SAFETY CONCERNS WITH OVER THE COUNTER DRUGS: MIND THE EVIDENCE GAP?

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INTRODUCTION

A recent paper reporting an association between cumulative anticholinergic drug use and incident dementia in subjects over the age of 65 years\(^1\) caused something of a media stir on both sides of the Atlantic. In the UK and US the news focus was on Over The Counter (OTC) drugs\(^2,3\), such as hay fever and sleep medicines, some of which contain drugs with anticholinergic properties. However the study's main finding was the observation of a 10-year cumulative dose-response relationship showing that higher anticholinergic use is associated with an increased risk for dementia and Alzheimer's disease. Furthermore the study was based on records of prescribed medicine use rather than OTC use. Indeed the increased risk was only found in people who took the equivalent of a fairly potent anticholinergic drug daily for 3 years – which would certainly not be a typical pattern of OTC drug use. In pointing out these salient facts to concerned patients, the NHS Choices website goes on to comment: ‘…. we can’t say if reducing the amount of anticholinergic medicines will reduce the risk of dementia to normal’\(^4\). And that epitomises the problem that OTC medicines often face when questions of safety arise.

The consequences can be dramatic. The recent switch of oral diclofenac back to prescription-only status in the UK is a case in point\(^5\). In this instance a European review of data, almost all of it from observational studies, suggested a small but significant increased risk of cardiovascular events associated with the drug, particularly if used at high doses and for long-term treatment. The UK Commission on Human Medicines (CHM), concluded that these side effects could not be ruled out even when oral diclofenac is taken for a short time or at a lower dose\(^6\).

This recent experience would suggest that absence of evidence is not to be taken as evidence of absence in considering possible OTC safety issues. Regulatory agencies will continue to apply the precautionary principle, and if there is any problem around a drug’s safety in prescription usage, then non-prescription status will surely be questioned. In these circumstances, it may be crucial to have evidence on the actual risks and benefits associated with OTC use if there is to be a balanced discussion on non-prescription status.

ADDRESSING THE EVIDENCE GAP

Each example of a safety problem leading to questions regarding OTC status is unique, however the types of data that might prove pivotal in those circumstances are common to all. The ideal time to collect such data is before a problem arises, and for drugs being considered for non-prescription status,
some data collection could be planned as a general part of the clinical development process. Here the major categories of evidence that might be relevant are considered.

**EVIDENCE OF BENEFIT**

Although challenges to non-prescription status almost always stem from a safety concern, it is important to consider the benefits that non-prescription status might confer in order to put these concerns into a broader context. Decisions on non-prescription status should include considerations of benefit and there are common domains that can guide the collection of relevant data. So far as possible these data should be quantitative or capable of modelling to quantify benefit, as illustrated below.

When considering a safety challenge, it may be particularly important to consider:

**Improved clinical outcomes through use of the non-prescription drug**

One common benefit of improved access to a drug through non-prescription status is that people may treat a condition earlier than otherwise. In some instances this may reduce the duration of illness or even help prevent progression. There may be observational data in the literature relating to proportions of sufferers that consult doctors, and the reasons for non-consultation.

Companies will often conduct consumer market research in people with the target indication, including data on propensity to consult and likelihood of taking self-medication. Such survey data are often undervalued by sponsors but with appropriate attention to study quality, behavioural survey data can and should be published. These data can then be used to help quantify the benefit of OTC status, either directly or through economic modelling.

**Benefit versus the alternatives**

In defending non-prescription status, it is important to understand and model quantitatively the counterfactual situation: i.e. how consumers of a medicine might behave if the drug ceased to be available without prescription. Broadly the result may be:

1. A greater use of alternatives available without a prescription. These may include:
   a. Drugs with adverse events of known frequency. It may be possible to model the increase in these events that might accompany a rise in usage of substitute drugs following a change of status for the drug under scrutiny.
   b. Alternatives with no proven efficacy e.g. ‘alternative’ remedies. In this case people may suffer adverse consequences relating to lack of efficacy such as increased duration of suffering or disease progression.

2. A change in consultation behaviour:
   a. Consumers may consult more (although this is an assumption that should be tested in consumer research). If that is the case then it is relevant to ask what the likely outcome of those consultations will be. It may be that doctors will prescribe the medicine that is no longer available OTC. If so, what dose will they recommend and how much will they prescribe? It is possible to answer such questions with a reasonable degree of certainty on the basis of historical practice. Studies that interrogate large databases, such as the Clinical
Practice Research Datalink (CPRD) in the UK. can give relevant information and are relatively quick and inexpensive to perform.

b. Consumers may choose not to consult. If a condition has historically low doctor consultation rates (because of embarrassment for example) then it is possible that people will revert to ‘suffering in silence’ should their chosen non-prescription alternative not be available. Again, behavioural surveys may be useful in modelling the impact of the change.

