British Journal of Psychiatry (1988), **152**, 140–147

Correspondence

Editor: Greg Wilkinson

Contents: The need to compare the effectiveness of the available antidepressant drugs/Pathology, phenomenology, and the dopamine hypothesis of schizophrenia/Behavioural Psychotherapy in General Practice – a response/Heroin abuse in India/No fixed abode/The dexamethasone suppression test in depressed Kuwaiti patients/Chronic schizophrenia and long-term hospitalisation/Incest and anorexia nervosa: what is the link?/Diethylpropion and psychosis.

The Need to Compare the Effectiveness of the Available Antidepressant Drugs

SIR: Since the clinical discovery of the antidepressant activity of imipramine, laboratory investigations have made available several methods – tailored on imipramine – which are considered predictive of human depression. These methods have resulted in an impressive number of new antidepressant agents which encompass a variety of mechanisms, including selective inhibition of noradrenaline uptake (maprotiline), serotonin uptake (citalopram), or dopamine uptake (amineptine). Other agents show the capacity to inhibit both noradrenaline and serotonin uptake (imipramine, amitriptyline), or both noradrenaline and dopamine uptake (nomifensine). Some others do not significantly affect monoamine uptake, such as iprindole or mianserin, or may even selectively increase the uptake of serotonin, such as tianeptine.

When given over long periods, the antidepressant agents, independently of their acute effect on monoamine uptake, may result in reduced sensitivity of β-adrenergic receptors coupled with adenylcyclase, reduced density of $5HT_2$ receptors, and enhancement of mesolimbic dopaminergic transmission (for review see Garattini & Samanin, 1984, 1987; Heninger & Charney, 1987).

Several other effects have been described for some, but not all, of the antidepressant agents. Examples are a decrease in the density of $GABA_A$ receptors, an increase in $GABA_B$ binding, and an interaction with the central benzodiazepine receptors.

There is no doubt, therefore, that about 20 antidepressant agents may claim to differ considerably. In contrast to this variety of biochemical effects, clinical trials on antidepressant agents show a stereotyped picture which essentially does not support such differences, but points more to a generally equivalent activity. Typically, most clinical trials will show that about 30% of the patients respond to placebo, 30% are relatively resistant, and the rest show statistically significant measurable benefits. Almost all drugs appear to be similar in the intensity of action and in the lag-time (3–4 weeks) necessary to achieve measurable improvement on one or more of the available rating scales for depression.

Despite hundreds of clinical trials and many more 'publicity' claims, most psychiatrists will admit that there is no real scientific basis for any *a priori* selection of a given drug for the treatment of any one depressed patient. There is instead a reasonable consensus on differences between antidepressant agents as regards their side-effects (Bollini *et al*, 1984; Blackwell, 1987).

How can this apparent discrepancy between the uniformity of clinical effects and the differences in the mechanism of action of antidepressant drugs be explained? We need more clinical trials with groups larger than those commonly used – and therefore with more potency in detecting differences in activity of different drugs – and perhaps a more sophisticated experimental design. It seems useful, for instance, to study the proportion of patients that is resistant to a given antidepressant agent, to establish whether there is any consistent pattern of selective sensitivity or of cross-resistance.

A clinical answer to these questions has long been due, since it is only through clinical evaluation that light will be cast on the significance of experimental work. Should adequate clinical trials prove the equivalence of the various antidepressant agents, laboratory work will have to look harder for common denominators which may not necessarily involve the action of antidepressant agents on monoaminergic systems. If, instead, differences between drugs can be reliably confirmed, then laboratory efforts to develop new drugs could be

potentiated. The importance of solving this problem may call for an unprecedented European-scale collaboration.

SILVIO GARATTINI
Istituto di Richerche Farmacologiche "Mario Negri"
Via Eritrea 62
20157 Milano
Italy

References

BLACKWELL, B. (1987) Newer antidepressant drugs. In *Psychopharmacology: The Third Generation of Progress* (ed. H. Y. Meltzer). New York: Raven Press.

BOLLINI, P., COTECCHIA, S., DE BLASI, A., ROMANDINI, S. & TOGNONI, G. (1984) Drugs: guide and caveats to explanatory and descriptive approaches. II. Drugs in psychiatric research. *Journal of Psychiatric Research*, **18**, 391–400.

GARATTINI, S. & SAMANIN, R. (1984) Drugs: guide and caveats to explanatory and descriptive approaches. I. A critical evaluation of the current status of antidepressant drugs. *Journal of Psychiatric Research*, **18**, 373–390.

