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## Prescriptions, licences and evidence

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Manchester or indeed psychiatrists. An understanding of the way in which this personal experience is obtained and maintained may help improve rational prescribing. One source of this experience is the pharmaceutical industry whose influence may be greater than we realise or are prepared to acknowledge. In acknowledging the possible influences of the pharmaceutical industry both positive and negative, we may be better able to judge how best to avoid prescribing pitfalls. As suggested by Hogerzeil (1995), the future prescriber should be equipped with problem-solving. Problem-based learning is now taking root in a number of medical schools including Manchester. It will therefore be interesting to see the impact of this on future prescribing. Basing prescribing decisions on personal experience is not necessarily a bad thing but ensuring that the right experience is obtained is important.

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## Prescriptions, licences and evidence

*David Healy and David Nutt*

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**Aims and method** There is considerable confusion at present among clinicians as regards the appropriateness of prescribing off-licence. Because of the nature of the registration process it is likely that a considerable proportion of prescribing will always be off-licence. This paper seeks to clarify when it is appropriate to prescribe off-licence. We convened a workshop on behalf of the British Association for Psychopharmacology involving clinicians and regulators from a variety of countries to explore this issue both generally and for specific childhood and learning disability clinical situations. Recent statements from the defence unions and consumer groups were also scrutinised.

**Results** Across senior clinicians and regulators from a number of European countries and North America, there is a consensus that prescribing off-licence is a necessary part of the art of medicine.

**Clinical implications** Current advice to clinicians on the issue of off-licence prescribing can sometimes over-emphasise the hazards and neglect the benefits that may stem from appropriate off-licence prescribing. Good prescribing involves specifying treatment goals and monitoring outcomes and it is more important to share this with the patient than it is to communicate the licensed status of the drug being prescribed.

### Off-licence prescribing: the origins of a problem

In 1951, the Humphrey–Durham amendment to the 1938 US Food, Drug and Cosmetic Act was passed. This gave the Food and Drug Administration power to designate certain drugs, in addition to narcotic drugs (opiates and cocaine), as prescription only. Narcotic agents had been made available on a prescription only basis before the First World War in order to control problems of addiction.

The rationale for the extension of prescription only status was quite different. In part this move was taken in order to assist in the 'labelling' of the antibiotics and other novel pharmacotherapeutic agents which emerged during the 1940s (Temin, 1980). Restrictions on the sales of drugs began in 1906 following scandals in the US food and drugs trades. The first restrictions required companies to specify on the label the ingredients in the medicaments they sold (Liebenau, 1987). These labelling restrictions were tightened in 1938, following a tragedy with sulphanilamide, by requiring companies to provide indications as to what their compound might be effective for. With the emergence of the new drugs following the Second World War, there was a feeling that there was too much information to fit easily on the label of the drug and that one way to ensure that patients received adequate information about their drugs was to require them to visit their physician in order to obtain those drugs (Lasagna, 1998).

There was a further tightening of the regulatory process following the thalidomide crisis; a more stringent efficacy requirement was introduced into the process of seeking a product licence, companies were further encouraged to develop agents for disease indications and prescription only status for non-narcotic drugs was maintained in the face of growing opposition (thalidomide had been available over the counter in many countries). These developments, per se, do little or nothing to forestall a similar catastrophe in future but by generally encouraging prescribing for disease indications, they may be useful by directing prescribing to areas where benefits can be gained against which risks can be off-set (Healy, 1997; Lasagna, 1998).

As a consequence of the above developments a disease indication was built into the labelling requirements. Companies were no longer allowed to market tonics, they had to show the compound was effective, for depression for example. Even though it might be a tonic, in the sense of improving appetite and sleep, compounds now had to become antidepressants or antipsychotics. It was at this point that the potential for confusion emerged. Despite the inclusion of a

disease indication in the labelling, the granting of a licence to a company to market a compound is still essentially designed to regulate the claims that a company can make. Pharmaceutical companies are constrained in their claims by what can be demonstrated to regulators. Put bluntly, the rules which apply to a dairy produce firm, for instance, who may be obliged to show that what they claim is butter is not simply lard injected with dye and made to look like butter, apply also to the pharmaceutical industry.

