Journal of Psychopharmacology Volume 11 Number 4 Supplement (1997) S25–S31

SAGE Publications, London, Thousand Oaks, CA and New Delhi

The enhancement of social functioning as a therapeutic principle in the management of depression

David Healy and Thomas McMonagle

North Wales Department of Psychological Medicine, Bangor, Wales, UK

It has long been considered that depression is a biochemical disorder resulting from dysfunction of monoamine systems in the brain and that antidepressants act upon these systems as 'magic bullets' to correct the lesion. An alternative hypothesis is that antidepressants act upon intact monoamine systems to produce functional changes that are not necessarily a reversal of the initial cause. If this is the case, one would expect that currently available classes of antidepressants would have overlapping spectra of therapeutic effects and that, while all may be effective in the majority of patients, some will be more useful according to individual needs. To date, the assessment of recovery from depression, using scales such as the Hamilton Rating Scale for Depression, has been physician centred. Such assessments leave open the possibility that patients may not have recovered in terms of their social adaptation and that, accordingly, the patients themselves and their relatives may not perceive them as having recovered. Findings of differences between antidepressants on the Social Adaptation Self-evaluation Scale highlight the importance of patient perception of treatment efficacy. These differences may indicate differences in efficacy not detected by conventional instruments, differences in tolerability, differences in the speed of onset of antidepressant activity, or differences in the behavioural profile produced by different classes of antidepressants.

Key words: depression; psychiatric status rating scales; psychological adaptation; reboxetine; self-assessment; social functioning

Introduction

Imagine a scenario in which a magician offers to provide the psychiatric community with the perfect antidepressant. The only requirement is that psychiatrists must stipulate what the drug should do in order to make the depressed patient well. An answer that it should simply 'make the patient well' will not suffice. There must be some specification of the means through which this drug will make the patient well. Probably few psychiatrists would currently be able to answer this question with confidence. In the field of ulcer therapeutics, however, a drug developer asking the question of gastroenterologists would not be faced with clinicians who simply say 'clear the ulcer up'. Clinicians or pathophysiologists might specify that the drug is required to reduce gastric acid secretion, increase mucus production, improve rates of wound closure or kill *Helicobacter pylori* organisms. There might, in other words, be differing preferences for a variety of therapeutic principles or an understanding that different therapeutic principles might apply in different patients, despite apparently identical clinical presentations. There would also be an understanding that rational therapeutics requires some specification of which functions are to be altered by treatment.

In the psychiatric field, however, clinicians are likely to be stumped by such questions, even though in the case of the antipsychotics, for example, there is a perfect correlation between the capacity of these drugs to reduce conditioned avoidance responses and their clinical activity. In the case of selective serotonin reuptake inhibitors (SSRIs), these drugs do something that cuts across syndromes of depression, obsessive compulsive disorder, social phobia and panic disorder, and this 'something' should be specifiable.

Therapeutic principles

Instead of specifying the functions that the psychotropic drugs affect, it has been assumed that these agents act directly on the core disturbances of an illness and that psychotropic drugs are 'magic bullets' targeting the 'lesion' in mood or other mental disorders. These assumptions were explicit in the first catecholamine and subsequent monoamine hypotheses. The success of the SSRIs has contributed to the impression that there is a serotonergic lesion in depression, and that while the SSRIs may not specifically correct that lesion, by acting on the serotonergic system, they come close to it and, by virtue of this, they make a significant difference. This impression has been created and sustained, despite the already existing evidence that drugs relatively selective to the catecholamine system, such as desipramine and nortriptyline, are also antidepressant agents. When faced with evidence that drugs which are relatively selective to either catecholamine or

serotonergic systems are both effective antidepressants, the traditional response has been to invoke a final common pathway in β-receptor downregulation or 5-HT_2 receptor changes, implicitly locating the 'lesion' in these receptors rather than specifying any functional consequences that might stem from receptor alteration.

