NICE work, but for whom: how should health technology assessment evolve?

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Summary

The National Institute for Clinical Excellence (NICE) intends to evaluate the clinical and cost-effectiveness of 30-50 new and existing technologies each year. The opportunity to appraise new health technologies and to influence their NHS reimbursement could be considered a first step toward explicit rationing. Taken with other developments such as clinical governance, the future may deliver more scientifically based clinical practice.

Economic evaluations have had (perhaps appropriately) little impact in the real world in the past, so which methods are going to be used by NICE to appraise treatments and are they up to the task? Two processes plucked out of the research ether by the proposed reforms are Development and Evaluation Committee reports and evidence-based clinical practice guidelines. The first approach involves a systematic review followed by a cost-utility analysis to provide an overview of value-for-money intended to guide health policy. The second approach makes a systematic assessment of the attributes of treatments (effectiveness, tolerability, safety, resource implications and delivery issues) from which relevant health care professionals try to formulate appropriate evidence-based recommendations. These two approaches are contrasted and their health policy implications are explored using the example of new drug treatment for schizophrenia, recently evaluated using both DEC and guideline methods.

Content description

Conceptual, resource allocation, health policy

Some background

Recent reforms to the English health service put great emphasis on developing the managed care of diseases, audit and self-regulation [1]. A substantial input to these processes is to come through the implementation of clinical and cost-effectiveness guidelines. The National Institute for Clinical Excellence (NICE) has been established to develop and present this information in a coherent fashion to the NHS [2,3].

Over the last decade, clinical guidelines have evolved rapidly from simple consensus or opinion pieces into a highly structured approach for assessing and summarising evidence and deriving appropriate treatment recommendations: [4,5] so called evidence-based guidelines. The incorporation of health economics within guidelines has been argued for from a number of sources [6-9] and a range of guidelines have been successfully produced [10-14] using a specially developed methodological approach [15]. The Department of Health continues to commission evidence-based guidelines on existing health care practices directly with the Royal Colleges in the interregnum, while NICE gets up and running.

A key task for NICE will be the *rapid appraisal* of new health care interventions in the period prior to licensing. New products may be accepted or refused NHS reimbursement, or allocated *continuing research status* on the basis of advice given by NICE to the NHS. Since 'health care intervention' is too long to bear much repetition, for simplicity this paper addresses pharmaceuticals (drugs). The review process proposed for new drugs mirrors that used for regionally funded *Development and Evaluation Committee* (DEC) reports.

Clinicians, as advocates for patients, want to give the best possible treatment in each situation, while economists appear preoccupied with efficiency concepts: sometimes there seems to be little common ground [16,17]. However, clinicians not managers or politicians make decisions about treatment in the NHS (and the consequent use of resources). The recent Viagra prescribing debacle illustrates the legal difficulties the Department of Health can experience when trying to limit the use of a licensed drug on the basis of cost [18]. With few exceptions, clinicians may defend their decisions on the basis that they believe they are providing appropriate patient care in each situation and with the information available. What approach should NICE use to improve value-for-money in our National Health Service? What might the challenges be to the advice NICE hands out?

Two models for decision making

The cost/QALY

Economic evaluation is commonly based on a 'decision-making' approach recognising that those taking decisions have a range of objectives besides efficiency [19,20]. Other factors, including decision-makers' personal values and specific notions of equity, may influence decisions. An index of output efficiency (the cost/QALY) is provided, hoping that decision makers will give such data a good

weight in the decision making process. (For simplification the cost/QALY is considered here but the debate may be generalised to cost-effectiveness concepts).

DEC epitomises the conceptual approach: a systematic review of available evidence followed by decision analysis to build up model scenarios of the process and outcomes of disease and treatment, leading to an overall cost/QALY. The Quality of life tool used in reports is the Index of health-related quality of life (IHQL). This is derived from the original two-dimensional (disability-distress) Rosser Index and developed so that distress is separated into physical and emotional components to give three dimensions in total: the validity of the ratings for the 175 potential health states is acknowledged to be unknown. Where clinical data are disease specific, these findings are mapped onto the IHQL to generate QALY scores. A Committee made up of senior clinicians and others considers the quality of available evidence and the likely value for money offered by the intervention and makes a recommendation. Five levels are possible: Strongly supported; Supported; Limited support; Not supported; and Not proven (sic). DEC reports are regionally 'funded by the Research and Development Directorate of the NHS Executive to provide rapid, accurate and usable information on the cost effectiveness of health technologies in response to the needs of NHS commissioners and providers.'

