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BJP 1993, 162:23-29.
Access the most recent version at DOI: 10.1192/bjp.162.1.23

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British Journal of Psychiatry (1993), 162, 23-29

Symposium: The Costs of Drug Treatment for Schizophrenia

Psychopharmacology and the Ethics of Resource Allocation

DAVID HEALY

The introduction of clozapine to current psychiatric practice is considered against a background of potential problems of resource allocation posed by the development of a number of 'budget-busting' drugs. It would appear that clinicians may increasingly have to operate within a climate in which the rights of individual patients to expensive treatments will seem to be pitted against the abilities of their communities to afford such treatments. Both clinicians and pharmaceutical companies have roles in the development of such conflicts.

The cost of drug treatment is ever escalating. Very often new compounds, such as the 5-HT reuptake-inhibiting antidepressants, are no more efficacious than older agents, even though they may cost substantially more. Increases in cost can be justified on the basis of the need to cover research, development, and marketing overheads. They may also be justified in terms of the newer compounds offering better safety or quality of life. Consequent benefits in terms of increased compliance and reductions in associated costs, such as intensive-care facilities for drug overdoses, when included in the equations of a cost–benefit analysis, may reduce somewhat the discrepancy in costs.

Such increases in cost provide little in the way of ethical difficulty. However, more recently a range of drugs has been developed whose costs are of an entirely different order to those of most agents used hitherto (Orme, 1991). So great are the increases that clinicians are faced with a novel ethical problem. Use of these agents, especially in a climate of indicative budgets, may entail cutbacks in other services. Clinicians may be forced to choose between treatments, and may have to allocate treatments to some rather than to all those who may benefit.

This paper focuses primarily on clozapine, a recently launched neuroleptic, whose costs far exceed those of other neuroleptics. Before doing so, the costs, benefits and impact of a number of other high-cost treatments are briefly reviewed to provide a context for the debate about clozapine.

Coronary artery bypass surgery

In 1964 the first coronary artery bypass graft (CABG) was performed in the US. By 1985, CABG was the most common elective surgery there (Halperin & Levine, 1985). The procedure was introduced to relieve the pain of angina pectoris, which it certainly did in a number of instances. The expansion in the numbers undergoing surgery, however, was based on what appears to have been an implicit understanding that this operation would cure angina, a claim that has never been proven (Petch, 1991).

Despite this lack of proof, by 1985, the costs of the operation and the supportive services surrounding it were estimated at $5 billion – a not insignificant proportion of the US health-care budget (Halperin & Levine, 1985). It seems probable that this resulted in part from hospitals gearing up to do such operations and then finding it more cost-effective to do more of them. The acceptance of this position may in turn have depended in part on there being an ever-increasing number of surgeons whose livelihoods depended on the operation, who were as a consequence vigorous advocates of its desirability (Valenstein, 1986; Petch, 1991).

In short, this development probably depended on decisions that were made intuitively and without an explicit basis. Where funding for health care is limited, the extensive provision of expensive procedures, such as CABG, must mean that other services will not be funded. It behoves us therefore to make explicit the basis for our treatment options.

Erythropoietin and interleukin-2

The first of the recently developed high-cost drugs to reach public attention was interleukin-2, the withholding of which on the basis of cost from Maureen Kendrick, a patient with cancer, in Christie's Hospital, Manchester at the end of 1990, led to considerable public outcry (Smith, 1991). Interleukin-2 appears to improve quality and length of life in patients with particular carcinomas. However, it is not a specifically life-saving drug, and it costs about £2500 per patient per year.

There have been similar debates within hospitals, that have not as yet received as much media attention, regarding other products of human genome engineering. One of these is Recormon, an analogue of naturally occurring erythropoietin, which when

given to patients with chronic renal failure appears to be quite clearly life-enhancing. Its use is particularly problematic. We appear to feel obliged to commit large amounts of money to keep patients with kidney failure alive with renal dialysis and transplantation programmes, even though quality of life is often poor. Recormon can significantly enhance that quality of life, yet it is likely to be withheld in many instances because of its cost, which is in the region of £4000–£6000 per annum.

