
Use of licensed medicines for unlicensed applications in psychiatric practice

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Royal College of Psychiatrists
Psychopharmacology Committee

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| Contents

Contributors	2
Executive summary and recommendations	4
What represents licensed and unlicensed prescribing?	6
Types of unlicensed prescribing and possible motivations	8
Potential benefits and risks	10
Guidance on unlicensed prescribing	11
References	14

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Executive summary and recommendations

Pharmacological treatment is an important component of much of psychiatric practice. Many psychotropic medications and psychological interventions are available for patients with mental health problems, but patients often remain troubled by distressing symptoms despite undergoing a series of pharmacological and psychological treatments. In this situation, doctors may wonder whether they might prescribe a medication outside the narrow terms of its market authorisation ('product licence') in an attempt to improve clinical outcomes. Many authorities agree that use of a drug outside the terms of its licence can be a necessary and beneficial part of clinical practice, whereas others have raised concerns about patient safety and medical liability.

The Royal College of Psychiatrists first issued guidance on recommended procedures for the use of licensed medicines for unlicensed applications in psychiatric practice in 2007. In the subsequent decade, evidence on this aspect of practice has increased and other bodies have also provided guidance (e.g. General Medical Council, 2013). The Royal College of Psychiatrists' Psychopharmacology Committee was therefore asked to consider and, if necessary, revise current College guidance and did so in consultation with representatives from the British Association for Psychopharmacology (BAP). We considered the potential benefits and risks of this aspect of clinical practice and believe that prescription of a drug outside the narrow terms of its market authorisation can be an appropriate part of overall management and in the best interests of a patient. The Committee strived to make ten balanced recommendations that it judged would be feasible to implement within current psychiatric practice.

Recommendations

1. First check that medicines with a licence (market authorisation) for the particular indication have either had an adequate therapeutic trial or have been considered carefully but excluded on clinical grounds (such as treatment contraindications or risk of drug–drug interactions).

2. Become familiar and be satisfied with the evidence base for the proposed pharmacological intervention, including its probable effectiveness, acceptability, treatment-emergent adverse effects, and drug interactions.
3. Obtain the advice of another prescribing clinician (and possibly a specialist pharmacist) with greater experience or expertise if the medicine to be used does not have an extensive evidence base to support its use for the proposed indication, or if you have particular concerns, or if you feel insufficiently expert in this field.
4. Consider the anticipated risks and benefits of treatment, giving particular thought in vulnerable groups such as children and adolescents, women of child-bearing age, elderly patients, physically ill patients, and patients with impaired insight and judgement; and document your thoughts on the likely balance of risk and benefit.
5. Explain fully the anticipated benefits and potential risks of the proposed medication to the patient (and if possible their relative or partner) stating that the medicine will be used outside the restricted terms of its product licence and make a record of this explanation.
6. In a situation where prescribing an unlicensed medicine is supported by authoritative guidance, describe in general terms why the medicine is not licensed for the proposed indication, but if you intend to prescribe an unlicensed medicine where that is not routine, provide the patient with a more detailed explanation.
7. Record the agreement of the patient to the proposed intervention. If the patient is unable to provide consent to a necessary treatment, document that it has not been possible to obtain formal consent.
8. Start the medicine at low dose and monitor its effects carefully. If it is well tolerated but not effective, give thought to cautiously increasing the dose, with further careful monitoring of its effects.
9. Tell other health professionals involved in the care of the patient that the medicine is being prescribed outside the terms of its licence and encourage them to discuss their observations of its beneficial and untoward effects.
10. If the medicine has no beneficial effects or the emergent risks and hazards outweigh the benefits, withdraw it (generally, best done gradually) and document the reasons why it is being withdrawn. If there is a persistent need for further treatment, consider possible alternatives (using the process described above) and after a suitable 'wash-out' cautiously introduce the next medicine.

What represents licensed and unlicensed prescribing?

In the UK, medicines receive a market authorisation (previously called a product licence) through arrangements determined by the Human Medicines Regulations 2012 and implemented through the Medicines and Healthcare products Regulatory Agency with regard to European Union authorisation regulations made under the European Communities Act 1972. When a pharmaceutical company wishes to receive an authorisation for a medicine, it submits a Summary of Product Characteristics (SPC) to the European Medicines Agency, describing how the product might be used for a specific treatment, based on conducted clinical trials. An approved SPC forms the basis of the patient information leaflet ('package insert') that accompanies the medicine. Prescribing for a 'licensed application' occurs when the prescription is within the terms (indication, dosage, etc.) described within the market authorisation: prescribing for an 'unlicensed application' occurs when the medicine is prescribed outside those terms. The doses, indications, cautions, contraindications and side-effects of a particular medicine provided in the *British National Formulary* (BNF) reflect the authorisation and SPC, but also take account of guidance and advice from professional bodies and expert clinicians. Access to an online version of the BNF is currently available by registering through www.medicinescomplete.com/about/subscribe.htm.

