Bandolier *Extra*

Adverse drug reactions in hospital patients

A systematic review of the prospective and retrospective studies

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Executive Summary

Adverse drug reactions (ADRs) in hospital are a significant cause of morbidity and mortality. We have examined the literature for evidence:

1   To estimate incidence of ADRs causing hospital admission or occurring whilst in hospital in the UK and in other countries.
2   To estimate the burden of ADRs (lengthened hospital stay, cost, capacity) for the UK.
3   To identify risk factors for ADRs.
4   To identify research into means of reducing adverse drug reactions.

We found a large literature, with 108 primary studies involving 412,000 patients. ADR incidence was lower since 1985 than before 1985. Across all studies since 1985 there was considerable consistency. Information from the UK was sparse, but indicated that the UK was similar to Europe, with ADRs affecting about 7% of patients or admissions. Rates in North America were half those in Europe before and after 1985.

The overall ADR impact on England is therefore estimated to be 4 out of 100 hospital bed-days, about 15-20 400-bed hospital equivalents at a cost of about £380 million a year to the NHS in England. One in 10 of all NHS bed days are taken up by the consequences of ADR or hospital acquired infection.

Factors associated with increased incidence of ADR were increasing age (especially over 70 years), increasing number of medicines and particular classes of medicine. Antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, and NSAIDs are responsible for between 60% and 70% of all ADRs leading to hospital admission or causing ADRs within a hospital episode.

Computer aids to prescribing have consistently been shown to cut ADR rates by about half in a number of settings. This has implications for the current health service IT development. We recommend urgent action to tackle waste from ADR and hospital acquired infection as part of quality control and clinical governance.

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Background

Lazarou [1] and colleagues have highlighted the public health importance of adverse drug reactions (ADRs) in hospital. They demonstrated that in-hospital ADRs ranked between the fourth and sixth leading cause of death in the USA. *'Primum non nocere'* - 'first of all be sure you do no harm' - has long been a principle of the practice of medicine, and there are many examples of pioneers like Osler and Semelweiss promoting this cause. Barr [2], addressing the American Medical Association in 1955, argued that "*one of the great hazards in the use of potent drugs is their inherent toxicity*", continuing "*the dangers of the drug appear to be greater now than ever before*". He went on to describe what he considered the outstanding example of digitalis.

Some 45 years later the active ingredient of digitalis continues to be implicated in many adverse drug reactions. Adverse drug reaction reporting systems exist, but these are recognised as consistently under-reporting the true incidence of ADRs. They cannot easily be used to assess true rates of ADRs especially those leading to hospital admission, prolongation of hospital stay, or death.

The last few decades have seen an immense growth in availability and consumption of medicines. Whilst most consumers derive far more benefit than harm, a proportion of patients experience undesirable effects from the use of medicines at recommended doses and frequencies. For some the effects are sufficiently severe to require hospital treatment and a few will die.

For example, non-steroidal anti-inflammatory drugs (NSAIDs) are responsible for 12,000 hospital admissions a year because of gastrointestinal bleeding [3], the equivalent of one 400-bed hospital working at capacity. They cause about 2,000 deaths a year because of gastrointestinal bleeding [3], of the same order as the 3,500 road deaths. NSAIDs kill 1 in 1,200 people who take them for two months or more [4], and the gastrointestinal harm costs the NHS about £250 million a year [5]. Each Primary Care Group of 100,000 people will have 50 hospital admissions a year in over-65s because of the combined gastrointestinal bleeding, heart failure and renal failure from NSAIDs.

In spite of this, adverse drug reactions are not generally considered to be a public health problem. Reviews tend to have been restricted to specific geographical regions and language of publication. The review by Lazarou and colleagues in 1998 [1] included 39 American studies and the calculated rate of serious ADRs was 6.7% (95%CI 5.2-8.2%). The rate of fatal ADRs was 0.3% (0.2%-0.4%) making ADRs a serious public health issue.

The Lazarou paper only considered North American work. It was decided therefore to undertake a systematic review of studies in the world-wide literature:

♦ To estimate incidence of ADRs causing hospital admission or occurring whilst in hospital in the UK and in other countries.
♦ To estimate the burden of ADRs (lengthened hospital stay, cost, capacity) for the UK.

♦ To identify risk factors for ADRs.
♦ To identify means of reducing adverse drug reactions and evaluate their potential impact.

Methods

A comprehensive search was made of MEDLINE (1966-1999), EMBASE (1980 to 1999) and International Pharmaceutical Abstracts (1970 to 1999), unrestricted as to language. We sought prospective or retrospective studies investigating ADRs. These included patients who were admitted to hospital as the result of an ADR and /or experienced an ADR during an inpatient stay. Search terms included "adverse drug" or "adverse reaction", "iatrogenic", "drug-related" or "drug-induced" and "hospital". We also examined reference lists of reviews and retrieved reports. Studies were sought with the following designs:

♦ Hospital medical record review whilst patient was in hospital or later review.
♦ Follow-up survey after release from hospital.
♦ Case-control, cohort
♦ Sample of patients versus all patients with ADRs.

The following information was extracted from each paper where possible: primary author, country, period and date of study, clinical setting, study method, number of patients, reported outcomes including an ADR rate, any estimate of the costs of ADRs, and a list of the main drugs implicated. There was no restriction in terms of the definition of ADR but we excluded events caused by administration errors, non-compliance, overdose, drug abuse or therapeutic failures. Information on deliberate or accidental self-harm with drugs was excluded. Duplicate publications of the same data were identified but were included in the analysis only once.

Definitions

For the purposes of this review, definitions of adverse drug reaction are those given below:

◊ **Adverse Drug Reaction**: an event that is noxious and unintended and occurs at doses in humans for prophylaxis, diagnosis, therapy or modification of physiologic functions [6]. This definition excludes intentional or deliberate overdose and drug abuse.
◊ **ADR rate**: proportion (percentage) of patients or admissions who had an ADR definitely or probably related to a drug.
◊ **ADRad**: Patients admitted to hospital due to an adverse drug reaction
◊ **ADRin**: Patients experiencing an ADR while in a hospital.
◊ **Type A reactions** are caused by known toxicity of the drug and related to dose and pharmacological effect, like bleeding caused by the anti-coagulant warfarin. This group of reactions is potentially preventable.
◊ **Type B reactions** are idiosyncratic or allergic in nature. Reactions that usually occur from the initial use of a drug

in a patient are not predictable and therefore not preventable.

