Medical management of deliberate drug overdose: A neglected area for suicide prevention?

D Gunnell, D Ho, V Murray

Objectives: Overdoses account for a quarter of all suicides in England. The number of people who survive the immediate effects of their overdose long enough to reach medical attention, but who subsequently die in hospital is unknown. The aim of this study was to determine the proportion of overdose suicides dying in hospital and describe their sociodemographic characteristics.

Method: Cross sectional analysis of routinely collected Hospital Episode Statistics data for England (1997 to 1999) to identify hospital admissions for overdose among people aged 12+ and the outcome of these admissions.

Results: Between 1997 and 1999 there were 233 756 hospital admissions for overdose, 1149 (0.5%) of these ended in the death of the patient such deaths accounted for 29% of all overdose suicides and 7% of total suicides. The median time between admission and death was three days (interquartile range one to nine days). The most commonly identified drugs taken in fatal overdose were paracetamol compounds, benzodiazepines, and tricyclic/tetracyclic antidepressants.

Conclusion: Around a quarter of all overdose suicide deaths occur subsequent to hospital admission. Further more detailed research is required to discover if better pre-admission and inhospital medical management of those taking serious overdoses may prevent some of these deaths.
hospital bed with a diagnosis of heart attack many weeks after the overdose admission was assumed to have died from an unrelated condition. Altogether we extracted HES records for 1590 possible cases of inhospital death after admission for overdose. After inspection of these we excluded 441 cases for one of the following reasons: (1) the patient was transferred to another trust (most commonly a mental health trust) after their overdose and died several days later, the diagnoses listed for their final episode of care appeared to be unrelated to the drugs they had taken in overdose; (2) patients with cancer whose episodes of care after overdose were coded as only relating to cancer; (3) two accidental poisoning deaths (where food poisoning (T codes T61–T62)) identified as the cause of death.

RESULTS
Between 1 January 1997 and 31 December 1999, 1149 people—569 (49.5%) females, 577 (50.2%) males, and three (0.3%) where sex was unrecorded—died in hospital after admission for overdose: a rate of about 380 deaths/year. Eight hundred and seventeen (71.1%) of the episodes were coded as intentional overdoses, in 49 cases (4.3%) the person’s intention was undetermined and for 283 (24.6%) the overdose was coded accidental. In the same three year period, there were a total of 233,756 hospital admissions for overdose; the estimated case fatality for hospital admitted overdose was therefore 0.49%. Over the same period there were 15,560 suicides, including 4003 overdose suicides in England (personal communication Office for National Statistics). The 1149 inhospital deaths therefore account for 29% of all overdose suicides and 7% of all suicides.

Figure 1 shows the age/sex distribution of inhospital overdose deaths. The mean age of male deaths was 56.5 years (range 15 to 94) and for females it was 58.2 years (range 15 to 94). The greatest number of deaths (n = 342) occurred among those aged 75+ (range 12 to 99). The greatest number of deaths (n = 342) occurred among those aged 75+, otherwise the deaths were fairly evenly distributed over the six age groups, with similar numbers of male and female deaths. Among those aged 75+, 114 (33.3%) of the deaths were coded accidental, this figure for all other age groups combined was 20.9%, indicating that the excess of deaths in this age group may be at least partially attributable to a higher proportion of genuine accidents ($\chi^2$ (2df) 19.9 $p<0.001$).

The main category of drug taken was coded for only 926 (80.6%) of the deaths. Two drug groups accounted for most of these cases: analgesics and antipyretics (n = 488 (52.7%)) and psychotropic drugs (n = 362 (39.1%)). Nineteen deaths (2.0%) were associated with pesticide ingestion. Table 1 gives the main specific drugs taken in overdose. The figures here are likely to be underestimates of the use of these drugs as for many records no specific drugs were listed. Fifty two deaths were caused by overdoses of anticoagulants, insulin and oral hypoglycaemics, cardiac glycosides or thyroxin; 26 (50%) of these were coded as accidental.

The median time between admission and death was three days (interquartile range one to nine days). Figure 2 shows the time (in days) between admission and death for subjects dying within the first 21 days of admission. Four hundred and thirteen people (35.9%) died within one day of their admission and 821 (71.5%) died within seven days. The median time between admission and death was two days for overdoses involving non-opioid analgesics/antipyretics and three days for overdoses involving psychotropic drugs.

