Dose optimisation in antidepressant drug development

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Abstract

There are four main obstacles in achieving optimal drug doses in the development of antidepressant drugs. The first is the large placebo response. This is known to be proportional to the initial severity of the illness such that subjects with less severe depressive illnesses show the greatest placebo response. Up to 40% of depressed patients with mild illnesses will spontaneously remit over 4 weeks of placebo therapy. Treatment with an effective antidepressant produces rates of 60–70% in this population. Thus, improvement directly attributable to a pharmacological action of the drug occurs in only 20–30% of treated patients. The second difficulty is that depression is probably heterogeneous in its response to antidepressant drugs. There is reasonable evidence that depression with psychosis is poorly responsible at least to existing antidepressant drug therapies but specifically responsive to electroconvulsive therapy. Patients with bipolar affective disorder may switch into mania when treated with antidepressant drugs and some bipolar patients develop chronic depression which is very resistant to drug therapy. The third difficulty, which is not unique to antidepressant drugs, is that 4 weeks of therapy is probably insufficient to observe maximal response and improvement in depression may continue for 6–8 weeks. Improvement in other disorders such as obsessional compulsive disorder may continue well beyond 8 weeks. The fourth difficulty is that the pharmacological mechanism of action of antidepressants has some uncertainty and so it is difficult to develop in vivo surrogate markers. Modern imaging techniques offer a way forward. For example, new drugs can be investigated for their ability to displace radioligand binding to the receptor identified with antidepressant response. Positron emission tomography radioligands are being developed for monoamine reuptake sites and this could be used to optimise drug dosage with new monoamine uptake blocking antidepressants. There is a strong thrust of evidence which implicates post-synaptic 5HT1A receptor in mediating the antidepressant effects of drugs and these can already be visualised in using the radioligand WAY100635. The ability of antidepressant drugs to increase 5HT release could be detected by a displacement of WAY100635 by increased endogenous release of 5HT. Pharmaco magnetic resonance imaging is an emerging technology for dose optimisation of

CNS drugs. The direct effect on neuronal metabolism in different regions of the brain can be monitored by following the local changes in blood flow. However, the technique is not yet quantitative. Another approach is to evoke regional neuronal activation using psychological tasks which engage different brain circuits or by the experimental induction of low mood itself. © 2001 Elsevier Science B.V. All rights reserved.

1. Introduction

The aim of dose optimisation is to identify doses of drug that show maximal clinical efficacy with minimal side-effects and toxicity. Clearly, the earlier in drug development that this happens, the more efficient the later stages of development. The earliest stage is the transition from pre-clinical to Phase I development. However, the scope of this seems particularly limited in the case of antidepressant drugs because of the lack of well-validated animal models of depression and the uncertainty of translating effective doses in animal models to optimal dosing in humans. What frequently happens is that the maximum tolerated dose is identified in toxicology studies and in simple behavioural screens followed by confirmation in Phase I trials. On the basis of these data the highest well-tolerated dose is selected for Phase II efficacy studies. If the drug is found to be active, dose-ranging trials are carried out with doses decreasing from the highest well-tolerated dose. Two real risks of this approach are that the drug will be used in unnecessarily high doses with the concomitant risk of long-term side effects and secondly, the doses will fail to meet increasingly stringent demands by regulatory authorities to justify the clinical dose-range. There is the additional theoretical possibility that the maximum well-tolerated dose may be on the descending limb of an inverted dose–response relationship. These have frequently been observed in animal behavioural models but not so far in clinical studies. Further discussion of the selection of optimal Phase I doses is beyond the scope of this study.

This chapter deals first with two sets of problems of early dose-optimisation for antidepressant drugs and then discusses some of the possible surrogates for clinical efficacy that might be used in early dose optimisation in the future.

2. Problems with early dose-optimisation

2.1. Overview

There are two groups of problems:
- Uncertain mechanisms of antidepressant action.

There are several types of antidepressant drug and they may have one or several acute direct pharmacological actions. It is still not clear what acute properties are essential for acute antidepressant efficacy. Antidepressant drugs take time to work—4-week studies are

usually required to detect efficacy and the full degree of efficacy may take 6 or more weeks to become manifest. This has led to interest in the delayed adaptive neurochemical effects of antidepressants as their possible mechanism of action.

• The nature of depression.

Depression is diagnosed on the basis of symptoms and there are no hard end-points which can be used in normal volunteers or early in drug development to provide a more objective or predictive measure of effect.

Depression is almost certainly a heterogeneous condition but in the absence of reliable biological markers or genetic polymorphisms, the identification of sub-groups with different aetiologies is very uncertain. It is likely that different sub-groups will have different optimal doses and neurochemical targets. A further problem is that depression has a very high spontaneous remission rate. This bedevils the evaluation of trials in depressed populations.

2.2. Mechanism of action of antidepressant drugs

2.2.1. Acute actions

All established antidepressant drugs have acute actions on monoamine synapses (Fig. 1) [1,2]. Table 1 lists the main classes of antidepressants. The reuptake blockers bind to noradrenaline or serotonin uptake sites or to both. For each type of uptake blocker there are old and new examples; newer agents generally being more potent and more selective for uptake sites over other actions such as muscarinic antagonism. Thus, venlafaxine and milnacipran are new combined noradrenaline and serotonin uptake inhibitors lacking many of the side effects of the older non-selective agents such as amitriptyline and clomipramine [3,4]. The older tricyclic antidepressant desipramine is selective for noradrenaline uptake sites and the new agent reboxetine is a cleaner
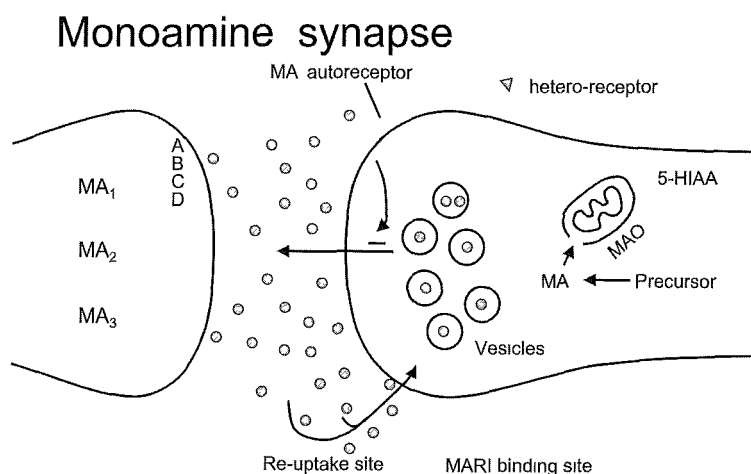

Fig. 1. MA = monoamine; MARI = monoamine reuptake inhibitor, MAO = monoamine oxidase.