An alternative response has been to postulate the notion of noradrenergic or serotonergic depressions with the implication that if the neurobiological status of particular patients could be pinpointed then the selection of the appropriate drug would enhance the chances of therapeutic success. On this basis, a good deal of research has been directed towards determining whether some individuals are 'noradrenergic deficient', as indicated by levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) and other catecholamine metabolites, or 'serotonergic deficient', which, it is assumed, will be revealed by evidence of reduced serotonin turnover in the form of lowered CSF 5-HIAA (Healy, 1987; Montgomery *et al.*, 1987; Healy, 1997; Montgomery, 1997). To date, neither efforts to distinguish different biochemical depressions nor to boost therapeutic responses by targeting those who have low levels of one or other neurotransmitter with an appropriate agent, has borne fruit. Moreover, the affective disorders have never looked like the inborn error of metabolism disorders that the above view of their nature would imply.

Implicit in these approaches is the notion that antidepressants are 'magic bullets' and therefore there is no need to specify any indirect functional changes, whether behavioural or physiological, that they need to produce in order to bring about recoveries. An alternative way of viewing these compounds is that, currently, we possess a variety of antidepressant principles or perhaps, more broadly speaking, anti-nervousness principles. If the nature of these principles can be specified more closely, it may allow us to deploy our therapeutic armamentarium more rationally.

Indeed, adopting this approach, it is possible to turn the argument about noradrenergic and serotonergic depressions around entirely and to suggest that it is expected that drugs which are active on the noradrenergic system would not work properly if there were abnormalities of the noradrenergic system. Equally, drugs active on the serotonergic system would be least likely to work effectively in the presence of abnormalities of that system. This argument is similar in form to the proposal that aspirin or other non-steroidal anti-inflammatory drugs would be least effective for arthritic conditions in individuals who had disorders of the prostaglandin pathways on which these agents act. On this basis, it might be argued that medications which are selective to a particular system are likely to be either ineffective or toxic to individuals with abnormalities of that system. Some indications of possible outcomes can be deduced from recent data presented by Brunner *et al.* (1993) on abnormal behaviour in individuals with monoamine oxidase deficiencies.

A consideration of the therapeutic possibilities of aspirin points to the fact that it can be anti-inflammatory, anti-pyretic and anti-thrombotic. Its useful deployment in clinical situations depends on understanding the nature of these actions rather than relying on the fact that aspirin acts on prostaglandin synthesis. What functional outcomes are there from actions on the noradrenergic or serotonergic systems?

In the field of personality biology, it has been traditional to suggest that the noradrenergic, dopaminergic and serotonergic systems have differing functions. A number of schemes have been produced (Cloninger, 1986; van Praag, 1992). According to most schemes, noradrenaline is particularly important in vigilance, serotonin in the regulation of impulse and irritability, and dopamine in the regulation of drive (Fig. 1).

If this scheme is followed, it becomes possible to suggest that drugs which act on the serotonergic system have an anti-irritability action of some form. This action might be expressed by a physician to a patient enquiring what the drug will do in terms such as 'it will make you sanguine'. This type of action will be 'anxiolytic' but it might be expected to provide a different type of anxiolysis to the anxiolysis, for example, that stems from the muscle relaxation provided by benzodiazepines. Benzodiazepines, in addition to other central actions, inhibit the feedback loop from muscular tension to mental state. This offers a therapeutic principle that can be expected to be useful in some but not all anxiety states. An action to reduce irritability offers a quite different therapeutic principle that might be expected to have benefits across a range of psychosyndromes, including some anxiety-based and some depression-based disorders. The drugs, in effect, may be operating to make someone sanguine, and where they are effective it may be because the introduction of sanguinity provides a space for other homeostatic mechanisms to come into play, which in turn promote a resolution of the index disorder.

While the monoamine hypotheses of the affective disorders embodied an implicit 'magic bullet' concept of the action of antidepressants, the idea that these drugs might contain a number of different therapeutic principles had been adumbrated by Kielholz (1968) and Carlsson (Carlsson *et al.*, 1969; Carlsson, 1982) amongst others. Drugs such as desipramine and nortriptyline were recognized to be more drive-enhancing than agents like clomipramine, which appeared to be doing something else. When the differing effects of these agents on catecholamine and serotonergic systems became clearer, it became obvious that there was a case for synthesizing the first SSRI, zimelidine, in the hope that a more selective action on the serotonergic system would underpin some other functional effect in mood disorders.

