, promotion, and publicity about a medicine. MHRA’s Yellow Card strategic activities aim to strengthen reporting of suspected ADRs to the Yellow Card Scheme and this is the reason for regular campaigns to raise awareness levels and increase ADR reporting.”

In November 2016, for example, the MHRA ran a social media campaign, as part of the Strengthening Collaborations to Operate Pharmacovigilance in Europe (SCOPE) Joint Action project, to promote suspected ADR reporting. “This was the first of its kind and initial results show the featured animation was seen by nearly 70,000 people each day of the campaign week in the UK,” says Mr Jadeja.

Healthcare professionals can stay up to date with the monthly Drug Safety Update (www.gov.uk/drug-safety-update). A watch list on the new Yellow Card app (see Box 1) allows healthcare professionals to sign up to receive news and alerts for particular medicines as well as report suspected side-effects. Nevertheless, Professor Loke calls for improved feedback to individuals who report a suspected issue, which may help encourage reporting. “Clinicians and patients often wonder what happens after they lodge a Yellow Card report,” he says. “They may feel that things simply disappear into the ether.”

In addition, the MHRA is looking to further integrate electronic Yellow Card reporting into healthcare professionals’ clinical IT systems. Indeed, NHS Digital and the GP Systems of Choice programme includes the development of integrated Yellow Card reporting as part of the mandatory contractual framework for GP practice IT systems. “Yellow Cards are already included in one GP clinical software called SystmOne. We envisage that rollout to other GP systems will contribute to a further increase in reporting in 2016/17,” adds Mr Jadeja.

Involving patients

The Yellow Card system records adverse events reported by wide range of sources, including healthcare professionals and the public. Patient ADR reporting using Yellow Cards was first considered in 1983 following the withdrawal of the NSAID benoxaprofen. In 2003, UK patients started reporting ADRs using NHS Direct. But relatively few patients reported ADRs using the new system.

So, following a pilot, patient Yellow Cards were launched officially in September 2005, supported by a nationwide campaign through GPs and pharmacists (reporting forms are now available at www.mhra.gov.uk/yellowcard). An evaluation of 407 reports received in the first six months suggested that patient reports were of a similar quality to those from healthcare professionals.6 “An independent review in 2011 reinforced MHRA’s existing view that patient reporting adds value to pharmacovigilance activities conducted by medicines regulators to protect public health,” Mr Jadeja says.

By 2015, patients accounted for 14% of total ADR reports received by the MHRA, accounting for over 23% of those received directly (see Figure 1) to the Yellow Card Scheme. “In 2015, suspected ADR reports received from members of the public contributed towards 15 safety signals being detected, including six signals where a member of the public’s report directly stimulated regulatory action,” Mr Jadeja comments. “For example, a patient report led to the product information for levonorgestrel being updated to include drug-induced hepatitis as a possible adverse effect.”

“Yellow Card coverage is very broad, in that it accepts reports for all types of drugs, and for any form of suspected adverse reaction,” says Professor Loke. “This is one of the scheme’s strengths. However, the breadth is also a weakness because the reports can be nonspecific, and lack detail. Hence, it is difficult to pick out the genuine signal amid the other chatter that arises in the system.”

Separating signal from noise

The MHRA evaluates reports weekly to identify previously unidentified potential hazards and new information on recognised side-effects. However, reported cases may be true ADRs, coincidental events or undiagnosed illnesses. So, the MHRA uses a variety of approaches to separate potential safety signals from other factors, such as age, medical history, and underlying or undiagnosed illness or infection.

One statistical approach – called disproportionality – identifies instances where an event occurs more frequently for a particular drug than might be expected based on the background information in the database. The MHRA also uses rule-based approaches to ensure important cases are always reviewed. This includes paediatric cases or those where a parent has taken the medicine and a child had the reaction, fatal cases and other particularly serious reactions. “Where we identify a potential safety issue, we can also look at prescription data across the NHS, or usage data by, for instance, analysing the Clinical Practice Research Datalink,” explains Mr Jadeja. “This gives additional information about the drug and event in a clinical setting.”
Professor Locke would like to see even greater integration of spontaneous reporting and other databases to improve regulators’ and researchers’ ability to detect ADRs. “An integrated system would allow any strong signals that emerge to be rapidly evaluated with a more detailed study using pharmaco-epidemiological techniques,” he says.

Data missing from papers
Detecting potential safety signals using spontaneous reports takes time. In the meantime, prescribers may not be able to rely on peer-reviewed papers: a recent analysis found that about two-thirds of the data about ADRs seems to be missing.2

Researchers identified 28 studies that compared data on side-effects included in published articles to unpublished data on websites, reports at conferences, from industry-held sources and so on. Fewer published documents included information about ADRs than the corresponding unpublished sources: medians of 46% and 95% respectively. For example, the published paper could lack numerical data or include selected – rather than all – the adverse events. Based on 11 studies, relying on the published document alone would miss a median of 64% of adverse events, although this ranged from 43% to 100%. Relying on the published papers would also miss 49% of serious adverse events, varying from 2 to 100%.2

“We don’t have access to the full dataset on adverse events,” says Professor Loke, one of the study’s authors. “This is a particular problem for systematic reviews and meta-analyses. It casts great doubts on the reliability of the results of the meta-analysis if only half the dataset were available. Perhaps the conclusions and treatment considerations would have been completely changed if the missing data had been incorporated. We know that most decision-making bodies, including NICE and even local formulary committees, have to rely on evidence synthesis as well as cost-benefit versus harm evaluations. However, the lack of data on adverse events makes it very difficult to reach a robust decision on the comparative safety of the available drugs for that condition.”

Professor Loke calls for “full transparency” regarding ADR data. “All trial results should be made available for public scrutiny as well as for evidence synthesis,” he says. “The authorities in the USA have taken a big step towards full transparency by making adverse events reporting mandatory in clinicaltrials.gov, and I hope there will be similar progress across the world. Until then, prescribers will be stuck with making treatment decisions on half the information.”

The twilight zone
Given that there will always be a lag before spontaneous reports yield confirmed safety signals, there is a pressing need to improve transparency and ADR reporting in peer-reviewed literature. So, while healthcare professionals are not prescribing totally in the dark, they are arguably working in the twilight. “Sometimes we are asked to prescribe drugs that are safer, or to use them first-line,” Professor Loke says. “But we actually don’t genuinely know whether the claims for safety are justifiable, given that much of the data is missing from public scrutiny.”

Nevertheless, more than 50 years after its introduction, the Yellow Card Scheme continues to offer an early warning signal for ADRs and other incidents. But the scheme needs be more widely used by healthcare professionals and patients, and fully integrated into the clinical IT infrastructure. “Supported by professional codes of practice, the scheme is reliant upon healthcare professionals being vigilant in identifying and promptly reporting suspected adverse drug reactions,” Mr Jadeja points out. “Don’t delay, report today.”

References

Declaration of interests
Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies and their agencies. He has no shares or other financial interests.

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