

# Use of licensed medicines for unlicensed applications in psychiatric practice

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# Executive summary and recommendations

Drug treatment is an essential part of much of psychiatric practice, in patients from a wide age range and across many diagnostic groups. Despite the availability of many classes of psychotropic drugs, a substantial proportion of patients will remain troubled by persistent, distressing and impairing symptoms, even after a succession of licensed pharmacological treatments. In this situation, many psychiatrists will consider the prescription of psychotropic drugs outside the narrow terms of their licence, as part of an overall plan of management.

As this aspect of clinical practice in psychiatry has recently come under some scrutiny, a working group of the Special Interest Group in Psychopharmacology (SIGP) of the Royal College of Psychiatrists was convened, to examine the nature and extent of the use of licensed psychotropic drugs for unlicensed applications in psychiatric practice, to consider any potential benefits and risks associated with this aspect of clinical practice, to outline when this may be an appropriate part of the management of individual patients, and to make balanced recommendations for a suggested procedure when prescribing licensed medication for unlicensed applications.

This College report summarises the discussions and conclusions of the working group, which incorporated feedback from the wider membership of the SIGP. It is recommended that unlicensed prescribing should occur when licensed treatments have been used or excluded on clinical grounds; and when the prescriber is familiar with any possible benefits and risks of the medication being considered, and feels confident with the proposed treatment. Whenever possible the agreement of the patient should be obtained, but if not possible, this should be noted. Prescriptions should be started cautiously, and the subsequent progress of the patient monitored closely. If the treatment proves ineffective it should be withdrawn carefully, and if effective the patient should be reviewed regularly. This aspect of prescribing practice may be a suitable area for review within continuous professional development peer groups and for clinical audit within mental health services.

## RECOMMENDATIONS FOR SUGGESTED PROCEDURE WHEN PRESCRIBING MEDICATION 'OFF-LABEL'

1. Check that medicines with a product licence have either had a proper therapeutic trial or been considered, but excluded on clinical grounds (such as contraindications and risk of interactions).

2. Familiarise yourself with the evidence about the proposed drug, including any possible drug interactions and potential adverse effects.
3. If the medicine to be used does not have a substantial evidence-base supporting its use for the proposed indication, or if you are not sufficiently expert in this field, or have particular concerns, obtain the advice of another doctor or specialist pharmacist.
4. Consider the risks and benefits of the proposed treatment. Particular consideration is needed with children, older patients, and in those with impaired insight and judgement. Document this.
5. Give the patient (or his/her relative, when relevant) a full explanation, including the information that the drug will be used outside its product licence. Document this explanation.
6. If agreement from the patient (or his/her relative, when needed) is obtained, document this approval. If a patient is unable to consent to a necessary treatment, note that it has not been possible to obtain consent.
7. Begin a cautious trial of treatment with the medicine. In out-patients, consider sending the patient a copy of any letter sent to his/her general practitioner, summarising why this approach has been adopted.
8. Monitor the patient closely. Continue with full documentation of its effectiveness and tolerance.
9. If the treatment proves unsuccessful, withdraw it, gradually if needed. Document the reason for the withdrawal of treatment, then consider alternatives, using the same process.
10. Consider writing up the case, to add to knowledge about the drug and its use.

# Purpose of this report

Drug treatment is an essential part of much of psychiatric practice. Many psychotropic drugs are available for the treatment of a wide range of mental disorders, but patients often remain troubled by persistent and disabling symptoms, despite a series of treatments. In these circumstances, many doctors will consider the prescription of drugs outside the narrow terms of their licence, in an attempt to offer their patients an improved chance of recovery.

However, concerns about the use and potential misuse of drugs have caused many patients, doctors and National Health Service (NHS) trusts to question current prescribing practice. The Audit Commission report, *A Spoonful of Sugar*, emphasises that NHS trust boards should recognise that 'medicines management' is a significant part of clinical governance responsibilities (Audit Commission, 2001). While most authorities agree that use of licensed psychotropic drugs outside the terms of their licence is a necessary part of psychiatric practice, instances of more unconventional prescribing, and worries about potentially unnecessarily restrictive policies, together led Professor Thomas Barnes, then Chair of The Royal College of Psychiatrists' Special Interest Group in Psychopharmacology (SIGP) to convene a working group, with the remit of examining this issue.

This report is based upon the discussions within this working group; on comments received during the workshop on this subject held during the Annual Meeting of the College at Edinburgh in July 2003; from comments made on a draft version of the report circulated to the wider membership of the SIGP in May 2004; and finally from comments made by other College members following discussion of the report at a meeting of the Public Policy Committee (January 2005). It should be stressed that this report focuses on psychiatric practice, and it is not intended to comment on the use of psychotropic drugs in the treatment of primary care patients, when a specialist mental health service has not been involved.

The accompanying vignettes in the chapter on unlicensed prescribing in practice provide six examples of the use of psychotropic drugs, in licensed or unlicensed applications. From these it can be conceptualised that there is a spectrum of prescribing, from an evidence-based consideration of the potential benefits and risks of a proposed treatment, to somewhat eccentric approaches that float free of evidence and defy detailed analysis.

# What is unlicensed prescribing?

In the UK, licensed medicines are those that have received a Marketing Authorisation (previously called a product licence). Licensing arrangements are determined by the Medicines Act 1968 and are currently implemented through the Medicines and Healthcare products Regulatory Agency. For each medicine, the doses, indications, cautions, contraindications and side-effects given in the British National Formulary (BNF), which is published by the British Medical Association & Royal Pharmaceutical Society of Great Britain, reflect those in the manufacturer's data sheets or Summary of Product Characteristics, which in turn reflect those in the corresponding Marketing Authorisation. The BNF also indicates when a treatment recommendation is for the use of a medicine outside the licensed indication for that product.

Absence of a licence does not necessarily indicate an absence of evidence for the proposed intervention; as an illustration, low-dose propranolol has proven efficacy in the treatment of antipsychotic drug-associated akathisia, but has no formal indication for the management of patients with that condition. Conversely, the prescription of psychotropic drugs within the terms of their licence is not a guarantee of safety or efficacy, for example, a patient with schizophrenia with severe depression could receive both the antipsychotic drug risperidone and the antidepressant paroxetine within the terms of their licence, but could be at risk of troublesome drug interactions.

Many medicines that are prescribed to patients are not licensed for the particular indication, age of the patient, or dosage, and their use in this situation has been termed as either 'off-label' or 'unlicensed' prescribing, or the 'use of licensed drugs for an unlicensed indication'. The use of a psychotropic drug in an unlicensed indication does not necessarily imply a safety hazard, and there are many instances where such use is uncontroversial and probably advantageous to the patient. As indicated earlier, it may be helpful to recognise that there is a spectrum of use of licensed psychotropic drugs in unlicensed applications, with some prescribing being regarded as 'near-label' (for example, the use of fluoxetine as a maintenance treatment in a patient with recurrent depression).

# What is the extent of unlicensed prescribing in psychiatric practice?

Many doctors believe that 'off-label' prescribing is often necessary when attempting to treat certain patients, for example in patients whose symptoms have proved resistant to a range of treatment approaches. It has been stated that the product licence for a drug does not necessarily represent the best use of that compound (Healy & Nutt, 1998). The extent of this aspect of prescribing in psychiatric practice is not fully known, but findings from research and surveys suggest it is common in general, old age, child and adolescent, learning disability and forensic psychiatry, in the UK and in many other countries.