### The United Kingdom Situation (1998)

Many doctors, however, feel that this process, which is aimed at controlling the marketing of a commercial product, also constrains them, so that they can only prescribe for indications for which drug companies have been given a licence. In January 1997, we convened a Round Table Workshop on behalf of the British Association for Psychopharmacology (BAP) on prescribing in child psychiatry and learning difficulties (BAP, 1997). One of the salient concerns of child and learning difficulty psychiatrists at this workshop was that the prescribing of psychotropic drugs for disorders in childhood and learning difficulties was typically unsupported by randomised controlled trial (RCT) evidence and commonly would have to take place in the face of datasheet statements that such prescribing is contraindicated. Following this meeting, on 27 February, the issue of off-licence prescribing for paediatric conditions became a matter of debate in the House of Commons and was reported in a number of the broadsheet newspapers (*Guardian*, 28 February 1997) in terms that suggested that it was possibly dangerous and certainly undesirable.

In addition, we have had the experience, on more than one occasion, when making recommendations to general practitioners (GPs) on referrals for sexual dysfunction of being told that the GP would not prescribe off-licence even though the drugs concerned were agents that GPs would otherwise readily prescribe (viz selective serotonin reuptake inhibitors; SSRIs). Unwillingness to prescribe was justified by saying that defence unions would not support the prescriber prescribing off-licence in the event that things went wrong. Finally, we have also prescribed some of the newer antipsychotics, such as risperidone, for cases of mania. This is off-licence prescribing. Can it be justified? Other examples would include the use of clozapine or other novel antipsychotics for treatment-resistant mood disorders or the use of sodium valproate for bipolar disorders. In instances such as these, some of our colleagues tell us that pharmacy departments are likely to query

prescriptions and that trust managements may indicate that they will not support prescribing of this kind.

Pursuing these issues with the defence unions has drawn a response that they would not presume to issue a verdict on whether such prescribing should take place. Decisions of that sort would be ultimately the function of the courts of the land and that each case would rest on its particular merits and weaknesses but that it is up to a prescriber to justify their prescription. A *Drugs and Therapeutics Bulletin* handling of the matter (Anonymous, 1992) states that:

"the responsibility for prescribing any medicine falls on the doctor but if a prescription is for an unlicensed medicine or for an unlicensed indication, the prescriber could be particularly vulnerable. . . . When prescribing outside a licence it is important that the doctor does so knowingly, recognises the responsibility that such prescribing entails and when obtaining consent to treatment should where possible tell the patient of the drugs licence status".

These responses would not appear to encourage off-licence prescribing.

In contrast, the Medicines Act and the EC Pharmaceutical Directive 89-341-EEC state that a doctor can prescribe an unlicensed medicine and use or advise the use of licensed medicines for indications or in doses or by routes of administration outside the recommendations given in the licence and that they can override the warnings and precautions given in the licence (British Paediatric Association, 1996). In practice, most clinicians prescribe off-licence extensively, as for instance when they use carbamazepine for epilepsy, mania, depression, the prophylaxis of bipolar conditions, aggressive disorders and other conditions. They do so, however, it would seem for the most part without a clear understanding that such prescribing is completely in order and they find themselves in difficulty when they are called upon to justify what they are doing, as happens increasingly often in a culture that asks clinicians to be evidence based.

### **Licences and evidence**

In an era that advocates the adoption of evidence-based medicine, it might seem reasonable to delimit clinical freedom on the basis of evidence. The response of insurers and mental health managers appears to indicate that they believe themselves to be following the evidence when advocating prescribing within licences. The issues on closer inspection, however, are somewhat more complex. In order to satisfy the efficacy requirement set down by the regulatory authorities, a company is free to seek the most

accessible population and most straightforward means to test their compound. Even though strong indications exist, for example, that many antidepressants have broad anti-nervousness properties, a company will pick one population such as subjects who are depressed. They can then take a relatively healthy group within the depressed population to test their product, excluding for instance subjects who are suicidal or severely depressed or otherwise complicated by concomitant physical illnesses or concurrent medications. As a consequence, all prescribing involves an extrapolation from a 'sample of convenience'. For reasons of convenience, companies have steered clear of populations of juveniles and it is this that has given rise to the uncertainties expressed at the BAP Round Table conference.