Analysis

We pooled studies to calculate the weighted mean ADR rate according to study design (prospective versus retrospective), geographical setting, clinical setting, before and after 1985 (an arbitrary date, to reflect changes in prescribing over the period of the studies and the emergence of care of the elderly as a separate medical speciality), and whether the ADRs were ADRin or ADRad. Weighting was by the number of patients or admissions. Calculations used Excel version 5.0 and were performed on a Macintosh G3. Graphical representation of data shows size of study according to the size of the symbol, and by year of publication for comparability between graphs, where the horizontal line represents the weighted mean for that analysis.

Results

The search strategy identified 138 potentially relevant papers. One review [7] described 10 studies not found by the search, and because they only appeared in the grey literature no attempt was made to obtain them. Several authors published aspects of a single study in a number of related papers.

Twenty-six papers were clearly not relevant because they did not assess ADRs, were letters, methodological papers, economic studies, or were not relevant for some other reason. Reasons for excluding studies are in Table 1. For instance, 15 primary studies had no evaluable data, and there were 12 duplicated studies. Detailed reasons for exclusion are in Appendix 1.

Details of the remaining 112 studies and review articles are in Appendix 2, together with the references. Excluding duplicates there were 69 unique studies with evaluable data covering over 412,000 patients.

Study design

Of the 69 studies, 54 were prospective with an ADR rate of 5.5% (193,000 subjects) and 15 were retrospective with an ADR rate of 7.7% (220, 000 subjects).
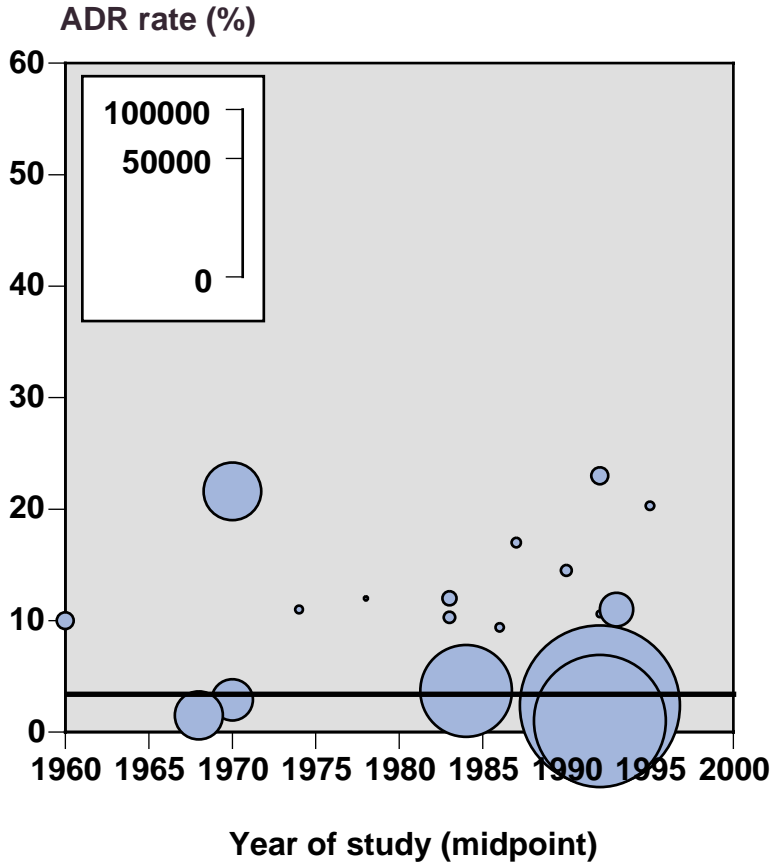
Geographical setting

Table 2 shows the country or region of origin, number of publications and numbers of patients. The size range is graphically illustrated for American studies (Figure 1), UK and Ireland studies (Figure 2) and European studies (Figure 3).

The analysis by world region is in Table 3. Most information was available from North America and Europe. European rates before and after 1985 were consistently higher (double or more) than those in North America, though in both cases rates after 1985 were lower than those before 1985. The amount of information from the UK was limited, but was in keeping with the European experience.

Table 2: Country of origin of included studies

Region of Study	No of publications	No of patients
North America	29	240,000
Europe excluding UK	22	114,000
United Kingdom	9	26,000
Australia / New Zealand	7	23,000
Middle East	3	9,000
Far East	3	3,292
South Africa	1	300
India	1	347

Table 1: Studies excluded from the review

| Reasons for exclusion	Number of studies
Had no evaluable data	15
Commentary/ letter	10
Methodology paper	8
Duplicate publication	12
Economic/medico-legal	3
Study did not assess ADRs (medication errors or drug interactions)	4
Review	9
Assessed management of ADRs	1
Assessed specific drug / drug class	2
Not a primary study	2
Presented different information from a published study	3

Figure 1: North American studies

ADR rate (%)

Weighted mean ADR rate:
4.6% (95% C.I. 4.5 to 4.7)

No. studies: 21

Total no. patients: 161,710

Mean study size:
7,700 (range 60 to 91,574)

Year of study (midpoint)

Figure 2: British & Irish studies
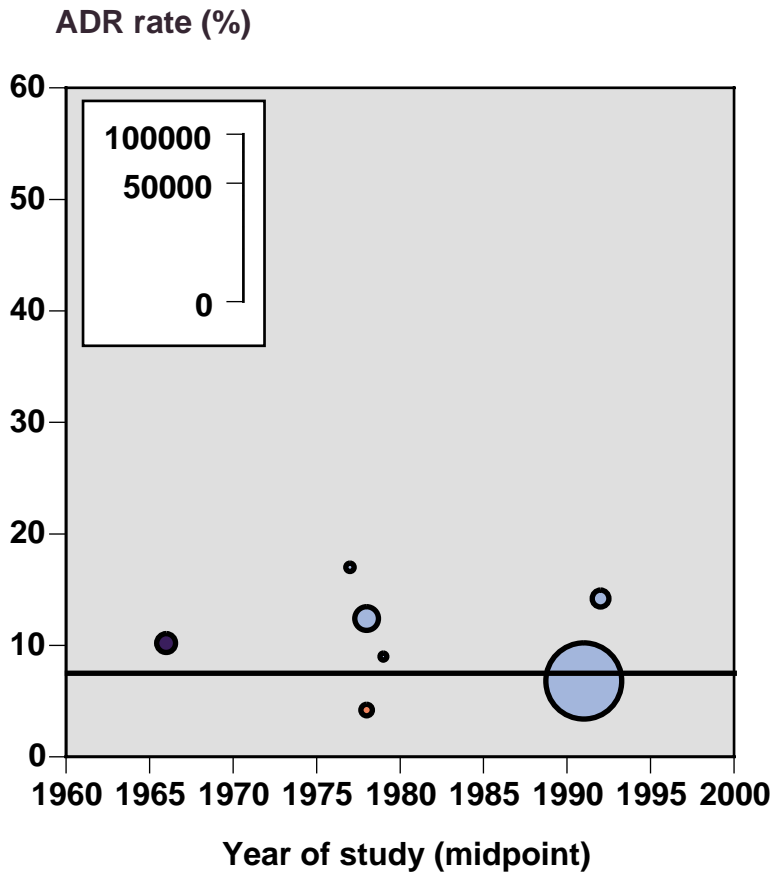
ADR rate (%)

