

Patient perspective

Adverse drug reactions (ADRs): a patient perspective on assessment and prevention in primary care

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ABSTRACT

A British Medical Association (BMA) report *Reporting Adverse Drug Reactions*, May 2006, estimated that 250 000 people a year are admitted to hospital suffering harmful effects of prescription drugs at a cost to the NHS of about £466 million a year. This is based on a 2004 study of hospital admissions. The BMA report draws attention to a crisis in public health that is largely being ignored and considers how medical education is failing both patients and doctors.

The number of patients suffering and deaths due to adverse drug reactions (ADRs), addiction and withdrawal problems is underestimated, often unrecognised and not well reported. Ignoring the problem is costly in financial and human terms. The following paper describes the importance of the patient experience and recommends the need for

systematic changes in practice and education of both the profession and the public in the recognition of ADRs. The paper includes recommendations for primary care trusts to be proactive in encouraging professional and patient Yellow Card ADR reporting, and to remind doctors of their moral duty to inform coroners of possible ADRs that may have preceded sudden death, suicide or fatal accidents. The paper concludes by emphasising the need for good practice in monitoring the side-effects of medicines, in order that patients gain the maximum benefits from their medicines

Keywords: adverse drug reactions, coroners, depression, harms, iatrogenic disease, medication errors, pharmacovigilance, side-effects, suicide

How this fits in with quality in primary care

What do we know?

Adverse drug reactions, dependency and withdrawal effects result in a wide range of physical and psychological symptoms which can be temporary or permanent. Ethnicity, gender and age differences affecting reaction to medicines are seldom considered in clinical trials and there is little research or data reflecting harms suffered due to variations in people. Those who suffer from serious iatrogenic, physical, neurological or psychological effects and their carers are seldom able to contribute to society or to work. The financial burden can lead to the loss of homes and businesses. The economic consequences put an enormous, largely avoidable, burden on the state as the cost of supporting people in hospitals, institutions and homes runs into millions. The human cost often leads to breakdown of relationships and deterioration in mental and physical health within families.

What does this paper add?

This paper describes the problems that patients experience in being heard, reviews some of their experiences of adverse drug reactions (ADRs) and the need to hold an audit of the extent of ADRs, withdrawal problems and addiction to prescribed medicines in the community. There is emphasis on the need for more focused education of professionals and proactive support from the primary care trusts in preventing iatrogenic disease. Systematic changes in practice and education can be strengthened to prevent ADRs and provide improved outcomes for patients. Recommendations for PCTs to be proactive in encouraging professional and patient Yellow Card ADR reporting, and to remind doctors of their moral duty to inform coroners of possible ADRs that may have preceded sudden death, suicide or fatal accidents are included.

Introduction

It is disturbing for patients and professionals alike to learn that doctor-induced illness (iatrogenic disease) is running at 6.5% cent of acute admissions to hospital. A report in 2006 published by the Board of Science of the British Medical Association (BMA) estimates that 250 000 people a year are admitted to hospital suffering harmful effects after taking drugs mainly prescribed by doctors in primary care, with a cost to the NHS of about £466 million a year.¹ If one included those not admitted to hospital, involuntary addicts to prescribed medication and those who die due to organ failure, suicide or avoidable accident while suffering adverse drug reactions (ADRs), the human and financial cost would be far in excess of the BMA estimate.

ADRs are common. Many patients are suffering ill-health and even death due to prescribed medicines, yet patients' concerns that the drugs are causing the problems are often ignored by health professionals. The voluntary sector is paying more attention to this public health crisis than the Department of Health appears to be. The public and the professionals need to be educated to recognise, prevent and report ADRs.

This paper describes the problems that patients experience being heard, reviews some of their experiences of ADRs and emphasises the need to hold an audit of the extent of ADRs, withdrawal problems and addiction to prescribed medicines in the community. There is emphasis on the need for more focused education of professionals and proactive support from the primary care trusts (PCTs) in preventing iatrogenic disease. Systematic changes in practice and education can be strengthened to prevent ADRs, and this will lead to improved outcomes for patients so these should be instigated immediately.