For example, in a postal questionnaire survey of 200 consultants, specialist registrars and staff grade doctors employed as psychiatrists within the NHS in one area of the UK (response rate, 58%), 65% of doctors reported prescribing medicines for unlicensed applications in the previous month. Most instances involved the use of a medicine outside its licensed indications (49%), but prescriptions of drugs at doses above those described in the then current BNF (19%), and for those outside the age range in their licence (12%) were also common (Lowe-Ponsford & Baldwin, 2000). A similar situation probably applies in many other countries, for example, in the USA, a prospective evaluation of prescribing for atypical antipsychotic drugs given to 73981 veteran patients found that 42.8% of patient prescriptions were for unlicensed indications (Rosenheck *et al*, 2001).

## GENERAL PSYCHIATRY

Unlicensed use of licensed drugs is a common feature of prescribing to patients in general psychiatry settings. A cross-sectional survey of prescription cards for 266 patients receiving in-patient care in acute adult psychiatric wards from 14 NHS trusts in another area of the UK found that 103 of 1387 prescriptions (7.5%) were outside the terms of the product licence. Of these, 75% were for indications not covered by the licence, and 25% were at doses above the maximum recommended dosage. A total of 81 patients were prescribed at least one medicine off-licence, typically for an unlicensed indication (Douglas-Hall *et al*, 2001). More recently, a cross-sectional survey of prescriptions for mood-stabilising drugs in 249 in-patients in a tertiary care unit found that 28.5% of patients were receiving prescriptions for unlicensed indications (Haw & Stubbs, 2005a); and an audit of antipsychotic drug prescribing over 5 years in a secondary care NHT trust found that approximately 40% of prescriptions were in 'off-label' applications (Hodgson & Belgamar, 2006).

Antipsychotic drug prescribing in patients receiving in-patient care in adult psychiatric wards was examined through a 1-day census of 47 mental health services in the UK (Lelliott *et al*, 2002). There were 613 of 3132

patients (20%) receiving a total dose of antipsychotic medication above that recommended by the then current BNF, but this usually resulted from polypharmacy. In only a small minority of cases ( $n=34$ ) was this due to the prescription of a single antipsychotic drug at a high dose; in the remainder high-dose prescribing was due to the combination of two or more types of antipsychotic drug. The majority of case notes did not include a stated indication for high-dose prescribing or note whether or not the patient had been informed of this (Harrington *et al*, 2002a). There was a substantial variation in prescribing practice, only some of it being accountable by differences in the patient case mix (Harrington *et al*, 2002b).

The extent of unlicensed prescribing in UK psychiatric out-patient practice is unknown. In a prospective evaluation of the prescriptions given to 209 patients attending 7 out-patient services in Italy, a total of 109 (52%) patients were given off-label prescriptions of atypical antipsychotic drugs (Barbui *et al*, 2002). This proportion (50%) was also seen in a consecutive sample of 259 psychiatric in-patients (Barbui *et al*, 2004). A similar situation was found in a prescription review in 173 patients attending pharmacies in Germany, in which 115 of patients (66.5%) were receiving antipsychotics for unlicensed indications (Weiss *et al*, 2000).

## OLD AGE PSYCHIATRY

Many licensed psychotropic drugs are used for unlicensed indications, when treating elderly patients with mental health problems. For example, at present there are no drugs that are specifically licensed for the treatment of psychotic and behavioural symptoms in patients with dementing disorders. However, in a postal questionnaire survey of 377 members of the Faculty of Old Age Psychiatry (response rate, 66%), most doctors described the use of psychotropic drugs for this application. Conventional and atypical drugs were used for treating patients with delusions, hallucinations, agitation, wandering, aggression or sexual disinhibition, and antidepressant drugs were employed in the management of patients with anxiety and lability of mood (Scott *et al*, 2002).

Little is known about actual prescribing practice in older people with mental health problems. In the German prescription survey described above, antipsychotic drugs were being prescribed in older patients (aged 49–70 years) almost exclusively for off-label indications (Weiss *et al*, 2000). In the UK, antipsychotic drug prescribing in 400 older individuals (aged 60–93 years) receiving in-patient psychiatric care was examined through a 1-week cross-sectional survey of 750 prescription cards of wards from 19 NHS trusts. Atypical antipsychotic drugs were prescribed to a total of 169 patients (42%), out of these, 85 (50.3%) had the diagnosis of a dementing disorder (Beck *et al*, 2001).

Consideration of capacity and consent to treatment in old age psychiatric practice is not the main focus of this report, but most patients with dementing disorders are unable to comprehend the reasons for using licensed drugs in unlicensed indications. Although it may be good practice to discuss a proposed unlicensed treatment with relatives or carers, it should be remembered that they do not have the right to consent to treatment on behalf of incapacitated adults. In this situation, doctors' practice is subsumed within a common law duty of care in England and Wales; whereas within Scotland treatment would be administered under the terms of Part 5 of the Adults with Incapacity (Scotland) Act 2000.

## CHILD AND ADOLESCENT PSYCHIATRY

Recent years have seen a substantial increase in the prescription of psychotropic drugs to children and adolescents (Bramble, 2003), and a number of medicines have received market authorisation for use in adolescents. However, the extent of unlicensed prescribing in UK child and adolescent mental health services is largely unknown.

In a questionnaire survey of community child and adolescent psychiatrists in the West Midlands ( $n=55$ ; response rate, 87%), 88% reported issuing prescriptions for antidepressants (typically selective serotonin reuptake inhibitors; SSRIs), and 63% for antipsychotic drugs (Doerry & Kent, 2003). Although not explicitly stated, it can be assumed that most of these prescriptions were for unlicensed indications. Two-thirds of the consultants reported prescribing the unlicensed compound melatonin. When compared to the findings of previous questionnaire surveys (Bramble, 1992; McNicholas, 2001) it seems that psychotropic drug prescribing has become a more common aspect of practice in child and adolescent psychiatry in the UK.

A similar situation applies in other countries; in an Australian nationwide cross-sectional postal questionnaire survey of 435 general paediatricians and 187 child and adolescent psychiatrists (response rate, 71%), 40% of doctors reported off-label prescribing of psychotropic drugs, including SSRIs, psychostimulants, antipsychotics and mood stabilisers (Efron *et al*, 2003). In a cross-sectional population-based study, evaluating prescription records from three health maintenance programmes in the USA over 5 years, the number of prescriptions of psychotropic drugs increased dramatically between 1991 and 1995, much of the prescribing being for unlicensed applications (Zito *et al*, 2002).

In paediatric healthcare settings, between 35% and 90% of the medicines prescribed to children receiving in-patient care are either not licensed for use in children, or are prescribed outside the terms of their product licence (Conroy *et al*, 2000). Adverse reactions appear to be more common with unlicensed than with licensed products (Turner *et al*, 1999). The findings of two recent primary care studies indicate that unlicensed prescribing for children is common. A retrospective cohort study of over 1.74 million prescriptions written for 400 000 children by 6886 primary care physicians in Germany found that 13.2% of prescriptions were for unlicensed applications: substantial proportions of the prescription for antidepressants (36.6%) and antipsychotics (10.2%) were 'off-label' (Bücheler *et al*, 2002). In another population-based cohort study of over 17 000 prescriptions for 6141 children in The Netherlands, 2667 prescriptions (15.3%) were for drugs not licensed for use in children, and 2381 (13.6%) were for licensed drugs, prescribed 'off-label', according to age, dosage, frequency or administration ('t Jong *et al*, 2002).

