Harms from medicines: inevitable, in error or intentional

Robin E. Ferner^{1,2}

¹West Midlands Centre for Adverse Drug Reactions, City Hospital, Birmingham B18 7QH and ²School of Clinical and Experimental Medicine, University of Birmingham, B15 2TT, UK

Correspondence

Professor Robin E. Ferner, West Midlands Centre for Adverse Drug Reactions, City Hospital, Dudley Road, Birmingham B18 7QH, UK.

Tel.: +0121 554 3801

Fax: +0121 507 5236

E-mail: r.e.ferner@bham.ac.uk

Keywords

adverse drug reaction, dose–response, forensic pharmacology, medication error, susceptibility

Received

16 February 2013

Accepted

29 April 2013

Accepted Article

Published Online

20 May 2013

Rational therapeutics requires a balance between benefits and harms. (i) Harm may be inevitable. Some adverse drug reactions cannot be predicted or prevented. (ii) Some harm occurs in error when a medicine is wrongly formulated, prescribed, dispensed or administered. Adverse drug reactions that might have been prevented, for example, by monitoring, fall into this category. (iii) Rarely, harm is inflicted deliberately, for example, in murder by poisoning. Here I consider adverse drug reactions, errors and deliberate drug-induced harm from the perspective of a clinical pharmacologist.

Introduction

Many clinical pharmacologists, and more pharmaceutical physicians, are optimists. They dwell on the benefits of therapy and not on its harms. Rational therapeutics, though, requires that the likely benefit of a treatment be balanced against the risks of harm. Aronson has coined the term ‘balanced prescribing’ to describe this aspect of rational therapeutics [1]. Some harms are inevitable even in an ideal world, while others might be avoided, or at least mitigated. The harms fall into the categories of adverse drug reactions, medication errors and intentional acts.

Adverse drug reactions

Consideration of dose–response, time course and susceptibility allows a rational polytomous approach to adverse drug reactions, which is more useful than a simple dichotomous approach.

Dichotomy

The first textbook of adverse drug reactions, *Die Nebenwirkungen der Arzneimittel: Pharmakologisch-klinisches Handbuch*, was written by Louis Lewin in 1881. Alexander, in his Translator’s Preface to the first English

translation [2], wrote of the importance of ‘the incidental, accidental or unexpected effects (Nebenwirkungen) of drugs upon the various organs and systems of the body . . .’

Adverse drug reactions, that is to say, harms from drugs, properly used, are sometimes the inevitable (‘incidental’) consequence of using the medicine. This is most obviously the case when a drug has two or more pharmacological actions, only one of which is beneficial. For example, when an opiate is given, its action in relieving pain cannot be separated from its action in causing nausea. Inevitability of this sort is entirely predictable and understandable from our knowledge of μ -opioid receptors.

However, the idea has grown up that there is another class of adverse drug reactions, inevitable because they represent some process that occurs only in individual patients. These adverse effects were labelled *idiosyncratic* by Gunn in his *Introduction to Pharmacology and Therapeutics* [3]. Clark expanded on the idea of idiosyncratic reactions in three papers on ‘*Individual variation in the response to drugs*’ published in the 1930s [4–6]. As Clark stated the matter, most people, given enough aspirin, would develop gastric irritation. ‘On the other hand in the case of about one person in 10 000, quite a small amount of acetylsalicylic acid may produce a general urticaria which is a wholly abnormal response that could not be produced in the rest of the population by any dose of the drug.’

Dose dependence

The dichotomous approach distinguishes 'predictable and understandable,' dose-dependent adverse reactions, labelled in the modern incarnation of this approach Type A, from others, Type B, which are 'unpredictable, not understandable in the current state of pharmacological knowledge and not dose-dependent.' [7]

This is curious. Many uncommon reactions are related to dose within the therapeutic range, and might be regarded as Type B or unpredictable adverse reactions, or both. For example, '[t]he neuropsychiatric effects of glucocorticoids involve affective, behavioral and cognitive manifestations. Serious neuropsychiatric effects occur in about 6% of patients who receive steroids. Although the effects of glucocorticoids are unpredictable, the administered dose is the most significant risk factor for the development of neuropsychiatric symptoms' [8]. The risk of gastrointestinal haemorrhage with non-steroidal anti-inflammatory drugs, which is explicable but unpredictable, varies several-fold across doses in the therapeutic range [9] and the incidence of a positive direct antibody (Coombs') test with methyl dopa depends strongly on dose [10].