UK

Northern Ireland

Republic of ireland
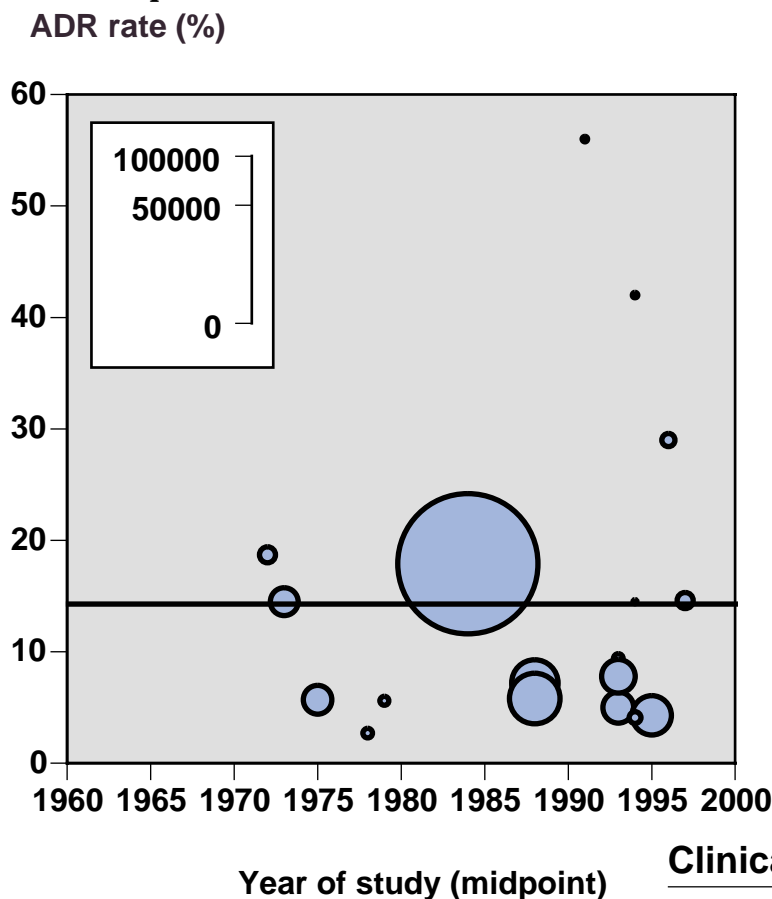
Weighted mean ADR rate:
7.5% (95% C.I. 7.2 to 7.8)

No. studies: 7

Total no. patients: 25,862

Mean study size:
3,695 (range 171 to 20,695)

Year of study (midpoint)

Figure 3: European studies

ADR rate (%)

**Weighted mean ADR rate:
14.1% (95% C.I. 13.8 to 14.3)**

No. studies: 21

Total no. patients: 113,841

**Mean study size:
5,421 (range 55 to 70,407)**

Year of study (midpoint)

Clinical setting

Table 4 shows ADR rates by clinical setting and date of study. The overwhelming bulk of information was in general medicine after 1985, where the fall in ADR rates after 1985 was apparent. The apparent large increase in ADR rate after 1985 for geriatric medicine may be due to either unreliability of data because of small numbers, or to a more systematic approach as geriatric medicine became more important as a specialty. The amount of information on paediatrics is probably too small to discuss, other than that it was generally in line with ADR rates in other specialties.

A recent systematic review and meta-analysis of adverse drug reactions in children [8] included 17 prospective studies and found an overall incidence of ADRs in children in hospital of 9.5%. The overall rate of hospital admissions due to ADRs was 2.1%. Significant proportions of these ADRs were life threatening (12% and 39% respectively). Unfortunately the review did not clearly define ADR, but included several studies published after 1999, and confirms the generally high rates of ADR.
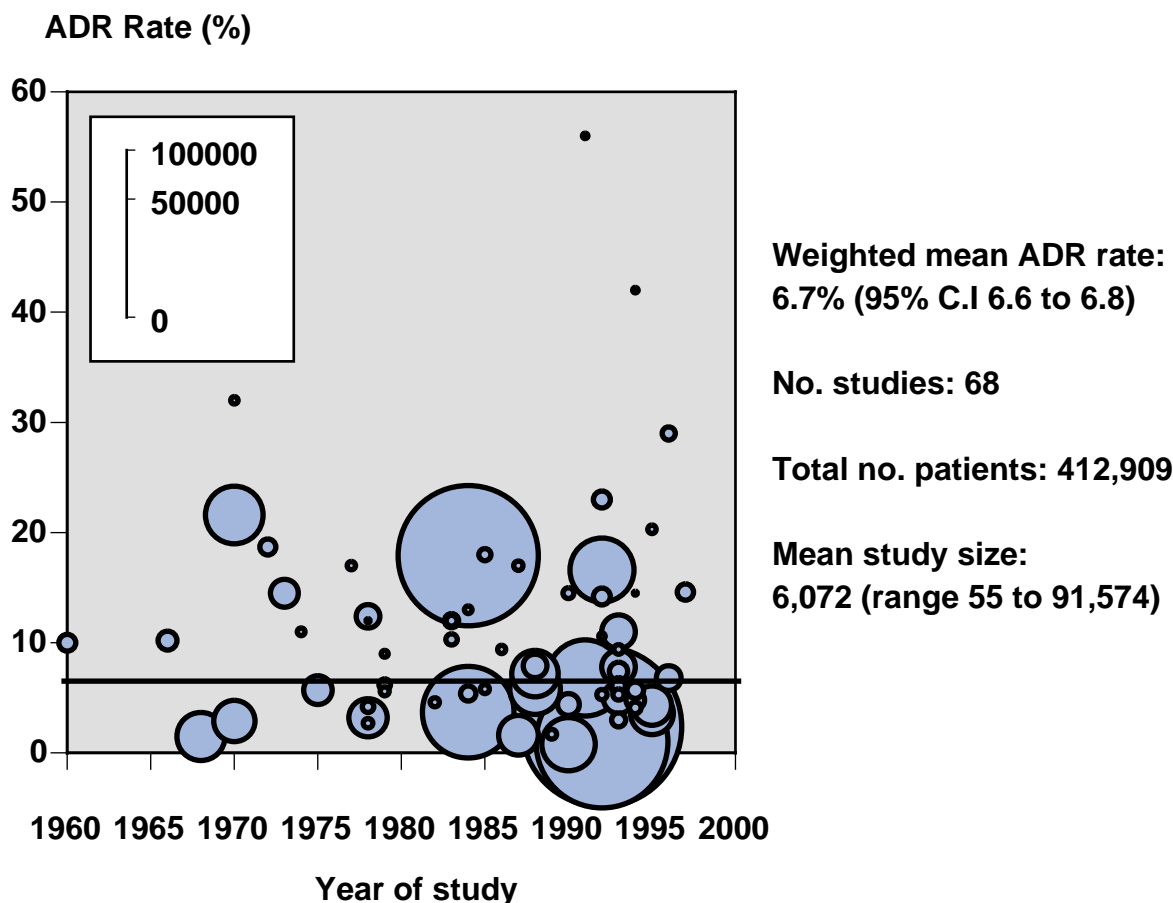
Table 3: ADR by geographical setting and time