NICE will simplify DEC recommendations to: Recommend as cost-effective; Recommend only for use in further research; or Not recommend, and further specify which health professionals should provide treatment. In another deviation from the DEC process, the pharmaceutical industry will be requested to submit evidence including their own cost-utility estimates. The appraisal group will have to reach an opinion about the validity of presented evidence and whether further external modelling is required.

Guidelines

When making decisions, clinicians weigh-up patients, carers and their own preferences, effects (good and bad) of treatment, patient specific information and, to varying extents (depending perhaps on the mode of reimbursement) cost. Thus, the goal of evidence-based guidelines is to help the clinician to explore the attributes of treatments in a manner relevant to doctor-patient interactions and thus to develop well-informed social preferences. A guideline group mimics this process by allowing clinicians to go through the process of interpreting the evidence and formulating summary recommendations. Evidence addressing effectiveness, tolerability, safety, resource implications and delivery issues are reviewed systematically, presented, discussed and refined [15]. Such a process still requires the assessment of costs and benefits of treatment to be methodologically sound, but the process stops at the point where the guideline members have enough information to proceed to formulate recommendations. This recognises that assumptions required to extrapolate from the results of studies in an effort to identify an overall answer (such as a QALY score) will introduce further uncertainties: each treatment and condition should be explored to the extent merited by available data. Current North of England (and some Royal Colleges) Guideline Groups grade recommendations (A-D) reflecting the underlying quality of evidence about the various attributes of treatment.

Little has been officially revealed about how NICE will pursue the production or dissemination of guidelines to date. But the NHS Executive clearly has concerns [3]:

"The guidance resulting from the appraisal process will be very different in nature and purpose from clinical guidelines. Nevertheless, it would be extremely confusing if the guidance on new interventions was inconsistent with any guidelines endorsed by NICE."

The policy issue

Should we be comparing these two decision-making approaches? DECs are aimed at evaluating new technologies before they have diffused widely into the health system. Guidelines could be considered an important element in defining acceptable practice and modifying clinician behaviour once treatment patterns become established. The bone of contention is whether we should evaluate new technologies, at the pre-licensing stage, with a DEC or guideline style approach. This issue is explored by considering the way that new drug treatment for schizophrenia was handled by a DEC report and by a national guideline. (The guideline has been approved by the Royal College of Psychiatrists and is currently being considered by NICE: thus its contents and recommendations are not finalised or in the public domain).

Drug treatment for schizophrenia

Before contrasting the two different approaches, and to promote informed debate, it is necessary to provide some of the background about the disease and its treatment. Additionally, the summaries presented of the DEC report and guideline are selective and no substitute for reading the full works directly.

... about the disease...