Dose-responsiveness is an inevitable consequence of drug-receptor interactions. Like all chemical processes, their rates depend on the concentration of reactants, and

the concentrations of reactants and products at equilibrium are in a fixed ratio. This is the Law of Mass Action, first proposed (in Norwegian) in 1864 [11]. Krönig & Paul, following Kahlenberg & True's studies in plants [12], applied chemical principles to disinfection at the end of the 19th century [13], and Chick extended their results, demonstrating that the rate of bacterial death was proportional to the number of surviving bacteria, 'in accord with the Law of Guldberg & Waage' (that is, the Law of Mass Action) [14].

The concept of receptors and the consequences of receptor theory were elaborated during the first half of the 20th century by Langley and others. Hill, working with Langley, showed in 1909 that the temperature coefficient of the effect of nicotine on muscle contraction could not be accounted for by physical diffusion, and the 'combination between nicotine and a 'receptive substance' ... is of an ordinary chemical nature' [15]. He also derived the hyperbolic form of the dose-response curve from the premise of a chemical combination of drug and receptor.

The first example I have found of a plot of response against the logarithm of the dose, which we now know well as the log dose-response curve, was published in 1926, when Clark used it to demonstrate the action of acetylcholine on frog rectus abdominis [16]. (Figures 1 and

Figure 1

The ontogeny of the logarithmic dose-response curve

Figure 2

Clark's drawing of the proportion of maximal contraction of frog rectus abdominis against the logarithm of the dose of acetylcholine (from reference [16]). The original title was 'Action of acetylcholine in producing isotonic contraction of the *Rectus abdominis* as a function of concentration'

2). He noted that 'the relation between the concentration and action of acetylcholine in most cases follows the formula $K \times x = y/(100 - y)$ and the simplest explanation of this fact is to suppose that a reversible monomolecular reaction occurs between the drug and some receptor in the cells.'

Clark was also aware of the work of Galton [17] and MacAlister [18] on the log normal distribution, which could be used to interpret many data on human attributes, including those attributes explained by Weber's law, later extended by Fechner, that the least discernible increment in stimulus was a constant proportion of the initial stimulus.

The acceptance that interactions between drugs and receptors were chemical, and that the log dose-response curve was consistent with this therefore came from two separate threads: the Law of Mass Action and the fact that many human phenomena followed a log normal distribution.

With this firm background in theory, it is perhaps surprising that the concept of dose-responsiveness was so readily abandoned for 'unpredictable' adverse drug reactions. Immunological reactions, such as anaphylaxis and delayed-type hypersensitivity, make up the bulk of these 'unpredictable' adverse reactions, and (as Aronson and I have discussed elsewhere) [19] are clearly dose-related; but not within the therapeutic range of doses. This leads to the simple conclusion that there is no need to abandon the

laws of nature, and in particular the Law of Mass Action, to explain adverse drug reactions. However, some adverse reactions reach maximal (asymptotic) intensity at concentrations way below those needed for any beneficial effect, and indicate *hypersusceptibility* to the adverse reaction and others are manifest only at concentrations higher than those generally used in therapy and represent (dose-dependent) *toxic* reactions. When an adverse drug reaction follows a dose-response relationship similar to the beneficial effect, the damage is 'collateral.'

Time course

Some adverse drug reactions, notably anaphylaxis, occur within minutes of the administration of the causative agent, as Richet described in his 1913 Nobel lecture: 'the symptoms characteristic of the second injection, namely swift and total depression of the nervous system, do not in any way resemble the symptoms characterizing the first injection.' Other reactions may not be manifest for years after exposure. Herbst described clear cell carcinoma of the vagina in young women who had been exposed to diethylstilbestrol *in utero* when they were, on average, nearly 20 years old [20]. Some adverse reactions usually occur, if they are going to occur, within a specific time frame. For example, clozapine-induced agranulocytosis is unlikely if it has not occurred in the first 6 months of treatment [21]. The time course of a reaction is therefore often of clinical significance and for many reactions is a defining characteristic.