Country/ Region	Pre/Post 1985	No of subjects	ADR rate % (95% CI)
North America	Pre	59665	8.1 (7.9-8.3)
North America	Post	172796	3.0 (2.9-3.0)
Europe	Pre	77628	17.2 (17-17.5)
Europe	Post	36203	7.3 (7.0-7.5)
UK	Pre	4156	10.9 (10-11.9)
UK	Post	21706	7.1 (6.8-7.5)
Middle East	Pre	No studies	
Middle East	Post	8771	4.4 (4.0-4.8)
Other	Pre	657	3.4 (2.0-4.8)
Other	Post	3639	4.9 (4.2-5.6)

Table 4: ADR by clinical setting and time

Speciality	Pre/Post 1985	No of subjects	ADR rate % (95% CI)
General medicine	Pre	60401	8.5 (8.2-8.7)
General medicine	Post	243803	2.9 (2.8-3.0)
Geriatric	Pre	11212	4.3 (3.9-4.7)
Geriatric	Post	3488	20 (19-21)
Paediatric	Pre	469	4.2 (2.4-6.0)
Paediatric	Post	837	3.1 (1.9-4.3)

Figure 4: ADR in all studies, by date of publication

Weighted mean ADR rate:
6.7% (95% C.I 6.6 to 6.8)

No. studies: 68

Total no. patients: 412,909

Mean study size:
6,072 (range 55 to 91,574)

Date of publication

The overall weighted mean ADR rate for evaluable studies was 6.7%. When these were calculated as studies published before 1985 and after 1985 the rates were 12.5% and 3.4%. This can be seen graphically in Figure 4. Nothing in the primary studies sheds any light on the reason for the apparent decline, but the obvious candidates are better understanding of possible ADR outcomes, better monitoring of prescribing, better conduct of studies, or better drugs.

Table 5 shows ADR rates for inpatients and for admissions caused by ADRs, including before and after 1985. Rates were similar for ADRin and ADRad, apart from ADRad before 1985 which had a relatively small number of patients.

Adverse drug reactions and the specialist setting

Cancer

Adverse reactions caused by cancer chemotherapy are specifically mentioned in seven general studies [9-15] and are the subject of a French cancer institute study [16]. ICD9 codes were used to identify patients who had experienced a potential ADR during a one-year period. One hundred and seventy one patients from 3429 in-patient stays (5%) presented with 313 different ADRs; 106 patients with 182 ADRs were classified as serious (resulting in death, requiring hospitalisation, prolonging hospitalisation, resulting in persistent or significant disability or life-threatening). Of serious ADRs 91% were of type A and predictable. In almost all cases the ADRs were due to cancer chemotherapy and were estimated to have increased hospital costs by 1.9% and drug costs by 15%.

Emergency Departments

Six studies (80,000 patients) examined the pattern of ADRs from the perspective of an emergency department. The largest study [17] of 62,000 visits to a US hospital reported that 1.7% of admissions were drug related but data were not available for ADRs. Anti-infectives were the greatest cause usually resulting in allergies with analgesic agents very closely behind. The authors reported that in many cases patients were unaware of potential adverse effects or allergic responses and this knowledge may have reduced the number of emergency department visits. A second US study [18] reported an ADRad of 0.015% although nearly 3% of all visits were drug related in some way. An Italian study [19] of 5497 patients visiting an emergency department over the course of one year found that 0.08% of patients were admitted due to an ADR. No detailed analysis of the drugs involved was carried out. Three other studies [11 20 21] were much smaller with fewer than 1000 patients. The key message that emerged was that ADRs were not a major issue for this patient population with other drug problems such as abuse, deliberate self-harm and non-compliance being of greater importance.

Table 5: ADR by inpatient or cause of admission and time

Setting	Pre/Post 1985	Number of studies	No of subjects	ADR rate % (95% CI)
ADRin	All	18	154154	3.7
	Pre	6	43897	4.0
	Post	12	110257	3.5
ADRad	All	37	133471	3.1
	Pre	15	20017	6.3
	Post	22	113454	2.6

Intensive care units

Using a broader definition of adverse drug events (ADE) that could include an administration error resulting in harm or an error at the drug ordering stage, Bates [9] reported a high incidence of ADEs in medical intensive care units of 19.4 ADEs per 1000 patient days. The mean number of drugs used was 15.5. The authors reported that 42% of ADEs in this study were considered to be preventable and observed that more severe ADEs were more often preventable. Leape [22] reporting on the same study shows the importance of pharmacists as full members of the intensive care team in reducing the numbers of ADEs but there is no data on the impact of pharmacists in preventing ADRs. A French study [23] from 1978 found that 12% (46 patients) of admissions to an intensive care unit were due to iatrogenic problems and almost a half of these were potentially avoidable. Iatrogenic disease was fatal in eight of 46 patients.

Psychiatry

One study [24] reported on adverse drug reactions in a female 55-bed ward at a psychiatric hospital in Italy. Patients had a mean age of 65 years with length of stay of 19.5 years. Prescriptions were reviewed quarterly and at the end of this one-year study. Just 12 ADRs were recorded with a mean of 228 prescriptions recorded on study days for the 55 patients. The most frequent effect was that of hypotension probably caused by zuclopenthixol, it was noted that 125 patients required laxatives to alleviate the anticholinergic properties of neuroleptics and antiparkinson drugs.

