The marketing of 5-hydroxytryptamine: depression or anxiety?

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Annotation

The Marketing of 5-Hydroxytryptamine: Depression or Anxiety?

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The discovery that tricyclic antidepressants blocked the re-uptake of both noradrenaline and 5-hydroxytryptamine (5-HT) was a significant step on the road to the development of the monoamine hypotheses of depression (Healy, 1987). The subsequent demonstration that the de-aminated metabolites of amitriptyline and imipramine, nortriptyline and desipramine, were antidepressants tilted the balance toward noradrenaline as the pertinent neurotransmitter, as these latter drugs were clearly inhibitors of noradrenergic rather than 5-HT uptake.

In 1964, Ciba Geigy chlorinated imipramine, in an attempt to produce a more effective antidepressant. However, not only was the resulting chlor-imipramine no more effective, it seemed to be markedly more toxic (Pinder, 1987), so much so that it was only licensed by the Food and Drugs Administration (FDA, Washington, DC) for use in the USA in 1990.

During the 1970s, Astra consulted Arvid Carlsson regarding the development of an antidepressant. He noted that, although a rational appraisal of the situation might suggest that desipramine and nortriptyline must be the core tricyclic antidepressants, clinicians appeared to prefer amitriptyline and imipramine (Carlsson, 1990). He pinpointed 5-HT re-uptake blockade as the effect that tertiary amine tricyclics have which their metabolites do not, and suggested accordingly that drugs specific for 5-HT re-uptake inhibition should be developed and tested for antidepressant efficacy. Clomipramine, then the most specific 5-HT re-uptake inhibitor, was used as a basis to design zimelidine, which was marketed in the early 1980s. Clinical trials suggested that it was an antidepressant but it was later withdrawn because of side-effects. Since then other 5-HT re-uptake inhibitors have followed.

Meanwhile, given the dominance of amitriptyline and imipramine in clinical settings, Ciba Geigy were faced with a marketing problem for clomipramine. They produced a parenteral preparation of clomipramine and encouraged prescribers to look at alternative indications. This 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 (for review see Healy, 1990). It appeared to be in some way anxiolytic – if anything more anti-phobic than anti-obsessional. However, the market for phobic/anxious depressions was at this time targeted by producers of monoamine oxidase inhibitors (MAOIs), whose sales had slumped as a result of both the MRC comparative trial of antidepressants in 1965 and the recognition of the 'cheese effect'. Clomipramine was subsequently marketed as anti-obsessional and it was for this indication that it was licensed by the FDA in 1990.

Whether the promotion of clomipramine as anti-obsessional was as market orientated as this analysis may suggest is uncertain, but the outcome today is that it and other 5-HT re-uptake inhibitors are marketed as specific for obsessive–compulsive disorders (OCD). It has been suggested that a large part of this impression derives from the fact that drugs which block 5-HT re-uptake are almost the only ones to have been studied properly in OCD (Marks *et al*, 1988). There has not been, for example, a proper study of neuroleptics in OCD, although prior to the introduction of clomipramine, neuroleptics appear to have been the standard treatment for OCD.

While there is some dispute about just how useful clomipramine is in OCD (Marks *et al*, 1988), there is an emerging consensus that it, and other 5-HT re-uptake inhibitors, in contrast to the non-5-HT re-uptake inhibiting antidepressants, are of some use. Are 5-HT re-uptake inhibitors then in some way anxiolytic rather than, or in addition to, being antidepressant? To try and focus further on this issue, I consider firstly the evidence in favour of a necessary action of antidepressants on 5-HT systems, and secondly the likely profiles of action of a number of recently developed 5-HT receptor agonists and antagonists.

