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New drugs for old: disinvestment and NICE

Methods for identifying drugs that can be discontinued need to be as rigorous as those for assessing potential new treatments. **Dyfrig Hughes and Robin Ferner** suggest some strategies to ensure best use of NHS resources

The aim of guidance from the National Institute for Health and Clinical Excellence (NICE) on medicines and other health technologies is to derive the maximum health benefit from finite NHS resources. The NHS in England and Wales is legally obliged to fund treatments recommended by NICE's technology appraisals but does not receive extra money to do so. This means that the funding of new, expensive medicines relies increasingly on releasing funds by displacing other treatments, but NICE does not specify which. One of the reasons that NICE was formed was to end inequitable geographical variation in the availability of new medicines (the postcode lottery). However, inconsistent decisions on which treatments to abandon will also lead to geographical variation. If the treatments being displaced are not the least efficient, overall population health is reduced. So how should we establish which medicines to discontinue?

Identifying medicines for disinvestment

Elshaug et al suggested several signals that might identify treatments offering poor value for money.[1] These include new evidence on effectiveness, safety, or cost effectiveness; variations in care (which may indicate differences in clinical opinion or the use of drugs outside licensed indications); technological development (such as change in formulation); and consultations with special interest groups. They also proposed criteria for prioritising shortlisted treatments for appraisal,[1 2] looking first at those that are associated with high overall costs; are not used for severe or life threatening conditions; have underused, more cost effective alternatives; are futile; or in which disinvestment may potentially reduce harm or would have limited effect on vulnerable populations.

NICE has taken a less systematic approach. It focuses on promoting technology appraisals and clinical guidelines that save money[3] and on activities for which the evidence base is weak or absent.[4] It has listed treatments where NICE guidance, when fully implemented, should save the NHS more than £600m (€690m; $970m).[3] These include drugs for hypertension (reducing expensive cardiovascular events), access to long acting reversible contraception (reducing the cost of unplanned pregnancies), and targeted use of drugs for Alzheimer's disease. However, NICE's estimates of budgetary impact are sometimes optimistic[5]: the use of donepezil, galantamine, and rivastigmine to treat Alzheimer's disease, for instance, has cost twice as much as it predicted.

NICE has also started using the Cochrane Library to identify treatments for which there is little or no evidence of benefit. Of the 102 interventions identified up to 2006, 27 are already covered by guidance—for example, anticonvulsants to treat acute pain and atypical antipsychotics in people with dementia. Guidance will shortly be available on a further 30 interventions, including use of corticosteroids in head injury, and 45 are being considered for further analysis by NICE.[6]

Prime candidates

In order to be licensed, medicines will have had to have proved at least minimal efficacy. However, there are many that have been superseded by newer, more effective medicines and others that bring only trivial benefits over existing therapies while costing much more. A medicine whose use is sanctioned as cost effective for one indication can be used in other circumstances where benefits are much smaller. These are all potential targets for disinvestment.

However, the most obvious target group for disinvestment is branded products with generic alternatives. Generic prescribing rates in England have risen from 35% in the mid-1980s to 83% last year.[7] Although the relative costs of generics have increased,[8] they are still much cheaper than their branded counterparts. A proposal to allow pharmacists to substitute generic drugs for prescribed branded products is currently under consultation.[9] If the policy is implemented, annual savings of £72m are expected by 2013.

The second (and perhaps the largest) category of medicines that produce little or no additional benefit but which cost more are the "me too" products—new entrants to an existing therapeutic class. There are many examples of therapeutic duplication within drug classes, with only minor differences between individual drugs. However, some "me too" drugs offer clinical advantages and promote price competition, which contributes to reducing costs.

Medicines developed through evergreening strategies—that is, by patenting incremental changes in products whose patents are about to expire—are also likely candidates for disinvestment (table).[10] Many such products are extended release preparations that require less frequent dosing. These might improve patient adherence, but evidence to support this, and any resulting improvement in health outcome, is often lacking.[11] Moreover, the licensed indications of an increasing number of new extended release formulations are limited to patients adequately maintained on the immediate release formulation, which might encourage inappropriate switching. It also creates the potential for serious medication errors—incorrect

Examples of drugs developed through strategies often used to extend patent protection (evergreening)