Susceptibility

The problem remains that many adverse reactions, including many serious ones, occur in some patients but not all. The idea of hypersusceptibility, defined above in terms of dose-response, dates back to the 1920s. Gunn in his student textbook *Introduction to Pharmacology & Therapeutics* [22], first published in 1929, stated that 'An individual may show an excessive reaction to a normal dose (hypersusceptibility), for example infants are hypersusceptible to opium ...' Twenty years before, it had been taken as a synonym for anaphylaxis: 'Anaphylaxis (*ana*, against, and *phylax*, guard, or *phylaxis*, protection), also called hypersusceptibility, supersensitiveness, is a condition of unusual or exaggerated susceptibility of the organism to foreign substances' [23]. It is clear that Gunn did not mean this, for he went on to say that an individual may show 'an unusual reaction (idiosyncrasy proper), for example, a usual dose of quinine produces in a small proportion of people a severe nettle rash.'

It is best to view 'susceptibility' as the patient-related factors that increase the probability of an adverse reaction. For some adverse reactions, there will be a division between those who may be susceptible and those who are not susceptible in any circumstances. For example, there is zero probability that a drug given to a post-menopausal woman will reduce fertility. Gender is therefore one of the

determinants of susceptibility, and age is another. Dopamine receptor antagonists cause dystonic reactions in children, but Parkinsonism in elderly people [24]. While the precise status of race, a hybrid and ill-defined characteristic made up of genetic, cultural, and social components, is unclear, and while the definitions used in pharmacoepidemiological studies are often omitted, there is evidence that race influences an individual's susceptibility to disease. The probability that a patient of African heritage will develop angioedema with an angiotensin-converting enzyme inhibitor is three times that for a similar European patient [25]. Japanese patients are particularly susceptible to amiodarone-induced lung disease [26].

Early examples of genetic susceptibility to adverse reactions, such as streptomycin-induced deafness [27] and haemolysis in people with glucose-6-phosphate dehydrogenase deficiency [28], have in recent years been augmented by more detailed studies of the human genome. These studies have uncovered, for example, a genetic predisposition to statin-induced rhabdomyolysis [29]. More intriguing, but less easily understood, are the very specific HLA-associations with toxic epidermal necrolysis in patients treated with abacavir [30], for example. It now seems that abacavir binds specifically to HLA-B*5701, changes the configuration of the antigen-binding site and causes it to recognize endogenous peptides as 'foreign' [31].

Medication errors

Clinical pharmacology texts tend to an idealized view of therapeutics, but in practice errors in the formulation, prescription, dispensing and administration of medicines are common. As a consequence, treatments are less effective and more dangerous than they should be [32]. Pharmacists who screened prescriptions written by junior hospital doctors identified error rates of 8.9% [33]. Whether this is an accurate estimate is matter of debate, because satisfactory operational definitions are lacking [34]. In consequence, others have quoted error rates in between 4.2% and 82% of patient prescription charts [35].

We have proposed the following definition. A medication error is 'a failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient' [36]. We amplified this by explaining that 'failure' means failure to reach an attainable standard (a benchmark). When Yu *et al.* examined definitions of medication error, this definition was best able to distinguish between scenarios that represented error and those that did not [37]. It is the basis for the definition adopted by the Australian Council for Safety and Quality in Health Care. One problem that arises in assessing the prevalence of medication errors is in counting the occasions on which errors do not occur, that is, in defining the denominator. Another difficulty is that in most circumstances, the potential outcomes for the

patient (successful treatment, failure to treat the condition for which the medicine has been prescribed, harm to the patient) are the same for both correct and incorrect treatment. It follows that observing the patient may not uncover medication errors.

As an alternative, we have examined errors in prescribing and administration by estimating the concentration of infusions of acetylcysteine, whose dose depends on patient weight. We found that proportion of doses between 80 and 120% of expected values was 0.6, and between 50 and 150% only 0.9 [38] (Figure 3). A subsequent study of morphine infusions showed that of the 464 infusion preparations, 161 (35%, 95% CI 30%, 39%) contained concentration errors [39].

It is not clear which step in preparing a solution for injection or infusion contributes most to the error. To examine this, we constructed a flow diagram of the process and undertook a systematic review to provide estimates of error rates at different stages [40]. This model showed that when a solution for injection is prepared, the risk of least one error is almost 0.7 and the most error prone step is reconstitution (drawing up and adding diluent to the drug powder). Removing this step by providing pre-prepared solutions might reduce the proportion of erroneous injections to less than 0.2, although some of this improvement might be attenuated by the introduction of new errors associated with choosing solutions of the correct concentration.