The paper includes recommendations for PCTs to be proactive in encouraging professional and patient Yellow Card ADR reporting and to remind doctors of their moral duty to inform coroners of possible ADRs that may have preceded sudden death, suicide or fatal accidents.

This paper looks at the troubled area from the patient's perspective and what can be done.

Drug-induced seizures reported to the Adverse Psychiatric Reactions Information Link (APRIL)

A young woman was standing at a London bus stop where a bus had broken down, and from a nearby emergency vehicle lights were flashing bright yellow. The lights disoriented her, she found she could barely

control her feet as she tried to walk away. Supported by a friend, they returned to the friend's apartment, where she had a seizure, shaking, then sleeping as she lay on the floor. As she awoke, her thoughts were disorganised, and she reached out for her pet dog, which in fact was 200 miles away being cared for in her absence.

Gradually, she pieced together the day's events and the reality of her position on the floor: she had had a seizure. This young woman is a talented journalist, a determined, intelligent and vibrant young lady, not yet 40. However, her life's ambitions and confidence have been thwarted by the fact she has seizures, triggered not only by flashing lights but also by chemicals. Seizures began within a month of being prescribed Prozac (fluoxetine), following the sudden death of her fiancé.²⁻⁴ Unfortunately, even when she reported this ADR, she had been told to continue taking Prozac together with other drugs to treat the seizures. She continued taking this combination of drugs for three years. As the ADRs increased, more drugs were prescribed. The resulting deterioration in her health led her to thoughts of suicide.

Extent of the problem of iatrogenesis

This is a real case, one of thousands that happen every year all over the country and reported to APRIL. There has been little research done to calculate the extent of the problem. In 2004 a team headed by Professor Munir Pirmohamed of Liverpool University found that of 18 820 emergency hospital admissions, 1225 (6.5%) were due to ADRs. These researchers estimated the rate of death in UK hospitals to be 10 000 a year, of which Pirmohamed reckons approximately 70% are preventable. But he also pointed out that there were exclusions in the study, for example, people aged under 16 years, obstetrics and gynaecology admissions.⁵

Medical education and prescribing issues

We must ask why so many preventable ADRs continue to happen. A contributory factor may be due to the current system of integrated medical education allowing students to qualify with little or no knowledge of pharmacology or expertise in medicines management or ADRs. Professor Stephen Evans said at a Royal College of Physicians' (RCP) conference that pharmacological knowledge could be used to predict ADRs. Many doctors who prescribe the medicines, have no such knowledge and may leave medical school

ill-prepared to prescribe.⁶ The situation is so serious that in April 2007 the General Medical Council (GMC) announced funding for a £100 000 research project that aims to investigate the prevalence and causes of errors in doctors' prescribing.⁷

Patients may know about some of the side-effects of a medicine, but may not understand the significance of their symptoms. Reliance on clinical trial data for details of expected ADRs is unreliable, as the subjects in trials may exclude important groups in the population. Females, children, elderly, ethnic groups are all under-represented.^{8,9} Genetics too can alter the way drugs are metabolised. Serious adverse events (SAEs) that occur in clinical trials are undisclosed and the Medicines and Healthcare Products Regulatory Agency (MHRA) stated that they remain the 'confidential' information of the company.

Lessons can be learnt from anecdotal cases of iatrogenic illness. Real-life case studies give valuable insight into problems. 'Evidence-based' information has been found to be unreliable where clinical trials funded by the manufacturer found in favour of the drug. The benefits as described in promotional material have to be balanced with the harms that people are actually suffering. Drugs are licensed with a flurry of promotional acclaim often preceded by disease-awareness campaigns.¹⁰ As time passes and the weight of evidence of harm against benefit becomes evident,^{11,12} warnings may be issued and some drugs withdrawn, though this can take years. In the meantime many may suffer or die.

