

Post-Release Drug Treatment Risks: Strategies to Minimise Harm to Patients

V M S Oh,*^{FAMS, FRCP, FACP}

Abstract

This paper examines the perceptions and causes of drug treatment-related error, and suggests some risk reducing strategies. Interest in medical error surged recently, culminating with an estimate by the US Institute of Medicine in 1999 of 44,000 to 98,000 annual care-related deaths. Public media pressure elicited responses from health care providers, purchasers, internists and health professionals' organisations. A search was made using PubMed, focusing on papers from 1980 to date giving data on trends and causes of in-hospital drug-related error. Papers with estimates of prevalence rates of drug-induced injury in large denominator populations were selected. One hundred and seven papers on drug-related error were identified; 36 clearly defined denominators and compared rates in different groups. Occurrence rates of drug-induced harm were similar (2.2% to 6.7%) in the US and British hospital surveys. The Harvard Medical Practice Study first reliably measured the frequency of care-related patient harm. More reliable and accurate information is needed on the base-line rates of drug-related injury. Whereas there are few precise estimates of drug-induced injury, the evidence suggests that between half and two-thirds of hospital-related harmful events are preventable. Most experts agree that hospitals need to change radically their approach to professional error from one of blaming individuals to overhauling the systems for monitoring, detecting and preventing drug-related error. Hospital managers should implement voluntary, non-punitive, and confidential systems for reporting error, and apply methods of safety enhancement which succeed in high-risk industries. A realistic and achievable target could be halving of current risk. Incentives can be given to event monitoring and pharmacotherapy quality assurance, to encourage timely and accurate reporting. On-line doctors' entry of drug orders and computerised adverse event monitoring also promote error reduction.

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Introduction

Physicians have long accepted unreliable evaluations of the risks attached to pharmacotherapy, i.e. treating our patients with drugs. The reasons for the uncritical attitude towards medication, which comprise 60% to 90% of all clinical interventions, depending on specialty, have not been systematically studied. We have had the randomised controlled clinical trial (RCT) for over 50 years.¹ Epidemiological tools to measure rates of unwanted events have been around for years. The mass transport industries, car designs and factory regulation have all attained acceptable standards of safety relative to benefit. Why, then, have health organisations not insisted on the most rigorous available evidence of medical risks and benefits and on error prevention? The obvious answer is that monitoring and control systems can be costly.

Medication Errors

A drug-related or medication error is a "failure in the treatment process that leads to, or has the potential to lead

to harm to the patient".² Estimates of error frequency vary, but up to 4% of inpatients experience a drug-related error.³ The evidence is that most mistakes, i.e. planning errors, arise from knowledge-based or rule-based errors made by carers in unfamiliar circumstances. Mistakes occur at rates depending on what people are doing and the conditions under which they operate.⁴⁻⁶ Therefore, there is room for correction through training and the sharpening of work systems.

Skill-based errors comprise action slips or memory lapses, which tend to occur when people are tired or distracted in unfamiliar settings. Of course, both mistakes and slips or lapses increase when the complex system of prescribing and giving drugs to patients breaks down. If strategic decisions go wrong, or work conditions promote error, the risk to the patient rises. The upside of this analysis is that we can improve the system to decrease risk.

Resistance to Systemic Change

What are the causes of the resistance to radical change in

* Professor and Senior Consultant Physician

Department of Medicine

National University Hospital

Address for Reprints: Professor Vernon M S Oh, Division of Clinical Pharmacology and Therapeutics, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

E-mail: mdcohms@nus.edu.sg

the way doctors function, and hospitals and medical organisations regulate practice? Medical practice has always been intensely personal, so the public expects each physician to strive conscientiously to avoid error. This expectation overlooks the fact that today's practice is so complex that latent error is inherent. Many of the protocols and processes we use daily cannot cope with near misses, because we did not consider human limitations when designing them. Therefore, it should no longer be an issue of punishing individual scapegoats—an absurdly wrong approach. There is an organisational inertia that prefers to focus on single doctors at the front dealing with patients. Some evidence suggests that 'backroom' factors, people who determine resources, also contribute crucially to most medical errors.⁷

Nearly all health professionals work hard to avoid mistakes. Those who make mistakes usually feel bad and undergo turmoil on facing the mistakes. Unfortunately it is clear that individual efforts, however heroic, can only go so far. Several hospital studies of care-related injury show that 50% to 67% of errors are avoidable.^{3,8} Such evidence supports the insight that medical systems and processes are faulty, and the faulty systems need 'ground-up' overhaul. Recognising a systems defect is hard. Summoning up the will to rectify entire systems is harder still.