Centoxin

A further agent likely to cause problems, centoxin, was launched in the Netherlands in May 1991 (Wolff, 1991). Like erythropoietin and interleukin-2, centoxin is a product of human genome engineering. Like erythropoietin and interleukin, it is costly. Its use lies in Gram-negative septicaemia, which has a high mortality despite modern antibiotic treatments. It is estimated that centoxin could save over 5000 lives per year in the UK alone. The cost per treatment is £2200. Given the numbers of potential Gram-negative septicaemias and the possibility of the drug being used prophylactically, the bill could amount to £100 million per year – up to 20% of current expenditure on drugs in the National Health Service (Taylor, 1991). Despite this, it is difficult to see how budgetary constraints could be allowed to stand in the way of using what appears to be an unambiguously beneficial treatment, unlike erythropoeitin and interleukin-2.

Tissue plasminogen activator

In marked contrast to centoxin is tissue plasminogen activator (tPA). In the US, this genetically engineered compound has been prescribed for fibrinolysis following acute myocardial infarction, in preference to an alternative, streptokinase, despite the fact that it costs 10 times more.

The largest clinical trials in medical history have looked at the comparative effects of tPA, streptokinase, and anistreplase for fibrinolysis following myocardial infarction. These have recently concluded, with results which indicate that all three agents are equivalent in fibrinolytic activity but that streptokinase is less likely than tPA to cause spontaneous cerebral haemorrhages (O'Donnell, 1991).

Following the publication of these results in the US, current affairs programmes, investigating why tPA should have been prescribed so widely in the US, at an increased burden to the health services of $100 million per year, suggested that its sales may have involved a triumph of marketing over research.

'Budget-busting'

The significance of these compounds is that the adoption of any of them, or more problematically a number of them, would seriously compromise funding in other areas of health care.

The differences in benefit obtained from the use of each of these compounds point to the fact that not all new and costly developments are necessarily equivalently good. In the case of the above drugs, it would seem that centoxin is clearly life-saving and hence possibly should be funded, interleukin and erythropoietin life-enhancing and therefore of lesser importance, and tPA of dubious benefit.

Psychiatry is not immune to such issues. Indeed, perhaps the most interesting resource-allocation issues surround a drug recently introduced into psychiatric practice – clozapine.

Clozapine

This drug was launched in the UK in January of 1990 under the trade name Clozaril, marketed by Sandoz. It costs in the region of £2000 per annum (compared to *c.* £300–£400 per annum for the recently released 5-HT reuptake inhibitors, for example). An unspecified proportion of this cost stems from blood tests that must be taken weekly for 18 weeks after the start of treatment and fortnightly thereafter because of a risk of agranulocytosis, along with insurance costs against possible fatal outcomes. However, it must be assumed that a significant part of the cost is accounted for by the company's profit.

In the US, the introduction of clozapine in February 1990 has caused considerable debate. In part, this is because of the even higher costs there, which, as of May 1991, had been running at approximately $9000 per patient year. Extrapolating from this, Terkelsen & Grosser (1990) have estimated that clozapine could cost the US in the region of $1.5 billion per year if it were given to all of those eligible to receive it. (For reasons outlined below, this figure may underestimate the eventual costs.)

Clozaril has been introduced with claims that it is a breakthrough in the treatment of schizophrenia – the first significant advance in the pharmacological management of schizophrenia for more than 20 years (Westlin, 1990). Such claims were not simply advertising copy, but rather have appeared in journal articles. Claims such as these have inevitably led to pressure on clinicians from families who have schizophrenic or psychotic members, who are concerned to get the best treatment for their relative, and who do not see why they should be denied the

benefits of any significant medical breakthrough – on the basis of cost (Pelonero & Elliott, 1990; Eichelman & Hartwig, 1990).