Table 1
Classification of antidepressants

Monoamine reuptake inhibitors (MARIs)	
imipramine	venlafaxine (mixed)
desipramine	reboxetine (noradrenaline selective)
fluvoxamine	citalopram (serotonin-selective)
Monoamine receptor-active drugs	
mianserin	mirtazepine
trazodone	nefazodone
Monoamine oxidase inhibitors (MAOIs)	
phenelzine	moclobemide

Original version of drug on left, latest example on right.

selective noradrenaline uptake blocker. The most recent selective 5HT uptake inhibitor is citalopram.

The monoamine oxidase inhibitors prevent the degradation of monoamines by the enzyme monoamine oxidase. Older agents were bound irreversibly to the enzyme while the new agents are competitive for the active site. This means that high doses of circulating monoamines induced by tyramine in the diet can compete with the drug for metabolism, thus preventing the cheese effect.

Monoamine receptor-active drugs do not work on the uptake sites but rather on monoamine receptors. Mianserin is pre-synaptic alpha2 antagonist, which is thought to work by increasing noradrenaline release. In addition it is a post-synaptic 5HT2C blocker. The recent version of this drug is mirtazapine, which has a similar profile [5]. Trazodone is also a 5HT2 antagonist, although it is probably a more potent 5HT2A than a 2C blocker. Nefazodone is a recent version of this drug with weak potency at 5HT- and noradrenaline-uptake sites [6]. The ability of these drugs to increase noradrenaline release may cause a secondary activation of 5HT neurones and thus increase 5HT release [1]. The 5HT2 antagonist properties may be important in their mechanism of action, resulting in a net increase in 5HT1-mediated effects [7].

2.2.2. Delayed actions

A number of homeostatic mechanisms prevent the rapid accumulation of monoamines in the synapse after acute treatment with antidepressants. Monoamine receptors located on nerve terminals (autoreceptors) sense concentrations in the synapse and suppress further release if concentrations rise (see Fig. 2). A more powerful restraint on the accumulation of monoamine in the synapse is probably exerted by autoreceptors on dendrites and cell bodies because they inhibit cell firing. They sense the concentration of monoamine released onto dendrites by terminals of collaterals or afferents from other monoamine cell groups. Repeated exposure to antidepressant drugs causes terminal and dendritic autor-ececptors to desensitise and so monoamine neurones adapt to increased concentrations of monoamine in the synapse [8,9].

There is now compelling evidence that the accumulation of serotonin or noradrenaline in the synapse on repeated treatment is the mechanism of action of antidepressant drugs.
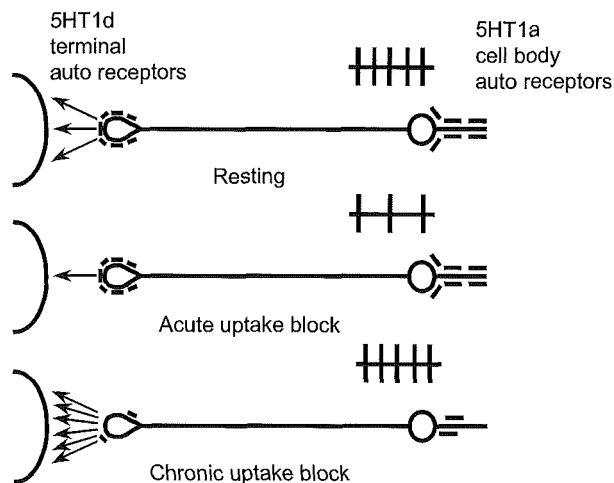
Autoreceptor down-regulation by antidepressants

Fig. 2. Top panel: Resting state with terminal 5HT1d and dendritic 5HT1a autoreceptors regulating release and firing rate. Middle panel: Rise in 5HT after acute uptake inhibition suppresses the firing rate so less 5HT is released and terminal uptake inhibition has little effect. Synaptic 5HT content shows little change in some areas after uptake inhibition. Lower panel: Autoreceptors desensitise and firing rate returns to normal. Uptake inhibition causes accumulation of 5HT in the synapse without activating terminal autoreceptors because they too are desensitised.

The key experiment was carried out by Delgado et al. [10]. They decreased brain 5HT function using the technique of acute tryptophan depletion. Subjects receive a large quantity of various amino acids in the form of a drink. When tryptophan is omitted from the mixture, circulating levels of tryptophan fall by up to 80%. This happens because the amino-acids induce protein synthesis in the liver, which removes endogenous tryptophan from the circulation. Delgado et al. [11] studied a group of patients who had recently recovered from a depressive illness with drug treatment. Acute tryptophan depletion caused an acute recrudescence of their symptoms of depression. This did not occur on a control day when the amino-acid drink contained tryptophan. Later it was shown that the phenomenon primarily occurred in patients treated with drugs acting on serotonin reuptake. These studies clearly indicate that SSRIs work by increasing 5HT concentration in the synapse. An analogous technique was developed for catecholamine depletion. Miller et al. used the drug alphamethylparatyrazine (AMPT), which inhibits tyrosine hydroxylase—a catecholamine synthetic enzyme [12]. Recently recovered depressives treated with noradrenaline selective uptake blockers had a recurrence of symptoms for a few hours whereas those treated with other antidepressants did not [13]. Taken together, the results indicate that increased noradrenaline or 5HT concentration in the synapse are parallel, apparently independent mechanisms of antidepressant action.

Studies in the 1980s investigated the delayed neurochemical effects of chronic antidepressant treatment on postsynaptic receptors in experimental animals. Many but not all antidepressant drugs on repeated administration cause delayed reductions in

beta receptors and 5HT2 receptors [7]. However, the monoamine depletion strategy clearly demonstrates that the important change is an increase in the level of synaptic 5HT or noradrenaline.

