

# The relevance of recent advances in psychopharmacology for social psychiatry

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## INTRODUCTION

Psychopharmacology is a large and wide topic ranging from the molecular biology of centrally-active molecules to the social and economic aspects of psychotropic drug usage. Psychopharmacology and social psychiatry are complementary and synergistic, particularly with respect to treatments for the mentally ill. Accordingly, I have concentrated on the topic of drug treatments and their relevance to social psychiatry and I have selected 4 therapeutic areas: antipsychotic drugs, drugs used in dementia, antidepressants and anxiolytic/hypnotics.

## ANTIPSYCHOTIC DRUGS

This is probably the area of greatest overlap with social psychiatry, encompassing as it does the management of schizophrenic patients both in the community and in hospital. The introduction of antipsychotic medication coincided with a change in public attitudes towards the mentally ill. These drugs facilitated the running down of mental hospitals with the decanting of psychotic patients of varying degrees of severity into the community into accommodation and professional supervision of varying degrees of adequacy. The problem of non-compliance was partly solved by the development and introduction of the depot neuroleptics which at least made non-compliance overt. But the problem remained of treatment refractory patients, which comprise up to a

third of sufferers from schizophrenia. This portion of the patients places disproportionate strains on the community psychiatric services and leads to frequent, short but largely ineffectual hospital admissions and poor quality of life (Awad *et al.*, 1995). A further problem involved the high incidence of unpleasant and even severe unwanted effects of typical antipsychotic drugs, including long term effects such as tardive dyskinesia (Gerlach & Casey, 1988).

The increased availability of clozapine around 1990 was hailed in the USA and some European countries as the needed breakthrough. Despite unpleasant adverse effects including oversedation, excessive salivation and the risk of fits and the need for regular blood monitoring, clozapine did live up to its promise of helping around half of patients unresponsive to or intolerant of conventional antipsychotic medication and having a low incidence of extrapyramidal symptoms (EPS). Even so, a troublesome minority of unresponsive patients remains.

For the responders, life can indeed be changed (Meltzer, 1996). As the psychosis comes under control, and cognitive functioning improves (Meyer-Lindenberg *et al.*, 1997), the patient becomes susceptible to psychosocial measures including the possibility of rehabilitation and renewed occupational capacity. Negative as well as positive symptom patterns respond. Assessments of the wider benefits of clozapine therapy have included quite complex pharmacoeconomic analysis. These show that in the USA at least, substantial savings start to accrue by the second year of treatment. This is largely due to the reduced frequency and duration of in-patient care in the responders more than compensating for the relatively high cost of clozapine therapy plus blood monitoring in all patients tried on the drug.

Thus, an increase in the overall improvement rate in schizophrenia is feasible. Unfortunately, the ove-

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rall impact has been limited, which reflects the low usage of clozapine in many countries because of fears about its safety and doubts about the practicalities of its use. Cost is also a factor.

The search has thus continued for newer drugs with the enhanced efficacy and low EPS of clozapine but without the adverse effects, in particular the risk of agranulocytosis. So far, the results have been disappointing. Although drugs like risperidone, olanzapine, sertindole, quetiapine and ziprasidone have a lower incidence and severity of EPS, they have not been demonstrated to help otherwise treatment resistant patients. Nor are negative symptoms usually ameliorated as with clozapine. Psychopharmacologists have to admit that they have not yet identified the pharmacological properties of clozapine, which render it unique clinically.

The use of clozapine in the community is beset by particular problems. Medication is dispensed on a weekly, or later less frequent basis, contingent upon a normal blood reading. Difficult schizophrenic patients can thus terminate their clozapine therapy by merely refusing to give blood. The entire debate about compulsory treatment orders revolves around the need for patients to take their antipsychotic medication. It pays insufficient attention to the minority who are refractory to all forms of therapy (including psychosocial measures) or who refuse clozapine. We can only hope that in the short-term a safer clozapine look-alike is introduced, and in the longer-term that schizophrenia can be prevented. Meanwhile, schizophrenia remains a serious condition with major psychopathology but also excess mortality (Brown, 1997).

## DRUGS FOR DEMENTIA

Alzheimer's dementia affects many areas of higher mental functioning and takes a heavy toll of the elderly, their carers and health services (McKhann *et al.*, 1984; Gray & Fenn, 1993). It has been pointed out many times that demographic trends over the next 30 years will increase that burden quite substantially (Hermann, 1992). Consequently, when medications are developed which purport to effect some symptomatic improvement, great interest is raised both by professionals and lay individuals.

For many years, the search for drugs to treat Alzheimer's disease was largely unfruitful. It was difficult to note any improvements in a downward pro-

gression and any effects detected were too small to be of any clinical importance. The first drug to be licensed for dementia in the USA and France was tacrine. Other countries have not yet accepted that the risk/benefit ratio is adequate enough for licensing. Controversy attended tacrine with wide variations in assessments both of efficacy and of safety (Davis & Powchik, 1995).