—— & —— (1987) Biochemical hypothesis on antidepressive drugs: a guide for clinicians or a toy for pharmacologists? *Psychological Medicine* (in press).

HENINGER, G. R. & CHARNEY, D. S. (1987) Mechanism of action of antidepressant treatments: implications for the etiology and treatment of depressive disorders. In *Psychopharmacology: The Third Generation of Progress* (ed. H. Y. Meltzer). New York: Raven Press.

Pathology, Phenomenology, and the Dopamine Hypothesis of Schizophrenia

SIR: The recent review by McKenna (*Journal*, September 1987, **151**, 288–301) is one more of a growing spate of hypothetical papers attempting to reconcile various pathological, clinical, and neurochemical findings into a unitary hypothesis for schizophrenia (Weinberger, 1987; Smajuk, 1987). Since there is no pretext for assuming that schizophrenia is a unitary and homogenous disease process, such exercises seem dangerous in that they limit rather than expand the avenues for research into the biology of schizophrenia. In addition, the three reviews cited make a case for differing unitary hypotheses; they beg the validity of each others claim's, and taken together argue for aetiological heterogeneity.

Notwithstanding this, there are also some specific points in Dr McKenna's argument requiring clarification. The hypothesis relies heavily on the assumption that the dopamine hypothesis in schizophrenia is unchallenged, ignoring the serious drawbacks to the dopamine theory (Hornykiewicz, 1982). In addition, the hope by Dr McKenna that the D_2 receptor binding seen in earlier single dose PET studies would be confirmed have not been realised. Using a more selective ligand (11C raclopide) and a more accurate semi-quantitative method, Farde *et al* (1987) were unable to show increased D_2 receptor numbers *in vitro* in drug-free schizophrenic patients. Finally, the heavy reliance of Dr McKenna's synthesis on prefrontal cortical dopamine and hippocampal dopamine systems extrapolated from animal studies is spurious, since in human tissue the levels of dopamine in these regions is negligible (Adolfsson *et al*, 1979) and D_2 receptor binding sites are not detectable *in vitro* or *in vivo* (DeKeyser *et al*, 1985, 1987), and, indeed, current attempts to identify a mesocortical dopamine system in man remains fruitless.

While Dr McKenna's article is an elegant review of the current status of the biology of schizophrenia, since the neurochemical substrates incorporated in his theory have not been demonstrated in man, care should be taken in its interpretation.

ROBERT W. KERWIN
Institute of Psychiatry
Denmark Hill
London SE5 8AF

References

ADOLFFSON, R., GOTTFRIES, G. C. & ROOS, E. (1979) Postmortem distribution of dopamine and homovanillic acid in human brain, variations related to age and a review of the literature. *Journal of Neurology*, **45**, 81–105.

DEKEYSER, J., DEBACKER, J. P., EBINGER, G. *et al* (1985) Regional distribution of the D_2 dopamine receptors in the mesoencephalic dopamine neuron system of human brain. *Journal of Neurological Science*, **43**, 1068–1071.

——, EBINGER, G. & HERREGODIS, P. (1987) Pathophysiology of akathisia. *The Lancet*, *ii*, 336.

FARDE, L., WIESEL, F.A., HALL, H. *et al* (1987) No D_2 receptor increase in PET study of schizophrenia. *Archives of General Psychiatry*, **44**, 671–672.

HORNYKIEWICZ, O. (1982) Brain catecholamines in schizophrenia. A good case for noradrenaline. *Nature*, **299**, 484–486.

SCHMAJUK, N. (1987). Animal models for schizophrenia. The hippocampally lesioned animal. *Schizophrenia Bulletin*, **13**, 317–327.

WEINBERGER, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry*, **44**, 660–669.

SIR: Dr Kerwin raises points concerning the existence of human limbic and cortical dopamine projections, the validity of the dopamine hypothesis, and the unitary nature of schizophrenia itself.

The existence of dopamine projections to the septo-hippocampal system and prefrontal cortex is generally accepted in primates, based on biochemical (e.g. Bjorklund *et al*, 1978) and histological (Porrino & Goldman-Rakic, 1982) findings. In man, the relevant evidence has been summarised by Camus *et al* (1986): both regions contain appreciable amounts of dopamine and its metabolites, which are significantly reduced in Parkinson's disease. Substantial numbers of D_2 receptors have been found in the human hippocampus. In the human prefrontal cortex, dopaminergic nerve terminals have been