In the case of drugs active on the noradrenergic system, there is a consensus that these agents act on drive and vigilance to a much greater extent than drugs active on the serotonergic system. In so far as they do, they would target different aspects of the depressive syndrome to the SSRIs. Equally though, through what may be characterized provisionally as an anti-anergic action, this may impact on the disorder so that homeostatic mechanisms can come into play to promote a wider resolution of the condition. If something similar to this scenario is correct then one might expect more severe forms of depression, in which psychomotor retardation is frequently more pronounced (Parker and Hadzi-Pavlovic, 1996; Sobin and Sackheim, 1997), to be more likely to respond to these agents. There are a series of recent studies on reboxetine (Berzewski *et al.*, 1997; Dubini *et al.*, 1997a), milnacipram (Lopez-Ibor *et al.*, 1996) and mirtazapine (Wheatley and Kremer, 1997), which all point to the fact that an action on the noradrenergic system does confer benefits in the management of severe depression.

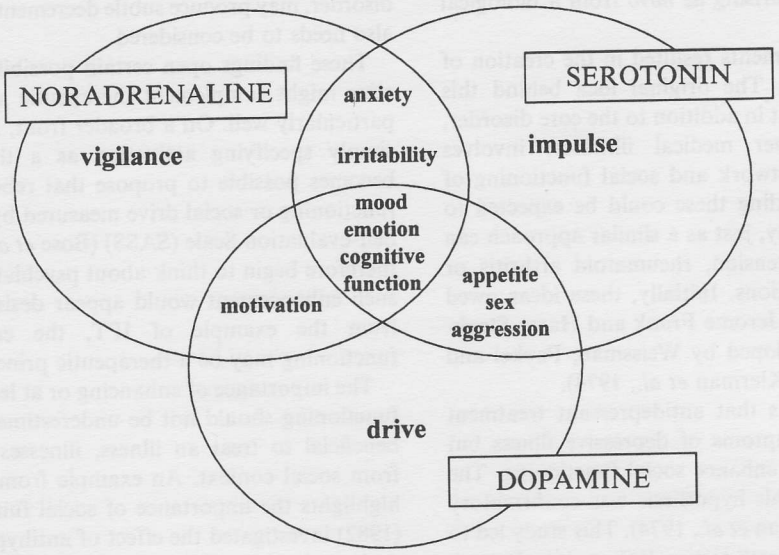

Figure 1 Schematic representation of different aspects of functioning attributed to noradrenaline, serotonin and dopamine

This analysis does not suggest that the use of these agents should be restricted to severe depression, merely that different therapeutic principles can be employed in different clinical situations. A further possibility is that mild to moderate depression characterized by lack of energy or complaints of being 'tired all the time' may be more likely to respond to agents like reboxetine, which are active on noradrenergic rather than serotonergic systems. Support for this concept comes from the social functioning data that demonstrates that reboxetine has a stronger effect on active social behaviour (e.g. gregariousness, community involvement) than fluoxetine (Dubini *et al.*, 1997a,b). Conversely, compounds active on the serotonergic system may be more useful in some cases of anxious depression. On the basis that both groups offer a therapeutic principle in depression rather than just in some depressions, both would be equally effective for the majority of cases of depression. Depression, like ulcers, is a trap and as with any trap there may be a number of ways out and the way out need not involve retracing the path of entry.

If the possibility that current antidepressants offer a number of therapeutic principles is accepted, further possibilities follow. The broad idea of actions on noradrenergic or serotonergic systems can be expanded further. In the case of agents like mirtazapine, for example, there may be more than one action on the serotonergic system – an agonist action on 5-HT_{1a} receptors and an antagonist action on 5-HT_2 receptors. This can be construed either in terms of blockade of 5-HT_2 receptors enhancing the efficiency of the action of the drug on 5-HT_{1a} receptors (i.e. there is only one therapeutic principle involved) or alternatively the action on 5-HT_{1a} receptors is an anti-irritability action while the blockade of 5-HT_2 receptors promotes sleep and appetite restoration, both of which can be expected to be therapeutic in depressive disorders. From this point of view, many psychotropic agents are in essence 'cocktail compounds', involving polypharmacy within the one compound.