In a consensus statement, the British Association for Psychopharmacology (1997) noted that it appears reasonable to extrapolate what is known about drug treatment responses in adults to children and adolescents in the case of patients with schizophrenia or obsessive-compulsive disorder, but that more caution is required in the case of patients with mood and anxiety disorders. The UK Royal College of Paediatrics and Child Health policy statement on the use of unlicensed medicines or licensed medicines for unlicensed applications makes a number of clear recommendations regarding this aspect of child healthcare (Royal College of Paediatrics and Child Health, 2000). These are summarised in Box 1.

**Box 1** Unlicensed medicines or licensed medicines for unlicensed applications: summary of the recommendations from the joint Royal College of Paediatrics and Child Health/Neonatal and Paediatric Pharmacists Group standing committee on medicines (Royal College of Paediatrics and Child Health, 2000)

- Those who prescribe for a child should choose the medicine which offers the best prospect of benefit for that child, with due regard to cost.
- The informed use of some unlicensed medicines or licensed medicines for unlicensed applications is necessary in paediatric practice.
- Health professionals should have ready access to sound information on any medicine they prescribe, dispense or administer.
- In general, it is not necessary to take additional steps, beyond those taken when prescribing licensed medicines, to obtain the consent of parents, carers, and child patients to prescribe or administer unlicensed medicines or licensed medicines for unlicensed applications.
- NHS trusts and health authorities should support therapeutic practices that are advocated by a respectable, responsible body of professional opinion.

## PSYCHIATRY OF LEARNING DISABILITY

As in other areas of psychiatric practice psychotropic drugs are often prescribed for unlicensed indications, in patients with mental health problems and behavioural challenges arising from developmental delay or arrest. Common indications include the management of sleep disturbances, increased arousal, and self-injurious behaviour; and problems related to behavioural changes resulting from epilepsy syndromes and dementing disorders. A recent cross-sectional survey of psychotropic drug prescribing in in-patients with learning disability found that 46.4% of patients were receiving at least one psychotropic drug for an unlicensed indication, most typically in an attempt to manage behavioural problems or to stabilise mood (Haw & Stubbs, 2005b).

The dearth of randomised controlled trials in this patient population means that most prescriptions are outside of product licences, although lithium has an indication for the management of aggressive or self-mutilating behaviour. Most of the common interventions are supported by retrospective case series analysis only. A review of the use of atypical antipsychotic drugs in individuals with autistic-spectrum disorders reflects current thinking in the wider field of developmental neuropsychiatry and learning disabilities (Barnard *et al*, 2002). Uncertainties regarding diagnosis and capacity to consent, and associated physical health problems must all be considered, when formulating potential treatment approaches (British Association for Psychopharmacology, 1997). Psychotropic drug prescription is usually only one component of a multifaceted approach to patient management.

## FORENSIC PSYCHIATRY

The unlicensed use of psychotropic drugs in forensic psychiatry settings can be especially contentious. The consensus statement from The Royal College

of Psychiatrists on use of high-dose antipsychotic medication, which has recently been revised, provides guidance on when doses higher than those described within the BNF may be indicated (Royal College of Psychiatrists, 2006). The practice of issuing 'as required' prescriptions on top of regular administration may result in overall daily dosages in excess of current recommendations (Milton *et al*, 1998). Similar concerns may apply to the concurrent prescription of oral and depot antipsychotic drugs, or concomitant prescription of conventional neuroleptics with atypical antipsychotic drugs. Treatment considerations will be guided not only by the Mental Health Act 1983 and the Code of Practice, but also by specific case laws. The rapid tranquillisation of acutely agitated patients with psychiatric disorders is outside the scope of this report, but useful reviews of pharmacological approaches are available (McAllister-Williams & Ferrier, 2002; Humble & Berk, 2003).

## PERINATAL PSYCHIATRY

No psychotropic medication is licensed for use in pregnancy or in breastfeeding mothers. The BNF and product information advise at least caution in their prescription at this stage or in most cases contraindication. Drug trials exclude pregnant or breastfeeding women and no randomised controlled trials of psychotropic medication have been conducted in pregnancy or lactating women. Despite this, prescribing of psychotropic medication is commonplace in women of reproductive age and up to 27% of women are receiving psychotropic medication at the time when their pregnancies are first diagnosed (Rubin *et al*, 1986; Williams *et al*, 1998). Although new onset serious mental illness (schizophrenia and bipolar disorder) is less common during pregnancy than at other times, significant numbers of women with pre-existing serious mental illness will require treatment during pregnancy. The withdrawal of medication at the diagnosis of pregnancy will be associated with the usual rates of relapse or recurrence of illness, particularly bipolar affective disorder. The prevalence of non-psychotic conditions during pregnancy is comparable to other times. Therefore, psychiatrists and general practitioners will find it necessary on occasion to prescribe psychotropic medication for new episodes of illness as well as continue to manage women with pre-existing disorders during their pregnancies.

The problems of the prescriber are further complicated by the variety of sources of information on the risks associated with medication. These include: data on request from the manufacturers, prescribing information leaflets, the BNF, advice from professional bodies such as the American Academy of Paediatricians, standard texts such as *Drugs in Pregnancy and Lactation* (Briggs *et al*, 2005) and the National Teratology Information Service, review articles and individual publications of case series. An understanding of the methodological limitations of the latter is essential for a critical interpretation of their results. Many thousands of exposed pregnancies will need to be studied over time before any significantly associated risk can be demonstrated compared with the unexposed control population. Under-powered studies may therefore either give false reassurance or may be unduly alarmist. Results expressed in terms of the relative risk associated with a given drug will need to be interpreted with knowledge of the baseline risks of the occurrence of any condition in an

unexposed group of pregnant women. It will also need to take into account the gestation of the pregnancy exposed and the age, weight and feeding patterns of breastfed infants.

Studies of the effects of drugs on the rates of major congenital malformations identified soon after birth are more numerous than those describing minor malformations and particularly neurodevelopmental problems and other effects of exposure in later pregnancy that may not be manifest for some time to come. The evidence base changes and may take some time to be disseminated into psychiatric journals. For example, there has been accumulating evidence of the additional hazards (over other anticonvulsant mood stabilisers) of valproate, published largely in paediatric and neurology journals for the past 20 years, however, this has only recently reached the attention of psychiatrists. A further problem is that evidence on the potential hazards of medication, particularly from conference proceedings, may be publicised in the media before publication in scientific journals. An example of this are recent concerns over paroxetine and other SSRIs in pregnancy which were widely published in the broadsheet newspapers before the Food and Drug Administration in September 2005 and the Committee on the Safety of Medicines in December 2005 issued a cautionary warning (Duff, 2005). Patients may well bring their concerns to their doctors, who can be caught unawares. Because of the changing nature of the evidence base, it is not wise to make categorical recommendations for one drug as opposed to another or to talk about psychotropic medications in terms of overall statements of safety or risk. The general principles of prescribing during pregnancy are described in Box 2.