A less tangible reason is that most doctors and administrators misjudge the magnitude of the risks accompanying both natural phenomena and unwanted treatment effects. Many medical interventions and diseases carry unexpectedly large or small risks of injury or death. Most people are inept at judging the relative risk of drug treatment, i.e. the likely benefit in relation to the anticipated damage. Because people cannot readily grasp numbers larger than thousands, quantitative risks expressed as 'one event per 36,000 a year' are not intuitively understood.

More importantly, the effects of many drugs at the community level are not precisely known. The relative risk of treatment is encapsulated in the catch-phrase 'risk: benefit ratio', but usually we lack precise measures of both risk and benefit and comparator information is missing. What risk estimates we do have for a given drug are often unreliable because of sampling error, or inaccurate baseline incident rates. New drugs are tested in a narrow age-range of patients under restricted conditions. Increasingly, we know that data on drug effects may not be valid between different populations because of pharmacogenetic differences, some of which are clinically important.

Formal Framework of Risk Estimation

In epidemiology, it is routine to describe a given treatment endpoint in terms of the odds ratio, defined as the ratio of odds of the endpoint occurring in the drug-treated group to the odds in the control group. However, for many drugs, the

effects are observed in patients without corresponding information from control persons. Therefore, it is best to think about *absolute risk*, defined as the number of patients who meet the criteria for a treatment endpoint (or adverse effect) divided by the total number of treated patients. If a control group is available and appropriate, it is still better to consider relative risk, i.e. the *risk ratio*, than the odds ratio. The reason is that the odds ratio greatly overestimates the relative risk for frequent events.⁹

Dose-dependent (type A) adverse drug reactions would qualify as frequent events because they are detected in 12% to 25% of in-patients.^{3,4,8} Dose-dependent drug reactions are overall more important than the hypersensitivity (type B) reactions, because they account for over 90% of drug-related deaths, and perhaps three-fifths are avoidable.^{3,10}

Uncertainties in Attributing Causes of Death

Drugs unavoidably carry some risk, either inherently or through unwise use. To normalise doctors' perception of risk, it is helpful to compare drug-induced risk with the risks that natural events carry. During the past century, life expectancy at birth increased by 25 to 30 years in developed nations, including Singapore. This benefit accrued in part by people taking risks, risks linked to such innovations as Caesarean sections and modern drugs. Today the risk of dying is low until the age of 50 years, beyond which it rises.¹¹ Within each year, about 1% of women aged 60 years and 10% of 80-year-olds will die. Against this natural background, it is hard to detect a causal relation between death and a given drug in older patients.

Misleading Presentation of Facts

As with all statistics, we need to beware of incomplete or misleading numbers. The airline industry regularly issues safety data that mislead through a well-known device. The risk of severe injury or death generally uses the denominator of 'passenger-miles' or 'passenger-kilometres', a meaningless product. Using this denominator, the risk appears very small, e.g. a world-average mortality risk of 3 per 10 billion km, compared with 10 per 10 billion km for railway travel, with its fewer passengers.¹² On this basis, air travel is often claimed to be much safer than surface travel. Expressing risk as an average ratio ignores the fact that aircraft crashes happen non-randomly, mostly as the culmination of several interconnected and preventable faults at landing or takeoff.