The efficacy of clozapine

However, the overall picture in the case of clozapine is even more ambiguous than it is in the case of erythropoietin. Clozapine is not a new drug. It was first manufactured in 1962. Promising clinical trials during the 1970s were aborted when a number of fatalities occurred consequent on agranulocytosis (Baldessarini & Frankenburg, 1991). Aside from its propensity to cause agranulocytosis, there are other drawbacks to its use. In a significant proportion of cases, clozapine causes convulsions. It does this in a dose-related manner. It may also cause significant weight gain and a number of other problems (Adams & Essali, 1991).

As regards efficacy, the current marketing of Clozaril depends on a rather slender research base. A number of studies from Europe have indicated Clozaril's efficacy for schizophrenia. This has been no more and no less than that of other neuroleptic agents (Fischer-Cornelssen *et al*, 1976; Povlsen *et al*, 1985; Baldessarini & Frankenburg, 1991).

Clozapine and treatment resistance

With the problems of launching clozapine in the US and the UK owing to its toxicity, company-sponsored research has focused on a treatment-resistance indication. This led to a trial in which patients were recruited who were initially treatment refractory and who were subsequently resistant to a six-week course of haloperidol (60 mg per day) (Kane *et al*, 1988). Subjects were then randomised to treatment with either clozapine or a combination of chlorpromazine plus benztropine. In the case of chlorpromazine, doses ranged up to 1800 mg per day. Of those on clozapine, 30% responded, whereas of those on chlorpromazine, only 4% responded.

A number of comments can be made about these findings. The first is that in a review of neuroleptic dosages and plasma levels, Baldessarini *et al* (1988) concluded that there was substantial evidence that neuroleptic regimes higher than the equivalent of 400–600 mg chlorpromazine a day or 30–40 mg haloperidol a day were associated with significantly worse outcomes. The adverse outcomes did not appear to be attributable to the initial severity of the index conditions leading to a consequent increase in medication. An implication of these findings is that higher doses of neuroleptics may produce treatment resistance in susceptible individuals.

In line with this suggestion, Bowers and colleagues, in a series of studies (Bowers & Swigar, 1988), have produced evidence that there are indeed patients who seem particularly susceptible to the adverse effects of neuroleptics. van Putten *et al* (1974, 1984) have also reported in a series of studies that some patients have significant symptoms of akathisia or increased nervousness, restlessness, and tension on neuroleptics. These patients appear to have a poorer outcome than those not experiencing such symptoms. There have also been reports that the outcome of haloperidol in doses of 5 mg per day (van Putten *et al*, 1990) or 10 mg per day (Rifkind *et al*, 1991) are as good as those from patients on higher doses. A study by McEvoy *et al* (1991) also suggests that the optimal dose of haloperidol is something of the order of 5 mg a day.

In support of these findings are recent studies by Farde and colleagues using positron emission tomography (PET) to assess D_2 receptor occupancy after neuroleptic intake (Farde *et al*, 1988). These have indicated that a therapeutic level of central D_2 receptor occupancy is achieved with 200–400 mg sulpiride per day or 6–10 mg haloperidol per day. Of interest were findings with clozapine, which appeared to result in D_2 receptor occupancy of no more than 60–70%, regardless of the dose given (Farde *et al*, 1988).

The significance of these findings for the debate about clozapine's efficacy is that Kane *et al* (1988) selected their treatment-resistant schizophrenic subjects on the basis of them being unresponsive to 60 mg haloperidol per day or its equivalent. The comparison group then took 1800 mg chlorpromazine per day. It is quite possible that this design helped select a group of subjects who would respond poorly to high-dose neuroleptics by virtue of these agents causing increased tension and restlessness. If this is the case, it is hardly surprising that this particular group of subjects should show a better response to clozapine, by virtue of its inability to bind to D_2 receptors to the same extent as would alternative high-dose neuroleptics (see also Baldessarini & Frankenburg, 1991).