Learning from anecdotal ADR reports

Dianette (Clairrette), cyproterone acetate and ethinylestradiol can cause depression

One-hundred and fifty young women contacted APRIL charity with reports of Dianette apparently causing depression, weeping and self-harming; some women had attempted suicide, most reported their depression lifted when the drug was stopped. Serious depression is labelled as a reason to stop Dianette, yet the shocking fact is that in most cases the women were prescribed antidepressants and beta-blockers and told by their general practitioner (GP) that the drug could not be the problem. The MHRA agreed with APRIL, in that depression should not be listed under mild side-effects, and have agreed that label changes are needed. APRIL awaits confirmation that this has occurred. Primary care trusts (PCTs) could remind clinicians once again that Dianette is not licensed as a contraceptive and is not considered safe for long-term use, as

some women had been taking it for up to 12 years, without being warned.^{13,14}

Zoton (lansoprasole), a proton pump inhibitor can cause depression

A nurse reported to her doctor that since taking Zoton she had felt depressed. The GP denied this could be possible and was shocked to learn that depression is indicated on the label as a possible ADR. This is just one of several reports sent to APRIL of the labelled ADR of depression being denied and of the symptoms lifting once the drug is stopped.

Statins may cause rhabdomyolysis and depression

A taxi driver had been prescribed a statin. This man is now receiving steroid injections to deal with a painful arm that is affecting his ability to earn a living. The pain started after he began taking the statin. The muscle-wasting condition rhabdomyolysis is a possible side-effect of statins. His condition should have been reviewed after a drug-free period. A CK (creatinine kinase) blood test could assess whether muscle damage exists, as renal failure can result from rhabdomyolysis. MHRA drug safety bulletin *Current Problems in Pharmacovigilance* states that 'patients receiving any statins should be asked to report muscle pain, weakness or cramps immediately, and stop treatment until this has been investigated. If symptoms are severe or if creatine kinase is greater than five times the upper limit of normal, treatment should be withheld'.¹⁵

A retired consultant feeling depressed and suffering from nightmares, stopped taking a statin and both problems resolved.

Roaccutane (isotretinoin) also known as Sotoret and Amnesteem linked to depression and suicide

In the tragic case of Jon Medland, a Manchester medical student,^{16,17} a consultation with a GP during which he expressed concerns about the adverse effects of Roaccutane and his feelings of suicidal ideation, led only to a prescription for antidepressants. Jon killed himself later the same day. Manchester City Coroner Leonard Gorodkin called for a review of the safety of Roaccutane during the inquest.

Anne and Fred Roberts were hoping that Roche would accept the invitation of Liverpool coroner Andre Rebello to attend the inquest of their son David.¹⁸ They are confident that the sudden change in mood and death by suicide of pharmacology student David, led directly from his taking Roaccutane for 8 weeks

prior to his death. Roche did not respond to the coroner's request. A Narrative Verdict was given.

GPs and coroners

The MHRA issued prescribing guidelines and warnings about Roaccutane in their drug safety bulletin *Current Problems in Pharmacovigilance* yet some coroners do not routinely investigate the medication a person was taking prior to a suicide, sudden death or accident. Many coroners are lawyers with no knowledge of the history of a particular medication. As it is not mandatory to investigate what led up to a death, or to elaborate on a death certificate, and possibly also because of pressure of work, the opportunity for collecting valuable data has until now been under-resourced. PCTs could ensure coroners have the latest drug warnings, label changes and MHRA bulletins.

What can be done?