Regulations relating to drug licensing vary across countries. The manner in which countries deal with the unlicensed use of medicines is not harmonised across the European Union, and some member states have passed legislation that promotes unlicensed use of medicines on economic grounds (Dooms *et al*, 2017). Since 1994 in France, an *autorisations temporaires d'utilisation* (temporary authorisations for use) procedure has provided an exceptional measure for making medicinal products available before formal marketing authorisation, in situations where there is a genuine public health need (as is currently the case for baclofen in the treatment of alcohol dependence). In the USA, the US Food and Drug Administration (FDA) approves new medicines that are shown to be safe and effective for specific indications, but it does not control or restrict how medicines are prescribed once they become available: unlicensed or 'off-label' use is when a drug is prescribed for an indication that has not received FDA

approval (Wittich *et al*, 2012). By contrast, in Australia, an unlicensed application is a medicine, formulation or dosage of medicine that has not been evaluated or approved and not entered on the Australian Register of Therapeutic Goods (Gazarian *et al*, 2006).

New indications for existing treatments appear regularly, and what is unlicensed use one month may come within the terms of a revised marketing authorisation the next, so becoming a licensed application. However, the absence of a licence does not necessarily indicate an absence of evidence for the proposed intervention: for example, sertraline has efficacy in acute treatment of generalised anxiety disorder but is not licensed for that indication (even though it is recommended for treating the condition by the National Institute for Health and Care Excellence (2011)). Conversely, prescription within the terms of a licence is no guarantee of either safety or efficacy: for example, there may be troublesome pharmacokinetic interactions between two drugs, each prescribed for a licensed application. Use of a drug for an unlicensed application does not necessarily imply a greater safety hazard, and there are many instances where prescribing for an unlicensed application is uncontroversial and probably advantageous (e.g. current prescriptions of venlafaxine in post-traumatic stress disorder or asenapine in schizophrenia). A number of factors influence whether a drug gains market authorisation; drugs that are 'off patent' or in orphan areas are unlikely to gain new licences for an indication, even though there may be good evidence for their use in a specific condition. By contrast, a new formulation of a drug may be developed and have potential clinical advantages, but its authorisation may not include all the listed indications of an earlier formulation.

When a drug first becomes available for clinical use, data relating to its potential application in young and elderly patients are extremely limited and consequently most prescribing for children and adolescents or for the elderly is for unlicensed applications. Pharmaceutical companies are strongly encouraged by regulatory authorities to undertake supplementary studies in children and adolescents, but there are no statutory requirements for drugs to be tested in these age groups. Modification of an existing product licence is a complex and costly process, so for commercial reasons pharmaceutical companies may be reluctant to pursue authorisation for potential additional indications, even when there is sufficient evidence of efficacy and safety from clinical trials. Pharmaceutical companies are also censured strongly if found to promote their products outside the terms of the market authorisation, although companies can distribute peer-reviewed articles about off-label use upon request by a prescribing physician (Wittich *et al*, 2012).

Types of unlicensed prescribing and possible motivations

Five forms of unlicensed prescribing ('the five Ds': demographic, disorder, dosage, duration, domain) are recognised.

- 1 **Demographic.** The age of a patient may lie outside the recommended range, with most medicines being evaluated during clinical trial programmes in patients aged between 18 and 65 years; and most medicines are not licensed for use in pregnant or breastfeeding women.
- 2 **Disorder.** A medicine may be prescribed for a condition other than that or those described within the SPC and market authorisation, for example the use of clozapine in a patient with a primary affective disorder.
- 3 **Dosage.** The prescribed dosage may be higher than recommended, for example a prescription of phenelzine at a dosage of 90mg/day for an out-patient or escitalopram at a dosage exceeding 20mg/day. Differing generic formulations of a drug may have varying maximum dosages, and only some formulations (e.g. extended-release versions) of particular drugs may be licensed for certain indications.
- 4 **Duration.** A prescription may be for a longer period than is recommended, for example prescriptions of benzodiazepine hypnotics for more than 4 weeks.
- 5 **Domain.** A drug may be licensed in one country but not another, for example quetiapine is licensed for treatment of generalised anxiety disorder in Australia but not in the UK.