**Box 2** General principles for the prescribing of psychotropic drugs during pregnancy

- Wherever possible, women receiving psychotropic medication should carefully plan their pregnancies and discuss with their GP and psychiatrist prior to conception whether to continue, change or stop their medication. This is particularly important for women receiving treatment for serious mental illness and where there may be a significant risk of relapse following cessation of medication.
- Unless there are positive reasons not to do so (for example evidence of previous relapse when changing medication), medication should be changed prior to conception to that which has the best safety profile in pregnancy.
- In general, because they have been in use for many years, there is more information available about the effects of older drugs compared to newer ones.
- Wherever possible, medication should be avoided in the first trimester. However, if women conceive while taking psychotropic medication it should not be abruptly withdrawn. A relapse of the maternal condition may involve increased risks through treating the relapse.
- Mild non-psychotic conditions are common in pregnancy and wherever possible psychological treatments are preferable to psychotropic medication. The threshold for prescribing psychotropic medication in pregnancy should be high and based on clear indications.

*continued*

*Box 2 continued*

- While the incidence of serious mental illness in pregnancy is lower than at other times, when these illnesses occur they should be treated energetically. The risk to both mother and the unborn child of not treating the illness may be higher than the potential risks to the unborn child of the medication.
- Pregnancy is not protective against a relapse of serious mental illness, particularly if medication has been stopped. Continuing medication is therefore in the best interests of both the mother and the infant. However particular attention needs to be paid to the choice of individual antipsychotic and mood stabilising agents.
- Psychiatrists, obstetricians and neonatal paediatricians should be aware of the potential of withdrawal effects in neonates if the mother has been taking antidepressants or antipsychotic medication prior to delivery (Sanz *et al*, 2005).
- The lowest dose possible should be used in divided dosage and polypharmacy avoided.
- Doctors prescribing psychotropic medication to pregnant and breastfeeding women should ensure that they have the most up to date information possible. A good source of balanced and regularly updated information can be obtained from The National Teratology Information Service (see their website at <http://www.nyrdtc.nhs.uk>).
- Doctors should always work in partnership with the women and their partners and be able to discuss the risks and benefits of their medication in a way that is easily understood.
- When prescribing medication in pregnancy or lactating women, the psychiatrist should clearly document the reasons why the medication is being prescribed, an indication that the risks and benefits have been addressed, that the woman has been involved in the decision and a note made of any advice or information received that has influenced the decision and choice of medication.

# Unlicensed prescribing in practice

There are four main types of unlicensed prescribing, relating to the medical disorder and demographics of the patient, and the dosage and duration of treatment ("the four 'D's"). Each type of prescribing is described over the course of Vignettes 1–6 presented below.

The first type of unlicensed prescribing is perhaps the best known and involved the prescription of a medication for an indication that was not then covered within the terms of the Market Authorisation. Vignette 1 illustrates how a proposed treatment approach can change from being an unlicensed to a licensed application, as the indications for a particular drug are extended; and therefore shows that reference to the twice-yearly editions of the BNF can sometimes lead to erroneous conclusions. New indications for existing treatments appear regularly, as shown by the expansion of indications for some of the SSRIs, so what is unlicensed prescribing one month may come within the terms of the Market Authorisation in the next. Conversely, drugs may 'lose' an indication as new clinical data emerge and become available to regulatory bodies; a recent example being changes to the licensing of SSRIs (other than fluoxetine) for the treatment of depression or obsessive-compulsive disorder in children and adolescents. A different example is the removal of the indication for fluoxetine in the treatment of women with premenstrual dysphoric disorder (PMDD), as a result of the harmonisation of the Summary of Product Characteristics for fluoxetine with Europe (an indication in PMDD persists in the USA).

## VIGNETTE 1

A general psychiatrist has just reviewed the case of a 35-year-old man with rapid cycling bipolar disorder. Despite full compliance with both lithium and an anticonvulsant, the patient continues to oscillate wildly between manic episodes with mood-congruent grandiose delusions and auditory hallucinations, and severe depressive episodes with marked suicidal thoughts and delusions of guilt. Once back in her office, the psychiatrist performs a literature search on the use of antipsychotic drugs in bipolar disorder, and reads the recent evidence-based consensus statement on the condition produced by the British Association for Psychopharmacology. She notes that there is good evidence for the use of a particular antipsychotic drug (olanzapine) in bipolar illness, both when prescribed alone and in combination with a mood-stabilising drug. Having consulted the BNF (September 2003 edition), she notes that this drug is not approved for use in the prophylaxis of bipolar disorder. She telephones the patient to discuss the treatment options, and to suggest that this antipsychotic drug might be helpful in reducing the risk of further episodes of illness. The patient

*continued*

*Vignette 1 continued*

readily agrees to this treatment option. The psychiatrist makes a full record of the clinical problem, a consideration of the risks and benefits of treatment, and includes a copy of the consensus statement in the patient's notes. She also makes a note to discuss this new treatment with the patient's wife, when she accompanies him to the next out-patient appointment.

*Comment*

Few would assert that the psychiatrist's care of this patient was less than exemplary. The choice of olanzapine was based upon consideration of the evidence, and on reflection of the potential benefits and risk. In addition the documentation was of a high standard and considerable efforts were made to involve the patient and his spouse in the treatment plan. Olanzapine received a licence for the treatment of manic episodes shortly after the described events.

The second type of unlicensed prescribing involves a prescription being given to a patient who lies outside the age range specified within the Summary of Product Characteristics. An example of this is shown in Vignette 2. The BNF (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2006, September edn) currently states that prescribing the noradrenaline reuptake inhibitor reboxetine to child and older patients is 'not recommended'. But it is unlikely that people differ much in their metabolism and response to treatment when they cross the threshold of their 65th birthday. Furthermore a randomised controlled trial has documented the efficacy of the antidepressant in the treatment of depression in older patients; so the use of that antidepressant in this clinical situation appears justifiable. However, it would perhaps have been better if the doctor had made a record of the reasons for the treatment decision, and the fact that it had been discussed with the patient.

VIGNETTE 2

An old age psychiatrist reviews the case of a 66-year-old woman in good physical health, with the diagnosis of recurrent unipolar depression. Her symptoms have not responded to treatment with a selective serotonin reuptake inhibitor, or a tricyclic antidepressant, each given for 6 weeks and at recommended dosage. The doctor is struck by the patient's marked lethargy and social withdrawal, and wonders whether she might benefit from treatment with the noradrenaline reuptake inhibitor reboxetine. He recalls the findings of a randomised controlled trial, demonstrating that it was significantly better in improving 'social function' than one of antidepressants the patient has already received. He consults the BNF to confirm the dose that should be employed, and is surprised to see that reboxetine is not recommended for use in older patients. He decides that the drug is nevertheless worth trying in this case. He discusses the rationale for using this antidepressant with the patient, who is agreeable to his suggestion. The doctor thinks about making a record in the medical notes for why he used the drug, but dismisses the thought, knowing the drug has been available for over 5 years.

*Comment*

It is unlikely that the efficacy and tolerability of reboxetine differ significantly in patients below and above the age of 65 years and the decision to prescribe it to this woman appears justifiable, although it might have been better if the doctor had made a note regarding unlicensed use in this patient.

