

## COMMENT

## What do 5HT Re-uptake Inhibitors do in Obsessive-Compulsive Disorders?

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In 1964, Ciba Geigy chlorinated imipramine, in an attempt to produce a more effective antidepressant (Healy, 1990). Chlorimipramine, however, was not obviously better. Ciba went on to produce a parenteral preparation of clomipramine, which led to its being given in large doses intravenously in a number of single-blind and non-placebo controlled studies for phobic and obsessional states (Capstick 1971 and 1973; Rack 1973; Marshall and Micev 1973; Walter 1973; Waxman 1973). It appeared to be in some way anxiolytic—if anything more anti-phobic than anti-obsessional—findings that have been replicated recently (Johnston *et al.*, 1988). There had been a prior hint of such an action. In 1967, Cordoba and Lopez-Ibor reported that clomipramine induced a state of indifference in subjects troubled by intrusive thoughts.

Clomipramine was subsequently marketed for depressions with obsessional features and for obsessional states—successfully. It appears to have become widely accepted that clomipramine has some specifically anti-obsessional activity. It also seems to have been accepted that this action of clomipramine derives from its 5HT re-uptake inhibiting properties. This has led to the subsequently introduced specific 5HT re-uptake inhibitors being researched and marketed for obsessional indications.

The first attempt to question the specificity of clomipramine to OCD came as a result of a study by Marks *et al.* (1988). They found that, quite apart from any effects on mood, clomipramine had a non-specific and relatively minor beneficial effect in obsessional states (Marks *et al.* 1988). Marks *et al.* (1988) also suggested that a large part of the impression that clomipramine and other 5HT re-uptake inhibitors were in some way specific for obsessional disorders derived from the fact that these were the only drugs on which proper studies had been conducted. The evidence simply did not

exist, they proposed, to suggest that other drugs were not as effective. In particular, there had not been a proper study of neuroleptics in OCD, even though prior to the introduction of clomipramine, neuroleptics appear to have been the standard treatment for OCD (Healy, 1990).

Since then, while there is still some dispute about just how useful clomipramine and the more specific 5HT re-uptake inhibitors are in OCD, there is an emerging consensus following further studies with clomipramine (Leonard *et al.*, 1989), fluvoxamine (Perse *et al.*, 1987; Goodman *et al.*, 1989) and fluoxetine (Jenike *et al.*, 1989) that these drugs, in contrast to the non-5HT re-uptake inhibiting antidepressants, such as desipramine, are of use in OCD, over and above any effects they may have in resolving a concomitant depressive disorder. What use and how are their effects brought about?

### 5HT AND ANXIETY

Unless the 5HT re-uptake inhibitors are of use in OCD, by virtue of their not being specific to the 5HT system, they must presumably act by altering the concentration of 5HT at one of the 5HT receptors. The development of specific drugs for 5HT receptor subtypes suggest that a common characteristic of drugs active on the 5HT system is one of anxiolysis (Healy, 1991).

The partial agonists for the 5HT-1a site, buspirone, gepirone, ipsapirone and flesinoxan appear to possess significant anxiolytic activity in a variety of animal models of anxiety (Glennon, 1990), although a case has more recently been made that such compounds may be antidepressant (see Healy, 1991). Of interest is a report that buspirone may be of use in obsessional states (Pato *et al.*, 1991). The 5HT-1c agonist, mCPP, appears, in contrast, to be anxiogenic and indeed makes obsessional disorders worse (Zohar *et al.*, 1988).

In the case of the 5HT-2 receptor, all current neuroleptics, in addition to having common actions on D-2 receptors, block 5HT-2 receptors (Glennon, 1990). While it is not clear just what this action contributes to the therapeutic effectiveness of neuroleptics, the recent demonstration that drugs biased more toward 5HT-2 than D-2 receptor antagonism may be of benefit in schizophrenia (Gelders 1989) suggest at least a potential 'tranquillising' effect of such an action.

More recently 5HT-3 receptor antagonists have been developed and these also appear to have an anxiolytic profile that differs from that of the benzodiazepines (Costall *et al.*, 1988; Jones *et al.*, 1988). The first clinical trial of a 5HT-3 receptor antagonist was reported, at the Summer meeting of the British Association for Psychopharmacology in 1990, as being superior to placebo in the treatment of generalised anxiety disorder (Lecrubier *et al.*, 1990).

These findings are consistent with the early behavioural work of Gray (1982), which suggested that the 5HT system appears to play a significant part in the mediation of anxiety. There has, in contrast, hitherto been little hint from basic research of any function mediated through the 5HT system, whose derangement might lead to OCD or whose modulation by drugs specific to the 5HT system might provide the basis of a specific anti-obsessional rather than a non-specific anxiolytic action on the part of 5HT reuptake inhibitors in OCD.