PCTs could remind doctors of their moral duty to report to the coroner any suspicions that medicines adverse effects may have led to an accident, organ failure or suicide, and the doctor's or the coroner's professional duty to report this to the MHRA. If there is uncertainty about whether a report should be submitted, it is best practice to report the ADR. The BMA publication *Reporting Adverse Drug Reactions* published May 2006 is aimed at and should be supplied to all health professionals.¹

GP meetings

Dr Andrew Herxheimer, founder and former editor of the *Drug and Therapeutics Bulletin*, Emeritus Fellow of the UK Cochrane Centre, believes that regular GP practice and PCT meetings should be combined into larger geographic areas, say every three months, so that doctors would benefit from the experience of colleagues in practices covering a wide area. It is understood that this already occurs in many areas as prescribing and clinical effectiveness forums, or to some extent within protected learning time schemes. However, Dr Herxheimer believes that even where PCTs may have instigated joint meetings, there is no guarantee that ADRs and dependency on prescription medicines will be high on the agenda for discussion. These topics should be encouraged for discussion, within the NHS and private health care, in meetings and conferences.

Value of sharing experiences of ADRs including akathisia, suicide, psychosis, cardiac and dependence issues

It has been estimated that 10–30% of chronic benzodiazepine users are physically dependent on them and 50% of all users suffer withdrawal symptoms.²⁷ It has been estimated that 2–3% of total drug prescriptions in the UK may cause QT prolongation.²² Psychosis, depression and suicide are labelled risks and some ADRs are dose or interaction related. All incidents that affect the wellbeing of the patient should be reported and case studies discussed with colleagues.

- One GP practice may possibly see, for example, only one case of akathisia or medication-induced suicide linked to antidepressants, including selective serotonin reuptake inhibitors (SSRIs),^{19,20} or Roaccutane or to drugs prescribed for attention deficit hyperactivity disorder (ADHD),²¹ or possibly due to sudden withdrawal from benzodiazepines, corticosteroids, antidepressants or neuroleptics.
- Another may have a patient suffering a sudden onset of psychosis due to sulphonamides, corticosteroids, ADHD or anti-malarial drugs.²²
- A GP may recognise cardiac arrhythmias, prolonged QT interval,^{23,24} raised blood pressure or cardiac death linked to methylphenidate, (COX)-2 inhibitors, hormone-replacement therapy (HRT), contraceptives, tricyclic antidepressants or anti-psychotic drugs.

Withdrawal support for tranquillisers and hypnotic/sedative drugs

The involvement of pharmacists in therapeutic audit of repeat prescriptions or polypharmacy is a positive step. However, recommendations to reduce medication should be supported by withdrawal expertise within the practice.²⁵

A pharmacist, nurse or doctor dedicated to helping patients to withdraw from antidepressants, corticosteroids, pain killers, antipsychotics, benzodiazepines, or newer hypnotic drugs, could disseminate experience and protocols widely. Thousands of pounds and untold misery could be saved and quality in primary care improved. It is well accepted that the elderly are suffering due to ADRs that in many cases could be prevented. The National Service Framework (NSF) for Older People states ADRs are implicated in 5–19% of hospital admissions, yet following guidelines and monitoring drugs for the elderly could prevent many of these incidents.²⁸ Falls due to overuse of benzodiazepines have been reduced when the dosage is reduced. Professor Heather Ashton is an expert on the effects of benzodiazepines and has confirmed that

cognitive dysfunction is caused by any drugs with sedative content.²⁶

For 12 years until 1994 Professor Heather Ashton ran a dedicated withdrawal clinic in Newcastle, for people wanting to stop their benzodiazepine tranquilisers and sleeping pills. Week by week and sometimes day by day she learnt more of the suffering encountered by over 300 involuntary addicts. Her experience led her to produce a withdrawal protocol which is now freely available on the internet. The manual, first introduced in September 2000, was officially used in British Columbia and supplied to every pharmacy by the College of Pharmacists. In 2001 The College of Physicians and Surgeons of Saskatchewan and The Saskatchewan Pharmaceutical Association provided every doctor's office and pharmacy in the province with this manual. PCTs could follow suit. Professor Ashton has always supported initiatives and willingly shares her expertise with clinicians.²⁷⁻²⁹ The Ashton Protocol is available free on www.benzo.org.uk.²⁴

Alcohol, dehydration, malnutrition and ageing exacerbate risk of ADRs

Alcohol may be the catalyst that triggers ADRs in some cases, if we are slow or non-metabolisers due to poor enzyme activity to clear drugs from the body, the intake of alcohol, which takes the same clearance pathways, increases the risk of ADRs.