A patient may therefore rather absurdly move from undergoing treatment for a licensed application to an unlicensed application if the diagnosis is refined, if she becomes pregnant, when she crosses an age threshold, moves from in-patient to out-patient status, or crosses a geographical border. It is probably helpful to conceptualise prescriptions as being on a spectrum, some being 'within-label', others 'near-label', and some 'very far off-label'.

Prescribing for unlicensed applications is frequent in all psychiatric specialties and in many countries (Baldwin & Kosky, 2007). Prescribing for unlicensed applications is also common in general practice (Ekins-Daukes *et al*, 2005), general medicine (Radley *et al*, 2006), paediatrics

(Ufer *et al*, 2004; Cuzzolin *et al*, 2006; Morales-Carpi *et al*, 2010) and palliative care (Culshaw *et al*, 2013). Several factors are relevant (Wittich *et al*, 2012).

- Probably the most common circumstance is when there is a persisting need for treatment and previous licensed medicines have proved either ineffective or poorly tolerated.
- A medicine may be known to be generally safe and effective in a broad patient population, but not approved for the treatment of a particular subgroup of patients.
- Sometimes, a clinician may wish to avoid potential hazards associated with polypharmacy by choosing to prescribe one medication to treat two or more comorbid conditions even though the chosen medicine is approved for treating only one of the conditions (e.g. sertraline to treat coexisting major depression and generalised anxiety disorder).
- A serious or life-threatening condition might impel a clinician to recommend a treatment that seems logical even though not licensed for that indication.
- A cost-conscious clinician might prefer to prescribe an unlicensed medication over a licensed medicine with a similar mechanism of action, comparable tolerability and efficacy, but differing pharmacokinetic properties and lower cost.
- Inadvertent off-label prescribing might occur when a pharmacist dispenses a medicine produced by another manufacturer for which the formulation has a lower licensed maximum daily dosage than the previously dispensed medicine.
- Finally, a clinician might feel impelled to prescribe for an unlicensed application if a patient declines treatment with medicines that have a licence for the condition.

Potential benefits and risks

Many authors contend that prescribing for an unlicensed indication can represent a thoughtful and often necessary part of clinical practice (Anonymous, 1992; American Academy of Pediatrics, 2002; Gazarian *et al*, 2006; Baldwin & Kosky, 2007). Others have argued similarly that it is usually uncontroversial and may enhance clinical outcomes (Healy & Nutt, 1998), and that the benefits typically outweigh any risks (Tan *et al*, 2004). Prescribing a medicine solely within the terms of its product licence may not necessarily represent its best use in practice (Cohen, 2001).

However, not all authors are so positive. For example, an expert panel review (based on the RAND/UCLA Appropriateness Method) of antipsychotic prescriptions for insomnia, anxiety, post-traumatic stress disorder or dementia (involving 29 scenarios for each drug) in 69 823 US veterans judged that 60% of prescriptions were probably inappropriate (Painter *et al*, 2017). Furthermore, awareness of potential associated hazards associated with off-label prescriptions is often limited (Ekins-Daukes *et al*, 2005), despite evidence that this form of prescribing can raise clinical and ethical concerns, and may have potential legal consequences (Collier, 1999; Blum, 2002; Neubert *et al*, 2004; Bartoli *et al*, 2015). Unlicensed use of medicines in children has been associated with both an increased incidence and a greater seriousness of adverse drug reactions (European Medicines Agency, 2004).

Several groups have therefore sought to develop mechanisms for ensuring the appropriateness of off-label prescribing (Ansani *et al*, 2006; Gazarian *et al*, 2006; Royal College of Psychiatrists, 2007; General Medical Council, 2013; Sharma *et al*, 2016; Doods *et al*, 2017). A balance must be struck between undue therapeutic conservatism and wilfully cavalier innovation, and between the duty to promote the health of individual patients and the desire to extend scientific knowledge and optimise clinical practice (Baldwin *et al*, 2015). It is important that any proposed intervention appears reasonable to medical peers and can withstand logical analysis, which implies that doctors have considered the anticipated risks and benefits of various treatment options, with regard to the supporting evidence base, patient preference and the nature of the clinical case (Haynes *et al*, 2002).

