Guidance on Off-label and Unlicensed Prescribing in Mental Health Services

Robust record-keeping and documentation is fundamental to all prescribing practice. When commencing new treatments, patients should be provided with sufficient information to allow them to make an informed decision.

Remember to **RECoRD**……

Rationale
Evidence-base
Consent
Review
Document

Background and definitions

In the UK, **licensed medicines** are those products that have received a 'marketing authorisation' previously referred to as a 'product licence'.

A **marketing authorisation** (MA) is required in order for a manufacturer to sell, advertise and promote a medicine for a defined population. Licensing arrangements are determined by the Human Medicines Regulations 2012 (a consolidation of legislation including the Medicines Act 1968) and implemented through the MHRA (Medicines and Healthcare products Regulatory Agency).

A summary of product characteristics (SPC) is a description of a medicinal product's properties and the conditions attached to its use.

Off-label and **unlicensed prescribing** are often used interchangeably, however, for the purpose of this guidance, the definitions are;

- **Off-label prescribing** occurs when medication use falls outside the terms of the Marketing Authorisation.
- **Unlicensed prescribing** is where a medicine has no Marketing Authorisation in the UK or the Marketing Authorisation has been withdrawn.

Off-label prescribing occurs when medication use falls outside the scope of the marketing authorisation with respect to one of five key domains[1];

1. Demographic. The age of the patient may lie outwith the recommended range
   e.g. the use of sertraline for depression in a 16 year old

2. Disorder. Prescribing for a condition which is outwith the marketing authorisation
   e.g. the use of hyoscine hydrobromide for clozapine-related hypersalivation

3. Dosage. Prescribing at a dose that is higher than recommended
   e.g. olanzapine prescribed at 30mg daily

4. Duration. Prescribing for a longer period of time than is recommended
   e.g. a benzodiazepine prescribed for longer than 4 weeks

5. Domain. Where a drug is licensed for a particular indication in one country and not another
   e.g. in some EU member states, valproate salts have a licence for prevention of migraine

In addition, the following situations would also constitute **off-label prescribing**;

1. Prescribing a medicine in a circumstance that is specified as contraindicated
   e.g. the use of haloperidol in combination with another mediation known to prolong the QTc interval

2. Where the form of a preparation is changed before administration e.g. crushing tablets and mixing with yoghurt as part of a covert medication pathway

3. Administering medication via a route not specified within the SPC e.g. down a nasogastric tube

Within mental health services, the vast majority of **unlicensed prescribing** occurs when;

1. The UK marketing authorisation has been suspended (usually for commercial reasons) with the product now imported from abroad e.g. pirenzepine for clozapine-related hypersalivation

2. The UK marketing authorisation has been suspended but where the company continues to make product available for named individuals e.g. sertindole

3. There has never been a UK marketing authorisation and the product needs imported from abroad e.g. ziprasidone

Outwith the regulatory framework of the marketing authorisation can be a body of literature related to off-label uses of a certain medication. Often the literature includes robust evidence including published RCTs. Modification of an existing marketing authorisation is a complex and costly process, therefore, pharmaceutical companies may be reluctant to pursue authorisation for potential additional indications due to commercial reasons even when there is sufficient evidence of efficacy and safety. The licensed uses of a medicine are therefore simply those for which formal approval has been sought and obtained by the manufacturer. The absence of a licence does not necessarily indicate an absence of evidence for the proposed treatment, neither is the prescribing of medicines within the terms of their marketing authorisation a guarantee of safety or efficacy.

Spectrum of off-label and unlicensed prescribing

It is helpful to consider off-label and unlicensed prescribing on a spectrum with some prescribing 'near-label' lower risk and others 'very far off-label' or unlicensed and potentially higher risk.

Medications whose off-label use is supported by evidence-based texts (e.g. BNF, BNF for Children, SIGN, NICE or BAP Guidelines) are generally considered lower risk provided the prescribing information in that text is followed.

The risks associated with some off-label medicine use may be due to poor evidence base or to the risk of adverse effects associated with the off-label treatment.

