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Newly licensed drugs

Should be on probation until their value is demonstrated

See pp 1158, 1159, 1169, 1184, 1195

The Medicines Act 1968 set up a licensing authority that grants a marketing authorisation (product licence) for a medicinal product only if it is effective and safe and of good quality. Once licensed, a drug can usually be prescribed by any doctor under the NHS. But general use of a newly licensed drug may be undesirable.

Firstly, the licensing process cannot define uncommon adverse effects. It is easier to measure common therapeutic benefits than rare, but important, reactions. The numerical problem is daunting. If n patients have been treated, and none has suffered a particular adverse effect, then we can be 95% sure that the true incidence of that adverse effect is between $0/n$ and $3/n$.[1] Licensing decisions are based on trials involving on average around 1500 patients,[2] so at the time of licensing, a serious reaction that affects as many as 1 in 500 patients could be undetected, and undetectable. Britain's Committee on Safety of Medicines asks for "yellow card" reports of any reactions to newly licensed medicines, marked with an inverted black triangle. A post marketing surveillance scheme, which monitors prescriptions and adverse events, exists only in general practice. Both schemes rely on the good will of prescribers rather than systematic study, and only a fraction of all important reactions is notified.

Secondly, relative efficacy plays no part in licensing decisions, though the licensing authority presumably considers relative safety. Most early studies of new medicines are performed against placebo rather than an established active agent. This makes it difficult to be sure of a new drug's true utility.

Thirdly, prescribers are not constrained to use drugs rationally and cost effectively. Rational prescribing should consider both the benefit and, in its broadest sense, the cost of a treatment. The cost of profligate use of new antibacterial agents, for example, is not simply the money wastefully spent but also the cost of increasing bacterial resistance.[3] Local mechanisms, such as practice and hospital formularies, and drugs and therapeutics committees, can have some effect, but the contributors to different formularies are likely to differ in expertise and in freedom from external influences, and they will not be privy to the information on which licensing decisions are based.

Licensing decisions are now made both by the UK Licensing Authority through the Medicines Control Agency and by the European Medicines Evaluation Agency, which runs in parallel with national agencies. The licensing authority is not a drugs wholesaler. It would anyway be unreasonable to hold a Dutch auction, in which a pharmaceutical company reduced the price of its product until the licensing authority would take it. But the NHS is interested in money, and it should see that newly licensed medicines be prescribed at NHS expense only if there are proportionate benefits.

Interferon beta-1b, which has recently been licensed through the European Medicines Evaluation Agency, is an example (see pp 1159, 1195). It probably reduces hospital admission by one day every three years on average in selected patients with multiple sclerosis but has no demonstrable effect on disability.[4] The published data concern just 124 patients receiving the 8 million unit dose of the drug. Treatment for one patient costs around £10 000 per year. The NHS might reasonably ask for evidence that the money should be spent on the drug, rather than on other services for patients with multiple sclerosis, or other patients. Several new agents for multiple sclerosis, such as copolymer 1, will pose similar problems.

The newer antiepileptic drugs provide another example where licensed drugs might have been treated more circumspectly by the NHS. Two papers (pp 1169, 1184) and an editorial (p 1158) in this week's *BMJ* cast considerable doubt on their long term value.[5-7] As Marson *et al* say, "the gold standard to determine future use of new drugs will be actively controlled studies"[5]: trials of relative efficacy by another name.

One answer would be to introduce a form of probation for newly licensed medicines, in which they are subject to careful scrutiny before they become available for all doctors to prescribe. A possible way to do this in Britain would be to allow the licensing authority to operate as before, but to decide separately whether a drug should be available for prescription within the NHS. That decision would necessarily require the manufacturer to show, on the basis of randomised clinical trials, that a drug was at least as effective as standard treatment. It would also permit the NHS to conduct its own trials into the costs and benefits of a newly licensed treatment, within the framework of NHS research.[8] This would need some integration, since cost effectiveness is a matter for the health service, and safety a matter for the licensing authority, but that should be possible. Prescribing outside the trials would be prohibited or discouraged by a ban on general prescription within the NHS. The Pharmaceutical Benefits Advisory Committee, which advises the Australian Minister of Health about which drugs should be available under the national pharmaceutical benefits scheme, is a useful model.[9]