These insights have led to attempts to hasten the onset of antidepressant effect by blocking terminal or cell body autoreceptors so that the monoamine neurone is insensitive to the increasing synaptic concentrations. Clinical experience is so far limited to the drug pindolol which is a 5HT1A antagonist in addition to its well-known beta receptor antagonist properties. 5HT cell body autoreceptors belong to the 5HT1A class and pindolol prevents the suppression of firing caused by acute antidepressant administration. This potentiates the rise in concentrations of 5HT in the synapse after single doses of antidepressants [14]. The clinical studies do not so far suggest that pindolol accelerates the onset of antidepressant action but may improve efficacy [15–20].

2.2.3. Non-monoamine approaches to antidepressant drug therapy

There are three main approaches to new mechanisms of antidepressant action. However, only neurokinin receptor antagonists have reached studies in patients where they show clinical promise [21]. Whether their efficacy is independent of monoamine neurones is not clear—it is possible that some interaction with monoamine neurones results in an increased concentration of noradrenaline or serotonin in the synapse. Other targets for potential antidepressant drugs include glutamate neurotransmission [22] and corticotrophin releasing factor [23]. A number of antagonists are available for both systems but these drugs have not yet been clinically evaluated. Again, it is possible that monoamines might be the mediating mechanism.

2.2.4. Implications for drug development

If all antidepressant drugs work by increasing monoamine neurotransmission in one way or another, then the attempt to develop agents which rapidly increase monoamine concentrations is clearly appropriate. More needs to be known about what happens downstream from monoamine synapses. There has been much interest in long-term effects of gene expression, for example, brain derived neurotrophic factor and cyclic AMP-dependent response elements [24]. However, the fact remains, that for reuptake inhibitors the primary therapeutic action appears to be enhancement of 5HT and/or noradrenaline neurotransmission.

2.3. The nature of depression

2.3.1. No hard end points

The diagnosis of depression is clinical. It relies primarily on subjective reports from the sufferer—low mood, anxiety, loss of pleasure, psychomotor inefficiency, sleep disturbance and loss of appetite. Objective rating of depressed appearance is highly unreliable.

2.3.2. Heterogeneity

Table 1 lists some of the many forms of depression that have been proposed. All of them are based on symptoms. Whether the symptoms reliably relate to aetiology is far

from clear. However, bipolar affective disorder has a very strong genetic component [25]. However, no genetic markers are yet unequivocally established. A single manic episode is sufficient to convert a diagnosis of recurrent depression to bipolar affective disorder and this occurs in perhaps 10% of cases of major depression followed up over 5 years [26]. Thus, patients currently diagnosed with major depressive disorder almost certainly include a proportion of an underlying bipolar affective disorder. Mood stabilisers such as lithium and anticonvulsants are effective in the prophylaxis of bipolar affective disorder but probably also in recurrent unipolar depression [27].

Psychotic depression is defined by loss of contact with reality due to delusions or hallucinations. There is evidence that this form of depression is specifically responsive to electroconvulsive therapy whereas non-psychotic depressive illness is not [28]. Conversely, antidepressant drugs appear to be less effective in psychotic depression than in other forms of depression [29]. Furthermore, there is evidence that the addition of neuroleptics to antidepressant drugs is beneficial [29].

These findings indicate that the proportion of patients with severe or delusional depression in a drug trial could influence selection of optimal dose. For example, in the study of Simpson et al. [30], 300 mg/day of imipramine was found to be significantly superior to 150 mg both in endogenous and in neurotic depression, but in the endogenous group, patients still had an average of 30% of their initial severity ratings whereas the neurotic subjects on the high dose ended the trial at less than 10% (see Fig. 3).

Various names have been used to describe depressive illnesses characterised by disturbances in neurovegetative functions (weight loss, sleep disturbance, retardation etc.) and they are grouped under the term endogenous in Table 2. However, the term "endogenous" appears to be misleading because life events occur with increased
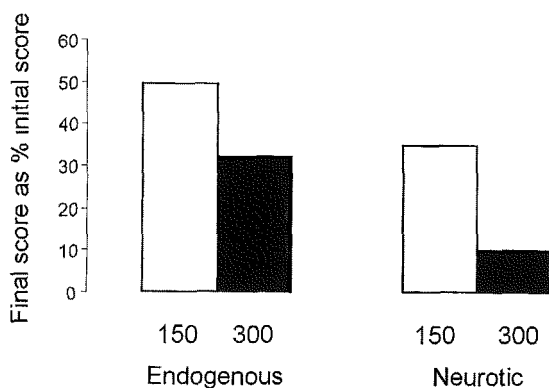

Fig. 3 Greater effect of 300 mg of imipramine than 150 mg in depression. Clear dose-effectiveness of imipramine but there was no placebo group. Endogenous patients did not fully recover despite the greater dose (Simpson et al.).

frequency in the 3 months prior to most forms of depression, irrespective of whether they could be termed endogenous or not [31].

Illnesses grouped with neurotic depression (Table 2) are characterised by a chronic, fluctuating course in the setting of unstable life styles and are characterised by symptoms of anxiety. There is evidence that such patients are specifically unresponsive to ECT [32].

Atypical depression has had various meanings. However, an influential view is that such individuals have disturbed personalities characterised by sensitivity to rejection [33,34]. There is some evidence that monoamine oxidase inhibitors may be more effective than reuptake inhibitors in patients with atypical characteristics.

It can be seen that depression is very likely to be heterogeneous in terms of aetiology and there is already evidence that it is heterogeneous in terms of response to therapy. Thus, dose optimisation studies may produce different results depending on the population investigated.

2.3.3. Spontaneous remission

Depression has a high spontaneous remission rate and this complicates the interpretation of clinical trials and studies of dose-effectiveness. Angst [26] has investigated predictors of response to uptake inhibitors and to moclobemide using meta-analysis. The main factor which predicts outcome is the initial severity of depression. This effect is mediated in part by the high spontaneous remission of symptoms in subjects with mild symptoms. The placebo response rate may be as high as 40% over a 4-week period. Antidepressant drugs probably have less overall efficacy in this group too.

Table 2
Depression is heterogeneous

• Bipolar
• Psychotic
delusional
• Endogenous
unipolar
vital
melancholic
endogenomorphic
familial pure
depressive disease
• Neurotic
reactive
situational
precipitated
depression spectrum
disease
• Atypical
psychopathic
sporadic
secondary

Various attempts have been made to classify depression on the basis of symptoms. They can be grouped into the five main groupings as shown in this table.