Antidepressants and 5-HT

By the mid-1980s increasing interest had developed about a possible role of 5-HT receptor functioning in depression. There were several reasons for this. Firstly, it had been shown that antidepressant-induced changes in adrenergic receptors did not take place, unless there was an intact 5-HT system (Sulser, 1984). Secondly, antidepressant treatment was shown either to sensitise post-synaptic 5-HT_2 receptors (De Montigny *et al*, 1988; Healy *et al*, 1985) or to influence receptor number (Cowen *et al*, 1986). Thirdly, it was also known from animal work that lithium has

pre-synaptic effects on the 5-HT system and sensitises post-synaptic 5-HT receptors (Price *et al*, 1990). In an attempt to study this effect in humans, De Montigny *et al* (1981) and Henninger *et al* (1983) added lithium to the tricyclic antidepressant regimes of treatment-resistant depressives and reported a rapid and remarkable improvement in mood. This was put down to the ability of lithium to sensitise 5-HT_2 receptors, with the implication that effective antidepressant treatment in general worked by this means (De Montigny *et al*, 1988).

Finally, based on this effect of lithium, a variety of treatment cocktails have been developed; the most notable of these have been the combinations of clomipramine, L-tryptophan and lithium (Hale *et al*, 1987) and phenelzine, L-tryptophan and lithium (Barker *et al*, 1987). A common feature of these regimes has been an attempt to selectively influence the 5-HT system (Leonard, 1988). The recent withdrawal of L-tryptophan from the market has led, it would seem, to a number of patients on such regimes relapsing (Ferrier *et al*, 1990).

It is, however, far from certain that there is any specific effect of manipulating the 5-HT system in treatment resistance. It is almost impossible to compare adequately the addition of lithium to the effect of adding another antidepressant or neuroleptic to an apparently ineffective regime. The initial claims in favour of lithium did not capture attention by virtue of any proven specificity to the 5-HT system or even to treatment resistance, but rather by a seemingly dramatic induction of clinical change – within 48 hours. This in turn appears to have done more than anything else to confer the impression of specificity to the 5-HT system. Such rapid responses are not now cited and would seem to have been a chance phenomenon.

In one of the largest studies of treatment resistance Shapira *et al* (1988) gave clomipramine and/or lithium to a group of 12 electroconvulsive therapy-resistant depressed subjects but found that the mean time to recovery was 2.2 months. Such delay hardly suggests a specific role for manipulations of the 5-HT system. Reviewing all studies in the area, Price (1989) has recently concluded that lithium augmentation brings about a response in around 50% of cases and that the mean time to response may be about three weeks. This suggests that there may be little difference between adding lithium to an ineffective regime or adding another antidepressant, such as mianserin, or a judicious dose of a neuroleptic.

Treatment-resistant subjects are also a difficult group from which to extrapolate. It can perhaps be noted that what in effect was the first study of lithium augmentation was conducted by Lingjaerde *et al* in 1974, on 45 clearly endogenously depressed subjects, who were randomly given a tricyclic antidepressant and lithium or a tricyclic antidepressant and placebo. They concluded that lithium appeared to enhance the effects of tricyclic antidepressants but the differences between lithium and placebo groups were not significant.

5-HT receptor agonists and antagonists

The initial monoamine depletion hypotheses gave way in the late 1970s to a variety of adrenergic receptor hypotheses, notably the alpha-2 supersensitivity and the post-synaptic beta receptor supersensitivity hypotheses (Healy, 1987). Comparable hypotheses, implicating 5-HT receptors, were held up by technical difficulties in identifying receptor subtypes.

In 1979, using radioligand binding methods, Peroutka & Snyder distinguished between a 5-HT_1 and 5-HT_2 receptor. The development of selective agonist and antagonist radioligands to further distinguish between 5-HT receptor subtypes has subsequently produced a profusion of new receptor subtypes. Some of these experimental compounds have been successfully refined further for use in man. It is with the behavioural profile of these latter drugs that we are now concerned.