Companies will also pick one illness group rather than attempt to demonstrate efficacy in a range of conditions. The demonstration of efficacy in other conditions may or may not follow subsequently. If efficacy has been demonstrated in only one condition, viz schizophrenia, and not also for instance in mania, even though neuroleptics are the first line of treatment for mania, the product licence will only be for use in schizophrenia. Despite this there will be overwhelming justification for prescribing the newer neuroleptics for mania on the basis that neuroleptics in general are the first line of treatment for mania and a restriction to schizophrenia in the circumstances is an artificial restriction, based more on factors such as market size and the difficulties of studying manic patients. Companies may even anticipate that off-licence use of the compound will establish the indication for them.

It should also be borne in mind that the indications for which a company chooses to seek a product licence, in addition to being determined by the ease with which efficacy may be demonstrated, will also be determined by other cultural and marketing considerations. For instance, given that the treatment effect size for SSRIs for premature ejaculation is greater than for depression (Waldinger *et al.*, 1994), an indication for premature ejaculation for one of the SSRIs would have been easier to obtain than one for depression. The decision to obtain a licence in such an area will hinge not on the ability to demonstrate efficacy but on wider perceptions within the company of whether there will be a market return on such developments or whether in some way the image of the company might be compromised by being associated with the proposed indication (Beaumont & Healy, 1993).

Depression is clearly an indication for which there are potentially extremely large market returns and therefore it attracts company

investment in market development. As a consequence of small treatment effect sizes, however, clinical trials have had to become multi-centred and indeed multi-national, and in the process capacities for independent psychopharmacological research, that might provide an evidence base for clinical practice, have been lost. This issue is directly relevant to the question of whether a significant minority of a prescriber's profession can be held to regard a particular therapeutic approach as reasonable. A good theoretical rationale for an approach may exist but prescribers may be faced with the fact that companies may not have carried out the relevant studies or alternatively a study may have been undertaken, as in the use of SSRIs for premature ejaculation (Waldinger *et al.*, 1994), but the results will not have been marketed.

In contrast to the relatively small treatment effect sizes of antidepressants for depression, in the case of attention deficit hyperactivity disorder, RCT evidence existed as early as 1962 (Conners & Eisenberg, 1963) (and strong indications existed as far back as 1937; Bradley, 1937) that stimulants were useful in the management of the condition. Indeed it has been argued that there are few other areas of medicine where the evidence of efficacy is so compelling (BAP, 1997). Yet both product licences and clinical practice lagged far behind.

A third scenario is provided by the cases of carbamazepine and sodium valproate where clinical practice supports the use of these agents in the management of recurrent affective disorders, even though at present the data have not been sufficient to support the registration of either product in this area. The failure to obtain a licence, in these cases, has been largely owing to the considerable difficulties in running clinical trials in the area of prophylaxis that would meet registration requirements. This does not mean that the compounds are ineffective; an alternative viewpoint is that clinical situations may often be too complex to mesh easily with regulatory desiderata. The widespread use of benzodiazepines during the first few weeks of treatment with an SSRI to ameliorate early treatment-induced side-effects or the use of mianserin or trazodone for the same purpose or as augmentation strategies will never be the subject of licence applications. Lithium augmentation is and is likely to remain an off-licence use for lithium.