Examples of off-label medicine use		
Near label Lower risk	**Off-label Intermediate risk**	**Off-label Higher risk**
Sertraline in GAD	Olanzapine > 20mg/day	Rechallenge with clozapine following neutropenia
Initiation of methylphenidate in an adult	Use of SGA for anxiety or in managing core symptoms of personality disorder	Combination of clozapine and carbamazepine
Semisodium valproate for maintenance of BPAD	Lorazepam IM for acute behavioural disturbance	IM ketamine for depression
Sodium valproate for treatment of hypomania	Bupropion for depression	Combination of haloperidol and citalopram
Metformin for antipsychotic-induced weight gain		
Amitriptyline for neuropathic pain		

Examples of unlicensed medicine use		
Unlicensed Lower risk	**Unlicensed Intermediate risk**	**Unlicensed Higher risk**
Pirenzepine for clozapine-related hypersalivation	Short-acting IM olanzapine	IM clozapine
Benzatropine for clozapine-related hypersalivation	Ziprasidone	Sertindole

Scope of off-label prescribing

A recent local audit within a GGC mental health rehab ward suggested that around 25% of prescribing was off-label .[2] Audit in other areas has suggested that up to 40% of all prescriptions of psychotropic drugs are off-label. [3] This may be even higher with specific psychotropic medications, for example, over 60% of risperidone use in a primary care study was for off-label uses. [4]

Medico-legal implications of off-label prescribing

Independent prescribers can prescribe any medication (licensed, off-label or unlicensed) so long as prescribing would be supported by a reasonable body of medical opinion.[5]

In general, off-label prescribing would not be deemed a breach of duty of care provided that the treatment was supported by a respected body of medical opinion (Bolam *v Friern Hospital Management Committee, 1957*). In addition, that medical opinion needs to withstand logical analysis (*Bolitho v City and Hackney health Authority*, *1997*). It is therefore essential to consider risks and benefits of various treatment options with regard to the evidence that is available and the nature of the clinical case. [6]

There is no legal requirement to disclose the off-label use of a drug to a patient but such disclosure is advocated strongly [1] and the GMC advice on prescribing states that sufficient information **must** be given to enable informed consent to be made to **any treatment**, including explaining the off-label nature of prescribing to the patient (or carer as appropriate) and the reasons for doing so.[5, 7]

Prescribers must now ensure that patients (or their carers if the patient lacks legal capacity) are aware of any 'material risks' involved in a proposed treatment, and of reasonable alternatives, following the judgment in the Montgomery case (*Montgomery* v *Lanarkshire Health Board 2015)*. 'The test of materiality is whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it.'

In emergencies or where there is no realistic alternative treatment to an off-label treatment and such information is likely to cause distress, it may not be practical or necessary to draw attention to the licence. In other cases, where prescribing unlicensed medicines is supported by published clinical guidance, it may be sufficient to describe in general terms why the medicine is not licensed for the proposed use or patient population. [7] However, in circumstances where the evidence base is less clear cut then it would be sensible to seek a second opinion to support the prescribing decision. [5]

Liability

Prescribing unlicensed medicines or medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber's professional responsibility and potential liability.[5] The prescriber is always responsible for the use of a medicine and the patient's welfare and in the event of adverse reactions may be called upon to justify the decisions that they have made. [8]

Consent & Documentation

Good record-keeping and documentation is fundamental to all prescribing practice. When prescribing is off-label or unlicensed, it is even more important to document the rationale for treatment, the evidence-base where appropriate, record the key elements of discussion with the patient and/or carer and consider ongoing review of the treatment.

Patients should be provided with sufficient information about the proposed treatment to allow them to make an informed decision. General advice about the off-label use of licensed medicines or use of unlicensed medicines from the Choice and Medication website[9] may be useful in aiding discussions with patients. Off-label (unlicensed) use fact sheet & Unlicensed medicines fact sheet. Choice and Medication also has some specific medicine information leaflets on off-label medicine use e.g. metformin for weight gain and for some unlicensed medicines e.g. pirenzepine, ziprasidone, sertindole. In addition, the use of off-label or unlicensed medicines in children is discussed in the following resource; Medicines for children unlicensed medicine advice

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Advice for T2 & T3 certificates in relation to off-label and unlicensed medicine use[10]

In general, T3 treatment plans should record the class of drug and route of administration and state that dose and frequency are within BNF guidelines; however, it is best practice for T2 certificates to specify the actual medication(s) rather than a class of medicines. [11]
It may be appropriate for the treatment plan to refer to guidelines or local protocols for off-label medication use e.g. dosing of lorazepam up to 8mg/24 hours in line with GGC guidance for acutely disturbed behaviour.[12] High dose antipsychotic therapy should state a requirement for monitoring in accordance with guidance from RCPsych or local GGC high dose antipsychotic monitoring policy.[13]
Where a proposed treatment plan contains novel treatments (including some higher risk off-label or unlicensed medicine use), it is the responsibility of the referring RMO to ensure that any relevant literature or references are available for the DMP to refer to and a clear rationale for the use of the medication is recorded in the casenotes. For full unlicensed medication, the specific medication and the fact that it is unlicensed should be included in the treatment plan (referring to the BNF in this case would be irrelevant).