Another strategy for reducing medication errors is to guide prescribers when they write prescriptions by combining electronic prescribing, that is, 'computerized prescriber order entry', with information, and in the most egregious cases, prohibition, that is, 'computerized decision support.' It seems obvious that errors will be reduced

Figure 3

The number of infusions of acetylcysteine against the percentage of the expected dose for 184 infusions; proportion of doses between 90% and 110%, between 80% and 120%, 50% and 150%, and 0% to 300% of expected values were, respectively, 0.4, 0.6, 0.9 and 1.0 (from reference [38])

by replacing a scrawled hand-written prescription with a legible one, and replacing the prescriber's fallible checking of those factors, contra-indications, dose limits, drug–drug interactions and so on, that might modify prescribing with automatically generated warnings, alerts, and interdictions. The evidence, however, lags behind the intuitive response [41]. Warnings of drug allergy do seem to be effective, but elsewhere data are less clear [42]. One reason may be that the senior doctors who make prescribing decisions do not use the systems [43]. Another is that the introduction of electronic prescribing systems can lead to new errors [44], or numb or irritate prescribers by displaying numerous alerts, which may then be ignored or cancelled [45]. Alerts should be less frequent and intrusive if it is possible to integrate demographic, clinical and prescribing information, so that they are only displayed when appropriate [46].

Intentional harm

The administration of medicines to cause deliberate harm is probably uncommon. When the perpetrator is a nurse or doctor, and the scene of the crime a hospital ward, several events may occur before the suspicion of poisoning arises. Even when poisoning is suspected, it may be difficult to prove that this is so 'beyond a reasonable doubt' (the standard required for a criminal conviction).

The role of the clinical pharmacologist in assessing such cases is usually to consider clinical, pharmacological and analytical data, and form an unbiased opinion as to the relation between them [47] [48]. The factors that are relevant to assessing adverse drug reactions are also relevant here: trivial doses do not kill, the time from administration to action of a dose of poison is characteristic and the harm done depends on the susceptibility of the patient.

The estimation of dose from post-mortem concentrations causes special and complex problems [49] [50]. The phenomenon of post-mortem distribution, which depends on the physical and pharmacokinetic properties of the drug, makes back-extrapolation very difficult. It also makes it unwise to define a 'fatal concentration' above which death must have been due to the drug [46].

For example, ethanol concentrations above 500 mg 100 ml⁻¹ of blood have been regarded as fatal [51]. Nonetheless, concentrations exceeded this in 5% of 693 cases [48] and a 24-year-old woman was reported to be conscious and talking with a blood ethanol concentration of 1510 mg 100 ml⁻¹ [52].

Part of the assessment is to examine the competing causes for the observed events. In the case of death of hospital patients, the co-existence of natural disease may make it uncertain what role the administration of a medicine played in terminal events. This is a particular difficulty in cases of alleged criminal negligence manslaughter

(negligence leading to death and so bad as to constitute a crime).

Conclusions

Harm from medicines is an important area of study and reflection for clinical pharmacologists, who have to balance possible benefit against potential harm. The identification of susceptible patients may reduce the inevitability of adverse drug reactions. The assessment of medication error rates is a problem that needs to be solved in order to demonstrate that methods of reducing error rates have been successful: medication errors seem refractory to attempts at prevention. The analysis of murder by drugs should take into account changes after death and competing causes. It is hardly surprising that an observer of the trial of Dr William Palmer in 1856 concluded that 'The contradictory deductions and tetanic complications of medical professors . . . make wise men tremble, good men sad and bad men bold'.

Competing Interests

REF is Director of the MHRA's West Midlands Regional Monitoring Centre and NHS Member of the NICE Appeal Panel. The views expressed in this review are his own and do not necessarily reflect those of any institution. REF also provides expert evidence in medico-legal matters.

Many teachers and colleagues have contributed to the views expressed in this review and I am very grateful to them. The ideas elaborated here have come in large measure from discussions with Jeffrey Aronson and would not be laid out so clearly, or at all, without our long debates and without Dr Aronson's helpful comments on a draft of this paper. I am also indebted to Professor Humphrey Rang who steered me towards Hill's 1909 paper.

REFERENCES

- 1 Aronson JK. Balanced prescribing. *Br J Clin Pharmacol* 2006; 62: 629–32.
- 2 Lewin L. The Incidental Effects of Drugs. A Pharmacological and Clinical Hand-Book. Translated by W.T. Alexander. New York: William Wood and Company, 1882.
- 3 Gunn JA. An Introduction to Pharmacology and Therapeutics. London: Oxford University Press, 1929.
- 4 Clark AJ. Individual variation in the response to drugs. *Lancet* 1934; i: 1149–50.
- 5 Clark AJ. Individual variation in the response to drugs. *Trans Edin Med-Chir Soc* 1935; 42: 1–18.