A fourth scenario concerns imipramine and panic disorder. Until recently this was the compound whose efficacy in panic disorder was best attested by means of RCT data. No company, however, would seek a product licence for imipramine in this area given its prior availability on the market. What are prescribers to do? In addition to advertising the benefits of

their compound for a particular condition, companies are not above advertising that their compound has an indication in an area such as panic disorder in a manner that all but implies it would not be good practice to prescribe an older unlicensed drug. Given that there are very few forces acting to bolster medical confidence, such marketing allied to statements from defence unions and consumers' associations to the effect that prescribers are likely to be particularly vulnerable, if straying off-licence, is likely to inhibit the exercise of clinical judgement to the benefit of patients.

### The art and science of medicine

Against this background, even though there was a lack of evidence drawn from paediatric and learning difficulty populations, the BAP Round Table consensus was that prescribing in childhood, for instance, can be undertaken on the basis that there is a continuity between conditions that emerge in childhood and persist into adulthood such as obsessive-compulsive disorder, schizophrenia and bipolar affective disorders (BAP, 1997). Few prescribers would shirk from prescribing an anticonvulsant to a child who was fitting, even though until recently no conventional anticonvulsant had a product licence for use in childhood. Prescribing in this case would be undertaken on the basis of continuity between childhood and adult conditions and would be guided by the response or lack of response of the child to treatment. Prescribing for child psychiatric and learning disability populations can validly proceed on the same basis, in the absence of a licence or RCT evidence and in the face of disclaimers on datasheets. Similarly, in the case of risperidone for mania, prescription could be justified on the basis that there is no *a priori* reason to believe that this compound which is essentially a neuroleptic is likely to be any less effective than other neuroleptics have been in the past for this condition.

Clinicians need to be fully aware of the limitations of product licences. They are useful in so far as they channel prescribing toward disease indications and are underpinned by some evidence of efficacy. Without such a regulatory framework, it is likely that the market-place would contain a number of frankly ineffective agents. But current product licences are not state of the art statements about the position of the evidence in the management of particular conditions and may not even indicate the best uses for the licensed compound. A licence should be seen as a statement that the compound can be shown to have some treatment effects and that it has accordingly been released

for use in the art of medicine. The freedom of medical practitioners to practise that art is governed by the Medicines Act rather than by a product licence. Unwise or abusive prescribing may at some point lead to legal restrictions on that freedom. This, however, needs to be carefully distinguished from the *de facto* restrictions that appear to have arisen to some extent following the advice of insurers or management employed risk assessors and may further erode clinical freedoms as increasing cost constraints within health services lead some countries and managed care organisations to move toward a position of only reimbursing prescriptions for licensed indications.

It is not uncommon to hear the proposal that first of all a physician should do no harm. This hallowed aphorism would seem to be one that increasingly provider organisations and defence societies are happy to endorse. The ultimate risk management strategy, however, is to do nothing at all for patients. As businesses, health care managers and medical insurers may feel that their jobs would be easier if prescribers restricted themselves to prescribing in accordance with product licences – and in a certain sense this is true. But it surely behoves them to consider whether they are simply in business or whether they are in the business of supporting medical practice. If they declare for the latter option, they should realise that the wording of their statements to enquiries from prescribers on this issue may have a considerable impact on the benefits that prescribers can bring to patients.

Any intimation that off-licence prescribing leaves prescribers particularly vulnerable is unfortunate on two counts. It is likely to deter efforts to help patients in need. It also, however, suggests that prescribing on licence is not ever likely to be a problem. In fact, problems with prescribing cut across the questions of licences and stem more from failures of prescribers to specify what treatment outcomes they are aiming at and from prescriber unwillingness to switch to another treatment strategy after a reasonable trial period than they do from prescribing on or off-licence. Inflexible prescribing may become abusive and indeed this may happen more easily with medications administered within the terms

of a product licence than it does with off-licence prescribing, where the prescriber is perhaps more likely to both make a deliberate calculation of risks and benefits and to monitor the effects of their intervention. Rather than advising prescribers to notify patients when they are prescribing off-licence, it would be better to advise them to explain to patients in all cases what the goals of treatment are, what criteria will be used to evaluate outcome and how long treatment will persist unchanged in the face of apparent non-response.

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