Modification	Candidates for disinvestment	Examples worth retaining
Single enantiomers	Esomeprazole, the S enantiomer of omeprazole, has no additional clinical benefit but is 11 times more expensive. The NHS in England spent £42m on esomeprazole in primary care last year. Globally, it is the third highest selling drug	Levobupivacaine, an isomer of bupivacaine, has anaesthetic and analgesic properties similar to bupivacaine but is thought to have fewer adverse effects
Formulation change	The film coated dispersible formulation of sumatriptan (Imigran Radis), introduced two years before the patent for Imigran expired, has no proved additional clinical benefits but costs almost three times more than generic sumatriptan	Neoral microemulsion formulation of ciclosporin overcomes many of the problems associated with the poor and unpredictable absorption of earlier oral formulations
Modified release	Modified release quetiapine (Seroquel XL) was introduced before the patent expired on the immediate release formulation without evidence of improved adherence or clinical performance	Modified release formulations of nifedipine avoid baroreflex mediated tachycardia and sudden hypotension
Change in route of administration	Transdermal glyceryl trinitrate patches are more likely to induce nitrate tolerance and are much more expensive than sublingual nitrate preparations	Risperdal Consta, a fortnightly intramuscular injection of risperidone, benefits patients whose adherence to oral treatment is unreliable
Combination products	Fosavance (alendronate plus vitamin D) costs more than treatment with generic alendronate plus calcium and vitamin D and does not remove the need for patients to take supplemental calcium	Many co-formulated antiretroviral therapies for HIV infection reduce pill burden and dosage frequency and enhance adherence
Active metabolite	Desloratadine, the active metabolite of loratadine, confers no additional benefit but is five times more expensive than generic loratadine	Fexofenadine, the active metabolite of terfenadine, retains its effectiveness but is devoid of cardiotoxicity
Different salt or molecule	Perindopril arginine confers no additional benefit but is three times more expensive than the generic perindopril erbumine	Peginterferon alfa is generally considered more effective than standard interferon alfa
Physicochemical characteristics	Paroxetine hydrochloride hemihydrate (Seroxat) offers no clinical advantages over the generic anhydrous form but is more than four times the cost	Norvir soft capsules do not contain the therapeutically inert crystalline form of ritonavir that was present in an earlier formulation

substitution of one formulation of tacrolimus for another resulted in acute rejection of transplanted organs.[12]

Evergreening strategies applied to six medicines (omeprazole, amlodipine, doxazosin, loratadine, mirtazapine, and ramipril) resulted in little or no therapeutic gain but cost the NHS between £164m and £369m.[13] Fortunately, courts are beginning to examine patent extensions more critically. In a recent ruling that Servier's patent on a new crystalline form of perindopril lacked novelty, Lord Justice Jacob of the Court of Appeal described the application as "the sort of patent which can give the patent system a bad name."[14]

Grey areas

Most medicines appraised by NICE bring additional health benefits at an increased cost to the NHS, when compared with existing treatments. NICE is well positioned to advise when such treatments are expected to make older treatments redundant (and therefore candidates for disinvestment). However, sometimes it makes sense to maintain an older treatment that is only marginally less effective but much cheaper than a new drug.[15] When it is possible to try one drug, and subsequently another if the first is ineffective, then, provided the cheaper drug is as safe, it is reasonable to start with the cheaper drug—for example, metformin rather than insulin glargine. The overall cost effectiveness of such a strategy will depend on how many patients can be treated satisfactorily with the less expensive treatment. Disinvestment is impractical when new treatments are not substitutes for old ones but are used in addition, or in sequence.

There are also medicines whose cost effectiveness is greatly improved by restricting their use to the subpopulations who are most likely to benefit. NICE already considers this in its appraisals, and most recommendations are for a narrower use than the licensed indication. The restriction of trastuzumab for use in women with HER-2 positive breast cancer is a case in point. But even with HER-2 testing, the opportunity cost of funding trastuzumab, in terms of the benefits forgone as a consequence of displacing other treatments with greater cost effectiveness, is substantial.[16] Further efforts to identify patients who have most to benefit are warranted to refine the use of older medicines.

Options for NICE

Since 2006 NICE has been charged with identifying existing interventions that are not cost effective as well as evaluating new treatments.[17] However, new formulations of existing treatments that provide no additional benefit—which represent the majority of evergreened products—are excluded from its appraisals programme.

The most obvious target group for disinvestment is branded products with generic alternatives

The criteria by which NICE appraises health technologies apply to disinvestment just as they do to investment. However, NICE could consider additional criteria. Currently, economic evaluations do not factor in the future prices of medicines because of the uncertainty involved. But as evergreens are typically introduced shortly before the patent of the original product expires—in the expectation of generic competition—it might be appropriate to base costs on the estimated price of the generic, rather than on the current price of the originator.[18] This would effectively make the evergreened product less cost effective and might help discourage the practice.