If there is no 'central' mechanism in depression that is the target for 'magic bullets', but rather a variety of psychophysiological functions that we can modify to facilitate the restoration of homeostasis, perhaps one of these other functions might be amenable to modification, even by non-drug interventions, with equal therapeutic effect. A re-evaluation of antidepressant actions in terms of distinct therapeutic principles therefore opens up the possibility that a number of other approaches, including cognitive, interpersonal or behavioural therapies, may also be considered to offer certain therapeutic principles, which may be complementary to pharmacotherapeutic interventions. Indeed, the possibility must be considered that these non-pharmacotherapeutic interventions may exert some of their effects through a mobilization of biological processes.

Social functioning in depression

Following the introduction of the antidepressants and monoamine hypotheses of depression, there was an assumption that antidepressants, in 'magic bullet' fashion, corrected the core features of the illness and, for a while, it seemed quixotic to even consider treating a biological disorder like depression with a psychotherapeutic intervention. This divide between pharmaco- and psychotherapeutic approaches to the affective disorders began to yield, however, to work from Yale University, USA, carried out by Paykel, Weissman and Klerman. Their work was influential for two reasons. First, it provided evidence that life events, or environmental dislocations, could trigger cases that, until then, had been termed endogenous depressive disorders, a form of depression

that was commonly seen as arising *de novo* from a biological dysfunction.

The second set of developments resulted in the creation of interpersonal therapy (IPT). The original idea behind this therapeutic approach was that in addition to the core disorder, depressive illness, like other medical illnesses, involves disturbances in the social network and social functioning of the affected individual. Tackling these could be expected to reduce the burden of disability, just as a similar approach can make a difference in hypertension, rheumatoid arthritis or other chronic medical conditions. Initially, these ideas owed something to the thinking of Jerome Frank and Harry Stack-Sullivan, but they were developed by Weissman, Paykel and Klerman in the early 1970s (Klerman *et al.*, 1974).

The initial expectation was that antidepressant treatment would improve the core symptoms of depressive illness but that IPT would be shown to enhance social functioning. The first acute study to explore this hypothesis was confirmatory (Klerman *et al.*, 1974; Weissman *et al.*, 1974). This study led to suggestions that it might be worth testing IPT against the core features of depression itself, which led to a subsequent study that demonstrated an efficacy for IPT against these features of the illness (Weissman *et al.*, 1979). This breakthrough led to the inclusion of IPT in the National Institute of Mental health (NIMH) randomized trial comparing IPT with imipramine and cognitive therapy in the management of depressive disorders (Elkin *et al.*, 1989). This trial demonstrated an effectiveness of IPT in major depressive disorders and, indeed, a superiority of IPT to cognitive therapy, findings that led to its inclusion in prophylactic studies of affective disorders (Frank *et al.*, 1990).

The findings from the NIMH study, which demonstrated an efficacy of IPT in major depressive disorders, clearly support a therapeutic principle as opposed to a 'magic bullet' argument. The data also support the hypothesis that treatments may be less likely to be effective if the system they act on is dysfunctional. When the NIMH investigators looked at what predicted successful outcomes with both IPT and cognitive therapy, they found that a better social situation favoured a better outcome with IPT while success with cognitive therapy was more likely in the presence of fewer dysfunctional thoughts (Sotsky *et al.*, 1991).

To date, therefore, IPT has been shown to enhance social functioning in major depressive disorders and to tackle the acute symptoms of the disorder. Accordingly, acting on perceived difficulties in interpersonal function offers a therapeutic principle in the management of depression. The converse question – whether antidepressant pharmacotherapy can impact on social functioning in addition to addressing the core features of the illness – has not been closely addressed. One might expect there to be some enhancement of social functioning simply by virtue of ameliorating the core features of the illness, but the differential effects found in comparative studies of reboxetine and fluoxetine indicate that something more than simply this may be happening (Dubini *et al.*, 1997b). Where both agents may produce some enhancement in social functioning simply by virtue of recovery from the underlying disorder, reboxetine appears to provide additional benefits to the depressed patient. The alternative explanation—that fluoxetine, while proving beneficial on core features of the disorder, may produce subtle decrements in social functioning—also needs to be considered.