Vignette 3 also illustrates the use of medicine outside the recommended age range, and for an unlicensed indication. Nearly all of the available SSRIs have proven efficacy in the treatment of obsessive-compulsive disorder, and some have efficacy in randomised controlled trials conducted in children and adolescents. The September 2006 edition of the BNF notes that two SSRIs can be used in the treatment of children with obsessive-compulsive disorder (fluvoxamine, aged 8 years and over; sertraline, 6 years and over). It may have been preferable for the doctor to explore this treatment option with the patient and his parents further, to enable a full discussion of the potential benefits and risks of treatment. No antipsychotic drug is currently licensed for the treatment of children with obsessive-compulsive disorder, and the evidence that antipsychotic drug treatment can boost the response to serotonergic antidepressants is derived from randomised controlled trials performed in adult patients. Instead, the psychiatrist chose to recommend that another doctor should issue an unlicensed prescription, and had not discussed the reasons for this recommendation either with the patient, his parents or their family doctor, with untoward results.

Another type of unlicensed prescribing is the use of a medicine outside the dose range recommended in the Summary of Product Characteristics and reflected in the BNF. This is illustrated in Vignette 4; unwittingly, the psychiatrist recommends that the patient increases the dose of an antidepressant that is already been taken at a dosage higher than recommended. Consideration of the current clinical situation was limited; there was no discussion about the potential benefits and risk of increasing the dose further; no thought was given to other treatment options; and no documentation of the treatment decision was made in the medical notes. The decision to recommend a dose increase could easily be criticised, and the general standard of care appears less than optimal.

### VIGNETTE 3

A child psychiatrist has been asked to review the case of a nine-year-old boy with distressing obsessional ruminations and compulsive rituals, which are disruptive both at home and at school. The boy talks about wanting to die, as he is so upset and feels different to everyone else in his class. The boy's parents are desperate for something to be done, but do not want their son to be put on a selective serotonin reuptake inhibitor, as they are fearful that he might act on his suicidal thoughts. The psychiatrist tries to reassure them, but her efforts are met with much resistance. Being fairly certain that atypical antipsychotic drugs can sometimes boost the response to selective serotonin reuptake inhibitors in patients with obsessive-compulsive disorder, she proposes to the boy and his parents that treatment with the atypical antipsychotic drug risperidone might be helpful. They seem agreeable to this suggestion. She then writes to the patient's GP, who angrily contacts the psychiatrist on receipt of the clinic letter, saying she was not prepared to prescribe the antipsychotic drug as there was no evidence for its efficacy in children, and that she had told the parents about this. The parents were furious when they heard this, and have decided that they will not bring their son back to the clinic.

#### *Comment*

It is possible that longer discussion of the rationale for the proposed treatment, with an acknowledgement that the antipsychotic drug was being prescribed for an unlicensed application, and discussion with the patient's general practitioner could have averted this unfortunate situation.

## VIGNETTE 4

While on a domiciliary visit, a general psychiatrist is telephoned by one of his current out-patients, a 25-year-old woman with depression, panic disorder and intermittent alcohol misuse. The patient complains of feeling more tense and restless than usual, and wonders whether this might be a side-effect of sertraline treatment. The psychiatrist reassures her, but also tells her to increase the sertraline dose further, believing that the patient's anxiety symptoms have worsened. Once back in the hospital, the psychiatrist remembers that the patient was already on a dose (250mg per day) that was greater than that recommended within the BNF (maximum daily dosage, 200mg). He makes a note in his diary to discuss this with the patient when she attends her next appointment, in 2 months.

*Comment*

The decision to increase the dosage of sertraline further may be justifiable, but the decision to make such a recommendation without fully assessing the patient, the lack of adequate note-keeping and the prolonged delay before the decision could be discussed in person could all be criticised.

There is another type of unlicensed prescribing, representing the use of a licensed medication for longer periods than those specified within the Marketing Authorisation. For example, most antidepressants are licensed for treating 'depressive illness'. Continuation and maintenance treatment with antidepressants in asymptomatic, remitted patients with recurrent depressive disorder might technically represent unlicensed use, but also clearly represents an aspect of good clinical practice. The Committee on Safety of Medicines currently advises that prescription of benzodiazepines should be limited to 4 weeks only (reflected in Section 4.1, BNF, September 2006), but many patients with chronic and disabling anxiety disorders who have not responded to other treatments may benefit from longer courses of treatment.

As stated above, no psychotropic medication is currently licensed for use in pregnancy or in breastfeeding mothers, and the BNF and product information materials advise at least caution in their prescription in these situations, or in most cases contraindication. Vignettes 5 and 6 relate to the use of psychotropic drugs during pregnancy.

## VIGNETTE 5

A 32-year-old married woman is referred by her GP. Three years previously she had suffered from severe depression with marked suicidal thoughts. After failing to respond to two other antidepressants she eventually recovered quickly and fully to venlafaxine. She continued to take venlafaxine for 2 years, fearful of a relapse. On the advice of her GP, she slowly withdrew from venlafaxine, stopping it 2 months before she conceived. In early pregnancy she became anxious then depressed. The GP was concerned about restarting antidepressants in early pregnancy and kept a close eye on her. But she became progressively more depressed.

When first seen by a psychiatrist, she was 26 weeks pregnant and was severely depressed with many biological symptoms, and frightened that suicidal despair might return. She was concerned about the effects of her mental health on the unborn child, and wished to start taking venlafaxine again as she felt it was the only drug that was effective for her, but was equally concerned about the effects on the unborn child. She was aware from the internet and from the media that there had been recent concerns about the use of antidepressants in pregnancy.

*continued*

*Vignette 5 continued*

The consultant's clinical decision was that her condition justified the use of an antidepressant and under ordinary circumstances would have restarted venlafaxine. He consults the BNF, which cautions against the use of venlafaxine in pregnancy. He contacts the manufacturer and reads the most up-to-date information about potential adverse effects including evidence of withdrawal in the newborn, which concludes with the same advice that it cannot be recommended for use in pregnancy. The consultant then contacts the National Teratology Information Service and obtains a summary of the most recent evidence regarding all antidepressants in pregnancy. He becomes aware that venlafaxine may be associated with problems in the newborn, but that the evidence of increased risks of major congenital abnormalities and later fetotoxicity is far from conclusive and described as 'a weak warning signal'. After a long discussion with the patient and her partner, they all decide to reintroduce venlafaxine. The consultant carefully records in the notes the reasons for the decision and refers to the advice and information that he has received.

*Comment*

The consultant's decision that the risk of not treating this ill patient with an antidepressant to which she had previously responded, both for her and her developing baby's sake, was outweighed by the benefits of so doing, would seem reasonable in the circumstances. He took care to seek the most up-to-date and balanced information that he could, discussed it with the patient and her partner, and documented the reasons for doing so. He should also inform the obstetrician of the potential for withdrawal effects in the newborn infant. The woman will need to continue her medication after delivery. The risk of relapse of her condition is substantial. If she continues to take venlafaxine she should not breastfeed.