Clozapine and negative symptoms

Kane *et al* also noted that the negative features of schizophrenia responded to clozapine, and this finding has since been cited as being a significant factor in clozapine's favour. The question of neuroleptic effects on negative symptoms has become a question of concern since Crow's influential distinction between type I and type II processes in schizophrenia, with its implication that negative symptoms do not respond to neuroleptics (Crow, 1980). However,

clozapine is not the first neuroleptic to show beneficial effects on negative symptoms, despite claims to this effect. In 1965, Goldberg *et al*, in a study of chlorpromazine, showed that chlorpromazine had significant effects not only on positive symptoms of schizophrenia but also on what they termed the 'Bleulerian negative symptoms' of the state (Goldberg *et al*, 1965). In a survey of the evidence on this issue, Meltzer *et al* (1986) concluded that it was not the case that neuroleptics do not affect negative states. They offered evidence that neuroleptics, particularly in low doses, may be of benefit (Meltzer *et al*, 1986).

There are further aspects to this problem. A possible reason for increasing awareness of negative symptoms in schizophrenia may be simply the consequence of the neuroleptic regimes we have been using of late. Doses of neuroleptics during the 1970s and early 1980s were much larger than had been customary during the 1960s. It is only in recent years that we have begun to revert to something like the doses used during the 1960s. An almost inevitable consequence of high-dose regimes, if the review by Baldessarini *et al* (1988) and the recent PET scan work is to be believed (Farde *et al*, 1988), would be the induction of negative states. The evidence that this has been the case has been marshalled by Drake & Sederer (1986) and Bartels & Drake (1988).

For patients formerly receiving high doses of neuroleptics, as was the case in the Kane *et al* (1988) study, treatment with an agent that cannot produce such negative states, by virtue of its inability to block a sufficient proportion of D_2 receptors, could well lead to an apparent improvement in iatrogenic negative symptoms (Baldessarini & Frankenburg, 1991).

Clozapine and relapse – insulin revisited?

There are further factors to the Clozaril story that need to be mentioned. One is the fact that clozapine's use at least initially appears to be associated with a reduced risk of relapse. It is difficult, however, to evaluate this, in that ongoing treatment with Clozaril has to date been associated with weekly or two-weekly blood tests. There is also the fact that patients are embarked on what has been billed as both a revolutionary new and high-risk treatment. The combination of excitement and close supervision of results can be expected to be associated with better response rates than the current neglect that is all too often visited on chronic schizophrenic patients. One would have to believe that people with schizophrenia were particularly unsusceptible to placebo effects to believe otherwise. Because of such factors, it seems difficult to see how a satisfactory double-blind study of maintenance treatment with clozapine could be conducted.

Indeed, a consideration of such issues might prompt a comparison between clozapine and insulin. The evidence that insulin was more effective than other treatments for schizophrenia at the time of its introduction was never compelling (Cramond, 1987; Shepherd, 1990). Yet the treatment was introduced widely; it appears that few self-respecting treatment facilities needed much persuasion on the question of setting aside considerable funds to establish insulin units (Cramond, 1987). These units in turn had a certain success rate. Retrospectively, however, it would seem that that success probably owed more to enthusiasm about a revolutionary new treatment and a general improvement in staff morale than anything else (Cramond, 1987). The fact that authorities pronounced favourably on this treatment may also have led those involved with the care of patients to take risks they might not otherwise have taken – leading to an Oedipus effect, whereby oracular pronouncements act to bring about the state they pronounce on (Shepherd, 1990). In due course, when enthusiasm fades and the oracle stops pronouncing, the rate of response to the treatment in question falls – this is certainly what happened with insulin (Cramond, 1987).

It can be suggested, perhaps somewhat facetiously, that the only possible trial of clozapine and relapse, given the current enthusiasm associated with this treatment, would be to have clozapine with its two-weekly blood tests compared with low-dose chlorpromazine, of the order perhaps of 50 mg a day, with two-weekly visits from a psychiatric nurse to hand over a cheque for £100 – this latter representing the amount of money being saved by using chlorpromazine.

Defensive prescribing

Eichelman & Hartwig (1990) suggested that, given the costs of Clorazil, it is particularly likely to be individuals with tardive dyskinesia who will be prescribed this drug, rather than individuals who may be more deserving of it, or who may be able to benefit from it more. The reason, at least in the US, is that clinicians are liable to be sued for tardive dyskinesia – a condition that clozapine seems less likely to cause. Given this, it is possible that hospitals will insist that clinicians preferentially prescribe clozapine for patients with tardive dyskinesia.