Examination of the six additional diagnosis fields included in the HES data enabled us to identify a number of conditions likely to have contributed to death. The most frequently recorded diagnoses (proportion of all deaths) were: hepatic failure: 197 (17.1%); cardiac arrest: 135 (11.7%); pneumonia: 104 (9.1%); cerebral anoxia: 49 (4.3%), and septicaemia: 37 (3.2%). Sixty three (5.5%) of the deaths had a diagnosis of malignant neoplasia recorded in one of their diagnosis fields.

DISCUSSION
Using HES data for England we have estimated that there are about 380 inhospital deaths a year after admission for drug overdose. These deaths account for around 29% of overdose suicides and 7% of all suicides. Thus while most people who commit suicide by drug overdose are already dead when they are discovered, we have identified that a sizeable proportion reach hospital alive, but die subsequently as a consequence of their overdose.

Paracetamol containing analgesics, benzodiazepines, and tricyclic/tetracyclic antidepressants were the commonest single drug groups involved. These drugs were also the most commonly taken medicines, except those associated with drug misuse, mentioned on death certificates for all (inhospital and community) poisoning deaths in England and Wales between 1994 and 1998. In a recent study by Calzada et al. (2002), it was found that the majority of deaths from paracetamol poisoning were due to self-harm, while the majority of deaths from benzodiazepine poisoning were due to suicide. The authors suggested that the use of these drugs as non-prescription medicines may be a contributing factor to the high number of deaths from these drugs. The authors also emphasized the importance of identifying and preventing such deaths, as it is estimated that up to 30% of suicide attempts involving these drugs are fatal. Further studies are needed to investigate the potential for preventing some of these deaths. Secondly, HES are collected for administrative rather than research
purposes and so there are likely to be some inaccuracies in the coding of both overdoses and deaths. The specific drugs taken in overdose were not coded for around a quarter of cases. Some reassurance concerning data quality was obtained from the observation that 145 (73.6%) of the 197 patients with diagnoses of hepatic failure had taken overdoses that included paracetamol containing compounds either alone or in combination with other drugs. Lastly, we used comparatively inclusive criteria to define suicidal overdose and so will have slightly overestimated inhospital mortality related to deliberate overdose. We thought it probable that few of the deaths in 12–74 year olds were truly accidental, however in older subjects accidental overdose/drug toxicity is more probable, possibly resulting from the effects of cognitive impairment and poly-pharmacy. While such deaths may not have been suicides, they nevertheless contribute to the overall burden of morbidity and mortality arising from drug overdose. Because of comorbidities, those aged 75+ are likely to be at greater risk from the adverse effects of overdose. This highlights the particular need for careful prescribing in this age group.

A number of studies have reported inhospital morbidity and mortality related to overdose of particular drugs. The most commonly reported complications are arrhythmias, seizures, hypoxic brain damage, aspiration pneumonia, and hepatoxicity. In some cases these complications may be preventable by following appropriate management guidelines and by use of sources of expert advice on poisoning. There is evidence, however, of variation in adherence to guidelines promoting best practice.

There are several approaches to reducing morbidity and mortality associated with drug overdose. These include: (1) population strategies aimed at improving population mental health; (2) encouraging general practitioners to prescribe drugs that are safer if taken in overdose; (3) minimising the amount of drug taken in overdose by restricting the quantity prescribed or sold over the counter; (4) disseminating hospital management guidelines on the treatment of overdose involving particular drugs; and (5) ensuring all those involved in the acute management of overdose are made aware of and use where appropriate, authoritative management advice from National Poisons Information Services.

Most suicide attempts occur within the context of acute psychological distress. With appropriate management, most episodes of depression improve and only 5% to 10% of people who survive deliberate drug overdose go on to commit suicide. It is therefore possible that improvements in the pre-admission and inhospital management of acute drug overdose may reduce long term sequelae among survivors, prevent a proportion of suicide deaths, and contribute to suicide reduction targets. It is acknowledged, however, that many inhospital deaths may not be preventable because the person has suffered profound cerebral anoxia or developed aspiration pneumonia before admission. Furthermore, overall mortality among hospital admitted overdoses is low (0.5%) and the costs of interventions to improve upon this low rate should be balanced against other approaches to prevention.