From Table 1 it will be clear that there is some overlap between the 5-HT_{1c} receptor and the 5-HT_2 receptor; it seems likely that these may in future be designated as 5-HT_{2a} and 5-HT_{2b}. A 5-HT_{1b} receptor exists only in animals. A 5-HT_{1d} and 5-HT_4 receptor have been proposed but at

Table 1
5-HT receptor agonists and antagonists

	Agonist	Antagonist
5-HT_{1a}	8-OHDPAT	Methsergide
	Buspirone	Spiperone
	Gepirone	Propranolol
	Ipsapirone	
	Flesinoxan	
5-HT_{1c}	mCPP	Ritanserin
		Mianserin
5-HT_2	d-LSD	Ketanserin
		Ritanserin
		Risperidone
		Mianserin
		Trazodone
		All neuroleptics
5-HT_3	2-methoxy-5-HT	Ondansetron
		Granisetron
		Zacopride

This table is based on the guidelines of the serotonin receptor club nomenclature committee, December 1989.

present remain radiolabelled binding sites only, without an obvious functional correlate (Peroutka, 1988; Gonzalez-Heydrich & Peroutka, 1990).

If the antidepressant action of 5-HT re-uptake inhibitors is mediated through the 5-HT system – it is not a foregone conclusion that this is necessarily the case – then presumably this must be effected indirectly by altering the availability of 5-HT to one or other of these receptors. If 5-HT has a role in either depression or anxiety, it might be expected then that drugs acting more directly on one or other of these receptors would be either clearly anxiolytic or antidepressant.

5-HT_1

The picture as regards drugs active at the 5-HT_1 site is complex. The recently introduced buspirone, which is a partial agonist for the 5-HT_{1a} site, has been marketed as an anxiolytic. Since its introduction a number of more specific agonists for this site have been developed – ipsapirone, gepirone and flesinoxan. These compounds all show efficacy in animal screening tests for anxiolytic compounds. They appear, however, to have a significantly different profile to the benzodiazepines, being inactive in some of the screening tests used to detect benzodiazepine-type anxiolysis (Gonzalez-Heydrich & Peroutka, 1990; Glennon, 1990).

In contrast to buspirone, however, flesinoxan and ipsapirone, which also appear in early pre-release studies to be anxiolytic in man, are currently being tested as antidepressants. One rationale offered for this stems from the finding that the prototypical 5-HT_{1a} agonist, 8-OHDPAT, potently reverses some of the behaviours in animals that constitute learned helplessness (Gonzalez-Heydrich & Peroutka, 1990). As this is a model of depression rather than anxiety, the inference drawn has been that 5-HT_{1a} agonists might be antidepressant. There are other ways, however, to interpret this switch in indications which will be developed below.

5-HT_2

In the case of the 5-HT_2 receptor, it appears that the hallucinogenic effects of LSD and mescaline are mediated through the 5-HT_2 receptor (Davis, 1987). These effects can be blocked in animals by ketanserin and ritanserin (Davis, 1987). There is also some evidence that 5-HT_2 antagonists such as ritanserin or risperidone are of benefit in schizophrenia (Gelders, 1989). All current neuroleptics, furthermore, in addition to having common actions on D-2 receptors, also block 5-HT_2 receptors (Glennon, 1990). The difference between their actions on these two receptor systems is that the doses used clinically for the different neuroleptics correlate closely with their ability to bind to D-2 receptors, whereas this is not so in the case of their binding to 5-HT_2 receptors.

The presence on this list of mianserin and trazodone, which have both been marketed as antidepressants, is of interest. In the case of mianserin, however, this agent also has a significant effect on adrenergic receptors. In the case of trazodone, of interest is the fact that one of its derivatives – mCPP, which is an agonist for the 5-HT_{1c}/5HT_{2b} receptor – is potently anxiogenic (Zohar *et al*, 1988).

5-HT_3

Several years ago, it appeared that 5-HT_3 receptor antagonists might be effective in schizophrenia, based on tests in animal models of schizophrenia (Costall *et al*, 1988). This led to the development of a number of compounds such as Glaxo's ondansetron, Smith Kline Beecham's granisetron and others which are shortly due to come onto the market. It has since become clearer that 5-HT_3 receptor antagonists have an anxiolytic profile that differs from that of both benzodiazepines and 5-HT_{1a} agonists (Jones *et al*, 1988).