**EVIDENCE OF EFFECTIVE RISK MITIGATION**

A decision to revoke non-prescription status implies that the risk mitigation strategies in place are no longer considered sufficient to reduce the likelihood of harm to an acceptable level. In the UK and most of Europe, the principal risk mitigation tools sustaining non-prescription status are the drug labelling and the role of the pharmacist in providing advice at the point of sale. Evidence relating to the effectiveness of these mechanisms is often produced when a medicine is considered for re-classification to non-prescription status and these data become important again when that status is challenged.

**Exclusion of at risk groups**

Sponsors of re-classifications to non-prescription status are typically required to produce data to show that the mechanisms supporting drug supply reliably exclude groups of people that are not suitable for the drug. In the United States ‘actual use’ studies are often mandated to show that people not only understand the drug label adequately, but also that they act in accordance with it in the great majority of cases. Outside of the US, studies more often concentrate on adequate consumer understanding of the label and appropriate interaction with the pharmacist at the point of sale.

Challenges to non-prescription status almost always arise from new safety concerns in particular patient groups e.g. the elderly or those at high risk of the safety concern in question. In these circumstances, the question posed is ‘Can these groups of people be reliably excluded from using this drug in the non-prescription setting?’ The exclusion of such groups would inevitably involve some changes to the circumstances of supply including e.g. changes to the drug label and (at least in Europe) the particular intervention of the pharmacist. There are considerable practical difficulties involved in ‘proving’ that changes to these mechanisms will eliminate the problem. For example it is unlikely that pharmacists will be deemed willing or able to take on monitoring of particular safety issues with individual non-prescription drugs in their routine daily practice. A defence of non-prescription status that depends on excluding patients in pharmacy may have little realistic prospect of success, even if new studies are conducted, because it is almost impossible to extrapolate results to the imperfect ‘real world’ with any degree of confidence.

**IN-USE EVIDENCE: THE POTENTIAL VALUE OF COHORT STUDIES**

Realistically the defence of non-prescription status will often depend on data already in hand. The most useful data in answering possible future challenges may be those gathered in the real-life non-prescription setting. One possible strategy is to collect data on a cohort of people actually purchasing and using a particular OTC medicine. In an ideal world such a cohort would be collected and followed prospectively, however this would be expensive to do and pre-supposes knowledge of the types of data
that will ultimately prove most useful. However, marketing departments of consumer pharmaceutical companies often survey users of their medicines, for example on-line, to discover what motivates their behaviour and what unmet needs they may have.

Similar but more robust methodologies might be used to select a representative cohort of users in order to answer safety-related questions. For example:

- What is the demographic profile of the user cohort?
- What co-morbidities do they have?
- What concomitant medications (prescription and non-prescription) are they using?
- What lifestyle risk factors are prevalent amongst them?
- What is their pattern of usage and level of consumption?
- Are particular types of misuse (e.g. exceeding dosage recommendations) prevalent or not?

A detailed profile of users and their behaviour from such an observational study may better equip a company to answer specific concerns. For example if a safety question relates primarily to the elderly, but the OTC users of the drug in question are almost exclusively young, then the ‘real-life’ risk can be better appreciated and any additional risk mitigation better planned.

**SUMMARY AND CONCLUSION**

The safety of all medicines, prescription or non-prescription, is constantly re-assessed in the light of new knowledge. Recent experience suggests that data from observational studies are often the source of new safety concerns relating to well-established non-prescription medicines. These data may relate to doses of drug, duration of treatment and patient populations that deviate from those typical in OTC usage. Such studies can only report associations and generate hypotheses. But in the absence of data that disprove a hypothesised causality, (which may be virtually impossible to generate), it can be extremely challenging to defend non-prescription status for a drug in the face of uncertainty. Nevertheless, data collected on the actual usage of the drug in the non-prescription setting can provide context and balance in any such discussion.

Defence of non-prescription status requires data both on the benefits of the drug and on the composition and behaviour of the users. Consumer pharmaceutical companies typically understand their consumers very well and need to consider how to formalise this knowledge into usable data. Sadly, many companies undervalue the behavioural data that they collect e.g. during market research, and fail to make this evidence base robust enough to be available in the published literature.

When OTC status is challenged, it is important to understand and present the unintended consequences that may result when the availability of a drug is restricted. Alternative routes of supply for the drug in question may not always lead to safer usage, and the use of substitute drugs with other safety issues can sometimes diminish any supposed net gain in patient safety.

Non-prescription medicines are, by their nature, well characterised. But that does not mean that their safety record is easy to defend. In the face of a challenge to non-prescription status, it is critical to
present data showing a clear understanding of how people use the drug in the OTC setting. Only with data is it possible to put hypothetical safety concerns into a real world context. Consumer drugs are understudied and few companies generate published evidence on their marketed products. In the face of increased challenges to OTC status they may need to mind this gap.

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Statement of Interests: The author acts as a paid consultant to consumer pharmaceutical companies on clinical issues relevant to the legal classification of medicines.

REFERENCES


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