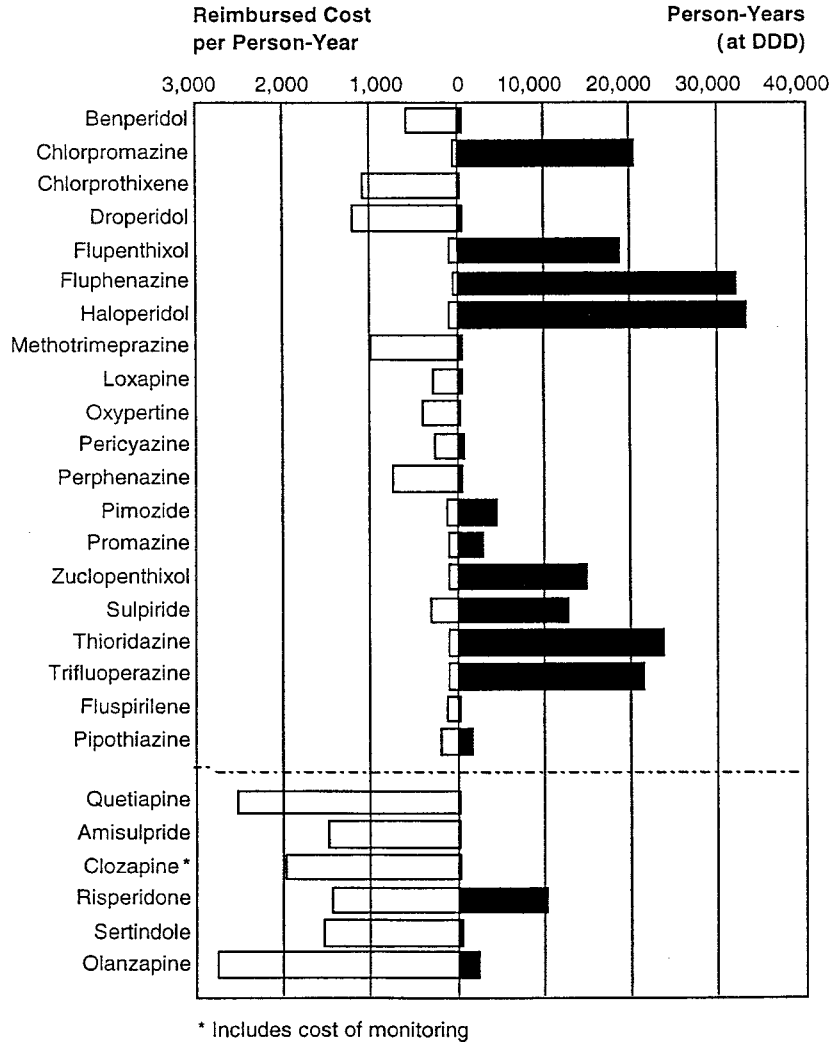
Schizophrenia is a psychotic disorder: a severe mental illness that affects perception, thinking, emotional responsiveness and psychomotor behaviour. In consequence, judgement may be seriously impaired. Patients suffering from schizophrenia may have so-called *positive* symptoms (such as delusions and hallucinations), *negative* symptoms (such as apathy and self-neglect), *depressive* symptoms and considerable functional impairment. First episodes often feature acute positive and behavioural symptoms requiring admission to hospital. About 50% of incident cases relapse and require readmission in the first two years [21].

The care of patients with schizophrenia is diverse, including hospital care (inpatient, day-patient, out-patient, depot injection clinics, secure units), community health care (CPNs, day care, GPs), social services (social workers, sheltered accommodation), non-professional carers (relatives and friends), and private and voluntary sector provision of care and services. In England, for patients receiving treatment, a recent review estimated 55% of patients to be living at home, a further 16% to be in

sheltered accommodation and 13% to be hospital in-patients. The most common points of contact for patients were specialist hospital outpatient clinics (44%), GPs (55%) and CPNs (21%).

In 1997, drugs prescribed (largely for) schizophrenia in England in primary care, cost £38.6 Million. [22]. Expenditure was divided approximately equally between conventional antipsychotic drugs and the newer 'atypical' antipsychotics. Quantity prescribing data, for each drug by dose and form, were adjusted using WHO Defined Daily Doses (DDD) [23] to estimate the number of patient years of treatment for each drug (Figure 1). By dividing volume by reimbursed cost for each drug, the cost of purchasing a year of treatment can be estimated reflecting the current mix of forms used, at DDD in English primary care.

Figure 1: Volume of use and reimbursed cost per year of treatment at DDD, England 1997



* Includes cost of monitoring

The use of Clozapine may be relatively underestimated, due to its pattern of use in secondary care. Primary care use accounts for most of the prescribing cost, since hospitals often receive substantial

supplier discounts not currently available in primary care and hospitals cease to be the source of medication for patients once discharged from inpatient care.

Conventional antipsychotic drugs cost, on average, less than £100 a year and form the mainstay of treatment for schizophrenia. The newer atypical antipsychotic drugs cost between £1400 and £2800 per year to prescribe and several are increasing their market share rapidly. It should be stressed that these cost estimates do not reflect other costs of care such as hospitalisation. Pharmaceutical treatment may be responsible for only a small part of the total cost of care [24]; nevertheless, it provides a useful yardstick for beginning deliberations. Are the substantially greater prescribing costs of the atypical antipsychotic drugs balanced by lower costs in other aspects of care (e.g. reduced inpatient stay) or justified by worthwhile improvements in health outcomes?

...some pharmacology...

The primary pharmacological effect of antipsychotic drugs is antagonism of dopamine D_2 receptors. Imaging studies *in vivo* have shown that antipsychotic efficacy requires a D_2 receptor occupancy of 60-70%, and that significant drug-related extrapyramidal side-effects (EPS) emerge at about 80% [25]. Hence, occurrence of EPS should be an indication to lower dose or switch to another drug - not to increase the dose. That might seem obvious but the conventional antipsychotics are often initiated at high doses. Antipsychotics also have a high affinity for a selection of other receptors which explains properties such as sedation, hypotension and weight gain; their differing binding profiles at these receptors is associated with their differing propensity to produce such effects. Patients may vary considerably in their D_2 receptor response. A recent meta-analysis [26] examined the relationship between dose of antipsychotic and outcome and observed no improvement in symptoms with increased dose, but an increase in the number of side effects, which in turn led to reduced compliance.