VIGNETTE 6

A 35-year-old married woman with bipolar illness asks for an appointment with her consultant psychiatrist to discuss her intention to start a family. She had two manic episodes requiring hospitalisation but has been well for 3 years taking sodium valproate 1200mg daily. She is concerned about risks associated with continuing valproate but equally concerned that stopping it might lead to a relapse. The consultant is aware from NICE guidelines on management of epilepsy and from attending a recent conference of the Royal College of Psychiatrists that valproate is associated with a risk of major congenital abnormalities and this risk is higher than with other anticonvulsant mood stabilisers. He is also aware that continued use of valproate throughout pregnancy is associated with neurodevelopmental and cognitive problems in the developing child.

He is unsure of the precise figures but confirms these by contacting the National Teratology Information Service. His conclusion is that there is clear advice that wherever possible valproate should not be used in women who are likely to become pregnant and its use in pregnancy should be avoided. He feels he has an obligation to share this information with the patient and her partner. He is also aware that she is at a significant risk of a recurrence of her condition should she stop medication and that it could take many months for her to become pregnant. He knows the pregnancy itself will not reduce the risk of relapse and that she has a 50% risk of becoming ill after delivery. He shares this with the patient and her partner. They all decide that if she is to embark upon a pregnancy she will need to withdraw from valproate and substitute it with another mood stabiliser. They decide to have a further consultation after the consultant has sought further information on the

*continued*

*Vignette 6 continued*

relevant risks associated with other psychotropic drugs. In the meantime, he advises the patient to take 5 mg of folic acid daily. At the next consultation, they discuss the information he has received so far. Other anticonvulsant mood stabilisers are considered to be less hazardous than valproate but still associated with an increased risk of major congenital abnormalities. Lithium carries a risk of an increased rate of the very rare Ebstein's anomaly but also of other more common cardiac malformations and other problems in later pregnancy. Olanzapine would appear to be a reasonable alternative but there is little data on its use in pregnancy and potentially may be associated with an increased risk of gestational diabetes. There is more information on the older antipsychotics but the patient had developed acute extrapyramidal side-effects on haloperidol and is reluctant to consider this option. On balance and after a long discussion the psychiatrist, the patient and her partner decide to slowly withdraw valproate, continue to take folic acid and start taking olanzapine. He arranges to see the patient on a regular basis and documents in the notes the reasons for the decision and the choice of treatment.

*Comment*

The psychiatrist made a careful and informed decision about the plans for conception and involved the patient and her partner fully. The GP should be advised to refer the patient to a feto-maternal medicine specialist once she is pregnant and to obtain an early high-frequency scan to reassure the patient that all is well in the first trimester. He should write to the obstetrician alerting him to the possibility of gestational diabetes. A perinatal management plan should be drawn up and communicated to both the midwife and obstetrician with regard to her high risk of a recurrence of her bipolar illness following delivery. If she is to continue with the olanzapine following delivery, she should be advised against breastfeeding. If sodium valproate is to be reinstated following delivery, it is probably safe for her to breastfeed but it should be prescribed in divided dosage and careful consideration given to contraception.

# The law and unlicensed prescribing

In Britain there is no statutory requirement to disclose to the patient when a drug prescription is unlicensed. However, it has been noted that prescribing of licensed medicines outside the recommendations of the Marketing Authorisation alters (and probably increases) the doctor's professional liability (Drug and Therapeutics Bulletin, 1992). When prescribing outside the recommendations of the product licence the doctor must be able to justify this action in accordance with a respectable, responsible body of professional opinion.

The recent emphasis on risk management and the requirement for evidence-based practice implies that some trusts might be encouraged to introduce systems and protocols to monitor and possibly direct the use of psychotropic drugs. In an attempt to reduce risk, some trusts have therefore suggested that doctors should not use licensed medicines for unlicensed applications. However, in 1993 the Department of Health stated that it would not expect that a health authority would seek to fetter a clinician's freedom to prescribe by expressly directing its medical staff against unlicensed prescribing. The Department of Health's lawyers also stated that, should a health authority so direct its medical staff, a court would be reluctant to support the authority in those circumstances.

In an attempt to clarify the legal position regarding unlicensed prescribing of psychotropic drugs for psychotic and behavioural symptoms in patients with dementing illnesses, contact was made with relevant pharmaceutical companies, three local authority commissioning managers for prescribing and community pharmacy, four NHS trusts, and two medical defence organisations (Lawrence *et al*, 2002). There was some divergence of opinion, reflecting differing standpoints on practice, risk and liability.

The pharmaceutical advisors stated that the final prescribing decision is a matter for the clinician, based on the availability of other therapeutic options and a careful assessment of the potential risks and benefits. This statement was echoed by the health authorities, although it was also stated that hospital doctors have to conform to the rules of their employing trusts. Representatives from the NHS trusts stated they would 'presumably' support clinicians if their actions could be demonstrated to be supported by the literature and considered reasonable by their peers, but also stated that informed consent should be sought before unlicensed prescribing. The two defence organisations were clear that doctors remain free to prescribe drugs for unlicensed indications, but noted that the prescriber is vulnerable to claims for negligence and liability; they also stated that doctors should obtain consent and tell the patient about the status of the drug (Lawrence *et al*, 2002).

In general, the courts would not hold unlicensed prescribing to be a breach of the duty of care, if that treatment was supported by a respected

body of medical opinion, as the Bolam test in medical negligence claims (Bolam v. Friern Hospital Management Committee [1957]) asks for proof that a body of doctors would act similarly to the doctor in question. The more recent case of Bolitho v. City and Hackney Health Authority [1997] states that medical opinion should also be capable of withstanding logical analysis, which in this instance would imply that doctors consider the risks and benefits of varying treatment options, with due regard to the evidence that is available.

More information on the licensing of drugs can be found on the website for the European Agency for the licensing of Medicinal Products (<http://www.emea.eu.int>) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (<http://www.ich.org>). The United Kingdom Medicines Act 1968 and its Regulations are no longer the source of the control in dealing with medicinal products, these matters being addressed by the European Union 1994 Authorisation Regulations (made under the European Communities Act 1994). All current European Union legislation for pharmaceuticals is currently available (November 2006) on <http://pharmacos.eudra.org>.

The General Medical Council publishes guidance on the principles that doctors must follow when prescribing medicines (General Medical Council, 2006). Box 3 shows examples of this guidance, explaining how these principles apply in situations that doctors often meet or find hard to deal with.

**Box 3** Guidance from the General Medical Council on unlicensed applications of licensed medicines. (Reproduced with permission from the General Medical Council, 2006)

PRESCRIBING UNLICENSED MEDICINES

18. You can prescribe unlicensed medicines, but, if you decide to do so, you must:
  - a. be satisfied that an alternative, licensed medicine would not meet the patient's needs
  - b. be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy
  - c. take responsibility for prescribing the unlicensed medicine and for overseeing the patient's care, including monitoring and any follow-up treatment (see also paragraphs 25–27 on prescribing for hospital out-patients)
  - d. record the medicine prescribed and, where you are not following common practice, the reasons for choosing this medicine in the patient's notes.