Of particular note is that 5-HT_3 receptor antagonists appear, in animals, to reverse effectively the anxiety that is induced by benzodiazepine discontinuation (Costall *et al*, 1990).

The marketing of 5-HT

In addition to perhaps 20 to 30 new 5-HT re-uptake inhibitors, there are a great number of new compounds, with relatively specific actions on the 5-HT system, that have begun to appear on the market. Are they anxiolytic or antidepressant or both? The overview, above, of the behavioural effects mediated through 5-HT receptors suggests that 5-HT has more to do with anxiety than depression. This, however, is an issue that is likely to be confounded greatly by the efforts of drug companies to market their products.

For example, the relative failure of buspirone to make major inroads in the marketplace suggests that it will be very difficult to market a general anxiolytic, in the post-benzodiazepine era. Such a compound would have to be both

as effectively anxiolytic as the benzodiazepines and remarkably safe. The safety factor comes into play when one considers that broad-spectrum anxiolytics may end up being prescribed for substantial sections of the population, so that the potential liability to the company should anything go wrong is considerable.

This must be one reason why so many 5-HT re-uptake inhibitors are being produced – and why the temptation to market them as antidepressants is all but irresistible. These compounds can be produced easily. They are far safer than the earlier tricyclics and MAOIs. They are so safe that it becomes a feasible proposition to take the current findings from social psychiatry and advise general practitioners that there are many more untreated depressives than was formerly thought; often conditions presenting as anxiety stem from an underlying depression, and current evidence suggests that antidepressants (in contrast to anxiolytics) need to be taken chronically, in order to reduce the risk of relapse. Marketing as antidepressants also produces a different (and more useful) set of expectations in both prescribers and consumers – that the drugs will not do much in the short term. There is, therefore, a good marketing rationale for producing 5-HT re-uptake inhibiting 'antidepressants'. From the beach-head of depression, raids can subsequently be launched on the hinterlands of anxiety, following the well-established precedent of the MAOIs and clomipramine.

Are 5-HT re-uptake inhibitors, therefore, not antidepressant? Currently in clinical trials for antidepressants, the Hamilton Rating Scale for Depression (HRSD) is the most commonly used instrument. A problem with the HRSD is that a considerable part of the total score may derive from questions that are concerned with anxiety. An effective anxiolytic agent may substantially reduce total scores and such reductions are then often uncritically interpreted as evidence of antidepressant efficacy.

On this basis all neuroleptics have been 'shown' to be antidepressants (Robertson & Trimble, 1982). Lundbeck, in particular, have conducted a successful marketing campaign for flupenthixol, using such data to suggest that it is in someway both a neuroleptic and an antidepressant (for review see Healy, 1990). Both diazepam and alprazolam have comparable antidepressant credentials (Tiller *et al*, 1989; Rickels *et al*, 1985); the companies concerned have, however, had other marketing targets (Healy, 1990).

Many of the more recently developed compounds active at 5-HT receptors will also provide substantial benefits for depressed patients as rated by the total Hamilton scale score. The 5-HT re-uptake inhibitors do just this. Are such agents specifically antidepressant? Against this possibility is the fact that there is no relationship between potency in inhibiting 5-HT re-uptake and antidepressant efficacy. Indeed, the recently developed and apparently antidepressant tianeptine appears to promote 5-HT uptake (Fattacini *et al*, 1990). It must be remembered as well that the original of the species, clomipramine, had a much wider range of actions than the more specific compounds currently being introduced.

There is a further possibility. It appears that there is a substantial overlap between the 5-HT and dopaminergic systems. Both 5-HT_3 receptor antagonists and D-2 receptor antagonists are antiemetic (Costall *et al*, 1988). Neuroleptics, 5-HT re-uptake inhibitors and 5-HT_{1a} agonists increase prolactin levels. Both neuroleptics and fluoxetine have been reported to produce akathisia (Lipinski *et al*, 1989). 5-HT_{1d} receptors are found principally in the basal ganglia (Peroutka, 1988). 5-HT_3 receptor antagonists modulate mesolimbic dopamine release (Tricklebank, 1989). There are grounds, therefore, to believe that drugs active on the 5-HT system may modulate dopaminergic systems or vice versa.