Many trials have used target dosing without dose adjustment for EPS when it occurs, which appears inappropriate in the light of current understanding about pharmacological response in humans and may constitute a major limitation in the usefulness of many conducted trials. A more appropriate procedure might involve the gradual titration of dose until EPS occurs and then reducing the dose to avoid unnecessary side effects.

Available antipsychotic drugs are dichotomised into older 'typical' and new 'atypical' categories, the first of which was clozapine and well-known additions are olanzapine and risperidone. An atypical drug is thought to be an effective antipsychotic at a dose significantly lower than that at which extrapyramidal side-effects (EPS) occur. However, there is no one property that atypical drugs have in common and a simple 'D_2 blockade' model is inadequate. Multiple and complex mechanisms are likely to exist to explain the lack of EPS as well as any differences in therapeutic efficacy which may be demonstrated when comparing with typical antipsychotics.

... about trial measures...

Recently, trialists have consistently used two scales to measure general psychopathology, positive, negative and depressive symptoms. The *Brief Psychiatric Rating Scale* (BPRS) is a 16-item, 7-point severity scale, containing 5 positive, 2 negative and 9 general symptom items. An overall BPRS score ranges from 16 to 112. The *Positive and Negative Syndrome Scale* (PANSS) is a 30-item, 7-point severity scale, comprising 7 positive symptom ratings, 7 negative symptom ratings and 16 general psychopathology symptom ratings. Overall PANSS scores range from 30 to 210. The positive and negative symptom groups are often reported separately: both score from 7 to 49.

Side-effects have been covered by a broader range of measures. The *Abnormal Involuntary Movement Scale* is used to rate tardive dyskinesia, a sometimes irreversible movement disorder that occurs at a rate of about 5% per year in patients on long-term conventional antipsychotic drugs. The AIMS includes 10 questions covering facial, oral extremity, trunk and global movement, scoring 0-4 and 2 questions on dental status scoring 0 or 1. The range of scores possible is 0-40 (dental scores excluded). The *Simpson-Angus scale* measures extra-pyramidal side-effects, excluding tardive dyskinesia. These include parkinsonian symptoms such as tremor and rigidity. The range of scores possible is 0-40. The *Barnes Akathisia Scale* measures akathisia, an uncomfortable feeling of inner restlessness caused by antipsychotic drugs. The scale rates objective movements (on a scale of 0-3), subjective awareness of restlessness (0-3) and distress (0-3) and a global clinical assessment (0-5). The range of possible scores is 0-14. Some studies simply report the event rates of specific side-effects, for example: dystonia, sedation and weight gain.

Mean changes in overall PANSS, BPRS and AIMs scores over time are hard to interpret since they implicitly give equal importance to all dimensions.

What the DEC report found

A recent DEC addressed whether olanzapine should be made available as a first and second line agent for the treatment of all people with schizophrenia [27].

The systematic review centres upon evidence of the efficacy of olanzapine from four published double blind randomised clinical trials of six weeks duration and from three extension phases of treatment responders. In these studies, higher response rates and fewer side effects were achieved when comparing olanzapine with either haloperidol or no treatment. Rather than analysing continuous scores reported in trials, they analysed response rates (patients experiencing >40% improvement in baseline BPRS score). The reviewers raise concerns about the role of dosing of the comparator drugs and approach used in trials to measuring side-effects, but do not pursue these concerns quantitatively.

No quality-of-life data were available directly from the olanzapine trials and so possible benefits for olanzapine were modelled using quality of life weightings applied to a hypothetical cohort. A decision tree modelled the likely course of treatment and relapse over one year by mapped BPRS response

rates and events onto health states. The model estimated gains for olanzapine of 0.049 QALYs in the first year of treatment compared to no treatment and 0.027 QALYs compared to haloperidol. Greater benefits were modelled using the disability weights for schizophrenia from the World Bank DALYs study: 0.068 and 0.038 QALYs when compared to no treatment or haloperidol respectively.