#### A 5HT-DOPAMINE INTERFACE?

A possible site of action of 5HT reuptake inhibitors in OCD lies in the substantial overlap there appears to be between the 5HT and dopaminergic systems. Both 5HT-3 receptor antagonists and D-2 receptor antagonists are anti-emetic (Costall *et al.*, 1988). Both neuroleptics, 5HT re-uptake inhibitors and 5HT-1a agonists increase prolactin levels. Both neuroleptics and fluoxetine have been reported to produce akathisia (Lipinski *et al.*, 1989). 5HT-1d receptors are found principally in the basal ganglia (Peroutka, 1988). 5HT-3 receptor antagonists modulate mesolimbic dopamine release (Tricklebank, 1989). There are grounds, therefore, to believe that drugs active on the 5HT system may modulate dopaminergic systems.

Of note is the fact that the first report of a possible benefit of clomipramine in OCD suggested that it helped by producing, after several weeks, a state of indifference to intrusive thoughts and

imagery (Cordoba and Lopez-Ibor, 1967). This has been echoed by subsequent reports (Toates, 1990). I have argued, elsewhere (Healy, 1989 and 1990b), that the beneficial effects of neuroleptics also consist of an induction of a state of psychic indifference—although one that appears to come on far more rapidly than that induced by clomipramine, albeit with the draw-back of being often accompanied by counterproductive side effects. Without more precise phenomenological descriptions from patients, it is not possible to say whether the effects of 5HT reuptake inhibitors differ from those of neuroleptics, other than in the time course of their onset. What perhaps can be said is that the phenomenology of 5HT-induced anxiolysis differs from that of benzodiazepine anxiolysis—so much so that it may be somewhat misleading to characterise both as anxiolytics, without some further specification of what that means.

A recent study by McDougle *et al.* (1990) is of interest here. This group added in a modest dose of pimozide or thioridazine to the medication of 17 subjects with obsessive-compulsive disorder, who were unresponsive to either fluvoxamine alone or the combination of fluvoxamine and lithium. They found a significant response in 9 of the 17 subjects.

#### A 5HT DEFECT IN OCD?

There has been a trend in recent publications to interpret the fact that 5HT reuptake inhibitors are of some use in OCD as implying a defect in the 5HT system in this disorder (Jenike *et al.*, 1989; Goodman *et al.*, 1989; McDougle *et al.*, 1990). This runs counter to the evidence that these drugs, or at least clomipramine, are broadly anxiolytic (Johnston *et al.*, 1988; Healy, 1990) and reports from patients that the benefit to be derived from them is more in the nature of 'tranquillisation' than an outright abolition of the disorder (Toates, 1990; Cordoba and Lopez-Ibor, 1967).

This seems part of a general trend in psychopharmacology: Where a drug proves useful in a disorder, the inference is made that there must therefore be some defect in the system on which this drug works. This type of hypothesising led to the dopamine hypothesis of schizophrenia, despite the evidence that neuroleptics on the one hand reduce agitation generally and on the other reduce it in schizophrenia, which can be taken to imply that the dopamine system must be working, as it should do, in schizophrenia (Healy, 1989).

A further example of this trend in the case of OCD can be found in the above mentioned paper by McDougle *et al.*, (1990), who interpreted the finding that neuroleptics may be useful in OCD to indicate that there may be defects of both dopaminergic and serotonergic systems in the disorder. However another possibility is that fluvoxamine produces a certain amount of psychic indifference and that this may be usefully supplemented by neuroleptic induced indifference in some instances—this would be especially likely where the neuroleptic was sensitively administered, so that side effects were avoided. If this latter explanation is correct, then neither defects in the 5HT or dopaminergic system need be implied by response to these drugs.

This tendency to assume that the efficacy of a drug implies that it must be correcting some specific psychophysiological disturbance seems to be stronger in psychopharmacology than in other branches or medicine, where the usefulness of compensatory or downstream therapies, such as the thiazide diuretics in heart failure and both steroids and non-steroidal anti-inflammatory agents in a variety of conditions occasions no corresponding rush to offer hypotheses of specific deficits. One factor at play here may be that at present, in psychopharmacology, the linking of particular clinical conditions to specific neurotransmitter deficits offers a basis for a clear research strategy and the possibility of attracting funding. From this point of view, while at present the more parsimonious hypothesis might be that drugs active on the 5HT system exert a non-specific beneficial effect in OCD, the hypothesis of a specific 5HT defect in the disorder has been more timely.

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