More detailed information, perhaps derived from a national confidential inquiry into inhospital deaths from drug overdose, is required to determine whether there are any aspects of management that could reduce mortality from this cause. Potentially important interventions might include protocols for ambulance crews concerning initial management/antidote administration and adherence to National Poisons’ Information Services Guidelines for the management of all cases.

**ACKNOWLEDGEMENTS**

ONS for information on overdose and total suicide deaths in England 1997–1999. Hospital Episodes Statistics (HES) data were made available by the Department of Health to the authors courtesy of the HES National Service Framework project (Professor Shah Ebrahim and colleagues), funded by a South and West Regional project R&D grant. Advice on using HES was obtained from Dr Steven Oliver. An extract of HES is held by the Department of Social Medicine, University of Bristol, the MRC HSRU are data custodians and also fund some of the support costs. The Department of Social Medicine is the lead Centre of the MRC Health Services Research Collaboration.

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**REFERENCES**


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The editors will decide as before whether to also publish it in a future paper issue.

An unusual cause of massive fatal epistaxis

A 90 year old woman was admitted to our accident and emergency department with spontaneous brisk epistaxis. On arrival she was profoundly hypotensive and unresponsive. Her airway and breathing were managed according to Advanced Life Support protocol. Volume resuscitation was started and intranasal packs used in an attempt to curtail the epistaxis. Unfortunately these measures were unsuccessful and the patient died shortly after presentation.

Postmortem examination revealed an 8x6x3 cm internal carotid artery (ICA) aneurysm in the base of the skull extending into the ipsilateral anterior and middle fossae and crossing the pituitary fossa to reach the contralateral anterior fossa. There was patchy erosion of the contralateral basal skull bones and a large defect communicating with the nasal space. The cause of death was recorded as epistaxis secondary to ICA aneurysm.

Epistaxis is a common symptom that can usually be managed conservatively by means of anterior and posterior gauze packing.1 It is rarely caused by ICA aneurysm.2 Attempted management of epistaxis secondary to ruptured ICA aneurysm using standard measures is often futile and mortality is high.3 For this reason other techniques have been devised for use in the acute situation, including internal carotid artery ligation at the neck4 and endovascular methods such as balloon embolisation,5 stent deployment,6 and the use of microcoils.7

It is intended to raise awareness of a less common but dramatic cause of epistaxis that is commonly fatal if undiagnosed.

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References

BOOK REVIEWS

Current management of scaphoid fractures. Twenty questions answered


In 1992 Nicholas Barton, the author fronting this book, wrote an article, published in The Journal of Hand Surgery, reviewing the management of scaphoid fractures by considering 20 questions. In this book he presents the state of play in 2002 by posing each of those questions to nine international experts. Mr Barton’s coauthors Günal and Calli collate the responses in the form of 20 chapters while Mr Barton summarises each chapter and adds his own opinions. The result is a very readable overview of the subject.

The questions deal with each stage in the fracture’s management from how to make the initial diagnosis, how best to treat it, when to operate, and through to what to do when it all goes pear shaped. The book will thus be of interest to anyone who deals with this troublesome fracture in any way and therefore to all of us in A&E. It is, however, bedtime reading rather than of any use when battling on the front line.

The review will also interest those of us who wear a managerial/c clinical director’s hat and who wish our juniors to work according to evidence based direction, the review does allow us to re-consider our own practice. Its relevance will, of course, vary between units depending upon how many chapters’ worth each department gets involved in scaphoid management.

I found this a useful and easy to read book. I am grateful to the EMJ for asking me to review it as I would have probably otherwise dismissed it as being orthopaedic interest only.

N Jenkins

Poisonous plants and fungi in Britain and Ireland—identification systems on CD-ROM


Poisonous plants and fungi is a fun, easy to use guide in identifying plants and fungi commonly seen in the areas we live. The pictures used on the CD ROM are excellent as they show the various plants/fungi in different stages of growth and seasons.

The CD ROM works by asking a series of questions about the plant/fungi in question. A process of elimination begins from your responses to the questions. This can be time consuming as you may be asked up to 20 different questions; this is done to reduce the result to less than five possible suspects. You may decide to skip questions, this will then result with a list of up to 229 suspects to search through.

Once a suspect is identified you can then search through the following list about the suspects, if still unsure you may then move to view the next suspect; photographs are available to view with a zoom facility, a summary on the plant/fungi, the toxicity of the suspect.