It would be logical to disinvest in treatments that cost more than £20 000-£30 000 per quality adjusted life year (QALY), which is the threshold above which NICE currently considers most treatments insufficiently cost effective to recommend to the NHS. But people tend to prefer not to lose what they have, even if this means forgoing a chance to have more. There is evidence for this in health interventions, and some have argued for a higher threshold for disinvestment in old treatments—say £30 000-£40 000 per QALY—than for investments in new treatments.[19] However, allowing this loss aversion to determine how healthcare resources are allocated introduces inefficiencies, does not maximise population health, and should not be considered.[20]

NICE has, until recently, operated on the understanding that a health gain of one QALY will be worth the same wherever that QALY arises. It now allows a higher value to be placed on QALYs gained from use of certain end of life treatments.[21] By analogy, society might accept that the NHS should place less value on QALYs for certain treatments, making them less cost effective and candidates for disinvestment. However, this approach would inevitably conflict with a wish for equity and would be difficult to justify and to put into practice.

Implementation

Implementing guidance on the withdrawal of NHS use of existing medicines on the grounds of cost effectiveness poses a different challenge from adoption of approved treatments.

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Most experience of withdrawal either relates to commercial factors or to directives issued by the regulatory authorities. In both cases, the process restricts the supply of medicines and not the demand.

Medicines that are of no value to the NHS should be relegated to the blacklist of medicines (schedule 1 of the NHS General Medical Services Contracts regulations, 2004) that cannot be prescribed on the NHS. This has been a particularly successful mechanism to reduce the prescribing of branded products but has not been updated since 2004. Most blacklisted products are tonics, vitamins, and nutraceuticals, but products that NICE decides should no longer be paid for could be added to the list automatically.

There are many cases, however, of medicines that are recommended for one indication, but not for another. The only way to ensure appropriate prescribing in these cases would be through electronic prescribing that allowed reimbursement to be linked to clinical indication.

Conclusion

NICE decisions on the economic value of medicines revolve mainly around their cost effectiveness, with no explicit recognition of the opportunity cost in terms of identifying what needs to be displaced to fund new treatments. There is a danger that although medicines approved by NICE are adopted uniformly, the treatments, interventions, and services that are displaced will be selected haphazardly. An explicit framework for the identification and appraisal of medicines for disinvestment should provide better value for money while reducing this source of inequity.

Dyfrig A Hughes reader in pharmacoeconomics, Centre for Economics and Policy in Health, Institute for Medical and Social Care Research, Bangor University, Bangor LL57 1UT
Robin E Ferner professor of clinical pharmacology, West Midlands Centre for Adverse Drug Reactions, City Hospital, Birmingham B18 7QH
Correspondence to: D A Hughes **d.a.hughes@bangor.ac.uk**
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Illness in prisons, and other blogs

Domhnall Macauley asks about illness in prisons. "What is happening in our own prisons? HIV, drug misuse, psychiatric illness, suicide, tuberculosis, hidden chronic disease. A quick glance at the literature reveals a litany of illness beyond belief in the developed world. When we read of medical scandals we wonder how it could happen under our noses. We listen to debates about hard to reach groups, forgotten minorities, and hidden morbidity. This is followed by investigations, reports, then regulation, while we wring our hands about yet another failing," he writes.

Guest blogger Seye Abimbola writes about scientific papers and commentary. "I am at present conducting a systematic review and meta-analysis that involves a detailed and critical quality appraisal of studies. It has made me realise all over again how impoverished the narrative of the classical scientific paper really is," he says.

Tracey Pérez Koehlmoos writes from Dhaka, where she was visited this week by two people from a big donor agency. "The big donor agency does not fund new chronic disease research, and I have witnessed that the eyes of donors will glaze over when I talk about the chronic disease programme that I have helped my institution to develop over the past two years because it seems to have no bearing on the millennium development goals," she says. On this occasion, however, they were interested to hear more.

Richard Smith has written twice this week. In his first blog he asks whether drug companies should be free to give information to patients. "If a patient rings a drug company asking for information about one of the company's drugs that he or she is taking, the company cannot answer. Companies are forbidden to 'come between' patients and their doctors. Is that right?" he asks. He also urges us to scrap peer review and beware of "top journals."

Also Venkat Narayan writes about how India is taking on new education challenges, and Emily Spry tells us about the doctors' and nurses' strike in Sierra Leone.

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