Very recently, another compound of similar type has been introduced. Donepezil (Aricept) is a piperidine-based acetylcholinesterase inhibitor that enhances cholinergic transmission. One controlled trial has been published in full and one in abstract and they involved 600 patients with Alzheimer's dementia. Small improvements in the cognitive subscale of the *Alzheimer's Disease Assessment Scale* (ADAS) were obtained with donepezil which were significantly greater than those with placebo. However, more clinically relevant scales such as Clinical Global Impression of Change, Activities of Daily Living and Quality of Life ratings were less consistently improved or unchanged (Rogers *et al.*, 1996). It is claimed that donepezil maintains its therapeutic effect over time but equally there appears to be no delay in the natural progression of the disease.

The social implications of a successful symptomatic treatment for dementia would be profound. It would enable patients to be kept longer in the community and lighten the burden of carers. But compounds acting on cholinergic pathways alone will probably have a very limited role to play as Alzheimer's dementia is much more than dropout of cholinergic neurones. The utilisation of psychosocial techniques of therapy will continue to be more important than pharmacotherapy.

Much effort is being expended in elucidating the pathological mechanisms in Alzheimer's disease and much success has already been achieved with respect to abnormal molecules and their accumulation. Prevention of Alzheimer's pathology would be a major breakthrough and could certainly occur within the next decade or two.

## ANTIDEPRESSANTS AND MOOD REGULATORS

Depression is amongst the commonest mental disorders. It is typically recurrent and episodic but may become chronic. Depressed patients tend to have poor physical, social and role functioning, poor perceived current health, and marked bodily pain (Wells

*et al.*, 1989). Indeed, these disabilities are comparable to or even worse than those associated with major chronic medical disorders such as angina, arthritis or diabetes. For example, depressed patients actually spend more days in bed.

The economic burden of depression has been variously estimated. One study came up with a total cost in the USA for 1990 of over 40 billion dollars (Greenberg *et al.*, 1993).

In this and the next area, the prescription of psychotropic drugs is essentially the province of the primary care practitioner. In the UK, for instance, only 10% of depressed patients who consult their general practitioner are referred on to a psychiatrist. Unfortunately, this is the area where least progress has been made despite the steady introduction of new drugs. What progress there is relates to more tolerable side-effect profiles rather than to enhanced efficacy. However, the data on efficacy are incomplete: very few studies have addressed the question of which drug to try should the first antidepressant fail (Sokolov & Joffe, 1995). That this is an important problem is evidenced by the databases for new antidepressants which generally show a response rate (defined as a halving of rating-scale score) of 60-75% as against a placebo response rate of 30-40% and even on occasion 50-60%. The «window of opportunity» in which to show an antidepressant's efficacy is thus disconcertingly small, a mere peephole! It is hardly surprising that it is rare to show a significant difference in efficacy between two active antidepressants, and when it does occur it may be a chance finding.

The side-effect profiles of the newer antidepressants are generally superior to those of the older drugs. This should not cause surprise after all if a new drug early in development showed a poor side-effect profile, its development would be stopped. However, the search for selectivity of action has had two outcomes with respect to side-effect profile. Firstly, drugs like the serotonin reuptake blockers (SRIs) increase central and peripheral serotonin (5-HT) and this in itself will produce a spectrum of adverse effects such as nausea, dizziness and disturbances in appetite and sexual function. This is despite selectivity avoiding anticholinergic effects such as dry mouth and constipation, anti-adrenergic effects like postural hypotension and antihistaminic effects such as drowsiness. Indeed, combinations of actions may even provide a better side-effect profile. For example, a drug like nefazodone combining reuptake block-

kade with 5-HT<sub>2</sub> receptor blockage has much less effect on sexual function and sleep patterns.

So the pendulum has swung back and the newest antidepressants combine two or more functions. Thus, venlafaxine blocks both 5-HT and noradrenaline (NA) reuptake and mirtazepine blocks alpha-2 adrenergic receptors as well as increasing 5-HT transmission. The exception is reboxetine which is a fairly selective NA reuptake blocker.

A very consistent trend has been the advocacy of longer and longer treatment durations. Twenty years ago, 3 months was about the minimum recommended, 10 years ago 6 months, and now many would keep a patient on antidepressants for a year or more. And patients with multiple episodes are recommended to stay on antidepressants indefinitely and at more or less full dosage.

The implications for public health concern the effects of these medications on functions such as driving, operating dangerous machinery, taking important decisions, remembering day-to-day matters, and so on. The tricyclics are notorious for their adverse cognitive effects as well as interactions with alcohol and danger in overdose. Newer antidepressants are much safer in this regard. At another level, the extraordinary interest shown in fluoxetine and its advocacy by both professional and lay commentators that it deserved widespread use betrays public ignorance about the therapeutic role of antidepressants and blurs the distinction between normality and its limits on the one hand and a clinically distinct abnormality on the other.