Surgical Units

Two different studies by Bates [9][25] reported ADE rates for surgical wards as 9 ADEs per 1000 patient days and 7 ADEs per 1000 patient days respectively. These numbers were lower than in medical or intensive care specialities in the same studies. An earlier 1982 [26] study across five hospitals in three countries reported a rate of 2.5 ADRs per 100 drug administrations. It is not easy to relate this to 1000 patient days and it should be noted that drugs included whole blood and packed red blood cells. A Veterans administration study from the 1960s [27] reported ADRs at the rate of 1.54%, the majority were allergic in nature with penicillins and X-ray contrast media responsible for 78% of all reactions.

Interaction between age and number of medicines

A number of studies examined ADR rates according to the number of medicines taken, and age, or the number of medicines taken in older people. Reasons why the older people are more liable to adverse drug reactions [28] include:

♦ The elderly receive more drugs.
♦ Illnesses in the elderly tend to be treated with drugs with a poor therapeutic ratio.
♦ Drug interactions occur due to polypharmacy.
♦ Poor compliance.
♦ Altered pharmacokinetics and pharmacodynamics.
♦ Elderly may have more type A reactions and fewer type B [29].

What is not disputed is that the elderly take more medications and that the incidence of all ADRs increases with the number of prescriptions, possibly exponentially. Most studies examining the interaction of age with number of medications were small (>1000 patients), and definitions of elderly varied.

♦ Carbonin [30] showed that in over 9,000 Italian patients, mostly over 60 years, the ADR rate increased from 1.2% with one medicine to 10% with nine and about 50% with 10.
♦ Grymonpre [33] examined ADR rates in Canadian patients over 50 years. The ADR rate was 5% with one or two medicines, rising to 20% or more above five medicines.
♦ Hurwitz [31] found that ADR rates were related to both increasing age, especially by 70 years and over, and with more than six medicines. This UK study (Belfast) was conducted in 1966, and may not therefore reflect contemporary trends.
♦ Leach [28] also reported increasing ADR rates, especially with more than four medicines, and in the over-80s, in Barnsley in 1986.
♦ Williamson [32] reported increasing ADR rising from 11% with one medicine to 27% with six medicines in 1998 patients in a survey of 50 UK geriatric units conducted before 1980.

Where ADRs were analysed according to type, the majority were Type A and therefore both predictable and avoidable [28][29]. Women were reported to be at greater risk of ADRs [33][34]. Other identified risk factors included three or more drugs [35], five or more diagnoses [35], admission with GI bleeding or haematuria [35], low cognition [34] and the number of new medications on discharge from hospital was a significant cause of ADRs in the community setting [34]. A range of medicines were implicated in studies; diuretics causing electrolyte imbalance [36], antibiotics causing diarrhoea [28], hypoglycaemic agents [37], warfarin and steroids [38], NSAIDs [39].

Adverse drug reactions with specific classes of medicines

Clear messages emerge from the literature relating to medications that are more likely to cause ADRs. The following appear frequently: antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, and NSAIDs, and each could be expanded to tell its own story in detail. In this overview we conclude from papers that estimate rates for all six classes of drugs that these are responsible for between 60% and 70% of all ADRs leading to hospital admission or causing ADRs within a hospital episode.

Antibiotics

Twenty studies provide some analysis of ADRs linked to antibiotics with this class of drugs responsible for approximately 7% of all ADRs [17][34][40][41]. Bates [9] states that antibiotics were responsible for 9% of preventable ADRs and 30% of non-preventable ADRs. Particular adverse effects were not generally reported, though one study claimed that reactions were predominantly allergy and diarrhoea caused by antibiotics. One case of deafness due to Netilmycin [42] is reported. Shapiro records three deaths thought to be due to super-infections related to antibiotics, though two of these patients had also been treated with high dose steroids. Classen reported a reduction in antibiotic related ADRs through the use of a computerised disease management programme [43].

Anticoagulants

Sixteen studies specifically mentioned anticoagulants, mainly with warfarin but with some references to heparin. In a large Australian study [15] 25 of 233 ADRs were linked to anticoagulants. The authors considered that 40% of these were preventable. A separate Australian study [44] of 90 admissions due to ADRs commented that warfarin was one of the three most implicated drugs (digoxin and NSAIDs were the others) and that warfarin frequently caused problems when used in combination with other medicines. Anticoagulants were implicated in serious adverse effects in a number of studies [44-47] including generalised haemorrhages, GI haemorrhage, haematuria and soft tissue haemorrhage. A number of studies reported deaths related to anticoagulant use [44][47][48]. Levy [48] reported that 23% of all patients receiving heparin complained of an ADR, and Miller [49] reported that 22% of all exposures to heparin resulted in an ADR. Bates reports that five patients in his study suffered the ill effects of a heparin pump being stopped and inadvertently not restarted (e.g. in order to collect blood samples to measure INR).

Digoxin and digitalis

Some 21 studies covered the issue of digoxin and digitalis toxicity and these drugs appeared as the second leading cause of ADRs in five studies [12][33][44][50][51]. Other studies describe ADRs with cardiac drugs and these have been excluded from this section. While digitalis is featured in early studies, it is clear that digoxin continues to be a difficult drug to manage. A 1995 study found three out of 16 admissions related to ADRs were caused by digoxin causing bradycardia, arrthymias, nausea, and vomiting [37]. The ADR rate was calculated as 16% by Miller [49], and 22% by Grymonpre [33] (ie if 5 patients are prescribed digoxin, one will suffer an ADR). Mackay [51] identified nine admissions due to digoxin among 68 ADR related admissions; on further examination the author concluded that the drug was contra-indicated or unnecessary in seven of these patients. Two older studies highlighted differences in ADR response to digitalis between genders. Hurwitz in 1969 [31] reported 11/90 men and 28/107 women suffered an ADR. Klein in 1976 [10] reported 60 patients requiring hospitalisation for digitalis related ADRs, of whom 48 were women.

Diuretics

Diuretics are commonly prescribed, particularly in the elderly. Fifteen papers reported ADRs associated with diuretics and while many of these were published before 1985, one elderly patient study [36] reported diuretics as the leading cause of ADRs. In this Dutch study of 105 patients, 56% of all admissions were taking a diuretic. Nineteen of 36 patients who were taking frusemide suffered an ADR usually in the form of dehydration or electrolyte disturbances. Overall diuretics were ranked between second and fifth as causes of ADRs leading to hospitalisation. An earlier study [49] stated that 12% of all exposures to frusemide and 18% of exposures to hydrochlorothiazide resulted in ADRs. Frusemide and thiazide diuretics were mentioned as commonly causing ADRs by a number of authors [12][26][32][49][50]. One study [35] reported orthostatic hypertension in two patients taking diuretics.