In moderate to severe depression the placebo response rate falls to 20–25% and the response rate in drug-treated groups rises to up to 75%. Since up to 25% of those on active drugs would have improved on placebo and 25% of patients do not remit over 4 weeks, it follows that only half of depression is amenable specific neurochemical actions of drugs. Overall, spontaneous remission in depression means that large sample sizes have to be used in dose optimisation studies.

3. Surrogates for efficacy

3.1. Overview

A surrogate marker for efficacy is a drug-effect measured in humans, which predicts that the drug will be effective in reducing symptoms. The two sets of problems discussed above suggest two approaches to surrogate markers in antidepressant drug development: markers for biochemical mechanisms of action and markers of the illness itself.

3.2. Biochemical surrogates

3.2.1. Introduction
Acute actions of antidepressants on uptake mechanisms can be detected in humans in vivo using peripheral autonomic markers such as potentiating constriction of the dorsal hand vein by noradrenaline [35] and by modulation of the pupillary light reflex [36]. The latter has the advantage of detecting a central blockade of noradrenergic function but the precise locus of effect is uncertain. Both these models have helped to demonstrate the previously disputed effect of venlafaxine on noradrenaline reuptake at therapeutic doses.

The neuroendocrine drug-challenge method has been used to detect acute central effects on monoamine function. For example, Porter et al. [37] showed that a single dose of venlafaxine potentiated the ability of tryptophan infusions to increase growth hormone secretion, indicating a central enhancement of 5HT1A-mediated neurotransmission. Surprisingly, the SSRI paroxetine was not effective but the dose may have been too low.

Radioligand binding in the living human brain can now be carried out using positron emission tomography (PET) and single photon emission tomography (SPET). This enables the in vivo imaging of acute pharmacological actions of putative antidepressants and their sites of action in Phase I volunteer studies. In the future, doses of new agents which affect reuptake, monoamine oxidase, post-synaptic monoamine receptors or autoreceptors will be determined by detecting displacement of appropriate radioligands [38]. This will be central to dose optimisation and indeed to identifying the neurochemical aetiology of depression.

3.2.2. Imaging the 5HT uptake site
There are two ligands for the 5HT uptake site that have been investigated: I_{123}-nor-beta-CIT and C_{11}-McN 5652. Two studies report decreases in depression [39,40]. While this

could indicate loss of presynaptic 5HT terminals in depression, there are other explanations and the functional consequences of such a change are obscure. The ability of new 5HT uptake inhibitors to displace radioligand binding to the uptake site is likely to be the method of determining effective doses in humans. However, much evaluation of the technique will be necessary. In particular, it is not known what degree of occupancy of the 5HT uptake site is necessary for efficacy. In a single depressed bulimic subject treated with 60 mg fluoxetine, Tauscher et al. [41] reported a 40% occupancy of uptake sites using beta-CIT SPET.

SSRIs have curiously steep dose response curves. Fig. 4 shows a compilation of studies of sertraline, fluoxetine and paroxetine in parallel-dose studies. For each of these three SSRIs it is clear that there is an effective dose and that further increases in dosage are not associated with increased therapeutic effect [42]. The minimum effective dose for fluoxetine and sertraline is not known with certainty. Five milligrams of fluoxetine per day appears to be effective and 20 and 40 mg produce no greater clinical response. Therefore, it is not clear why the standard therapeutic dose of fluoxetine is 20 mg. It would be very interesting to know whether 20 mg of fluoxetine produces a greater degree of occupancy of 5HT uptake sites than 5 mg. Reduced efficacy at 60 mg may reflect the increased incidence of side effects at high doses. Furthermore, the drop-out rate is twice as high as at lower doses. Even so, looking solely at patients who complete, the degree of improvement at 60 mg is not greater than at lower doses. The minimum effective dose of paroxetine appears to lie somewhere between 10 and 20 mg but again increasing doses
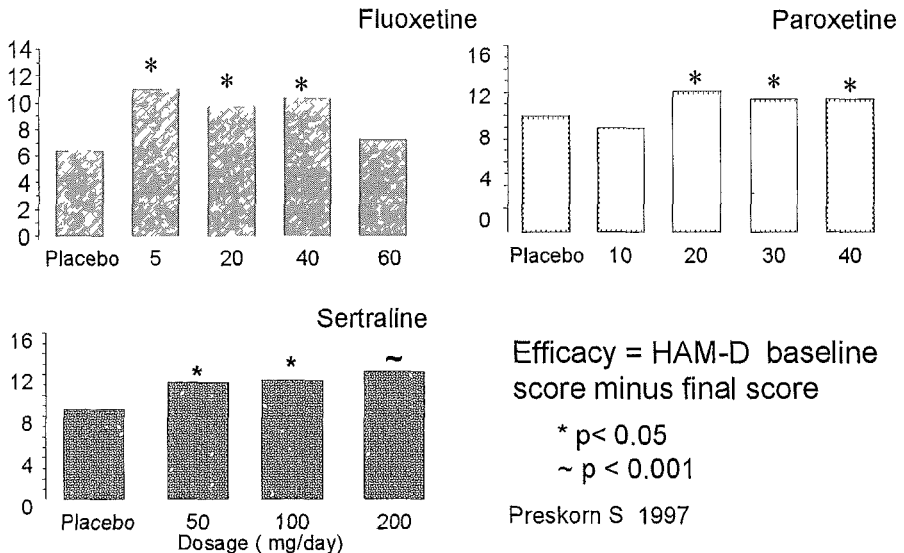
SSRI Dose-effectiveness

Fig. 4 Dose response data for SSRIs. All SSRIs have flat dose response curves.

produce no greater clinical effect. It is clearly a crucial research issue to know whether doses greater than 20 mg produce greater occupancy at the uptake site.

The lack of dose–effect relationship in clinical studies of SSRIs raises the possibility that some factors restrain the effectiveness of SSRIs at higher doses. Deakin [7] has suggested that enhanced neurotransmission through 5HT2 receptors may underlie some symptoms of depression, such as anxiety. If this is correct, then higher doses of SSRIs may cause increased stimulation of 5HT2 receptors, which counteracts the therapeutic effects of enhanced 5HT1A receptor stimulation. Another possibility is that because of feedback mechanisms, there is simply a threshold of SSRI dose that is required to increase synaptic 5HT concentrations and that when this occurs there is a maximal effect on symptoms. To gain further improvement, it may be necessary for enhanced noradrenaline neurotransmission to occur. Both of these possibilities can be evaluated using radioligand binding techniques.