These findings open certain possibilities. Drugs like reboxetine might complement therapeutic approaches such as IPT particularly well. On a broader front, however, as opposed to simply specifying activation as a therapeutic principle, it becomes possible to propose that reboxetine enhances social functioning or social drive measured by the Social Adaptation Self-evaluation Scale (SASS) (Bosc *et al.*, 1997). Clinicians can therefore begin to think about psychiatric conditions in which such enhancement would appear desirable. As we have seen from the example of IPT, the enhancement of social functioning may be a therapeutic principle in its own right.

The importance of enhancing or at least not impairing social functioning should not be underestimated. While it is always beneficial to treat an illness, illnesses rarely come divorced from social context. An example from hypertension research highlights the importance of social functioning. Jachuk *et al.* (1982) investigated the effect of antihypertensive treatment on patients in a novel manner. They observed satisfaction with treatment from the point of view of the physician, the patient and the relatives. Physicians were completely satisfied with the treatment that appeared to be 100% successful based on their criterion for evaluating the outcome, a drop in mercury on the sphygmomanometer. Patients had mixed views on the outcome; only half reported satisfaction with treatment. The origins of the patients' satisfaction were poorly characterized. It may simply have reflected satisfaction at the physician's satisfaction. The assessment of relatives, however, was uniformly poor. Only one of 75 relatives assessed treatment as providing a benefit. Seventy-four considered the outcome to be worse. Relatives did not see the changes in the mercury column, but saw instead a patient who had either become a hypochondriac or who had developed side-effects from treatment. They saw an individual who, for one reason or another, had become symptomatic where they had not been before, and these symptoms impinged on social functioning in a way the target illness had not (Jachuk *et al.*, 1982).

The success of treatments in many areas of medicine has depended on assessments that only take into account one point of view – that of the treating physician. This bias arguably renders many studies less empirical and less scientific than they often claim to be. This is as true of the assessments of therapeutic outcome in depression as it is for hypertension. Instruments such as the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Bech, 1989) are intensely individualistic in their focus. The potential problems with an over-reliance on selective rating instruments were highlighted by Nathan Kline as early as 1956, when he suggested that taking this kind of approach to the evaluation of treatment rather than looking at larger frame social outcomes risked creating a version of the rabbit in the hat trick (Kline, 1959). Adapting Kline, there has to be a hint of suspicion that the demonstrable efficacy of certain tricyclic antidepressants is reliant on the fact the that HAM-D conveniently incorporates many clinical features relieved by tricyclic antidepressants. A similar case can be made for cognitive therapy and the BDI.

In contrast, a range of other features related to social functioning, such as sensitivity to criticism from significant

others (Hooley *et al.*, 1986), have been shown in repeated studies to predict chronicity of affective disorders but, to date, have not been incorporated in assessment instruments.

Depression is a quite different illness to hypertension in that in hypertensive disorders the undetected illness has little or no impact on family or work functioning, unless it leads to stroke or cardiovascular accident. The impact of adverse effects on social functioning as a consequence of treatment may, therefore, be particularly salient in the case of hypertension. Depressive disorders, in contrast, necessarily have an extensive impact on work and family functioning. A treatment that would further compromise social functioning may not be as readily noticed against a background of prior difficulties. The introduction of an assessment of social functioning into pharmacotherapeutic studies of depression is, from this perspective, welcome and may in due course be a potent instrument for evaluating the relative pharmacoeconomic benefits of different treatments (Weissman, 1997).