PRESCRIBING MEDICINES FOR USE OUTSIDE THE TERMS OF THEIR LICENCE (OFF-LABEL)

19. You may prescribe medicines for purposes for which they are not licensed. Although there are a number of circumstances in which this may arise, it is likely to occur most frequently in prescribing for children. Currently pharmaceutical companies do not usually test their medicines on children and as a consequence, cannot apply to license their medicines for use in the treatment of children. The use of medicines that have been licensed for adults, but not for children, is often necessary in paediatric practice.
20. When prescribing a medicine for use outside the terms of its licence you must:
  - a. be satisfied that it would better serve the patient's needs than an appropriately licensed alternative

*continued*

*Box 3 continued*

- b. be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy. The manufacturer's information may be of limited help in which case the necessary information must be sought from other sources
- c. take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring and any follow up treatment, or arrange for another doctor to do so (see also paragraphs 25–27 on prescribing for hospital out-patients)
- d. make a clear, accurate and legible record of all medicines prescribed, and, where you are not following common practice, your reasons for prescribing the medicine.

# Conclusions

The recommendations of the group are given in the Executive summary (see pp. 6–7). It is important to strike the right balance; between undue therapeutic conservatism, that might limit patient choice and reduce the chance of optimal clinical outcomes; and over-enthusiasm for idiosyncratic approaches that may deny patients access to the best evidence-based treatments. Where a proposed off-label treatment could be considered innovative or hazardous, a doctor may be advised to adhere to these suggestions assiduously; but elaborate measures would be less important where the proposed treatment is not controversial or particularly novel.

Clearly, in situations where much of current prescribing is for unlicensed indications (for example, in many aspects of practice in old age psychiatry) it simply will not be possible to fully document the reasons for certain prescribing decisions, in every patient. The absence or non-availability of surviving relatives can also make it impossible to discuss particular aspects of prescribing practice with a suitable carer. In this scenario, doctors might wish to document where and why it has not been possible to consult with relatives.

As in all aspects of evidence-enhanced healthcare, treatment decisions should not be solely based upon evidence from randomised controlled trials; other influences are also important, such as the preferences of the patient, the clinical judgement of the doctor and the treatments that are available locally. Many traditional medical interventions (for example, the use of warfarin as an anticoagulant) are not supported by evidence of efficacy from randomised placebo-controlled trials, but by the evidence of clinical effectiveness over many years. The restriction of prescribing to licensed indications or to clinical situations with evidence from randomised controlled trials may unwittingly inhibit the use of effective drugs from an earlier era of drug registration.

Whenever possible, potential treatment approaches should be considered with due regard to the potential benefits and risks, and discussed fully with the patient, and if relevant with his or her family members. In general, treatment decisions should not be rushed, and the reasons for a change in approach should be adequately documented in the medical notes. It is possible that in especially urgent clinical situations (for example, when there is a need for rapid tranquillisation in patients with behavioural disorders experiencing acute psychotic episodes), some of the steps will be taken quickly, although in these cases other treatment approaches involving the licensed use of medicines can often be instituted, while the possible unlicensed use of medicines is considered.

General practitioners are typically involved in the continuing care of psychiatric out-patients and often have input to the management of their patients undergoing in-patient psychiatric care. In this situation, it is

probably best for psychiatrists to liaise with their primary care colleagues at the time of instituting a new unlicensed treatment approach in out-patients, and before discharge from hospital of in-patients. Most GPs would be prepared to continue such a treatment recommendation from a colleague, providing the rationale and practical arrangements have been clarified. A similar situation applies when doctors working in tertiary referral specialist centres make treatment recommendations to colleagues working in more standard settings.

These recommendations were largely supported by the 40 members of The Royal College of Psychiatrists who attended the workshop on 'unlicensed use of licensed psychotropic drugs' held in the Edinburgh 2003 Annual Meeting. There was agreement that unlicensed prescribing could be a suitable area for multidisciplinary audit (possibly through collaboration with hospital pharmacists); and consensus that judicious unlicensed prescribing can extend treatment options, improve clinical outcomes, and develop the evidence base for psychiatric practice. There was also a belief that prescription of psychotropic drugs (in licensed and unlicensed indications) cannot be separated from the knowledge and experience of the doctor who is doing the prescribing. For example, a psychiatrist whose practice is largely psychotherapeutic, and who prescribes only infrequently, might be advised to adhere more narrowly to licensed prescribing than another doctor with an interest in psychopharmacology, for whom complex prescribing choices are an aspect of daily clinical practice.

# Further considerations

Further considerations relating to the use of licensed psychotropic drugs in unlicensed indications are summarised in Box 4.

Pharmaceutical companies typically evaluate potential new medicines in patients aged between 18 and 65 years. There are no current statutory requirements that potential new drugs are tested and licensed specifically in other populations, such as children and older people. As such, the data about a drug when it first becomes available are usually insufficient to inform the potential use of that drug in those patients at the extremes of the age distribution. Doctors working with patients from these age groups are therefore placed in a somewhat difficult position, and might therefore benefit from discussing these issues within their peer groups, with the aim of clarifying their position on unlicensed prescribing.

The process of obtaining modifications to a product licence is lengthy and costly, and for that reason, pharmaceutical companies may be deterred from pursuing potential new indications for an already available drug, particularly if the patent is soon to expire. By contrast, doctors become more prepared to use tried and tested treatments in potential new clinical applications, similar to those for which the product already has a licence. In these situations, there is much scope for data collection and local pharmacovigilance, but this requires the support of drugs and therapeutics committees, and the provision of trust resources.

It is important that these novel uses in case series of patients are submitted for scientific publication, as the resulting generation of an evidence base allows doctors to cite 'custom and practice' on the effectiveness and acceptability of proposed treatments when there is no evidence of efficacy from randomised controlled trials.

Finally, the College might consider a range of activities, relating to psychotropic drug prescribing. For example, the Research Unit might support large-scale surveys of current psychiatric prescribing practice, in an attempt to establish the proportion of prescriptions that are 'off-label'. In addition, the individual College Faculties might convene working groups to consider these issues in more (Faculty-specific) detail, and issue periodically updated recommendations.

**Box 4** Further considerations relating to use of licensed drugs in unlicensed applications

- Doctors might wish to discuss individual practice relating to unlicensed prescribing in their continuous professional development peer groups.
- Trusts might wish to audit local prescribing to gain information on the extent of, and reasons for, prescribing for unlicensed applications in individual patients.

*continued*

*Box 4 continued*

- Doctors may wish to collaborate in evaluating the benefit and acceptability of prescribing for unlicensed applications in their practice, and submit the results of these assessments for publication in scientific journals.
- Faculties of The Royal College of Psychiatrists may wish to convene Faculty-specific working groups to consider the issue of unlicensed prescribing in more detail.
- The Research Unit of The Royal College of Psychiatrists might wish to commission large-scale research into unlicensed prescribing in psychiatric practice.