Dehydration is dangerous for users of sulphonamides and other drugs and malnutrition is a precursor to malabsorption of drugs. When patients are asked about their lifestyle and use of alcohol, the possible interaction with medication should be noted and discussed with the patient.

Nurse specialist advice to patients

In practices where this is not already being done, advice on nutrition and lifestyle changes is an area that a specialist practice nurse could be allocated to. This could be combined with therapeutic audits and monitoring for ADRs. A reduction in cost of drugs, hospitalisation and home care would make this a long-term economic benefit and enhance the quality of life for many people.

Assessing ADRs

If there is any doubt about symptoms being signs of ADR, then withdrawal, change of treatment or a blood test could help assessment. These actions could save distress, suffering, and in some cases long-term iatrogenic illness or even death. PCTs could highlight the need for this kind of vigilance. Dr Jeff Aronson, at the RCP conference, pointed out that the risk of late

reactions increases as time goes by. These could be a result of a drug accumulating in the body, such as retinopathy with chloroquine. Delayed reactions can occur after exposure, even after the drug has been withdrawn.

Yellow Card ADR reporting system for clinicians and patients

The ADR Yellow Card reporting system was conceived in 1964, in response to the deformities and deaths affecting the babies of mothers who took thalidomide. The current pilot scheme of allowing patients to report ADRs is improving the rate of reports to the MHRA. Dr June Raine stated the standard of patient reports is high and welcomed.

Pharmacovigilance is an area where PCTs could be proactive in encouraging patient and professional Yellow Card reporting of ADRs

Without a good reporting system supported by health professionals, we will not be able to assess the extent of long-term adverse effects such as cancer, diabetes, dementia, movement disorders and dependency.

One would hope reporting of ADRs would highlight signals early on. Yet the low level of reporting by health professionals means harms are not being highlighted in time to save lives. Patients and clinicians may report online at www.yellowcard.gov.uk.

Drugs in pregnancy

Now, 43 years since Professor Bill Inman set up the ADR reporting system, following the discovery of harm to unborn babies, apparent adverse effects on unborn or breast-fed babies, of mothers taking drugs such as SSRIs and other antidepressants, are again coming to light. Babies are being born with heart defects linked to these drugs. Food and Drug Administration (FDA) and MHRA advisory warnings have been issued to warn of these concerns.^{30,31} Anti-epileptic drugs and Roaccutane are also known to harm the fetus.

Midwives may not be aware of the risks of SSRIs and other drugs to neonates, and training could be offered to practice nurses and midwives to ensure mothers on medication have the right support to withdraw if safe to do so and to plan future pregnancies, drug free if possible. Without support for withdrawal this is difficult, as some people suffer distressing withdrawal effects including risk of suicide when coming off antidepressants, corticosteroids or benzodiazepines.

Professor David Healy's withdrawal protocol for SSRIs and other antidepressants is available free, and lists withdrawal symptoms that should not be confused with the return of the original illness.³²

Conclusion

Medicines are saving lives and helping people to have a better quality of life in many instances. However, in order to try to reduce the extent of ADRs, good practice in primary care should focus more on actual patient experience. Although it appears we have gone a long way towards this goal, we must ensure that the setting up of patient and public involvement groups and patient participation groups is not just paying lip service to hearing the patient experience. It is not enough to permit patients to voice their concerns, it has to be seen that concerns are being addressed in a proactive way by all professionals in primary care. PCTs should be proactive in promoting patient and professional Yellow Card reporting of ADRs. They should provide access to therapeutic audits and dedicated medication-withdrawal support, and facilitate training for ADR recognition and monitoring. PCTs have a responsibility to pay attention to ADRs as a possible cause of patients' ill-health. Sharing information, a willingness to learn from patients' experiences and focusing on the holistic care of the patient should lead to improved quality in primary care.

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Received 27 April 2007

Accepted 13 May 2007

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