Communication with other prescribers

The legal responsibility for prescribing falls to the clinician who signs the prescription. It is therefore essential that there is clear communication between a recommending specialist and the patient's GP about the rationale for use of an off-label or unlicensed medication over a licensed alternative. Offering information to GP colleagues on indication, evidence-base, safety, patient need etc with the prescribing request is important in order for the patient's GP to be adequately satisfied with the clinical decision. Note: as a rule, the majority of full unlicensed medicines (i.e. with no UK marketing authorisation) used in mental health services, e.g. pirenzepine for clozapine-related hypersalivation, named-patient sertindole, ziprasidone will be supplied by MHS for patients in primary care.

Process for unlicensed medicine use in GGC MHS

GGC MHS have blanket unlicensed medicine protocols for the following medications[14];

- Short-acting intramuscular olanzapine Protocol for olanzapine IM
- Pirenzepine for clozapine-related hypersalivation Protocol for pirenzepine
- Benzatropine for clozapine-related hypersalivation Protocol for benzatropine
- Thioridazine for 'legacy' patients Protocol for thioridazine

Any other unlicensed medicine request need a full unlicensed medicine form completed and submitted to the MH Prescribing Management Group for consideration. GGC ULM form

In the main, the off-label use of medication does not require any supplementary documentation. However, where the off-label use is considered higher risk, a full ULM form should be completed and submitted to MH-PMG for consideration.

References

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Appendix I: excerpt from GMC guidance Good practice in prescribing and managing medicines and devices GMC Good practice in prescribing and managing medicines and devices

67. The term 'unlicensed medicine' is used to describe medicines that are used outside the terms of their UK licence or which have no licence for use in the UK. Unlicensed medicines are commonly used in some areas of medicine such as in paediatrics, psychiatry and palliative care. They are also used, less frequently, in other areas of medicine.
68. 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.
69. Prescribing unlicensed medicines may be necessary where:
    a) There is no suitably licensed medicine that will meet the patient's need. Examples include (but are not limited to), for example, where:
        i) there is no licensed medicine applicable to the particular patient. For example, if the patient is a child and a medicine licensed only for adult patients would meet the needs of the child; or
        ii) a medicine licensed to treat a condition or symptom in children would nonetheless not meet the specific assessed needs of the particular child patient, but a medicine licensed for the same condition or symptom in adults would do so; or
        iii) the dosage specified for a licensed medicine would not meet the patient's need; or
        iv) the patient needs a medicine in a formulation that is not specified in an applicable licence.
    b) Or where a suitably licensed medicine that would meet the patient's need is not available. This may arise where, for example, there is a temporary shortage in supply; or
    c) The prescribing forms part of a properly approved research project.
70. 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.

Information for patients about the licence for their medicines

71. 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.
72. Some medicines are routinely used outside the terms of their licence, for example in treating children. In emergencies or where there is no realistic alternative treatment and such information is likely to cause distress, it may not be practical or necessary to draw attention to the licence. In other cases, 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. You must always answer questions from patients (or their parents or carers) about medicines fully and honestly.
73. 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.

Appendix II: excerpt from RCPsych CR210 Use of licensed medicines for unlicensed applications in psychiatric practice RCPsych CR210

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 authorative 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.

Appendix III: excerpt from GG&C Unlicensed Medicines Policy GG&C ULM policy

HEALTH BOARD
It is the responsibility of the Health Board to ensure that medicines are prepared and administered correctly. While any liability associated with the use of unlicensed or off label medicines will be accepted by the employing authority. This policy describes best practice for employees of the acute division NHSGG&C.

PRESCRIBER
The prescriber is always responsible for the use of a medicine and the patient's welfare and in the event of adverse reactions may be called upon to justify the decisions that they have made. (see GMC advice, appendix 4). In the case of unlicensed/ off label medicine prescribing it is important to be aware that information regarding efficacy and safety may be less robust and this should be considered where there is a licensed alternative.

PHARMACIST
A pharmacist assumes professional responsibility as purchaser of the medicine, particularly if this involves specifying an unlicensed medicine to be purchased.

MANUFACTURER
If an untoward incident occurs with:-

- a licensed medicine prescribed and administered according to the Marketing Authorisation, liability rests with the manufacturer.
- off label use of a licensed medicine i.e. prescribed or administered out with Marketing Authorisation then the manufacturer is unlikely to be found liable for any harm caused by that medicine, unless harm is directly attributable to a defect in it, rather than the way it was prescribed.
- an unlicensed medicine with no Marketing Authorisation within the UK then the manufacturer is not liable (unless the medicine is shown to be defective).