When modelling costs of care, potential net savings for olanzapine were consistently predicted due to reduced inpatient and intensive community care. If it was assumed that patients who did not respond to their first two neuroleptics all needed continuing hospital or intensive out-patient treatment, then olanzapine was the first choice therapy with a cost advantage of £7,800 per QALY over haloperidol. When the requirements for hospital or intensive community care were reduced, the cost advantage of olanzapine fell to £2,500 per QALY.

Findings applied to a prevalent cohort of patients for one year only, pending further evidence. The analysts acknowledged some very significant assumptions: (i) that the short duration of the trials truly represents a longer time period; (ii) that the trial patients, particularly those enrolled in extension phases, are representative; and (iii) that potential savings from reduced hospitalisation can be realised.

In summary, the DEC Report 'supported' the use of olanzapine as a first and second line agent, asserting 'good evidence of excellent value for money' despite the limitations of the available evidence.

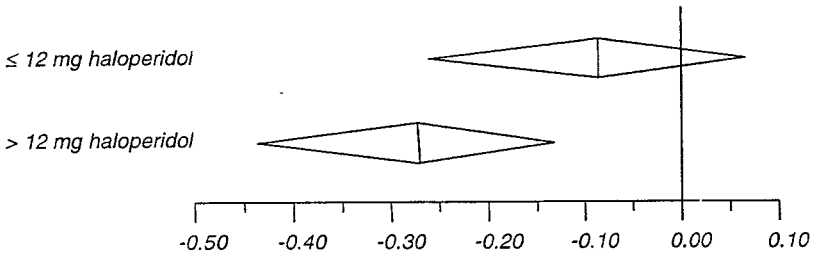
What the National Guideline found

Trials of atypical antipsychotics showed considerable variability in efficacy and tolerability when compared with conventional neuroleptic drugs, limiting the value of simple combined estimates from trials. Analysis by drug suggested small benefits in reduced psychiatric symptoms favouring some antipsychotics. However, most trials were short term (6-8 weeks) and provided limited evidence on how best to treat patients in the longer term. There was no evidence of specific effects for atypical drugs upon negative and depressive symptoms. Benefits, when they occured, seemed equally to involve all classes of symptoms

Observed differences in the results of trials may be explained by variation in the dose of the comparator conventional neuroleptic used. Consequently, the effect of the dose of comparator drug received on psychiatric symptom scores was modelled for trials of atypicals comparing with haloperidol and chlorpromazine using multilevel modelling based upon Gibbs sampling. In both instances, statistical modelling revealed a linear dose effect with benefits for the new drugs disappearing at low doses of comparator drug. This can be seen when simply dichotomising into fixed low dose and higher dose-ranging trials (Figure 2). The apparent benefits of the atypical antipsychotics on overall symptom scores are no longer present when compared with low dose

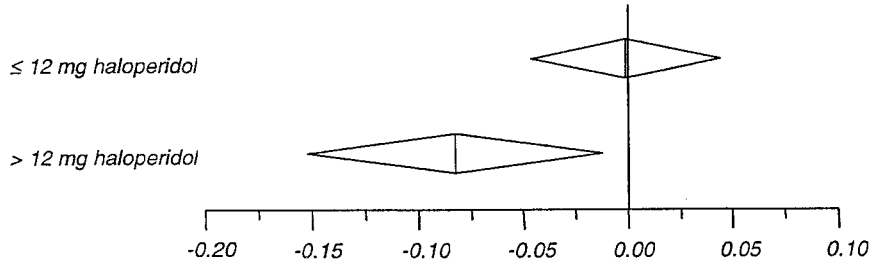
haloperidol, indicating that conventional drugs are frequently used in doses that are inappropriately high.

Figure 2. Overall symptom score by level of dose of comparator drug in trials of patients with schizophrenia or related disorders, (Standardised Weighted Mean Difference and 95% Confidence Intervals)



Although drop out is reduced in trials comparing atypical antipsychotics with conventional neuroleptics used at higher doses, at lower doses, conventional neuroleptics appear similarly tolerated to the newer drugs (Figure 3).