3.2.3. Imaging 5HT1A receptors

Various lines of evidence suggest that enhanced neurotransmission through 5HT1A receptors is a key mechanism of antidepressant action [9]. The radioligand $_{11}$CWAY100635 reveals the distribution of post-synaptic 5HT1A receptors in cerebral cortex and 1A autoreceptors can also be seen in the mid-line raphe. Using this technique in volunteers and patients, it should be possible to address the key issues: (i) is there a change in 5HT1A receptor number in depression?; (ii) do antidepressant drugs modify 5HT1A receptor binding?; (iii) is it possible to find agents which block the cell body autoreceptors without blocking the post-synaptic receptors?; (iv) what doses of antidepressant drug increase 5HT concentration in the synapse?

Drevets et al. [43] and Sargent et al. [44] reported reduced 5HT1A binding in un-medicated patients with major depressive disorder both to post-synaptic receptors throughout the cerebral cortex and also to presumed 5HT1A autoreceptors in the raphe. These studies raise the possibility that depression is associated with a reduced expression of 5HT1A receptors. However, if SSRIs work by increasing synaptic 5HT availability, then this might be expected to displace WAY-100635 binding further in patients treated with antidepressants. However, this has not so far been observed [44]. These findings are preliminary and clearly further studies are required to determine whether increased synaptic 5HT is capable of displacing WAY-100635 radioligand binding to post-synaptic receptors.

Rabiner et al. [45] have shown that pindolol and buspirone displace WAY-100635 from cortical and autoreceptor binding sites in the raphe. They found that a dose of 10 mg of pindolol selectively decreased ligand binding to autoreceptors in the raphe with minimal effect on post-synaptic sites in the cortex. Greater doses decreased binding at both sites. The selective autoreceptor dose of 10 mg is appreciably higher than the 2.5 mg t.i.d. dose, which has been used in SSRI augmentation studies. Inadequate doses of pindolol may be one reason for the equivocal results of the benefits of pindolol augmentation [46].

3.2.4. 5HT2 receptors

PET and SPET ligands are available for studies of the 5HT2A receptor (setoperone, altanserin and ketanserin) but studies of depression have so far been small-scale. Three

studies report decreased binding in depression [47–49] but an early study reported increases in parietal cortex [50], and another study found no differences [51]. The results contrast with increases reported in post-mortem brain [52]. Drug effects on in vivo 5HT2 binding have been little studied. The central 5HT2A antagonist effects of nefazodone were demonstrated by its ability to displace radiolabelled setoperone binding in vivo [53]. Chronic treatment with desmethylimipramine and clomipramine have been reported to decrease 5HT2A binding [48,54] and this is compatible with the ability of many antidepressants to down-regulate 5HT2A binding in experimental animals [55]. SSRIs do not down-regulate 5HT2A binding in animals and Massou et al. [56] reported increased binding in vivo in six patients treated with SSRIs compared to eight untreated patients.

Another approach to probing neurotransmitter sensitivity is to monitor the brain's functional response to acute drug challenge. Populations of neurones activated or inhibited by the drug can be revealed by measuring regional cerebral blood flow using PET, or more recently blood oxygen level dependent magnetic resonance imaging (BOLD MRI). Regional glucose metabolism can be followed using FDG PET. Mann et al. [52] reported that DL-fenfluramine, which releases 5HT causing 5HT2C effects, induced increased regional brain metabolism in prefrontal cortex and that this effect was reduced in depression. Unfortunately, this was not replicated by Meyer et al. [51] possibly because they used the more selective 5HT releasing isomer D-fenfluramine. Fenfluramine is no longer available but other challenges can be used. For example, Hommer et al. [57] used the drug mCPP, which directly activates 5HT2C receptors, and showed increased metabolism in ventral frontal cortex in normal subjects. We have recently shown that acute intravenous mCPP administration also causes increases in the BOLD signal in ventral frontal cortex using functional MRI.

3.2.5. Noradrenaline

Much the same approach as those described for 5HT could be taken towards the noradrenaline synapse. It is likely that radioligands will be developed with affinity for the uptake site and for post-synaptic receptors. Such techniques will establish the role of noradrenaline in the pathogenesis of depressive illness and could be used to identify pharmacological effective doses in Phase I normal volunteer studies.

MRI can be used to visualise functional activity in noradrenergic systems. Coull et al. [58], for example, used the drug clonidine to inhibit the firing of locus coeruleus cells. This drug is a pre-synaptic alpha2 receptor agonist, which inhibits noradrenaline cell firing. Remarkably, using MRI it was possible to visualise an area of reduced activity in the locus coeruleus in the brain stem. Again, it is theoretically possible to investigate pre-synaptic alpha2 receptor functioning using this approach.

As noted earlier, noradrenaline and 5HT appear to be independent routes towards antidepressant efficacy. Therefore, it seems possible that their combination could be synergistic. Nelson et al. [59] compared depressed subjects taking desipramine with those in which fluoxetine was added to desipramine. They showed substantially superior response in those treated with the combination. Care has to be taken with the interpretation of such studies. Fluoxetine is an inhibitor of the cytochrome oxidase system, which metabolises desipramine, and the enhanced response could simply be a function of

increased circulating desipramine concentrations [42]. Nevertheless, there is evidence that drugs with combined actions on noradrenaline and 5HT systems may have enhanced efficacy. For example, there is reasonably good evidence that high doses of venlafaxine combine noradrenaline–serotonin uptake inhibitor, and that they have superior efficacy compared to treatment with a serotonin-selective uptake inhibitor [60]. Furthermore, in contrast to SSRIs, venlafaxine has a clear dose response curve with increasing doses producing an increased effect. As speculated above, this may be because the combination of two mechanisms of action permits a more graded response. A simpler explanation may be that venlafaxine at lower doses is primarily a serotonin-selective agent and only at higher doses inhibits noradrenaline reuptake. Thus, the combination of effective higher doses results in the greater efficacy at higher doses. The latter interpretation is supported by the lack of a dose–effect relationships of milnacipran despite its combined noradrenaline–serotonin uptake inhibition action; it is roughly equally potent at both uptake sites. Like SSRIs, this drug has a very steep dose–response curve with no efficacy at 50 mg/day and equal efficacy at 100 and 200 mg/day.