Of note here is the fact that the first report of a possible benefit of clomipramine in OCD suggested that it helped by producing a state of indifference to intrusive thoughts and imagery (Cordoba & Lopez-Ibor, 1967; Healy, 1990). I have argued, elsewhere (Healy, 1989), that the beneficial effects of neuroleptics also follow from the 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 drawback of being often accompanied by counterproductive side-effects. Without more precise phenomenological descriptions from patients, it is not possible to say whether these effects differ, other than in the time course of their onset.

A case can be made therefore that manipulating 5-HT functioning may, in certain circumstances, be indirectly neuroleptic. On this basis, current cocktails for treatment-resistant depressions, which manipulate 5-HT systems, may be equivalent to adding a neuroleptic to an established antidepressant regime.

The way forward?

When new compounds are produced, there is a *prima facie* case for conducting a series of open studies in clinical populations to establish their actual effects in man as opposed to the effects proposed by current theories or by extrapolation from animal

experiments. This, however, is not the way the modern pharmaceutical industry works.

The production of a drug requires a prior determination of market returns balanced against liabilities. This initial requirement tends to act as a mould into which subsequent developments must be fitted. This will often apparently lead to companies ignoring information about unexpected clinical benefits which might complicate the figures. A recent example concerns calcium-entry blocking agents (Healy, 1990). Company information, until recently, suggested that these agents do not cross the blood–brain barrier. However, it was observed that such agents may ameliorate tardive dyskinesia (Barrow & Childs, 1986), an observation subsequently replicated, which has not, it would seem, been taken up and promoted by the companies concerned. This is presumably because the balance-sheet of gains and liabilities might be incalculably disrupted by doing so.

This example of clinicians noting the effects of a drug on a condition other than the one it was prescribed for contains an important pointer. To date, all significant developments in psychopharmacology have happened serendipitously (see Sneader, 1990; Kuhn, 1990; Sandler, 1990 and for review Healy, 1990). None have been the result of a double-blind placebo-controlled study. At present, the interpenetration of psychopharmacology with the pharmaceutical industry, although of immense benefit in many respects, tends to obscure this and to suggest instead that all the significant research has been done before a drug comes to the marketplace – apart from the formality of a set of clinical trials. This is simply not the case. All too often the clinical trial, today, merely sets the seal on a marketing process rather than acts an independent piece of research.

Clinicians need to research 'independently' the effects of these new compounds. We need also to come up with operational criteria for antidepressants (and other psychotropic drugs), so that simply achieving effects in clinical trials cannot be passed off as evidence that the drug in question is an imipramine-equivalent, for example. There are a number of recent developments that perhaps may help in this. One has been the development of rating scales, such as the Montgomery-Asberg Depression Rating Scale (MADRS), which are much less likely to throw up false positives with anxiolytics.

Another is the development of multiple-baseline methods, which could potentially replace the placebo-controlled trial (Kazdin, 1982). Such methods would permit studies on small numbers of patients rather than the hundreds needed for adequate placebo-controlled studies. These smaller numbers could then consist of clearly endogenomorphically depressed subjects; the kind of individuals who would seem least likely to respond to an anxiolytic.

Finally, Quitkin *et al* (1984) and Kravitz *et al* (1990) have suggested that a true antidepressant response can be differentiated on the basis of a pattern analysis as opposed to a consideration of overall success rates compared to placebo. A clear delay in response of up to two weeks has traditionally been taken to be characteristic of antidepressants as opposed to anxiolytics or neuroleptics. Ironically, this may indicate the best basis for claiming that the 5-HT_{1a} agonists are antidepressants, in that response to these compounds takes two to three weeks to appear.

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