A print option is also available, and you can exit at any point and restart your search.

The CD ROM also allows the medical practitioner to look at poison syndromes, asking specific questions about symptoms and time of onset, then giving you a possible poison syndrome and the plants/fungi involved.

There are some botanical words that may leave you baffled, do not worry as there is a glossary that you can access through the help icon. (I did this many times!)

From an emergency department perspective this is a useful tool, but the editors do state this is only a guide and the content should not be used for diagnostic purposes and therefore a need to contact the poisons information is still required.

It should be remembered that the plants/ fungi covered are only aimed for Britain and Ireland and therefore cannot be used for those returning from foreign travel. The CD ROM is in colour, and the editors also state that a colour blind person should not use this.

This software is excellent for teaching anyone about various toxins found in common plants and fungi. Teachers in schools or parents at home could use it. However, in the emergency department setting it should be
Medication errors. Lessons for education and healthcare


“Never judge a book by its cover!” This proverb has particular relevance to Professor Naylor’s book as “medication errors” discurses a wide range of challenging issues. In particular, as well as an account of drug errors, the book is also pertinent and detailed commentary on adverse event reporting, risk management, and, consequently, clinical governance.

About one million patients a day in the UK visit their hospital interacting with 700,000 healthcare staff. Many of these patients receive medication and even with a low error rate of 0.0001%, this would still result in a hazard to around 250,000 patients a year. Of such, drug errors are undoubtedly an important public health risk and the single most common form of medical error.

The book defines the extent of this global problem in all healthcare environments. Professor Naylor is both incisive and controversial in his analysis of the causes, risk factors, and cost of medical errors. The effect of high intensity workloads, especially in critical care settings is explored. He also discusses a wide range of challenging issues. In particular, as well as an account of drug errors, the book is also pertinent and detailed commentary on adverse event reporting, risk management, and, consequently, clinical governance.

In summary, this is a book that should be available in every hospital library rather than in the emergency department book list.

A S Gloster

Emergency nursing care: principles and practice


Prepare yourself for a whistle stop tour through A&E!! This book gives a good overall view of emergency nursing. It provides a valuable insight into issues as diverse as the emergency care of the child and adolescent to dealing with major disasters.

It is easy to read and well set out, although in certain sections the clarity of the book is marred by the overuse of tables. The book provides background information as well as acting as a quick reference guide to assist the practitioner in practice.

The text is also account the many recent changes in emergency care policy driven by the Department of Health and therefore is “up to date” and relevant on a national basis. It is well referenced and offers a good guide and evidence based practice.

It would be an ideal text for anyone wishing to enter the Faculty of Emergency Nursing, especially at level W and as such is an excellent book for students and staff new to emergency care. In addition aspects of this book, for example, “Emergency Care of the Older Person”, would be particularly useful to personnel involved in prehospital care such as paramedic practitioners.

Anyone wishing advice in a specific area of emergency care, for example, minor injury, would need to access specialist text. However, this is true of any general A&E text, as it would take someone with the proportions of Arnold Schwarzenegger to lift a book with everything in it.

The authors have succeeded in writing a book that fills a gap in the market, “unchattered” by irrelevance, and will be valued by many emergency care practitioners.

J Perrin

Recent advances in anaesthesia and intensive care


This is the 21st edition of this book spanning over 70 years of anaesthetic care. In this edition the title and contents have been changed to reflect the increasing importance of intensive care. The book is, of course, aimed principally at clinicians in anaesthesia and intensive care. The book covers in detail very specific but a wide ranging list of anaesthetic related topics. These include among others the pharmacology of COX2 inhibitors, neumopathic pain, education and training in anaesthesia, prone ventilation, and advances in resuscitation. The chapters are well written and are detailed reviews of the current literature relating to recent advances in each topic.

This is not a book that will be read from cover to cover by the emergency physician. The chapters are detailed and are not formatted in a manner that allows the casual browser to dip into them and glean relevant information. It would, however, be a useful reference source for clinicians looking for up to date reviews on specific subjects.

The chapters on asthma and recent advances in resuscitation are reasonable summaries of the current concepts and issues in these clinical areas and are pertinent to all individuals practising emergency medicine. Some of the non-clinical chapters such as those on education and training, managing medical mishaps, and the legal aspects of anaesthesia have generic information that is also of relevance to our specialty.