What really matters to the public, however, is the risk of death per passenger journey. The insurance and airline industries use this denominator. The re-worked risk becomes a world average of 550 per 100 million aircraft journeys, or 5 deaths per million departures. Actually this risk exceeds that of travel by road, 4.5 per million, or by railway (2.7 per 100 million journeys).¹³ The risk is similar to death from

falling objects or a tropical lightning strike.^{14,15} It is slightly lower than the risk of dying from pregnancy—a physiological condition—or from penicillin-induced anaphylaxis.¹⁵

Lay Persons' and Physicians' Perceptions of Risk

We need to recognise that a doctor's understanding of risk may be similar to the slightly irrational perception held by the public and fed by the media. For instance, in the USA tobacco-related disorders kill the equivalent of 3 jumbo-jet loads (1200 persons) and road crashes kill 100 people every day, while alcohol abuse in pregnancy injures about 3100 babies every year (average for 1979 to 1998).^{12,15} The public accepts these avoidable deaths with little concern. By contrast, the comparatively minuscule risk of serious damage or death from vaccines provokes high-profile media responses, despite the great health benefits that vaccines confer.

Ordinary folks get their news from simplified and stark media-bites that focus on victims. By playing on emotions rather than rational thought, such presentations have a lasting effect on both lay people and doctors. We forget that only the worst cases reach public attention and medical journals. Consider, then, the following example. If the mortality risk for an untreated zoonosis, say a porcine retrovirus disease, is 5%, then 5000 of 100,000 infected persons would die in an epidemic. Given a drug which effectively treats the infection but which carries a 1 in 10,000 risk of a lethal drug reaction, 10 persons might die from the treatment. However, 4990 of those people, who would have died if left untreated, would recover.

When the mass media focus selectively on the 10 drug-related deaths to sell the news, they mislead the public into ignoring the benefit to 4990 others. Moreover, dramatised reports on the 10 deaths might cause about 1 in 5 (20,000) patients to reject treatment with the drug; 1000 of the treatment refusers would then die instead of 2 (reacting to the drug), a net loss of 998 lives.

Effects of Selective or Biased Reporting

This kind of selective reporting prevails in communities in which the public media hold great influence through wide coverage. Recently, an Institute of Medicine (USA) survey summarised the in-hospital risks for care-induced illness and death, based largely on the Harvard medical practice study, and the Utah and Colorado medical practice study.¹⁶

From the population estimates of annual risk, which are expressed as a 95% confidence interval, the media seized on the upper confidence limit of 98,000 deaths. For inpatients, this figure produced an annual mortality risk of about 1 in 80. The lower limit of 40,000 would have given

a risk closer to 1 in 200 inpatients dying each year, which is similar to earlier estimates.³ In Singapore, we are less likely to be misled, with media reporting on health matters being less sensational. The stronger causes of rejection of western drug treatment are sociocultural beliefs, e.g. a greater confidence in traditional folk medicines than in western drugs.

What then can be done? We should encourage the production of the best available estimate of the absolute risk in terms of the numerator ('victims') and the denominator (total exposed persons). Such an approach works well both for the risk of a disorder, the effects of a given drug treatment and the consequence of restricting the use of the drug of interest. In such analysis, we regard all members of the community as strictly equal. For as soon as we introduce the idea that young persons with correctable disease might deserve more (and thus more expensive) care than elderly persons with painful terminal disease, we enter a bioethics debate outside the remit of this article.

What are Acceptable Levels of Risk?

Most ordinary folk understand the stark balance of 50:50. If your chance of losing money in a wager is 20%, i.e. the odds are 4:1 against winning, you might hesitate. So some analysts present risk information in such terms. For instance, an estimate based on 0.27 deaths per million aircraft departures in the USA in 1990 to 1994 translates into a 50% risk of death if you fly continuously for 20,000 years.¹² Most of us readily accept this level of threat to wellbeing. However, such an average figure inflates our sense of security. In fact, the threat is much greater for someone making a short hop between dangerous airports in a chartered single-engine aircraft in bad weather. But we lack a precise risk estimate. Similarly, we lack estimates of risk for people exposed to specific medical events under different conditions.