Guidance on unlicensed prescribing

In the UK, the Medicines Act 1968 provides exemptions that enable doctors to use or advise the use of licensed medicines outside the recommendations of the licence, and to override the warnings and precautions given in the licence. However, in these situations (as in other aspects of medical practice) the doctor must be able to justify this action in accordance with a respectable, responsible body of professional opinion. In contested practice, the recommendations of regulatory authorities and professional bodies will be examined to make informed decisions about potential culpability. In the area of psychiatric practice, suitable authorities could include the General Medical Council (GMC), the Royal College of Psychiatrists, the Royal College of Paediatrics and Child Health (for psychotropic drug prescribing in children and adolescents) and the BAP.

In its 2013 guidance the GMC stated,

‘You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient’ (para. 68).

It continues:

‘When prescribing an unlicensed medicine you must: (a) be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy; (b) take responsibility for prescribing the medicine and for overseeing the patient’s care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so; (c) make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine’ (para. 70).

Later paragraphs in the GMC guidance (paras. 71–73) state, ‘You must give patients (or their parents or carers) sufficient information about the medicines you propose to prescribe to allow them to make an informed decision’; continuing, ‘[...] where prescribing unlicensed medicines is supported by authoritative clinical guidance, it may be sufficient to describe in general terms why the medicine is not licensed for the proposed use or patient population’; and, ‘if you intend to prescribe unlicensed medicines where that is not routine or if there are suitably licensed alternatives available, you should explain this to the patient, and your reasons for doing so’.

There is no legal requirement to disclose off-label use of a drug to a patient, but such disclosure has been advocated strongly (Frank *et al*, 2008; Wilkes & Johns, 2008) and the GMC guidance recommends that the decision to prescribe an unlicensed medicine in preference to a licensed alternative should be accompanied by an explanation to the patient. Any risk of increased liability relating to off-label prescribing may be mitigated if the prescribing physician is well informed about the product, bases its use on a firm scientific rationale and sound medical advice, and maintains records of the product's use and effects (Fugh-Berman & Melnick, 2008). Again, the GMC guidance emphasises both the need to be familiar with the evidence for the safety and efficacy of the proposed unlicensed application, and the need to document the unlicensed nature of the prescription and its utility in practice (General Medical Council, 2013).

Guidance from the Royal College of Paediatrics and Child Health states that where available 'an appropriate licensed preparation should be prescribed and supplied in preference to an unlicensed preparation' (Fox & Sammons, 2013). However, the Medicines for Children guidance highlights situations when off-label prescribing may be safe and acceptable and the best choice for a patient – such as the medicine being formulated in a way which can be taken more easily by a child or because the unlicensed medicine is safer than a licensed one (Medicines for Children, 2015). In a position statement, the BAP offers guidance on the prescribing of psychotropic medication to children and adolescents:

'Prescribing an off-label medicine may have advantages over a licensed one. Hence, licensed drugs and formulations should not always be prescribed and supplied in preference to an off-label drug or formulation. A prescribing decision (including a decision not to prescribe) should incorporate knowledge of the overall evidence base and the needs of the individual child' (Sharma *et al*, 2016: p. 420).

The BAP guidance also states, 'When the evidence base for an off-label medication is lacking or the benefit/risk profile appears potentially unfavourable, obtain a second opinion from another doctor (and perhaps another member of the multidisciplinary team) before prescribing'; and, 'Explain the potential benefits and side effects to the patient and their parents/carers and document this discussion' (Sharma *et al*, 2016: p. 420). As with the GMC guidance, the BAP position statement is clear that unlicensed prescribing should be based on sound knowledge and accompanied by a documented record of the explanation to the family.

In 2007, the Royal College of Psychiatrists' report CR142 included ten recommendations for a suggested procedure when prescribing off-label. The College's Psychopharmacology Committee and representatives from the BAP have examined these recommendations and have considered both accumulating evidence on licensed and unlicensed prescribing and guidance from other organisations. Many authorities agree that prescription of a drug outside the narrow terms of its market authorisation can be an appropriate part of the overall

management of individual patients: and the College supports this aspect of clinical practice, when it is in the best interests of a patient. A correct balance must be struck between the extremes of restrictive conservatism that may hinder good clinical outcomes and wilful experimentation that could put some patients at unnecessary risk. We have revised the original recommendations to take account of recent developments, while striving to ensure their practicability within current psychiatric practice (see pp. 4–5).

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