- 6 Clark AJ. Individual variation in response to drugs. *BMJ* 1937; 2: 307–10.
- 7 Rawlins MD. Clinical pharmacology. Adverse reactions to drugs. *Br Med J (Clin Res Ed)* 1981; 282: 974–76.
- 8 Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics* 2012; 53: 103–15.
- 9 Lewis SC, Langman MJ, Laporte JR, Matthews JN, Rawlins MD, Wiholm BE. Dose-response relationships between individual non-aspirin non-steroidal anti-inflammatory drugs (NNSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. *Br J Clin Pharmacol* 2002; 54: 320–6.
- 10 Breckenridge A, Dollery CT, Worledge SM, Holborow EJ, Johnson GD. Positive direct Coombs tests and antinuclear factor in patients treated with methyl dopa. *Lancet* 1967; 2: 1265–7.
- 11 Waage P, Guldberg CM. Studier over Affiniteten. Forhandlinger i Videnskabs-selskabet i Christiania 1864: 35–45. (Henry I. Abrash, Translator). *J Chem Educ* 1986; 63: 1044–7.
- 12 True RH. The physiological action of certain plasmolyzing agents. *Bot Gaz* 1886; 26: 407–16.
- 13 Krönig B, Paul T. Die chemischen Grundlagen der Lehre von der Giftwirkung und Desinfection. *Zeitschrift für Hygiene und Infektionskrankheiten* 1897; 25: 1–112.
- 14 Chick H. An Investigation of the Laws of Disinfection. *J Hyg (Lond)* 1908; 8: 92–158.
- 15 Hill AV. The mode of action of nicotine and curari, determined by the form of the contraction curve and the method of temperature coefficients. *J Physiol* 1909; 39: 361–73.
- 16 Clark AJ. The reaction between acetyl choline and muscle cells. *J Physiol* 1926; 61: 530–46.
- 17 Galton F. The geometric mean, in vital and social statistics. *Proc Roy Soc Lond* 1879; 29: 365–7.
- 18 McAlister D. The law of the geometric mean. *Proc Roy Soc Lond* 1879; 29: 367–76.
- 19 Aronson JK, Ferner RE. Clarification of terminology in drug safety. *Drug Saf* 2005; 28: 851–70.
- 20 Herbst AL, Green TH Jr, Ulfelder H. Primary carcinoma of the vagina. An analysis of 68 cases. *Am J Obstet Gynecol* 1970; 106: 210–8.
- 21 Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis – incidence and risk factors in the United States. *N Engl J Med* 1993; 329: 162–7.
- 22 Gunn JA. An Introduction to Pharmacology and Therapeutics. London: Humphrey Milford Oxford University Press, 1929; 11.
- 23 Anderson JF, Rosenau NJ. Anaphylaxis. *Arch Intern Med* 1909; 3: 519–68.
- 24 Bateman DN, Darling WM, Boys R, Rawlins MD. Extrapyramidal reactions to metoclopramide and prochlorperazine. *QJM* 1989; 71: 307–11.
- 25 McDowell SE, Coleman JJ, Ferner RE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. *BMJ* 2006; 332: 1177–81.
- 26 Wolkove N, Baltzan M. Amiodarone pulmonary toxicity. *Can Respir J* 2009; 16: 43–8.
- 27 Pražić M, Salaj B, Subotić R. Familial sensitivity to streptomycin. *J Laryngol Otol* 1964; 78: 1037–43.
- 28 Carson PE, Flanagan CL, Ickes CE, Alving AS. Enzymatic deficiency in primaquine-sensitive erythrocytes. *Science* 1956; 124: 484–5.
- 29 SEARCH Collaborative Group, Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R. SLCO1B1 variants and statin-induced myopathy – a genomewide study. *N Engl J Med* 2008; 359: 789–99.
- 30 Mallal S, Phillips E, Carosi G, Molina J-M, Workman C, Tomazic J, Jagel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; 358: 568–79.
- 31 Alfirevic A, Park BK, Pirmohamed M, Naisbitt DJ. Explanation for HLA-B*57:01-linked immune-mediated abacavir-induced hypersensitivity. *Pharmacogenomics* 2012; 13: 1567–9.
- 32 Routledge PA. Safe prescribing: a titanic challenge. *Br J Clin Pharmacol* 2012; 74: 676–84.
- 33 Dornan T, Darren Ashcroft D, Heathfield H, Lewis P, Miles J, Taylor D, Tully M, Wass V. An in depth investigation into causes of prescribing errors by foundation trainees in relation to their medical education. EQUIP study. 2009. Available at http://www.gmc-uk.org/about/research/research_commissioned_4.asp (last accessed 9 June 2013).
- 34 Lisby M, Nielsen LP, Brock B, Mainz J. How are medication errors defined? A systematic literature review of definitions and characteristics. *Int J Qual Health Care* 2010; 22: 507–18.
- 35 Ross S, Bond C, Rothnie H, Thomas S, Macleod MJ. What is the scale of prescribing errors committed by junior doctors? A systematic review. *Br J Clin Pharmacol* 2009; 67: 629–40.
- 36 Ferner RE, Aronson JK. Errors in prescribing, preparing, and giving medicines: definition, classification, and prevention. In: *Side Effects of Drugs Annual*, ed. Aronson JK. 22. Amsterdam: Elsevier Science, 1999; xxiii–xxvi.
- 37 Yu KH, Nation RL, Dooley MJ. Multiplicity of medication safety terms, definitions and functional meanings: when is enough enough? *Qual Saf Health Care* 2005; 14: 358–63.
- 38 Ferner RE, Langford NJ, Anton C, Hutchings A, Bateman DN, Routledge PA. Random and systematic medication errors in routine clinical practice: a multicentre study of infusions, using acetylcysteine as an example. *Br J Clin Pharmacol* 2001; 52: 573–7.
- 39 Parshuram CS, To T, Seto W, Trope A, Koren G, Laupacis A. Systematic evaluation of errors occurring during the preparation of intravenous medication. *CMAJ* 2008; 178: 42–8.
- 40 McDowell SE, Mt-Isa S, Ashby D, Ferner RE. Where errors occur in the preparation and administration of intravenous