The NHS might also wish to see evidence of cost effectiveness before agreeing to support major changes in the use of established licensed drugs. For example, using lipid lowering agents such as pravastatin in the primary prevention of coronary heart disease[10] could be examined.[11]

The Committee on Safety of Medicines has a good record of protecting the public from frankly dangerous medicines, while allowing potentially useful drugs to be marketed. More careful monitoring after a drug has been marketed would make it easier to detect "rogue" drugs like benoxaprofen (Opren). Local controls on prescribing have been less successful in ensuring that drugs are used rationally. The NHS should not be obliged to pay for new drugs unless they are at least as good as older ones, nor for expensive drugs whose benefits are uncertain. A good starting point would be a trial of the costs and benefits of interferon beta-1b before patients are exposed haphazardly to unknown risks, and before large sums of money are spent for poorly quantified benefits.

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Drug trials in epilepsy

New drugs have been poorly assessed

See pp 1158, 1169, 1184

A new generation of antiepileptic drugs has emerged in the past 10 years, including gabapentin, lamotrigine, felbamate, and vigabatrin. These are said to be valuable adjuncts to the first line drugs when epilepsy is inadequately controlled. No agreement exists on the criteria that define treatment failure. One view is that a treatment has failed when seizures are unacceptably frequent despite plasma drug concentrations in the "therapeutic range." However, this range is defined as the range of concentrations at which most patients have a sizeable reduction in the frequency of seizures without substantial dose dependent side effects. Since some patients require and tolerate larger doses, treatment failure might be better defined as inadequate efficacy at the highest tolerated dose.

Drug treatment for epilepsy is usually long term and should therefore be as simple as possible. Ideally, patients should start treatment with a single drug.[1] In the countries where they are now available, vigabatrin and lamotrigine were approved on the basis of supplementary treatment. Randomised controlled trials were performed in patients whose epilepsy was inadequately controlled by standard doses of a first line drug.[2-4] This dose was continued along with either the new antiepileptic drug or a placebo. A systematic review of 28 of such randomised placebo controlled "add on" trials appears in this week's issue (p 1169).[5] It concludes that the new antiepileptic drugs are significantly better than placebo in reducing seizure frequency, but that comparative trials will be needed to see if one drug is better than another. However, trials of supplementary drugs cannot measure the efficacy of a new drug. What they assess is the overall effect of the combination, which may be due to simple additive effects but which may also result from synergistic or even antagonistic effects.

The trials of vigabatrin and lamotrigine give other grounds for concern. The groups were not homogeneous at baseline: some patients were receiving a single drug and some multiple drugs, and some met one and some the other of the two criteria for treatment failure cited above. The drug combinations tested were also highly diverse. Most important, the main end point used was a reduction in the frequency of attacks by 50% or more; no account was taken of the clinical benefit experienced by the patients. Yet in a recent trial of lamotrigine no correlation was found between reductions in the frequency and severity of seizures and patients' wellbeing.[6]

None of the trials lasted more than three years. As these new antiepileptic drugs are costly, they should not be prescribed routinely without data on how many patients actually benefit and for how long. Also in this issue (p 1184) Walker *et al* show that most patients who initially respond to supplementary lamotrigine or vigabatrin gradually abandon the new drugs.[7] Studies will be needed to determine the reasons, which might include reduction in efficacy, side effects, or cost.

More detailed questions remain unanswered. The initial assessment file on vigabatrin left some doubt about potential side effects since studies on animals had reported ocular and neurological toxicity.[5] In France vigabatrin was initially reserved for use in hospital neurology units, which had to include the patients in a cohort study to identify any such toxicity. Unfortunately, no conclusions can be drawn from data published so far because of methodological problems (Mauguiere *et al*, personal communication, 1995).

Drug regulatory agencies should not be approving new drugs for which no benefit has been proved for patients using relevant outcome measures. In the case of the new antiepileptic drugs I believe that problems with the design of the trials have undermined the reliability of the available data. When marketing approval is authorised on the basis of relatively short trials (so that patients can benefit rapidly) I believe the assessment should be continued to determine the cost effectiveness and risk-benefit ratios in the long term. The regulatory agencies should reassess the files on these new antiepileptic drugs at regular intervals, and meanwhile their licences should include a requirement for a programme of continuing evaluation.

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