Figure 3. Drop out by level of dose of comparator drug in trials of patients with schizophrenia or related disorders, (Risk difference and 95% Confidence Intervals)



Atypical antipsychotics are associated with a reduced risk of extra pyramidal side-effects even in trials where lower doses of haloperidol are used. An analysis based on the extension phases of three randomised trials comparing olanzapine and haloperidol suggests a significant reduction in irreversible tardive dyskinesia in chronic patients at high risk of 5.9% per year (95%CI: 2.05% to 12.46%), although there are no direct data on the relative incidence of tardive dyskinesia in lower dose trials of conventional neuroleptic drugs, or in lower-risk patient groups. There have been reports of suspected malignant neuroleptic syndrome in trials of at least one atypical drug currently licensed. Information on the relative incidence of treatment emergent side-effects is surprisingly limited for atypical drugs. That is to say the side-effects of older drugs are well known and carefully measured, the newer drugs have their own side-effects but these appear inconsistently reported.

Directly randomised comparisons of atypical drugs are thus far inadequate to provide reliable evidence on their relative effectiveness. However, there is limited evidence of improved tolerability with olanzapine compared with risperidone.

In long term trials of one or two year duration, average improvement in psychiatric symptom scores for the newer drugs does not exceed a 4% gain. Gains in tolerability, side-effects, and quality of life remain unclear and may be confounded by the dose of comparator drug given. Two large US studies presenting net costs of care present imprecise findings (wide confidence intervals on net costs). The net cost of prescribing atypical antipsychotic drugs in the UK setting remains uncertain and it should not be assumed that savings from reduced hospitalisation or use of other services will offset their higher acquisition cost. None of this (unmodelled) evidence makes it plausible that there are robust cost savings or quality-of-life gains to be obtained from the general use of atypical antipsychotics.

Data are very limited to inform decision making about the treatment of first episode schizophrenia. In this patient group, trial data are required to explore the influence of the choice and dose of drug given, presenting a profile of costs and consequences relevant to the UK health care setting.

In overview, the guideline recommended beginning treatment with low-dose conventional antipsychotics with careful monitoring. Previous history or emergence of unacceptable EPS symptoms treatment should trigger a switch to an atypical drug.

Differences

...in concept...

The decision making approach assumes the existence of an audience of social decision makers, who weigh the costs and benefits of policy changes to all affected parties and who apply the results of cost-effectiveness studies. However, commissioners specifying health services (covering often, in one service agreement, provision of a whole medical speciality) have struggled to apply economic evaluations of individual technologies: studies considering the impact of cost-effectiveness studies suggest little impact [28-32,17]. The introduction of NICE with its evaluative role and of clinical governance in a monitoring role could potentially change the state-of-play. NICE could advise refusal of NHS reimbursement for new products on the basis of an unfavourable (modelled) cost/QALY.

The DEC approach illustrates the persisting belief that complex cost and benefit profiles associated with treatments can be aggregated, thus handing 'an answer' to aid decision-making (at least with respect to efficiency). This has been unproductive in the past because the methods and data have not been adequate to provide a simple answer [33-38]. Whether this situation improves in the future with more generic quality-of-life measurement being conducted in trials remains an interesting empirical issue (but not the topic of this paper). Of more immediate importance, practising clinicians (the key audience until now) do not approach individual treatment decisions in terms of economic outcomes, such as cost-utility ratios. This is not to say that the cost/QALY may not seem appealing to NICE. The issues remain qualitatively, should NICE think so simplistically about health care and quantitatively, are current cost-utility estimates as informationally robust and certain as they often appear?

...in detail...

The most obvious difference between the approach of the DEC report and the guideline (besides the use of QALYs) are that the guideline examined all atypicals (not just olanzapine) and went to considerably greater lengths to get 'underneath' the trials and find out what was really going on. The three short-term trials of olanzapine compared with haloperidol all featured fairly high doses of comparator drug thus enhancing the likelihood of a favourable outcome for the new drug. Although no quality-of-life data were available for olanzapine they are available for other atypicals. With one partial exception, these other studies failed to show any improvement in QOL, which if considered may have made the modelling more cautious. Similarly, long term trials with economic outcomes were available for other atypical drugs, which should have led the DEC analysts to question the consistent cost-savings their model predicted for olanzapine. When adjusted for dose, there is no great difference in outcome between atypicals and typicals and as a result, net cost savings lack plausibility.

The DEC report moved directly to response rates (an arbitrary categorisation of patients into success and failure on the basis of a 40% improvement in BPRS score rather than a physical measure of response). The quite spectacular performance of olanzapine using this metric is quite at odds with the rather modest changes seen in mean psychiatric scores. The use of response rates was presumably to facilitate modelling and the DEC reviewers asserted this was the right way to analyse the data because of a wide dispersion of scores. Statistically, it is inefficient and potentially misleading to dichotomise continuous measures and pragmatically, it is a concern because the cut-off point can heavily influence the impressiveness of findings.

