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Prescribing drugs outside their licensed indications (‘off-label’ prescribing)

Prescribing psychotropics CHAPTER 14 Prescribing drugs outside their licensed indications (‘off--label’ prescribing) A Product Licence is granted when regulatory authorities are satisfied that the drug in question has proven efficacy in the treatment of a specified disorder, along with an acceptable adverse effect profile, relative to the severity of the disorder being treated and other available treatments. Licensed indications are preparation- specific, outlined in the SPCs, and may be different for branded and generic formulations of the same drug.1 In the USA, product ‘labelling’ has a similar legal status to EU licensing. The decision of a manufacturer to seek a Product Licence for a given indication is essentially a commercial one. Potential sales are balanced against the cost of conducting the necessary clinical trials. Drugs may be effective outside their licensed indications for different disease states, age ranges, doses and durations. The absence of a formal Product Licence or labelling may reflect the absence of controlled trials supporting the drug’s efficacy in these areas. In some cases (e.g. sertraline or quetiapine in generalised anxiety disorder [GAD]) there is sufficient evidence but a licence has not been sought by the manufacturer. Importantly, however, it is also possible that trials have been conducted but have given negative or equivocal results. Clinicians often assume that drugs with a similar mode of action will be similarly effective for a given indication. This may encourage the assumption that the official labelling for one drug indicates efficacy and safety of another, similar drug. However, apparently similar drugs may differ in respect to active metabolites and in regard to receptor affinity. Prescribing a drug within its licence or labelling does not guarantee that the patient will come to no harm. Likewise, prescribing outside a licence does not mean that the risk–benefit ratio is automatically adverse. For example, sertraline and fluoxetine are no less effective for GAD than alternative, licensed drugs.2 Prescribing outside a licence, usually called ‘off-label’, does confer extra responsibilities on prescribers, who will be expected to be able to show that they acted in accordance with a respected body of medical opinion (the Bolam test)3 and that their action was capable of withstanding logical analysis (the

Bolitho test).4 In the UK, both have effectively been superseded, or at least clarified, by the Montgomery vs Lanarkshire Health Board appeal case decision5 which stated: An adult person of sound mind is entitled to decide which, if any, of the available forms of treatment to undergo, and her consent must be obtained before treatment interfering with her bodily integrity is undertaken. The doctor is therefore under a duty to take reasonable care to ensure that the patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternative or variant treatments. 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. Thus, in the UK at least, the prescriber has a duty to make a patient aware of any material risks associated with the prescribing of any medicines and to outline alternatives.

946 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 14 The General Medical Council allows doctors to prescribe off-label but only where the prescriber is satisfied that there is enough evidence or experience to support efficacy and safety.6 In the USA, it is lawful to prescribe off-label 'within a legitimate health care practitioner–patient relationship'.7 Marketing of off-label use is forbidden but information may be provided following an unsolicited request.8 Off-label prescribing represents a significant proportion of prescribing in mental health conditions in the USA.9,10 A similar degree of off-label prescriptions is seen in other countries.11–13 Off-label prescribing in psychiatry is less likely to be supported by a strong evidence base than off-label prescribing in other areas of medicine.14 In psychiatry, small (underpowered) studies (with wide confidence intervals) often influence practice, particularly with respect to treatment-resistant illness (a great many examples can be found in this book). When these small studies are combined in the form of a meta-analysis, considerable heterogeneity is often found, suggesting publication bias (i.e. that some negative studies are not published). Treatments may therefore become incorporated into 'routine custom and practice' in the absence of robust evidence supporting efficacy and/or tolerability, and these treatments may sometimes continue to be used despite the findings of later, larger and more definitive negative studies and meta-analyses. An example of widespread off-label prescribing of a psychotropic in non-mental health conditions is amitriptyline – 93% of UK primary care prescriptions are off-label.15 The psychopharmacology special interest group at the Royal College of Psychiatrists published a consensus statement on the use of licensed medicines for unlicensed uses.16 They noted that unlicensed use is common in general adult psychiatry, with cross- sectional studies showing that up to 50% of patients are prescribed at least one drug outside the terms of its licence. They also note that the prevalence of this type of prescribing is likely to be higher in patients under the age of 18 or over 65, in those with a learning disability, in women who are pregnant or lactating and in those patients who are cared for in forensic psychiatry settings. The main recommendations in the consensus statement are summarised in Box 14.1. Box 14.1 Recommendations before prescribing 'off-label' ■ ■Exclude licensed alternatives (e.g. they have proved ineffective or poorly tolerated). ■ ■Ensure familiarity with the evidence base for the intended unlicensed use. If unsure, seek advice from another clinician (and possibly a specialist pharmacist). ■ ■Consider and document the potential risks and benefits of the proposed treatment. Share this risk assessment with the patient, and carers if applicable. Document the discussion and the patient's consent or lack of capacity to consent. ■ ■If prescribing responsibility is to be shared with primary care, ensure that the risk assessment and consent issues are shared with the GP. ■ ■Monitor for efficacy and adverse effects; start a low dose and increase slowly. ■ ■Consider publishing the case to add to the body of knowledge. ■ ■Withdraw any treatment that is ineffective or where emergent risks outweigh the benefits. The more experimental the

unlicensed use is, the more important it is to adhere to the above guidance.

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