The risks of hospital care are of a higher order. Whereas physicians may confidently cite the major benefits of modern drug treatment of disease, there is considerable room for improvement in overall hospital care. The increasing range and complexity of today's medicine carry significant amounts of harm to patients. In a 1991 report, medical care caused damage to patients in 3.7% of 30,000 hospital admissions in New York State (NYS).³ Over half of the damaging events were avoidable and nearly one-seventh (0.50% of admissions) were fatal. Advanced hospitals carried risks of injury and death 1370 and 185 times higher than an American air journey. In a highly regarded hospital (Brigham and Women's Hospital, Boston) linked with a prestigious institution, the Harvard University Medical School, potentially serious drug-related errors occurred in 6.7% of patients; happily only 1% of these

errors killed patients.¹⁷

The respective risks for drug-related injury and death are thus about 2480 and 25 times higher than that of death from airplane crash (US statistics for 1990 to 1994). Why do people accept the higher risk level of drug treatment? Here is a question for social investigators.

Imagine the following welcome message when you next enter hospital for treatment. “As your personal nurse, I welcome you to the Superlative Hospital, a tertiary-care institution. You will sleep in 4 nights over 5 days. I am confident you have a 95% chance of leaving here without injury. The medicines we serve you are 7% likely to make you ill and only 1% likely to kill you. In fact, just 1 out of 200 patients like you might not leave alive. Please make yourself comfortable and enjoy the region’s best medical care”. How many patients would happily stay, even knowing that the message does not apply equally to everyone?

If the same risk levels applied to air travel, some people would reject it. More people would likely decline flying than staying in hospital, given that most of us value health more than flying. What is the highest risk level most of us can reasonably accept?

Realistic Care Standards and Death Risks

Many of us demand the low level of risk associated with flying in a carefully serviced aircraft run by a large and reputable airline. But some usually-cautious professionals also enjoy the frisson of helicopter-glacier skiing—a very dangerous sport. Therefore, it seems reasonable to expect hospital care to carry a mortality risk no higher than about *1 in 10,000* admissions. This risk level typifies death from best-practice general anaesthesia, and best-practice treatment of bronchial asthma, peptic ulcer disease, leukaemia and drug-related agranulocytosis. Non-medical events with a similar risk include falls, burns, suicide and road or railway accidents. Even by this moderate standard of 1 death in 10,000 admissions, the risk of care-related death in NYS hospitals is 50 times greater and the risk of medication-related death at Brigham and Women’s Hospital is 7 times greater.

At the next higher risk level, people in Singapore, as in most developed urban societies, die of influenza-related illness, diabetes or liver cirrhosis,^{11,15} at rates between 1 in 1000 and 1 in 9,999. So, we may reasonably expect hospitals to cause injury in no more than *1 in 1000* admissions. The risk of care-related injury in NYS hospitals is about 40 times higher and the risk of drug-related harm to patients is about 70 times higher than the author’s proposed ‘reasonable standard’.

In the period 1996 to 1998, the mean number of admissions to the 23 hospitals in Singapore was about 370,000, consisting of 280,000 and 90,000 admissions to 10 public

and 13 private hospitals, respectively.¹¹ If the American figures, rounded down, were extrapolated to Singapore hospitals, then each year, 3% (about 11,100) Singaporean patients would receive care-related injury and an estimated 0.4% (1480) would die from health care errors. Drugs would harm around 6% (22,200 patients) and perhaps 0.05% (185 patients) would die from medication errors. Now we see that the Americans may have just cause for concern.

It is difficult to know if hospital patients in Singapore experience significant risks of drug-induced harm. We do not have data from large prospective studies in Singapore hospitals. Some limited reports, however, suggest that local patients experience lower risks of injury and death. For instance, the highest number of adverse drug events that nurses reported to the Pharmacy Department at the National University Hospital (NUH) from 1993 to end-June 1999 was 95 (in 1995), with only one death in 1996 [personal communication]. The adverse medication event in 1995 was 95 per 44,000 admissions, equivalent to 2.2 events in 1000 admissions (0.22%) and near the ‘reasonable standard’ of 1 per 1000. The fatal drug event rate was 23 per 100,000 admissions (0.0023%), also close to the reasonable expectation of 1 per 10,000 above.