In summary, this is a book that should be available in every hospital library rather than in the emergency department book list.

A Gray

ABC of spinal cord injury, 4th edn


An old adage states that anyone can become an expert if they choose a small enough field. Emergency physicians have to know a little bit about the emergency management of everything, our expertise being limited not by condition but by time. I found it refreshing to read the ABC of Spinal Cord Injury, which illustrates perhaps the limits of specialisation and the holistic approach that such patients need, not only from the medical specialties but from the nursing, physiotherapy, occupational therapy and community support teams.

The book is clearly written and illustrated in the BMJ ABC series format. The chapters are arranged to follow the time course sequence of a patient with spinal injuries. Emergency physicians may be most interested in the first five chapters, covering epidemiology and prehospital care, initial management and assessment, radiological investigations, medical management, and early complications. I have great difficulty remembering each individual muscle group or exact dermatomes while in the resuscitation room so I was particularly grateful to read about the American Spinal Injury Association (ASIA) impairment scale and the associated form allowing clinicians to accurately record neurological deficit. A copy of this form would be a welcome addition to the emergency medical notes, comparable to the Lund and Browder charts that we use for burn patients. Other current topics in the emergency management of spinal injury such as the use of corticosteroids in the acute phase and the use of emergent MRI are also discussed.

Perhaps one of the disadvantages of the book to the emergency physician is hinted at by the title, ABC of Spinal Cord Injury. The number of patients that we see with potential spinal injuries is great but thankfully few patients will turn out to have significant injury. “Clearing” the spine is a vital skill for the emergency physician to learn, but cannot be covered by a book dealing with only the injured patient.

A few minor criticisms. There is wide spread use of acronyms and jargon. AUS is not the country with kangaroos but bilateral urinary sphincter and SARS (sacral anterior root stimulation) in a spinal injury unit.

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would not provoke immediate isolation. Interestingly while poikilothermia is used by both a physician and a nurse author, only the nurse fully explains its meaning. The greatest value of this book lies in reading the chapters outside your own area of expertise. I recommend this book to all clinicians involved in the management of patients with spinal cord injuries. Most particularly, we should all jump out of our little boxes of specialisation and read the chapters by the paramedical specialists and about the care of patients with spinal injuries in the developing world. While the book will not cover every question that the experienced clinician needs to ask it will raise awareness that management of patients with spinal cord injury is life itself and is best approached with a broad mind.

P J Harmbrey

Fundamentals of anaesthesia, 2nd edn


This book is intended for anaesthetists in training. The editors set out to generate a text book encompassing the primary FRCA syllabus with their first edition and have now come up with a new and improved version. If you are sitting the primary FRCA exam, then this book has a lot to offer: there are four sections and 963 pages in all, and it measures up to the competition. The first section is all about clinical anaesthesia, and is the most relevant to emergency department doctors. The second and third sections cover physiology and pharmacology, while the final section deals with physics and clinical measurement. Much of the later sections are not really necessary for us in the emergency department, and to tell the truth I expect our somewhat short attention spans will not extend to details of light transmission and absorbance. If this is your thing, though, you will not be disappointed.

The editors have taken a lot of trouble to ensure there is consistency of style, which makes reading it easier, and the layout is reader friendly. Tables and figures are monochrome or highlighted with shades of peacock plum which becomes a little dull after a while. If I were using this book to work for an examination, more colours would help make it all seem worthwhile.

I suspect most emergency department doctors own or intend to own a reference book on anaesthesia. The choice depends on what you do in your department: if RSI is de rigueur, then a book like Fundamentals would be a good back up to the Manual of Emergency Airway Management. If you devolve this responsibility to the anaesthetist on call, then a smaller book would be more appropriate, and you would cross you fingers that the anaesthetist has read and understood a book like Fundamentals of Anaesthesia...

A Fletcher

Clinical research


Until recently books and articles on how to research have been scarce. Those available have been challenged to bridge the gap between that of the authors and the novice reader. The result has been a tendency to turgid texts with confusing examples, requiring an exceptional tenacity of the reader.