Hypoglycaemic Agents

Eleven studies report incidences of hypoglycaemia related to insulin and sulphonylureas. Reported rates of admissions due to ADRs caused by these agents were 6% [17], 7% [13], 11% [52] and 12% [40] all based on small numbers. Where defined, the majority of hypoglycaemic incidents were related to insulin. A Danish study by Hallas [40] reported 14 out of 157 admissions due to hypoglycaemia related to insulin use. A North American study [53] reported that 15% of drug related admissions were due to hypoglycaemic agents but some of these related to diabetic ketoacidosis in patients who had stopped taking their insulin. Two Hong Kong studies [54][55], where diabetes mellitus is common, reported higher rates of hypoglycaemia with sulphonylurea drugs; two thirds of admissions were due to sulphonylureas. Two patients in a Boston USA study died from the effects of hypoglycaemia related to insulin [47].

Non steroidal anti-inflammatory drugs

Twenty four studies describe ADRs relating to NSAIDs. A number of studies [9 12 14 17 40 42] describe NSAIDs as the leading cause of ADRs while others [33 34 51] rank NSAIDs lower, often fourth or fifth in causing ADRs.

A Scottish study [39] identified 144 drug related problems in 1011 elderly admissions; 17 patients reported an ADR with NSAIDs of which about half were preventable. Some 96 patients in the total cohort were taking NSAIDs, 70% without any form of gastric protection prophylaxis. The majority of admissions due to an ADR were for gastrointestinal side effects. An Australian study of 5623 admissions reported a high incidence of GI bleeds associated with NSAIDs [44]; of 20 patients in this category, 10 had been taking the medication for less than three weeks, and six patients were receiving two or more NSAIDs. Chan [54] also found a high incidence of GI bleeding in Hong Kong; NSAIDs were responsible for 28% of drug related admissions and aspirin for a further 12%. A study in Taiwan placed NSAIDs as a joint leading cause of drug related admissions together with Chinese crude drugs [42]. These Chinese crude drugs were difficult to identify and were often contaminated with corticosteroids or NSAIDs according to authors.

The most common adverse effects reported are GI bleeding and gastritis with a low incidence of allergy [17], renal impairment and erythema multiforma [11]. Hallas [40] calculated the rate of ADRs with NSAIDs to be 71 (95%CI 44-107) per 1,000,000 defined daily doses, and Tramèr [4] calculated one death for every 1200 patients taking NSAID or aspirin for more than two months. A number of reviews have documented the impact of NSAID gastrointestinal adverse events [56], but fewer describe heart failure [57 58] and renal effects [59 60].

Adverse drug reactions and gender

Gender differences were described above for ADRs relating to digitalis or digoxin. A Wisconsin based study [34] stated that women were twice as likely to report an ADR than men. Grymonpre [33] noted that women were more liable to develop adverse reactions to medicines. In a cohort [12] of over 6,000 patients, the 177 patients admitted due to an ADR were split 63% female and 37% male, very similar ratios were reported by Klein [10], Hallas [40], and Sceintman-McIntyre [17]. Higher rates of ADRs for women were mentioned in a number of other studies [38 44].

Cultural & geographical differences

El Bagir [61] reported that the most common ADRs reported by 56 patients admitted to a hospital in southern Saudi Arabia were upper GI bleeding and hepatic injury. Anti-tuberculosis drugs were the most common cause of hepatic damage. NSAIDs were the most common cause of GI bleeds. Anti-tuberculosis therapy was also a problem in a paediatric study conducted in India [62] though numbers were small. This group was one of a number reporting single deaths due to Stevens-Johnson syndrome due to sulphonamides during the period of the study.

In Lebanon [14] the authors report that there is very little restriction on drug use. Most (74% of 917) adults and (85% of 190) children reported self medication with NSAIDs. In spite of this, the authors note that this self-medicating behaviour did not seem to increase the development of ADRs. NSAIDs and cancer chemotherapeutic agents were cited as common problems in adults with children experiencing ADRs from NSAIDs and antibiotics. A study from Jordan [13] where drug regulation is similar to Lebanon showed that 26% of drug induced admissions were caused by self treatment, though the greatest cause of admissions were related to the adverse effects of chemotherapy and NSAIDs were the fifth leading cause of admission.

Two studies by Chan [54 55] report on adverse drug reactions in Hong Kong. Nearly 30% of ADRs were due to sulphonylurea drugs leading to hypoglycaemia, and 18% due to NSAID related GI bleeds. The authors note ADRs also due to combination OTC products not commonly available world-wide and also a few patients reporting problems with Chinese herbal medicine. These studies had particular problems identifying drugs ingested by subjects (59% and 42%) because the medicines were not labelled. A study from Taiwan [42] of 666 patients reported an ADR rate of 5.7% with type A and type B reactions in approximately equal proportions. Of the 38 patients who experienced an ADR, causes were as follows: anti-infective agents 17, cardiovascular drugs 5, herbal medicine 5, analgesics and NSAIDs 4, other drugs 7. NSAIDs and Chinese herbal medicines were leading causes of ADRs requiring admission to hospital with five patients each. Symptoms associated with Chinese herbals included: weight gain, oedema, tarry stools, pre-renal failure, hypokalaemia and hypertensive crisis, the ingredients of these mixtures could not be identified.

A useful review of 14 Australian studies [7] published between 1988 – 1996 reported that 2.4%-3.6% of all hospital admissions were drug related, and that 15%-22% of all emergency admissions among the elderly were drug related. We have not been able to access some of the original articles in this review as they form a part of the grey literature and could not be obtained.

Discussion

The Lazarou review has been criticised recently [63] on a number of points, including heterogeneity of studies, choice of numerators and denominators for calculating incidences based on events rather than patients, and the value of extrapolating small numbers of fatal ADRs to a whole population. The Kvasz critique fails to acknowledge the consistent magnitude of adverse drug reaction events reported in many studies in many clinical areas and many different countries. While some of the criticisms may be justified, there is a consistent pattern of ADRs that, even in more contemporary settings, are high and of real significance to individuals and institutions. While the *impact* of ADRs is not well described, there is little doubt that they contribute to diminished patient experience, longer stays, and higher costs.

Based on patient data not events, we estimate the weighted mean rate of ADRs to be 7.5% (26,000 subjects) in the UK and Republic of Ireland compared to 3.5% (232,000 subjects) for North America.

Impact on the NHS in England

A complete estimate of the impact of ADRs on the NHS would be a large undertaking. What we have done in this report is to provide a simple estimate of the likely order of the effect. To estimate the impact we have chosen to use statistics from the Department of Health site (http://www.doh.gov.uk/public/stats1.htm) accessed on August 31 2001 for the year 2000.