The DEC report recommendations relate to treatment of first episodes of schizophrenia. Very little trial evidence applies to new patients; cases enrolled mostly have some history of disease or treatment resistance. New patients are most likely to achieve a response to the older drugs and least likely to suffer from unwanted side effects, particularly when appropriate dose titration is used. The same predicted cost-effectiveness estimates couldn't apply to these patients as to chronic or relapsed patients.

In contrast, the guideline recommends a structured and sequential approach to the use of new drugs that has, interestingly, been well received by opinion-leading psychiatrists and endorsed by the Royal College of Psychiatry Guidelines Group. Additionally the guidance is likely to be considerably more cost-effective than the blanket use of olanzapine indicated by DEC.

The modelling in the DEC report appears heroic, but much the same data was potentially available to DEC and the national guideline. Neither is this an isolated case. For the treatment of Alzheimer's Disease with Donepezil Hydrochloride (Aricept), a regional guideline group concluded on the basis of the available phase II and III trials that there was insufficient evidence to recommend its use, or to continue secondary care initiated prescribing [13]. This finding can be contrasted with the DEC report, which suggested, using a Cost per QALY framework, that treatment might be cost-effective [39]. Its overall conclusion was 'borderline' and that treatment should be carefully targeted. The DEC findings were remarkable (£21,000 - £200,000/QALY gained) given the small and clinically questionable effect

upon cognitive function, no improvement in quality of life in direct measurement, and no evidence that the drug achieves any worthwhile effect at the stage where dementia has become severe enough to merit residential care [40].

...in practice...

It would be unfortunate for NICE if apparently marginal health benefits were translated by modelling into apparently cost-effective technologies. The rapid appraisal of drugs is one aspect of a string of reforms designed to foster both collaboration in the NHS and continual updating of skills and performance by health professionals: it should not be considered in isolation. For clinicians to modify there behaviour there should be transparency in the methods use to influence them and credibility in the messages these methods contain. It is essential for NICE to communicate its information to clinicians in a language consistent with the way they treat patients: a cost/QALY clearly won't do. Currently, in law, any recommendations given by NICE appear to be only advisory. The Secretary of State's initial attempt to curtail GP prescribing of Viagra proved not to be legally binding. The subsequent decision to restrict the use of Viagra, as a schedule 11 drug (for use in defined patient groups only) on the basis of its total cost impact [41] is being challenged by Pfizer, since this restriction was conceived for drugs with limited effectiveness. NICE has thus far ducked the issue of where resources will be released from when new high-use expensive but cost-effective drugs appear, thus presenting a substantial strain on existing budgets. Such challenges could be considered necessary birth pains when trying to reorientate the NHS toward explicit rationing. Such a process cannot be expected to be simple or fast in a healthcare system founded upon clinical freedom and implicit rationing.

A NICE approach?

A formal rapid appraisal of new pharmaceuticals should be better than no appraisal at all. The most marginally beneficial and costly drugs can be sent back to the industry for a rethink rather than have uptake determined by the abilities of marketing personnel. However, appraisal must be rigorous to be of value. There are difficulties coming to an informed opinion about the value of a new drug, but why compound them with the invalidated assumptions required to estimate a cost/QALY. The approach appears to promote tunnel vision in its protagonists, using the evidence selectively in order to get to the 'big answer'. Rather than examining a single drug, significant information may be gained by considering other related products, particularly those with a similar pharmacological action. This implies a more extensive review, but would bring benefits in terms of the validity of recommendations.

The objective of appraisal should be to enable clinicians, patients and managers to reach informed decisions about treatments. Guidelines groups spend a considerable amount of time debating and interpreting the meaning of the attributes of treatments. The National Institute for Clinical Excellence appraisals should similarly profile systematically the attributes of therapy (effectiveness, tolerability, safety, resource implication and cost), and comment on the absence or inadequacy of critical

information. This profile should include best estimates of effect (and their uncertainty) on a range of relevant outcomes, thus avoiding questionable modelling assumptions and correctly identifying research priorities for pharmaceuticals allocated to a *'continuing research'* category. It may be useful to run a Cost/QALY modelling exercise during each appraisal to gain experience of the performance of such an approach, but it may be asking too much to expect doctors, patients or the public to be impressed.

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