3.2.6. Conclusion

It can be seen that experimental drug-challenge methods and new imaging techniques can be used to detect effects on CNS monoamine function, which are directly relevant to antidepressant actions. These should allow the detection of maximal and minimal doses of candidate drugs for actions on CNS monoamine function early in drug development.

3.3. Candidates for psychobiological surrogates

3.3.1. Overview

Biochemical surrogates involve probing neurochemical mechanisms of antidepressant effect; psychobiological surrogates would probe the psychobiological processes which become disturbed in depression. It is likely that mood itself is regulated and various strategies exist for inducing depressed or elated mood [61]. There have been several conceptions as to the psychological process which underpin depression, including changed sensitivity to reward and punishment, attentional biases to negative cues, and impairments of regional brain function as measured by cognitive function tests and regional cerebral flow and metabolism. None have been used as a basis of early dose optimisation but there would seem to be rich possibilities in psychobiological surrogates. They would have the great advantage of freedom from any assumptions about neurochemistry, yet firmly based on pathogenic mechanisms.

3.3.2. Mood induction

Clearly, in depressive illness, depressed mood is out of proportion to circumstances but it is likely to involve similar brain circuits that operate in normal variation in mood. Indeed, this is corroborated by functional imaging studies of depressed mood induced in normal volunteers. This is reliably accomplished by instructions to think about negative autobiographical memories while listening to melancholy music. Increased blood flow occurred in ventral subgenual cingulate cortex in depressed mood induction and this

region corresponded to an area of increased flow in depressives compared with controls [62]. Furthermore, greater flow/metabolism in ventral frontal cortex has been associated with response to antidepressant drugs [62,63] and to sleep deprivation [64]. It will be of considerable interest to determine whether single or repeated doses of antidepressant drugs in normal volunteers reduce the ability to induce depressed mood and whether they influence brain function in ventral frontal cortex. This could offer a reasonably simple approach to detecting new antidepressants that makes no assumptions about neurochemical mechanisms of action, which is nevertheless based on the pathophysiology of depression.

3.3.3. Affective and cognition basis of depression

From experiments in animals in the 1950s onwards, there has been increasing understanding that the brain contains specific systems which detect the occurrence of rewards and punishments. This has influenced thinking about depression and the idea that depression involves a "pervasive loss of interest and pleasure" is now enshrined in the diagnostic manual of the American Association of Psychiatrists (DSMIV). The underlying idea is that brain reward systems are subsensitive in depression. While this has been useful in developing surrogates for depression in animal models, it has proved difficult to demonstrate reduced sensitivity to reward in depressed humans or to manipulate it in volunteers. Functional brain imaging may offer new ways forward. Elliott et al. [65] have shown activation of the ventral tegmental area and of the nucleus accumbens in volunteers when they are winning money in a card guessing task. These regions have been strongly implicated in dopamine mechanisms of reward in animal studies. Dopamine-mediated reward effects were demonstrated by Koepp et al. [66] who showed that winning a space invaders task displaced raclopride binding to dopamine receptors in ventral striatum detected by PET—the inference is that rewards released dopamine which displaced raclopride binding. These techniques have the potential to visualise and quantify reward (and punishment) mechanisms in human volunteers and depressed patients and their response to antidepressant treatment. Such effects could then form the basis of early dose optimisation of antidepressants in volunteers.

There are various cognitive concepts of depression which could form the basis of surrogate markers of efficacy. For example, several studies suggest that patients automatically detect negative words and do so more rapidly than normal subjects. In a recent study, elated subjects were quicker to detect positive words. Whether antidepressants in normal subjects influence cognitive biases in normal volunteers has yet to be determined. Such an effect could contribute to the detection and dose-optimisation of new antidepressants with novel mechanisms of action.

4. Conclusion

The goal of dose optimisation based on mechanisms of antidepressant action and on reversing pathogenic processes in depression is clearly some way off. Nevertheless, the techniques for imaging neurochemistry in vivo are developing quickly and hold great promise for the future efficient development of antidepressants. Psychobiological surro-

gates for antidepressant efficacy have the promise of detecting agents with non-mono-amine mechanisms but there has yet to be a serious response to the challenge of developing this approach.

Appendix A. Discussion 18

M. Danhof: Looking at your data, you showed that basically there are lots of adaptation in the system. Earlier we discussed the concept of carefully dosed titration, particularly to avoid side effects. I understand that in the treatment of depression, doses are gradually increased until you reach side effects. To what extent could that affect effectiveness, considering the fact that you are having a very adaptive system? You might as well be chasing your disease by going in very slowly, would that be something that you could reveal using this type of technology?

W. Deakin: In reality what happens is that one looks at what the maximum tolerable dose is likely to be from the animal side and you try that in phase I; you check that that's roughly right, and then you go into the clinical trials near the maximum tolerable dose, and then what happens is that studies are carried out at lower doses. The problem with titration is that you have to wait 6 weeks before you know where you are. There is a study where authors started off with 20 mg of fluoxetine, and if they hadn't shown any sign of improvement at 2 weeks, they upped it to 40 mg. There was no benefit. That is a kind of titration, but we are still talking about a lag of at least 2 weeks before the effect of the changed dose can be evaluated.

M. Danhof: Unless you had a useful biomarker, showing basically inhibition of serotonin reuptake, then you might be able to jump in with the dose that immediately very effectively inhibits reuptake, and basically hits the targets much earlier. But in the way, basically avoid functional adaptation in the system.

W. Deakin: It would be one approach, for example, calculating what dose you'd need to block 80% of the SSRI sites. But all that would be doing is telling you where you start, I think, and you wouldn't be titrating. What we don't know, and what we need to establish, is what degree of uptake blockade you need: does it have to be 90%, for 4 weeks, or does it have to be maybe 25% block of the 5HT uptake site, or is some effect on noradrenaline also necessary? The promise of the technique, is to get the dose and combination so obtaining minimal pharmacological effects for maximum clinical effect.

M. Pirmohamed: You will be aware of Robert Kerwin's data on clozapine response in schizophrenia with the different genetic polymorphisms. The problem with that data is that it has not been possible to replicate in different populations, and so clearly comes back to some of the things we were talking about this morning. There have also been some studies of response to anti-depressants being associated with certain receptor polymorphisms. Do you think there is a genetic component to psychotropic drug response, and would it be better to combine some of the polymorphism studies with some of the functional assessment that you've shown with the PET scan, or maybe MRS?