Admissions with ADR (ADRad)

There were 14,600,000 A&E visits in 2000. We estimated that 10% of these were likely to be admitted, and that of the admissions 2.6% would be because of adverse drug reactions. The figure for ADRad of 2.6% was obtained from worldwide studies, and predominantly from North America where ADR rates tend to be about half those in Europe and the UK (Table 5).

The calculation gives a figure of 38,000 admissions caused by ADRs. If 12,000 were for NSAID-related gastrointestinal bleeds with a median in-patient stay of 14 days, and the remaining 26,000 had a median in-patient stay of only three days, then the total bed-days used would be 246,000, equivalent to two 400-beds hospitals at average occupancy. If the ADRad were higher, closer to the overall ADR figure of 7% for Europe and the UK, this would result in four to six 400-bed hospitals having their entire capacity subsumed in dealing with admissions caused by ADRs.

Inpatient ADR (ADRin)

There were 186,290 beds, at 83% occupancy, giving 56,436,556 bed-days available for patients. For calculating the possible impact of ADRs on inpatients, we made the following assumptions:

1 That average length of stay could be between a low of five days and a high of 10 days (it was eight days in 1994/5 [64]).
2 That the ADRin could vary between a low of 3.5% (worldwide post 1985 studies, Table 5) to a high of 7.3%, the overall ADR figure for Europe and the UK (Table 3).
3 That the average additional stay resulting from an ADR

could be a low of two days [43][65] and a high of four days (found with severe ADRs [43]).

The range of results found for bed-days and 400-bed hospital equivalents for inpatient ADRs are shown in Table 6. The range is wide, from 3 to 27 hospital equivalents. Shorter inpatient stay, higher ADRin rates, and more days for each ADR all contribute to a larger ADR burden. Our best guess is that a sensible estimate lies with an average hospital stay of five days, the actual 7% ADR rate, and two additional days per ADR. This would yield an ADR inpatient burden of 1.6 million bed days and 13.6 hospital equivalents.

Overall impact

The overall ADR impact on England is therefore best estimated at 15-20 400-bed hospital equivalents. This is to be compared with hospital acquired infections, which affect about 8% of inpatients (and has a 13% mortality rate) and consumes resources equivalent to 24 400-bed hospitals [64]. At an average inpatient cost of £200 per day in patients without hospital acquired infection (1994/5 costs [64]) the cost of ADRs is of the order of £380 million a year to the NHS in England, and consuming about 4% of bed-days available.

This, though, is a rather simple calculation using average costs, rather than higher costs of a service under pressure, because the 4% of bed days contributes significantly to more expensive professional time and services for relatively sicker patients. For example the current audit commission report on temporary nursing staff estimates that on a typical day 20,000 bank and agency staff work in NHS trusts, covering 1 in 10 of all shifts [66]. This emphasises the fact that where capacity is constrained, anything that reduces demand will have a significant beneficial impact on an organisation.

Other lessons

Some clear messages do emerge from the literature that could be used to monitor patients at risk. Anticoagulant drugs often give rise to bleeds, digoxin is still causing toxicity, diuretics lead to dehydration and electrolyte disturbances, hypoglycaemic agents cause hypoglycaemia and NSAIDs are producing serious gastric irritation. This knowledge is not new but perhaps highlights a lack of focus in terms of managing the potent ADRs. In addition we have demonstrated that the elderly are at risk partly because of the number of medicines which they may be expected to take at any one time, and that the elderly female patient is at a slightly greater risk than the elderly male.

Table 6: Range of estimates of impact of inpatient ADR

Estimate	Average length of stay (days)	ADRin (%)	Average extra days	ADR-related extra bed-days	400-bed hospital equivalents
High	5	7.3	4	3,295,895	27.2
Middle	8	5.4	3	1,142,840	9.4
Low	10	3.5	2	395,056	3.3
Best guess	5	7.3	2	1,647,947	13.6

Other points to note are geographical differences related to attitudes to medicines or different patterns of disease and also the potential harm caused by Chinese herbal medication.

Reducing ADRs

We looked for further publications from key centres reported above to determine what actions, if any, had been taken. The Agency for Healthcare Research and Quality (AHRQ) has a recent review available on the Internet [67]. Another systematic review [68] of computer-based clinical decision support systems (CDSS) showed that there are many studies in a wide variety of different clinical areas that work to reduce harm from medication. In this latter review studies were sought that used CDSS in a clinical setting by a healthcare practitioner and assessing the effects in a prospective setting with a concurrent control.

Sixty-eight studies were found. Of 15 studies of drug dosing systems, 60% found benefit. Of 19 studies on preventive care systems, 74% found benefit. Of 26 studies in other clinical areas, 73% found benefit. Two US examples show that computer systems can contribute significantly to reduce adverse drug events in hospitals [69][70].

Boston [69]

In the Brigham and Women's Hospital, a 726-bed tertiary referral centre, the use of a physician computer order-entry (POE) system was evaluated, in which doctors wrote all drug orders online. The study had the design of a baseline period during which an audit of medication errors was examined, followed by implementation of the POE system and re-audit. Incidents were identified by three mechanisms: nurses and pharmacists reported incidents, an investigator visited wards twice daily to solicit information, and patient charts were examined daily by an investigator. The main outcome was the number of nonintercepted serious medication errors. These were either an error or preventable by systems currently in use, or had the potential for harm but did not result in injury.

Use of the POE system prevented more than half of the serious medication errors. There were just under 11/1000 patient days at baseline, and under 5/1000 patient days during use of the POE system. Potential errors not intercepted fell most, by 84%. Preventable errors fell by 17%. The authors concluded that their system could be extended to different drug types, like sedatives, which actually rose, which had not been included in their original system, and by extending the system in other ways. They also show that the cost of running a POE system for their large, complicated, hospital, would be of the same order as money saved directly. When other costs, like extra work caused by serious drug errors, or malpractice litigation, were included, it could save $5-10 million a year. The system could both save money and improve quality of care.

Phoenix [70]

The Good Samaritan Regional Medical Centre in Phoenix is a 650-bed referral centre. It has an integrated hospital information system, and a multidiciplinary team of professionals met and identified 37 drug or class-specific areas where adverse drug events might be expected. The system was modified so that if circumstances arose where an adverse drug event might occur (digoxin toxicity was one example), then a pharmacist or radiologist was alerted. If necessary, the physician attending the patient was contacted.

Over six months there were 9306 non-obstetric admissions. There were 1116 alerts. Physicians needed to be contacted 794 times, and 596 times the event had not been recognised. The average time taken for each contact was 15 minutes. The rates of clinically unrecognised events varied for different clinical circumstances. For instance, more than half of the potential problems for renal toxicity with the use of radio-contrast media had been previously recognised, but it was felt that potential benefit outweighed potential harm. Using some literature data on costs, the authors calculated that the potential saving to their 650-bed hospital was some $3 million a year, and could be more if the system were extended to other areas.