The adverse drug event rate in NUH in 1995 was 33 times smaller and the drug-related mortality rate (1996) was 290 times smaller, than that in Brigham and Women’s Hospital (Boston) at about the same time. The low figures for 1995 to 1996 probably flowed from the different methods used to obtain the data and possibly from greater vigilance in Singapore hospitals. However, it is unsafe to assume that no injuries were wrongly attributed to natural causes. The harder one looks for adverse events, the more such events will be flagged. Some overseas reports suggest that 50% to 67% of adverse drug events are avoidable.^{3,18,19} So we have no room for complacency, whatever the exact numbers of adverse drug events in Singapore hospitals.

Why are Drug Treatment Errors Important?

Medication errors produce unwanted adverse drug events. Apart from the intangible cost of unnecessary distress and mortality caused by avoidable error, we should consider the financial cost. Based on the adjusted cost of extra stay in a Boston teaching hospital, each preventable adverse drug event produced a loss of US\$4680 (SGD\$7860) in 1997. For a 700-bedded acute care hospital, the annual cost was about US\$2.8 million.²⁰ Even discounting to SGD\$6000 per event for lower costs in Singapore and assuming one-half of the rate of adverse drug events in Boston, the estimated cost of preventable adverse drug events for all Singapore hospitals is SGD\$19 million per year, which is 1.2% of the recurrent health care expenditure.¹¹

How to Promote Error Reporting?

If 50% to 67% of the injuries and deaths are avoidable, we can reasonably aim at reducing these numbers by one-half. What matters is that hospital managers should make serious attempts to (a) measure the present levels of risk to patients, and (b) decrease levels of risk of injury and death related to drug treatment and other modes of treatment. When medication errors are found, the usual response is to try to blame and punish someone; this is futile. Recrimination and reprisal produce not safety but secrecy and defensiveness, as well as great agony. The impressive progress in safety in high-risk activities such as aviation and space engineering shows that the surest way forward is through confidential event reporting,²¹ and the refinement of work procedures, equipment and support systems.

The American Medical Association²² and the American College of Physicians²³ have both opposed mandatory reporting of medical errors which produce serious harm or death. Both bodies argue that compelling doctors to record mishaps opens them to recrimination because anonymity cannot be guaranteed. The British Medical Association and Royal Colleges are likely to take the same view. Some work suggests that carers elsewhere report only 10% of mishaps and near misses in drug treatment.²⁴ Common sense as well as these considerations strongly argue for voluntary reporting of adverse drug events in Singapore.

How Best to Implement Drug Treatment Guides?

Although a few physicians habitually evaluate the evidence of treatment outcomes before advising their patients, most do not. Most important is the need to persuade physicians to demand an accurate and realistic evaluation of the factual odds. The present initiative in Singapore, as elsewhere, promotes clinical guidelines but physicians tend to ignore guidelines whose contents are similar to their current practice.²⁵ Put simply, they do not believe that minor work alterations will affect patients' outcomes.

If a costly treatment is effective, we can judiciously ration its use. If it is weakly effective or non-effective, we should ruthlessly discard it. Producers of drug-treatment guidelines must work towards delivering the known odds simply and directly to physicians at the bedside, because if they do not, physicians will simply ignore the facts.^{26,27} Doctors must work together with the writers of guidelines to maximise the likelihood that patients will receive drug treatments that really are the best that medical science can offer.

Apart from guidelines, our scapegoat culture needs a root-and-branch change. Hospital managers ought to (a) implement non-punitive systems for reporting error,²⁸ (b) improve workplace safety for all carers to encourage

solidarity of purpose, and (c) use the most effective methods of ensuring safety that already succeed in, say, mining and deep-sea or space exploration. The National Patient Safety Foundation and the Institute for Healthcare Improvement, USA, has joined with the Veterans Health Administration to undertake wide changes in reporting systems²¹ and care procedures to decrease medical errors. There are similar initiatives in Europe and Britain. We should interact with other groups to save losses in life, wellbeing, as well as finances.

There is no reason why hospitals and other care purchasers should not introduce positive measures to promote reductions in such losses, e.g. incentive payments to departments. Similarly, government could offer increased subsidies to hospitals that show evidence of significant reductions in harm to patients and thus financial loss.