medicines: a systematic review and Bayesian analysis. *Qual Saf Health Care* 2010; 19: 341–5.

- 41** Roshanov PS, Fernandes N, Wilczynski JM, Hemens BJ, You JJ, Handler SM, Nieuwlaat R, Souza NM, Beyene J, Van Spall HGC, Garg AX, Haynes RB. Features of effective computerised clinical decision support systems: meta-regression of 162 randomised trials. *BMJ* 2013; 346: f657.
- 42** Schedlbauer A, Prasad V, Mulvaney C, Phansalkar S, Stanton W, Bates DW, Avery AJ. What evidence supports the use of computerized alerts and prompts to improve clinicians' prescribing behavior? *J Am Med Inform Assoc* 2009; 16: 531–8.
- 43** Baysari MT, Westbrook JI, Richardson KL, Day RO. The influence of computerized decision support on prescribing during ward-rounds: are the decision-makers targeted? *J Am Med Inform Assoc* 2011; 18: 754–59.
- 44** Redwood S, Rajakumar A, Hodson J, Coleman JJ. Does the implementation of an electronic prescribing system create unintended medication errors? A study of the sociotechnical context through the analysis of reported medication incidents. *BMC Med Inform Decis Mak* 2011; 11: 29.
- 45** Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, Weingart SN. Overrides of medication alerts in ambulatory care. *Arch Intern Med* 2009; 169: 305–11.
- 46** Ferner RE, Coleman JJ. An algorithm for integrating contraindications into electronic prescribing decision support. *Drug Saf* 2010; 33: 1089–96.
- 47** Ferner RE. Toxicological evidence in forensic pharmacology. *Int J Risk Saf Med* 2012; 24: 13–21.
- 48** Ferner RE. *Forensic Pharmacology-Medicines, Mayhem and Malpractice*. Oxford: Oxford University Press, 1996.
- 49** Skopp G. Postmortem toxicology. *Forensic Sci Med Pathol* 2010; 6: 314–25.
- 50** Ferner RE. Post-mortem clinical pharmacology. *Br J Clin Pharmacol* 2008; 66: 430–43.
- 51** Jones AW, Holmgren P. Comparison of blood ethanol concentration in deaths attributed to acute alcohol poisoning and chronic alcoholism. *J Forensic Sci* 2003; 48: 874–9.
- 52** Johnson RA, Noll EC, Rodney WM. Survival after a serum ethanol concentration of 1 1/2%. *Lancet* 1982; 2: 1394.