Examples of computer decision for antibiotic prescribing

Pestotinik [71] in an observational study covering a 7 year period (1988-1994), over 63,000 hospitalised patients received antibiotics (39% of total hospital population). The proportion of patients receiving antibiotics increased from 32% in 1988 to 53% in 1994. The team used clinical decision support systems to develop and implement local consensus guidelines. These were based on evaluations and literature, national guidelines and local expert opinion together with analysis of the hospital database.

The guidelines were incorporated into the knowledge base of the hospital information system to provide decision support at the time of care with feed back to the physicians that was patient specified and related to actual clinical condition. All aspects of antibiotic use ware covered including prophylaxis, empirical use (e.g. in suspected infection and therapeutic use.) Measures were based on defined daily dose (DDD) per 100 occupied bed days. The authors reported a number of achievements.

1. Percentage of patients receiving first prophylactic antibiotic dose within two hours of incision increased from 40% in 1985 to 99% in 1994. The average number of prophylactic doses decreased from 19 in 1985 to 5.3 in 1994.
2. Reporting from the microbiology department was improved and clinicians more readily followed the advice. The rate of antibiotic associated ADRs decreased from 27% in 1989 to 19% in 1994. Mortality rates for patients treated on antibiotics decreased during the same period from 3.7% to 2.7%. Length of stay for antibiotic treated patients did not change over the time. Antibiotic cost per treated patient (adjusted for infection) decreased from $122 to $52 between 1988 to 1994. Antimicrobial resistant patterns remained stable.

While the study may be criticised as observational rather than an RCT, and the changes may have occurred as a result of the failures, the work does suggest that computerised record system can have an impact on antibiotic use and related adverse effects.

Another study [72] tested a computerised system on a 12-bed intensive care unit. The study was carried out comparing two years before the intervention period with one year after. The programme led to a significant fall in the number of patients reporting allergy (35 vs 146), a reduction in excess drug dosages (87 vs 405), and reduction in antibiotic mismatches (12 vs 206). Length of treatment with antibiotics and adverse events were also significantly reduced when the computer regime was followed there was a sizeable reduction in costs, where this advice was ignored costs were increased ($134 vs $515).

Finally, a pharmacist intervention programme [73] to reduce the number of days and adverse effects by targeting five antibiotics (vancomycin, gentamicin, imipenem, cefazolin & cefuroxime) showed that it was possible to reduce excessive dosages by some two days (4.7 days to 2.96 days). Lower doses were used during this intervention phase with associated lower costs. Adverse reactions were reduced for the five antibiotics from 82 (1.3%) in the two years pre intervention period to 14 (0.5%) in the study period.

Effective interventions exist both for reducing the volume of antibiotics administered and the number of adverse drug events. These results are encouraging and may be of value in reducing the number of adverse events for medicines other than antibiotics. With the current moves to introduce clinical computing the role of advanced medical information systems should not be ignored.

What is missing in this review?

Economics

This review has not examined the health economics of ADRs. These have been examined in the AHRQ report [67]. The report concluded that:

♦ Adverse drug events (ADEs, a wider definition than ADR) in the USA result in more than 770,000 injuries and deaths each year and cost up to $5.6 million per hospital, depending on size.

♦ Patients who experienced adverse drug events were hospitalised an average of 8 to 12 days longer than patients who did not suffer ADEs, and their hospitalisation cost $16,000 to $24,000 more.

♦ Between 28% and 95% of ADEs can be prevented by reducing medication errors through computerised monitoring systems.

♦ Computerised medication order entry has the potential to prevent an estimated 84 percent of dose, frequency, and route errors.

This shows that ADRs are equivalent in impact to hospital acquired infection in the length of stay and cost of treatment.

The AHRQ report has useful references and is well written. Archetypal is a case [43] where in trying to save $5,000 a year on a cheaper version of a drug a hospital incurred an additional $50,000 a year because of extra ADRs. Only the presence of an ADR tracking system demonstrated this.

Definitions

In this report we excluded errors arising from administration errors, non-compliance, overdose, drug abuse or therapeutic failures. These may not be negligible. The reports that we included distinguished between medication causing adverse reaction and adverse reactions leading to hospital admission.

This remains, though, a highly complicated area, and we need better definitions between adverse events that are known to occur and those that are unexpected, between adverse events that are common and those that are rare, between adverse events that are reversible and those that are not, and then between correct medicine correctly administered, and incorrect medicine incorrectly administered. Setting out clear definitions for future research is needed so that professionals are clear about what is needed to reduce ADRs.

Primary care perspective

Most prescribing is primary care, and the scope of this review was not adequate to cover all aspects of this.

Changing systems and attitudes

Again, this was beyond the scope of this review. However, an excellent book *"To err is human"* from the National Academies of Sciences, Engineering, Medicine and Research in the USA addresses exactly these issues [74]. Though clearly set in a US context, much could be taken and applied immediately to British healthcare.

Conclusions

Adverse drug reactions impose significant burdens on hospitals through prolonging patient stay and by increasing admission rates. Four out of every 100 bed-days, equivalent to 15-20 400-bed hospitals in England, deal just with ADRs. There is considerable evidence that relatively simple measures involving computer-aided decisions support systems could reduce the impact of ADRs by about half; more intensive measures could reduce it further. A greater understanding about predictors and management systems is needed to institute quality assurance procedures to ensure ADR incidence is minimised. ADR plus hospital acquired infection, essentially mistakes, account together for almost 1 in 10 bed-days.

Suggestions

Short Term

Knowledge Management

♦ Explore ways of incorporating results into management and design of hospital prescribing systems.

Research and Development

♦ Formally test the added value of US-based IT systems to reduce adverse drug events.

♦ Use operational research tools to model the likely impact of improved prescribing tools on the NHS to determine key sensitivities and more effective implementation.

Risk Management

♦ In collaboration with CHI, NHSLA and NPSA explore the scope for systematic incorporation of ADR reduction mechanisms into CHI's and other regulatory framework.

Longer term

1 Examine whether lessons already being learnt in the USA at AHRQ and elsewhere could be applied to Britain.
2 Seek to get findings incorporated into the introduction to the British National Formulary
3 Ensure NHS IT systems make full use of clinical decision support systems.

Acknowledgements

Appendices

Appendix 1 is a list of excluded studies with reasons for exclusion.

Appendix 2 is a list of included studies and reviews, with details of the studies and results.

Both appendices can be found as separate PDF files.

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