New drugs, or at least old drugs with a new role, have also been introduced as mood stabilisers, to lessen the frequency and severity of mood swings in bipolar, manic depressive patients. But lithium, the doyen of mood stabilisers, has again become a focus of controversy with denials that it has any proven efficacy on the one hand and contrary claims that it is almost a panacea on the other. Its toxicity is also a matter of concern, particularly in combination with antipsychotic drugs (Goldman, 1996). It seems fairly clear that the burden of bipolar illness is still with us and the long-term prognosis in the more serious or treatment-resistant cases is no better than that of schizophrenia (Coryell *et al.*, 1993). The advent of carbamazepine and valproate sodium has not provided a total solution and polypharmacy is increasingly resorted to. Newer anticonvulsants being assessed for mood stabilizing properties include gabapentin and lamotrigine.

## TRANQUILLISERS AND HYPNOTICS

Marked country-by-country variations are noticeable in tranquilliser use, some countries like France having 3-4 times the prescription rate of say, the UK (Quera-Salva *et al.*, 1991). Public and professional attitudes vary widely but slowly concern is mounting even in high-prescribing countries. The main concern is the risk of dependence on benzodiazepines (Kan *et al.*, 1997).

Another area of concern relates to drugs, driving and the economic consequences (Leger, 1994). The correlation between the level of alcohol concentration and driving ability and accident rate is sufficiently strong to dispense with clinical evidence of inability to drive. Thus, testing positive on the breathalyser is itself sufficient proof of excessive alcohol and impaired ability to drive, the latter not having to be established separately. With psychotropic drugs, however, the correlation between plasma concentration and psychomotor impairment is a weak one. Thus, evidence of impaired ability to drive has to be convincing for a conviction. It is tempting, therefore, to suggest that roadside testing for drugs — licit and illicit should be developed as a parallel technique to a breath alcoholmeter. But although the technology might be forthcoming the interests of justice would not be served in trying to make drugs and driving into an absolute offence.

On the hypnotic front, two developments have occurred more or less in parallel. Duration of action or at least, elimination half-lives have become less and less, thus flurazepam 48 hours, nitrazepam 36 hours, flunitrazepam 24 hours, temazepam 12 hours, triazolam 3 hours. The newer compounds include zopiclone 5 hours, zolpidem 2 hours and (in development) zaleplon 1 hour. Residual effects the next day are minimal or undetectable with the recommended doses of the short-acting compounds. Also, compounds have become more selective, often like zolpidem, only binding to subpopulations of benzodiazepine receptors (Besnard *et al.*, 1996). This may confer on the newer molecules properties such as less interference with sleep patterns, less rebound and withdrawal and perhaps even less abuse potential.

Despite this hypnotics are widely used, particularly in the elderly, surveys show that 20-30% of elderly in institutions take sleeping tablets regularly and as many as 10-20% of elderly in the community do likewise (Morgan, 1990). Surely this is unnecessary. Unfortunately, sleep and insomnia are topics which are

generally ill-taught to doctors because they are not the province of any one specialist. Doctors are not instructed how to assess a patient who claims to suffer unsatisfying sleep. Nor are they taught to differentiate the commoner causes of insomnia. Instead, they reach for their prescription pad. However, guidelines do exist for the management of patients with insomnia and non-pharmacological measures are often sufficient (Lader, 1992).

## OVERVIEW

The past two decades have been a period of consolidation for the practical therapy of various psychiatric conditions. Even where new classes of compound with new indications have been introduced, the science behind the practice has been well-established: an example is the treatment of dementia.

The major problem is the gap which still exists between the basic neurobiology of the brain and our understanding of the mechanisms of action of the whole range of psychotropic drugs, most of which were discovered by accident. On the one hand, the brain remains largely *terra incognita*, a dauntingly complex assembly of millions of constituent entities, the neurones. On the other hand psychiatric disorders comprise a heterogeneous group of conditions, with abnormal symptoms and behaviour but not signs. Theories of pathogenesis range from the molecular to the analytic. The psychotropic drugs should provide a bridge between the laboratory and the clinic but the construction is flimsy and threatens to collapse under the weight of theory. For example, the characteristics of the benzodiazepine-GABA-chloride ionophore-receptor are known in exquisite detail but how effects on this complex translate into an anxiolytic or an anticonvulsant effect remain unclear.

What are the implications for Social Psychiatry? Quite simply, the empirical and eclectic approach combining the best of all therapies has to be relied on in the present and the foreseeable future, as in the past. Practical studies in the tradition of «evidence-based medicine» are needed to evaluate various treatment strategies. In that way, we can do the best for our patients, their carers and for Society in general.

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