The authors of this comparatively small book are from an anaesthesia/intensive care background and are used to teaching specialist list registrars on research issues. Their stated objectives are to provide comprehensive, concise, and easily accessible information on all aspects of audit and research for the busy trainee preparing for specialty examinations. Emergency medicine is not represented in the 23 contributors therefore rendering the book of generic research interest rather than specific to emergency medicine. With the possible exception of the final chapter on Intensive Care National Audit and Research Centre (ICNARC) the book remains highly relevant to the emergency medicine trainee.

The authors have achieved their objectives. There are 41 short easy to read chapters through 206 pages covering the inspiration (research ideas) to publication (peer review) of research issues. There are ample home chapters offering overviews (medical research as part of postgraduate training, and research process). There are 16 chapters on statistics. There are examples and diagrams as appropriate. In all the style is neat, trim, and lean as each chapter tightly divides into headings, subheadings, and bullet points. Despite being concise the material is intellectually accessible and does not leave the reader lost somewhere along the explanation of concepts. In achieving this, the authors demonstrated their teaching experience and it is this accessibility that I liked most about the book.

Though appropriately targeted at the specialist registrar, I would also recommend other staff to look through to lighten up those dark areas of their knowledge or just where the memory has dimmed. Each chapter has suggested further reading.

For as broad a title as Clinical Research, one might anticipate a section on how to evaluate clinical research, but this is not included. How to go about and how to evaluate research are in a sense sides of the same coin and there are ample texts on evaluation elsewhere. A short chapter though offering a generic approach or approaches to research interpretation might be seen by specialist registrars to have pulled many issues together, helping their knowledge and exam prospects, and above all their future clinical practice.

This book however is still an excellent one. I can envisage it becoming essential reading for specialist registrars in emergency medicine and others like the rest of us, to have learnt quickly and move on. Others wanting to understand research issues will find the contents demystifying whether new to clinical practice or well established. It would be an excellent book for medical libraries. I am very grateful for the editors of this journal for bringing it to my attention. Now, how does that logistic regression thing work again? Oh yes, here is the chapter, in three pages.

A Good

ABC of clinical electrocardiography


I thought that the ABC of Clinical Electrocardiography was excellent when published as a series of articles in the British Medical Journal. Collecting these articles together has created a book that is a pleasure to read. It is pitched at exactly the right level for the emergency medicine practitioner—comprehensive, but without getting distracted into the esoteric.

The format of the book is easily readable, with every page having many examples of ECGs, or diagrams, to illuminate the text. Key points are collected together with the liberal use of headings to break otherwise complex subject into digestible pieces. This format means that the book might also appeal to the interested undergraduate who wanted to go beyond the basics of ECG interpretation. The structured and visual format will make this book a useful quick reference in the clinical setting.

The book does exactly what it says on the cover. There is no information about the man in the street or the underlying clinical conditions, which has enabled the ABC of Clinical Electrocardiography to remain concise and to the point.

The first chapter contains a revision of the basic patterns of rhythm disturbances and their diagrams. The rest of the first half of the book deals with common arrhythmias and myocardial infarction. Coverage of these subjects in some detail seems to be very appropriate. I liked the fact that a chapter on exercise testing was included, as this investigation is likely to be moving much closer to the emergency department in the future, and may well come under the remit of the emergency physician in a clinical decision unit. Subsequent chapters are about conditions affecting the right and left heart, and conditions causing ECG abnormalities from a non-cardiac causes. The paediatric chapter contains more information than most of us will need, but may be useful for those working emergency department near paediatric cardiac centres.

In the introduction Francis Morris suggests that ECG interpretation is all about pattern recognition. This book certainly improved my pattern recognition skills.

T J Coats

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An authors’ error occurred in this paper by Dr Guillot and others (2004; 21:35–8). Incorrect totals for the number of suicides in England 1997–1999 were given. The figures wrongly included deaths coded E988.8 (accelerated death registration, most usually homicides). The correct figures (excluding those coded E988.8) are 4889 in 1999 (not 5292 in 2000 as stated in the text: see lines 6–7, para 1 introduction). Paragraph 1, lines 11–15 of the Results section should read: “Over the same period there were 14419 suicides, including 4033 overdose suicides in England. The 1149 in-hospital deaths therefore account for 28% of all overdose suicides and 8% of all suicides.” These corrected figures of 28% and 8% should also have appeared in the abstract (results line 2) and the Discussion, paragraph 1 lines 3 and 4.