W. Deakin: Cohen's data highlights an interesting problem. Kerwin says that he can predict something like 90% of the response of schizophrenics to clozapine on the basis of three 5-HT polymorphisms. But what he hasn't shown is that might be true for

haloperidol, and it might be true for placebo response. So you've got to show it's a differential prediction, particularly in psychiatric disorder where there is high placebo response. Yes, there is some evidence that there are polymorphisms for the 5-HT uptake site, some of them are functional. There is a recent paper in the Lancet that says that there may be a sub-group of patients with depression who have one of these polymorphisms and who are simply unresponsive to SSRIs. That will tell you, if you've got this polymorphism, don't waste your time with 6 or 8 weeks, and go for a noradrenalin reuptake inhibitor. That's certainly a way forward. We did a study with fenfluramine, a drug which works at the 5-HT reuptake site, it pumps out serotonin and you can measure a prolactin response after it; so we had a functional model of the uptake site, release and interaction with 5-HT$_2$ receptors; we did all the polymorphisms including for the uptake site and 5-HT$_2$ receptors. We also did dopamine receptor polymorphisms. No polymorphism or any combination predicted any significant variance so we were a bit discouraged by that.

X. Carné: One of the problems that you have dealt with is the placebo effect. You know that FDA and EMEA they have different, slightly different opinion about the use of placebo control group on a long way, in phase III clinical trials. In my hospital there is always a big discussion with psychiatrists, concerning if it's ethical to accept some months of treatment with placebo in depressed patients. They say that's a very heterogeneous disease, as you told us, there are many different diseases in the same concept. They add that at the beginning, many years ago—treated with tricyclic anti-depressants—these patients were real depressed people; but now in all the trials psychiatrists are recruiting less depressed people, less real diseased people because they are afraid of the suicide or other problems. In fact, people in the trials in the 1990s or right now have weaker depression than before, and that's an effect of the need to include a placebo control group in phase III trial. What do you think about that?

W. Deakin: They might be right; there are immense practical problems now that perhaps it didn't happen some time before. Nowadays patients are sort of less in control, and there is no doubt that psychiatrists are worried about that during placebo control trials. But I'm not sure about the evidence really, because there is no evidence for a drift downwards in the initial Hamilton depression ratings, as a measure of severity. If it was true that severity was decreasing then the entry criteria would be different and the level of depression as rated would be markedly decreasing. I don't think that's right, still trials are going on, and it is possible stratify by level of severity; so you still have a highly severe group in the studies. It's harder and harder to do it, but there is no question about it, placebo is absolutely essential because of the high rate of response to it. I'm very much against trials where you compare a new depressant with one that you know works, without a placebo group. Because time and again trials with active comparators and placebo fail to show a difference from placebo. And so you can't interpret the trial of the new agent, so if you don't have the placebo group, you don't know where you are.

K. Wesnes: Does dietary-induced tryptophan depletion in volunteers produce short-term depression of mood?

W. Deakin: No. It does if you have some predisposition. There is evidence if you have a previous or a family history; then you do see a reduction, but it's not enough in people with no vulnerability.

S. Jackson: I was interested in the MRI data. A thought occurred to me with fluoxetine; because it's got fluorene atom in it, is imageable with spectroscopic MRI, and I just wondered if anyone's done that.

W. Deakin: I'm not aware of that, and it's good idea. What sort of concentrations would the drug be in the brain—I guess you're talking about micromols?

S. Jackson: But I think with that kind of power of machines now, it could be done in a reasonable length with a small amount of drug; you need a longer time to image, obviously, and I think it could be done in the time you could reasonably expect someone to lie on the scanner.

M. Reidenberg: Back to the tryptophan issue, I was struck by the data you showed. How variable are tryptophan levels in people with depression, some of whom are anorexic, and does that influence drug response?

W. Deakin: Some of our and other studies have shown that the depressed people had lower tryptophan. We did a huge study in the community, with 500 women. Very briefly, we were interested in stress hormones, so they spat at 11 o'clock at night and 9 o'clock in the morning to get the diurnal variation. We had 2000 samples of spit with saliva, but we did their tryptophan as well. And having a recent severe life event—this is a sort of biological social psychiatry project. If they'd had a severe life event in the last month, their tryptophan levels were decreased. I find immensely interesting that maybe one could protect them from getting depression by some fairly simple dietary manipulations. Though having said that, it is very difficult to increase brain 5-HT function by giving tryptophan; you've really got to eat grams of the stuff before anything happens. The answer is that tryptophan levels are variable, there is a consistent line of evidence that depressed people have lower levels of tryptophan, and actually that predicts a good response to anti-depressants as well, but the amounts of variance in clinical status that is explained is pretty tiny.

L. Sheiner: The contrast between the last two talks is interesting. Without taking any credit away from Bill Evans and his colleagues, one cannot help but notice how crucial to their work was simply making careful observations of input and output variables in the process of their controlled trials. They then used these data to suggest answers to the simple question: Why do some patients get better and others do not? The hypothesis they entertained, that variation in exposure to drug or active metabolite might be the cause, was not that novel. The key to their success was the careful looking at experience, and then testing the hypotheses so generated with subsequent controlled trials. It was the cycle of using each therapeutic trials for learning as well as confirming, to suggest sensible therapeutic modifications for the next cycle that was so successful. The progress possible with this straightforwards learn—confirm paradigm, as we've all seen, was quite startling. On the other hand, we look at the picture on depression presented by Bill Deakin, where there seems to be a lot less certainty about what the target is. In his case it's not a particular set of cells that you are trying to kill; perhaps there's some receptor, but we are not even clear which of the neurotransmitters or some combination of effects we want to have. In contrast to Bill Evans' work, new drugs that have different mechanisms of action seem to be more promising and more attractive than getting the old drugs' use exactly right, and maybe that's the right idea, maybe getting old drugs exactly right is not going to work as well in depression field as it did in oncology. But the