This preference is likely to be reinforced if anyone institutes litigation following the development of a 'rebound psychosis' with injury to self or others, in association with an attempt to ameliorate tardive

dyskinesia by reducing the neuroleptic regime – injuries that might have been avoided with clozapine.

Alternative therapies for treatment-resistant psychoses

Against this background, Pelonero & Elliott (1990) and Eichelman & Hartwig (1990) point out that few other treatments have been investigated in the same comprehensive manner for treatment-resistant psychotic conditions as clozapine. There is some evidence that both lithium and carbamezapine may be useful adjunctive therapies in treatment-resistant disorders, but it seems unlikely that the sponsorship will be forthcoming for research on either of these agents to the extent that it has been in the case of clozapine, owing to the lack of potential market return on such research.

As 5-HT_2 receptor antagonism possibly plays a part in clozapine's beneficial profile (Meltzer, 1991), a number of other agents appear deserving of investigation in treatment-resistant schizophrenia. These include mianserin, trazodone, and the recently introduced 5-HT reuptake inhibiting antidepressants (Healy, 1991*a*). Given the phenomenology of responses to these agents, it seems quite possible that these would be of some benefit in treatment-resistant schizophrenia (Healy, 1991*b*). The advantages of these agents lie in their greatly reduced costs and better safety profiles compared with clozapine.

There is a further set of therapies deserving of note. In recent years, a number of studies have reported on the efficacy of cognitive therapy for chronic delusions (Lowe & Chadwick, 1990; Healy, 1990). Such research would appear to be of immense significance where the neuroleptic-resistant psychoses are concerned, but further research in this area is unlikely to be funded to anything like the extent that the clozapine studies have been. And even if it were funded, the outcomes would be unlikely to receive the publicity that Sandoz have given Clozaril.

Après clozapine . . .?

This article does not pretend to review the clinical pharmacology of clozapine in comprehensive detail – interested readers should see Baldessarini & Frankenburg (1991). Nor is there any wish to suggest that clozapine does not have dramatic effects in a significant proportion of otherwise treatment-resistant cases. The studies above and the testimony of an increasing number of eminent clinicians point to undoubted benefits. The purpose of this article is to assess the place of clozapine in current practice in the light of the recent emergence of a number of 'budget-busting' drugs.

As with compounds such as erythropoietin, a number of hospitals in the USA and in the UK have attempted to draw up guidelines to limit the number of people who can be prescribed clozapine at any one time, and to delineate what should be considered a reasonable trial period, after which a failure to respond will lead to a discontinuation of treatment. The reason for this stems from the potential costs, set against a background of budgetary constraints. It would seem that for the first time, there is a perceived need to allocate resources between treatment options and within patient populations; it also seems that in many cases clinicians are being called upon to act as gatekeepers for society's resources (Williams & Beresford, 1991). It would seem therefore that clinicians are being asked to balance their duty to individual patients against a duty to society in a way they have never as clearly been called on to do before.

Despite its cost, clozapine might at first sight not appear to pose as large a problem as other budget-busters, in that along with the constraints of clinical guidelines there is the fact that it is licensed only for treatment-resistant schizophrenia. However, licences are relatively meaningless, with clinicians, on the basis of clinical judgement, daily prescribing many compounds in ways not covered by their licence. There is no good reason why a clinician seeking the best for a patient should not prescribe clozapine for treatment-resistant obsessive–compulsive, or bipolar disorders, or indeed for the many individuals who show a marked sensitivity to conventional neuroleptics. In a climate where guidelines are simply that, there seems every likelihood that many clinicians will prescribe clozapine liberally, on the basis of the hitherto dominant ethic that a clinician's duty is to individual patients rather than to communities. On this basis, clozapine could cost far more to the exchequer than any of the other budget-busters.

A further aspect of clozapine's price is that it can be expected to influence the cost of any new neuroleptics produced, as the cost for new compounds is set with reference to the price of available reference compounds ('a going rate'). The development of high-cost neuroleptics and other psychotropic compounds could be extremely problematic, in that these compounds are likely to be prescribed widely in primary care.