Biology is social

Quite apart from illness being a social event, biology is also inherently social, as sexual differentiation, the organization of social life in accord with circadian rhythms, and the findings of interaction between social rank and endocrine status (Sapolsky, 1990, 1991, 1992) all clearly indicate. In recent years, we have been studying the role of circadian rhythms in affective disorders. This has led to the development of a shift-work model of affective disorders (Healy and Waterhouse, 1991). Investigating this further, we looked at aspects of social, neurobiological and psychological functioning in a group of 100 healthy student nurses prior to a first block of night work and, subsequently, following a three-month block of night work (Healy *et al.*, 1993; Adeniran *et al.*, 1996). Night work produced all of the major core symptoms of depressive disorder – disturbances of sleep, appetite, interest, motivation and concentration. It produced hopelessness concerning the future and social dislocation. It also produced a sensitivity to interpersonal criticism that had not been predicted a priori. Indeed, night work produced both an increased sensitivity to criticism from significant others and, in addition, the level of sensitivity to criticism from significant others prior to starting night work predicted how symptomatic the individual would become during the subsequent block of night work. This led us to suggest that these findings complemented the evidence that therapeutic manoeuvres which focused on perceived social functioning were of benefit in cases of depression and perhaps provided some hints regarding mechanisms that might mediate these effects.

It was not possible to tease out the direction of effects from our study, but there appeared to be a close relationship between circadian rhythm disruption, the production of the irritability, and perceived changes in the quality of relationships with significant others. In retrospect, this should not be surprising as human biology is social. The impact of significant others on our biology and in stabilizing that biology in productive patterns has been neglected to date. When taken into account, however, it should be clear that this impact must necessarily be considerable.

A new scale and treatment that offers the opportunity to explore these relationships further is therefore welcome. The findings with reboxetine on the SASS are consistent with suggestions from a range of other studies, which indicate that treatments acting on catecholaminergic systems produce better results than agents acting on serotonergic systems when the outcome measures involve self-report instruments such as the Zung (Zung, 1965) or the BDI (Bech, 1989). But what could differences in outcome on such scales mean?

One possibility is that the scale may reflect the impact of the broad functional changes produced by the drug. This returns us to the main argument of this paper, which is that antidepressants are not simply antidepressants, they are antidepressant by virtue of some functional change they induce. In the case of drugs active on the serotonergic system, we have characterized this provisionally as inducing sanguinity. Sanguinity may be therapeutically useful but it may also have its drawbacks. It suggests detachment, in contrast to an action to enhance drive. These differences may be reflected in instruments such as the SASS or other self-report measures.

A second possibility is that the differences that have been demonstrated on self-report measures, such as the SASS, reflect speed of onset of antidepressant action. There is a substantial body of evidence associating actions on catecholaminergic systems with earlier onsets of antidepressant effects (Potter and Manji, 1994), despite the fact that earlier onset effects have been difficult to demonstrate in clinical trials using conventional assessment instruments such as the HAM-D or the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). These latter instruments measure a different domain of functioning to that measured by the SASS or other self-report measures. The SASS may be more sensitive to changes in functions that contribute to an impression of recovery. Further data on the effects of reboxetine and fluoxetine on perceptions of social functioning in studies with a longer trial period, or in patients who have failed to respond as assessed on measures such as HAM-D, might help address this issue.

A third possibility is the SASS may be sensitive to the impact of side-effects. Impairments of sexual functioning, for example, while not showing on assessments of recovery from depression, or indeed on formal side-effect measurements, may be evident in areas of social functioning. Indeed, estimates of social functioning may provide a means to assess the overall impact of both primary and secondary effects of treatment. To date, there has been no satisfactory method to weight the dry mouth caused by tricyclic antidepressants against the jaw dyskinesias that may be caused by SSRIs (Fitzgerald and Healy, 1995). Assessments of social functioning, amongst others, by offering some measure of an individual's assessment of the overall impact of treatment, may in fact perform this function.