question is what are the key differences; why did Evans and colleagues have such success taking old drugs and using them better in childhood ALL? Why is psychiatry searching for new drugs, when it is not all sure that the old drugs are being used optimally? I would venture to say that one of the reasons—and certainly not the only one—are the points that Bill Deakin made when he was talking about depression: the softness of the end points, and the heterogeneity of the disease. In the case of ALL, one has morphological and genetic differences between the different kinds of diseases, in depression one has only symptomatology to tell them apart, and obviously that's not doing as good a job as one might hope. But maybe another reason is the fact that Bill Evans is working at a hospital that specialises in certain diseases and runs multiple trials of therapies for those diseases. Not only are dense data gathered in the course of patient trials, but those data are available for subsequent analysis and reanalysis. And perhaps equally important, data from multiple separate trials can be combined to try to draw broader conclusions. I'll give just one example of this type of learning, one that Bill Evans talked about at the end of his talk: seizures associated with poor prognosis possibly due to the use of anti-seizure medications. Now, it's a perfectly reasonable hypothesis that anti-seizure medications affect the metabolism of teniposide, but the use of those medications is a post-randomisation decision, associated with the need to treat seizures. One could certainly say, if one wanted to be very hard-nosed about it, that perhaps there is something else about seizures that is a poor prognostic factor, something which has nothing to do with drug metabolism. Thus, the relationship between seizures and poor prognosis need not be mediated through the metabolic effects of the anti-seizure medications and so Bill's action to change those drugs isn't necessarily justified. But, here's the crucial point: The St. Jude's investigators will examine their future experience, as they change the use of anti-seizure drugs, and if need be, will even do a prospective trial. Thus, the tentative conclusion that the mechanism is metabolic is acceptable when planning for future testing, not when making public policy. That is precisely the way observational data and hypothesis generating analyses should be used, and we should encourage it. I think it is rarely practiced as formally as we see it being practiced at St. Jude's, and if their experience is any indication of the success the approach can have in other areas, then we should be encouraged indeed.

M. Reidenberg: I think there's another big difference between these two presentations. We are talking about chemotherapy, about killing cancer cells, which, theoretically, is based on the Skipper hypothesis of fractional kill and dose escalation. I'll contrast that with psychiatry and what I'll call pharmacodynamics, which is based on modulating function that normally is present. Its conceptual basis goes back to some of B.B. Brodie's ideas at around the same time as Skipper. I think there are enormous theoretical and conceptual differences between a chemotherapeutic approach and what I'll call a pharmacodynamic approach. And I think that also is important in understanding the differences between these two presentations.

W. Evans: I was just going to agree with Lewis Sheiner's comments. On the anti-convulsant therapy, you're right, we don't know for sure the mechanism, but it's pretty easy to avoid the problem going forward, even in the absence of knowing for sure whether there was drug metabolism or not; you can avoid the drug metabolism in part of it and see if the problem goes away, by these new anti-convulsants that don't induce. If the problem

doesn't go away and there's still difference, then you are back to trying to figure out what is the problem. On getting more information out of existing data, I wish that we had started saving DNA samples on these patient when I first started working at St. Jude's from the normal cells, 25–30 years ago. We didn't, but we've done that for the last decade or so, and we do have this, now, wealth of biological material in a fairly large group of not uniformly treated patients, but patients that were treated according to protocols, and so we can go back again, I think now, and mine this as additional genetic polymorphisms come up, we can learn quicker by going back in those patients where we already know the outcome. So this is what we hope to do next.

L. Scheiner: What's the fraction of childhood leukaemia that is treated on protocols in institutions that are likely to keep good and fairly standard records?

W. Evans: In the U.S. and Europe I think it's close to 90% for children, whereas it's close to 9% for adults. So, it is just the opposite, in fact, in these two age groups.

L. Scheiner: I think that's part of the reason we are mobilised to create good databases for certain diseases and not for others. We'll never find out whether this kind of pay-off from collecting good data and being able to look at it could be paying off in the same way in other areas if don't get the data together, and make it available.

W. Deakin: The record-keeping is a big difference, because in depression nobody keeps any sort of rating scale of how people have got on in depression. We would not be in a position to pull together all the data in the big teaching hospitals in the UK, about outcome of depression in the different hospitals and relate that to treatment or to genetic polymorphisms, I really think that's something that we have to get our act together on. Even the simple rating of good, better, moderate or fantastic improvement could be of interest. The blood samples would be an enormous benefit, and we are trying to do that in the British Association of Psychopharmacology, with some of the trials that we are organising across the country. That has to be a way forward.

N. Holford: Bill Evans is looking at a very clear end point: it's death and he's also measuring drug concentrations, which he can measure reliably. On the other hand in depression, sometimes you're not even sure if the patient is depressed. The fuzziest thing for me are the images you showed and the Hamilton D scale that you use actually is much more attractive to me, as it seems to have numbers that go from zero to 70. My point really is that it seems that psychiatrists actually throw away most of their data when they do these studies. Anti-depressant studies typically have measurements of Hamilton D over repeated occasions, and as you showed, you only look at the last one throwing away 90% of the data. My question is, why?

W. Deakin: It's a question I often raise myself. I try to persuade the drug companies to do a rating at week 1 and at 4 and 8. Why do we need all these intermediate ones? One reason is that they're always hoping that they'll get an early onset at week 1, so they always want one there to see if they can just sort of pull their drug apart from other drugs with an early onset of action. I think that's one driving force, but it's never analysed. That's the problem. There's a lot of interest in trying to spot genuine drug responders, people who show some response in week 1, is there something about those people that distinguishes the ones that have a response at week 1 where it's not sustained. There is a lot of interest in pattern analysis, and people are looking at that, but actually, in terms of big trials, it's very little used.

L. Sheiner: The point that Nick Holford is making is a good one: serial measurements are very useful because they're connected in time. You expect to see trajectories, but when you know what that trajectory ought to look like, because you've got drug levels, or because you've got some kind of mechanistic basis for understanding, you're a lot more confident about using those dynamic measurements.

W. Deakin: One interesting thing that comes out of it is that if you look at the clinical time course of people who respond to placebo (20–30% respond to placebo) the time course is the same for responders to drug. All the anti-depressant drug seems to do is trigger a natural recovery that sometimes happens under placebo. I think that's an insight. It isn't necessarily that way, for some of the combined noradrenaline and 5-HT reuptake blockers, the responders improve quicker, in some studies, than the responders to placebo. It looks like it's doing better than natural recovery. So that's one use of the recurrent data.

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