Consider Glaxo's Zofran, which was launched in June 1991. Current costs for its use as an anti-emetic are up to £270 for a ten-day supply. This works out at £9500 per annum. There is some evidence that Zofran and other 5-HT_3 receptor antagonists may be useful in schizophrenia (Meltzer, 1991). Costs

will undoubtedly drop if current trials lead to a successful licence application for the treatment of schizophrenia – but by how much?

There is a further aspect to the cost of clozapine that needs assessment. Even in the case of those who do well on it, there is a hidden cost, other than the £2000 per annum. This lies in the time taken to supervise treatment delivery and the taking of blood tests, etc. A detailed assessment of such hidden costs should be undertaken, as well as an audit of any diversion of resources that may occur as a consequence of the funding of Clozaril.

Considerations such as these suggest that presenting any ethical conflict regarding the prescription of budget-busting drugs in terms of clinicians having to decide between their responsibilities to individual patients and to their communities is misleading. Rather than the primary tension stemming from conflicts between aspects of the clinicians' role in society, the ambiguities stem as much, if not more, from the position of modern pharmaceutical companies in society. Ironically, in the early years of the century, in an attempt to differentiate their activities from those of the patent medicines industry, companies characterised this position themselves as 'ethical' (Healy, 1991*c*).

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British Journal of Psychiatry (1993), **162**, 29–32

Comment

Psychopharmacology and the Ethics of Resource Allocation

NICK BOSANQUET and ANNA ZAJDLER

Economists in the UK have developed a particular view of ethical choice which puts the main focus on short-term, static decisions. As resources are scarce, decisions have to compete (O'Donnell *et al*, 1988). Although economists have also stressed the moral imperative of improving efficiency, the theme of choice as inexorable has come through much more strongly. Economists in the UK have been more hesitant about giving any clear advice on how to deal with the special problems of supply efficiencies and professional monopoly in health services.

Health economics in the UK has little to say about gains from innovation and how to increase them. Such gains may not always lessen discontent and unease about services, as expectations will generally run ahead of performance, but they will lead to solid objective measures of improved health status and even some greater subjective satisfaction for some. It could be argued that services for mentally ill people are a special case, given the difficulty of achieving results and the great distress of severe mental illness, but it is just in such a field – where clients are least able to speak for themselves – that society needs to ensure that pressure is put on providers to improve services. The last two decades have seen some great and unexpected breakthroughs in terms of better services for people with learning difficulties. Through a new vision, a new philosophy, could the 1990s be a decade which sees major and unexpected gains for patients with mental illness?

Pharmaceutical research and innovation has been one positive force for change – in fact in psychiatry it has been of greater importance than in the treatment of physical illness, which takes many other forms. Even recently there have been some advances, particularly in the treatment of depression. The chances of new advances will be greatly improved by a positive attitude to joint development and to new kinds of understanding between professionals and researchers in the industry. The real ethical imperative is to increase the incentives for more effective services.

David Healy has produced a powerful but negative critique, taking the static approach to choice. His article may well cause unease, but it does not specify the choices and opportunities open to managers and professionals. The problems he sets out are real but secondary to the issue of how to speed up innovation.

Decisions about investment in a specific therapy have to start from a realistic view of the total costs of a service. Care for people with mental illness already cost £1.76 billion in 1989, even without allowing for expenditure of £500 million incurred by the National Health Service (NHS), the Department of Social Security and the Social Services for the support of elderly people with mental confusion and dementia. At current prices, total expenditure would be £2 billion (Office of Health Economics, 1989). The main items of spending are set out in Table 1. Over the longer term, hospital expenditure for in-patient care has risen fairly slowly, even though it still accounts for the largest single item. There has been a significant increase in support in community and primary care. Spending is high, and much of it is for long-term recurrent support.

Schizophrenia involves treatment costs as well as costs to patients and society through loss of working time. One recent estimate put these at £2.7 billion, without taking into account early mortality and