# References

- Audit Commission (2001) *A Spoonful of Sugar – Improving Medicines Management in Hospitals*. Audit Commission.
- Barbui, C., Danese, A., Guaiana, G., *et al* (2002) Prescribing second-generation antipsychotics and the evolving standard of care in Italy. *Pharmacopsychiatry*, **35**, 239–243.
- Barbui, C., Ciuna, A., Nose, M., *et al* (2004) Off-label and non-classical prescriptions of antipsychotic agents in ordinary in-patient practice. *Acta Psychiatrica Scandinavica*, **109**, 275–278.
- Barnard, L., Young, A. H., Pearson, J., *et al* (2002) A systematic review of the use of atypical antipsychotics in autism. *Journal of Psychopharmacology*, **16**, 93–101.
- Beck, S., Paton, C., Euba, R., *et al* (2001) Atypical antipsychotics in the elderly. *International Journal of Psychiatry in Clinical Practice*, **5**, 257–261.
- Bramble, D. (1992) The use of antidepressants by British child psychiatrists. *Psychiatric Bulletin*, **16**, 396–398.
- Bramble, D. (2003) Annotation. The use of psychotropic medications in children: a British view. *Journal of Child Psychology and Psychiatry*, **44**, 169–179.
- Briggs, G. C., Freeman, R. K., Yaffe, S. J. (eds) (2005) *Drugs in Pregnancy and Lactation* (7th edn). Lippincott, Williams and Wilkins.
- British Association for Psychopharmacology (1997) BAP consensus statement. Child and learning disability psychopharmacology. *Journal of Psychopharmacology*, **11**, 291–294.
- British Medical Association & Royal Pharmaceutical Society of Great Britain (2006) *British National Formulary* (September edn). BMJ Books & Pharmaceutical Press.
- Bücheler, R., Schwab, M., Mörike, K., *et al* (2002) Off label prescribing to children in primary care in Germany: retrospective cohort study. *BMJ*, **324**, 1311–1312.
- Conroy, S., Choonara, I., Impicciatore, P., *et al* (2000) Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ*, **320**, 79–82.
- Doerry, U. & Kent, L. (2003) Prescribing practices of community child and adolescent psychiatrists. *Psychiatric Bulletin*, **27**, 407–410.
- Douglas-Hall, P., Fuller, A. & Gill-Banham, S. (2001) An analysis of off-licence prescribing in psychiatric medicine. *Pharmaceutical Journal*, **267**, 890–891.
- Duff, G. (2005) *Paroxetine (Seroxat) – Safety in pregnancy* CEM/CMO.2005/11. Department of Health.
- Drug and Therapeutics Bulletin (1992) Prescribing unlicensed drugs or using drugs for unlicensed indications. *Drug and Therapeutics Bulletin*, **30**, 97–99.
- Efron, D., Hiscock, H., Sewell, J. R., *et al* (2003) Prescribing of psychotropic medications for children by Australian paediatricians and child psychiatrists. *Pediatrics*, **111**, 372–375.
- General Medical Council (2006) *Good Practice in Prescribing Medicines*. London: GMC. Available at [http://www.gmc-uk.org/guidance/current/library/prescriptions\\_faqs.asp](http://www.gmc-uk.org/guidance/current/library/prescriptions_faqs.asp)
- Harrington, M., Lelliott, P., Paton, C., *et al* (2002a). The results of a multi-centre audit of the prescribing of antipsychotic drugs for in-patients in the UK. *Psychiatric Bulletin*, **26**, 414–418.

- Harrington, M., Lelliott, P., Paton, C., *et al* (2002b). Variation between services in polypharmacy and combined high dose of antipsychotic drugs prescribed for in-patients. *Psychiatric Bulletin*, **26**, 418–420.
- Haw, C. & Stubbs, J. (2005a). A survey of the off-label use of mood stabilizers in a large psychiatric hospital. *Journal of Psychopharmacology*, **19**, 402–407.
- Haw, C. & Stubbs, J. (2005b). A survey of off-label prescribing for inpatients with mild intellectual disability and mental illness. *Journal of Intellectual Disability Research*, **49**, 858–864.
- Healy, D. & Nutt, D. (1998) Prescriptions, licence and evidence. *Psychiatric Bulletin*, **22**, 680–684.
- Hodgson, R. & Belgamar, R. (2006) Off-label prescribing by psychiatrists. *Psychiatric Bulletin*, **30**, 55–57.
- Humble, F. & Berk, M. (2003) Pharmacological management of aggression and violence. *Human Psychopharmacology*, **18**, 423–436.
- Lawrence, R. M., Scott, K., Duggal, A., *et al* (2002) Medico-legal implications of drug treatment in dementia: prescribing out of licence. *Psychiatric Bulletin*, **26**, 230–232.
- Lelliott, P., Paton, C., Harrington, M., *et al* (2002) The influence of patient variables on polypharmacy and combined high dose of antipsychotic drugs prescribed for in-patients. *Psychiatric Bulletin*, **26**, 411–414.
- Lowe-Ponsford, F. & Baldwin, D. S. (2000) Off-label prescribing by psychiatrists. *Psychiatric Bulletin*, **24**, 415–417.
- Maxwell, S., Walley, T. & Ferner, R. E. (2001) Using drugs safely. Undergraduates must be proficient in basic prescribing. *BMJ*, **324**, 930–931.
- McAllister-Williams, R. H. & Ferrier, I. N. (2002) Rapid tranquillisation: time for a reappraisal of options for parenteral therapy. *British Journal of Psychiatry*, **180**, 485–489.
- McNicholas, F. (2001) Prescribing practices of child psychiatrists in the UK. *Child Psychology and Psychiatry Review*, **1**, 94–97.
- Milton, J., Lawton, J., Smith, M., *et al* (1998) Hidden high-dose antipsychotic prescribing effects of p.r.n. doses. *Psychiatric Bulletin*, **22**, 675–677.
- Rosenheck, R., Leslie, D. & Sernyak, M. (2001) From clinical trials to real-world practice: use of atypical antipsychotic medication nationally in the Department of Veterans Affairs. *Medical Care*, **39**, 302–308.
- Royal College of Paediatrics and Child Health (2000) *The Use of Unlicensed Medicines or Licensed Medicines for Unlicensed Applications in Paediatric Practice. Policy Statement Produced by the Joint RCPCH/NPPG Standing Committee on Medicines*. Royal College of Paediatric and Child Health.
- Royal College of Psychiatrists (2006) *Consensus Statement on the Use of High-dose Antipsychotic Medication (CR138)*. Royal College of Psychiatrists.
- Rubin, P. C., Craig, G. F., Gavin, K., *et al* (1986) Prospective survey of use of therapeutic drugs, alcohol and cigarettes during pregnancy. *BMJ*, **292**, 81–83
- Sanz, E. J, De-Las-Cuevas, C., Kuru, A., *et al* (2005) Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet*, **365**, 482–487.
- Scott, K., Lawrence, R. M., Duggal, A., *et al* (2002) Prescribing patterns of psychotic and behavioural symptoms in dementia: a national survey. *Psychiatric Bulletin*, **26**, 288–290.
- 't Jong, G. W., Eland, I. A., Sturkenboom, M. C. J. M., *et al* (2002) Unlicensed and off-label prescription of drugs to children: population based cohort study. *BMJ*, **324**, 1313–1314.
- Turner, S., Nunn, A. J., Fielding, K., *et al* (1999) Adverse drug reactions to licensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatrica*, **88**, 965–968.
- Weiss, E., Hummer, M., Koller, D., *et al* (2000) Off-label use of antipsychotic drugs. *Journal of Clinical Psychopharmacology*, **20**, 695–698.

Williams, L. V., Pearce, G. L., Martin, R. M., *et al* (1998) The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. *British Journal of Obstetrics and Gynaecology*, **105**, 882–889.

Zito, J. M., Safer, D. J., dosReis, S., *et al* (2000) Trends in the prescribing of psychotropic medications to preschoolers. *Journal of the American Medical Association*, **283**, 1025–1030.

Bolam v. Friern Hospital Management Committee [1957] WLR, 582.

Bolitho v. City and Hackney Health Authority [1997] 3WLR, 1151.