Making Prevention Strategies Work

We should bear in mind that aviation is probably not as complex or human error-prone as medical practice. Even as checking systems minimise pilot errors, so the 'tilting point' moves to the least well-maintained electric or hydraulic control system. In medical practice, drug treatment involves so many people and sub-systems that the probability of error would appear greater. Among medical errors, drug mishaps are the commonest.^{8,16,12}

To get safer treatment, we have to improve the systems of drug prescription and delivery, plus checking procedures. Because human error creeps in through fatigue, computers can minimise error in drug ordering and dispensing and unit dosing. Online entry of physician drug orders,²⁹ and the input of clinical pharmacists³⁰ can probably reduce error further in many activities, not just in intensive care units.

Where We Are

The perception of drug treatment risk is often unbalanced. The current lack of public interest will not endure. As the nation moves on with developing a pharmaceutical and nutraceutical industry, safety expectations will rise.

We know little about the risks of drug error, and what we do know is imprecise and difficult to apply to individual patients. As the median age of the community rises, the natural rates of disease and death increase, so making it harder to recognise drug-related disorder or mortality. We should expect reasonable levels of risk in relation to both hospital care and drug treatment, say 1 in 1000 admissions for injury and 1 in 10,000 for death respectively, corresponding with mortality risks linked to best-practice treatment of common disorders and general anaesthesia respectively. Nonetheless, reports from highly regarded US teaching hospitals suggest the risk of death due to

medication error is 7 times and the risk of drug-related harm is about 70 times greater than these proposed standard risk levels. Limited pharmacy data suggest low risk levels for drug-related injury and death in Singapore hospitals, but we need systematic and rigorous audits to detect events that might otherwise be wrongly attributed to natural causes.

What Can We Usefully Do?

We need to make innovations in some crucial areas. Physicians should provide the community with realistic and balanced ideas about treatment-related benefits and risks through health education programmes already in place.

For risk management, we have first to establish, as accurately as possible, the background rates of drug-related harm in the denominator population, which should comprise as large a proportion of the community as practicable. This requires a nation-wide pharmacovigilance system devolved to hospitals and clinics. Hospital audit criteria can help enforce a minimal level of data entry into the system. Post-marketing monitoring of unwanted drug events by pharmaceutical companies can contribute to the database, but will only be useful for newly marketed drugs.

Then we should recruit human factors specialists, systems engineers and other professional analysts to help in individual hospitals to:

- 1) ensure regular professional checks on the safety of medical, in particular drug-based, treatments;
- 2) establish procedures and systems to enhance safety, based on careful studies to identify dangerous behaviours and threats to the safety of patients and staff;³¹
- 3) set up computer-guided systems to minimise the effects of mistakes in the prescription and administration of drugs;
- 4) exploit information technology to train and retrain both people and systems, e.g. by using simulators.

All these national and institutional initiatives will carry appreciable costs, but such costs may also be regarded from a fresh viewpoint. Data collection should be considered outcomes research and quality improvement. A joint venture between the health administration and the pharmaceutical industry can turn the pharmacovigilance system into an investment. Computerised adverse event monitoring is the technology to embrace. When all the groundwork is completed, Singapore can then lead in devising methods using hand-held computers or mobile telephones to guide professionals to deliver low-error drug treatments to patients. This can create a niche enterprise for people with the right stuff.

Conclusion

Community education in the balanced perception of healthcare related risks and benefits is important. Hospital managers and physicians together should make serious attempts to measure accurately the levels of risk to patients and decrease the risk of injury and death from drug treatment, because medication is highly prone to error. Clinical treatment guidelines should give doctors, wherever possible, accurate and explicit risks as well as benefits in simple numerical terms. All healthcare professionals should aim at halving the rate of medication-related errors. We need non-punitive systems for reporting error and adverse drug events to a central vigilance database and computer-led checking procedures to enhance safety. Singapore could lead the world in devising ways for computers to guide professionals in giving minimum-error drug treatment to patients.

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