Finally, another possibility is that the SASS measures the impact of selective therapeutic principles on particular personality types. Personality in one sense is the ultimate expression of biology in action in a social context. Eysenck and colleagues in the 1950s and 1960s were able to demonstrate that a range of sedatives and stimulants had predictably different impacts according to personality (Claridge and Healy, 1994). Extroverts were sedated by much smaller doses of a sedative than introverts. This was taken as indicating distinct differences in

the constitutional/biological underpinnings of personality, a position that has subsequently been developed by Kagan (Kagan, 1994). Eysenck's early work was recast by Gray (1982) in terms of behavioural activation and behavioural inhibition systems, with disturbances of either having the potential to lead to nervous disorders. Noradrenaline has traditionally been associated with the behavioural activation system and serotonin with the behavioural inhibition system. Some of the dramatic 'better-than-well' responses, which appear to occur in a small proportion of patients taking agents selective to the serotonin system (Kramer, 1993), may stem from this source. Similar effects in a different set of depressed patients may occur with agents selective to catecholamine systems. For a small number of depressed patients, therefore, there may be dividends in selecting treatments according to the premorbid personality type of the sufferer.

In summary, using reboxetine and early clinical trials in depressive disorders as a case study, we have introduced the notion that antidepressant treatment should be conceived as offering a range of therapeutic principles that can best be deployed if the nature of those principles is understood and the potential benefits offered are matched to the disabilities of the treatment population. As long as all antidepressants have equivalent results on major outcome measures, a therapeutic principle as opposed to 'magic bullet' argument is more difficult to sustain. In contrast, the fact that reboxetine differs from fluoxetine on the SASS poses problems for a 'magic bullet' argument. The full potential of an alternative therapeutic principle approach will require a mapping of the argument onto the profiles of action for both other antidepressants and available antipsychotic agents.

Address for correspondence

Dr David Healy
North Wales Department of Psychological Medicine
Hergest Unit
Bangor LL57 2PW
Wales
UK

References

Adeniran R, Healy D, Sharp H M, Williams J M G, Minors D S, Waterhouse J M (1996) Interpersonal sensitivity predicts depressive symptom response to the circadian rhythms disruption of night work. Psych Med *26*: 1211–1221

Bech P (1989) Clinical effects of selective serotonin reuptake inhibitors. In Dahl SO, Gram LF (eds), Clinical pharmacology in psychiatry. Springer-Verlag, Berlin *7*: 81–93

Berzewski H, Van Moffaert M, Gagiano C A (1997) Efficacy and tolerability of reboxetine compared with imipramine in a double-blind study in patients suffering from major depressive episodes. Eur Neuropsychopharmacol *7 (Suppl. 1)*: S37–S47

Bosc M, Dubini A, Polin V (1997) Development and validation of a social functioning scale, the Social Adaptation Self-evaluation Scale. Eur Neuropsychopharmacol *7 (Suppl. 1)*: S57–S70

Brunner H G, Nelen M, Breakefield X O, Ropers H H, van Oost B A (1993) Abnormal behaviour associated with a point mutation in the structural gene for monoamine oxidase A. Science *262*: 578–580

Carlsson A (1982) Rationale and design of a selective inhibitor of 5-HT re-uptake. Br J Clin Pract *19 (Suppl.)*: 19–21

Carlsson A, Corrodi H, Fuxe K, Hökfelt T (1969) Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-alpha-ethyl-metatyramine. Eur J Pharmacol *5*: 357–366

Claridge G, Healy D (1994) The psychopharmacology of individual differences. Hum Psychopharmacol *9*: 285–298

Cloninger C R (1986) A unified biosocial theory of personality and its role in the development of anxiety states. Psych Dev *3*: 167–226

Dubini A, Bosc M, Polin V (1997a) Do noradrenaline and serotonin differentially affect social motivation and behaviour? Eur Neuropsychopharmacol *7 (Suppl. 1)*: S49–S55

Dubini A, Bosc M, Polin V (1997b) Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. J Psychopharmacol *11(Suppl.)*: S17–S23

Elkin I, Shea T, Watkins J T, Imber S D, Sotsky S M, Collins J F, Glass D R, Pilkonis P A, Leber W R, Docherty J P, Fiester S J, Parloff M B (1989) National Institute of Mental Health treatment of depression collaborative program: general effectiveness of treatments. Arch Gen Psychiatr *46*: 971–986

Fitzgerald K, Healy D (1995) Dystonias and dyskinesias of the jaw associated with the use of SSRIs. Hum Psychopharmacol *10*: 215–220

Frank E, Kupfer D J, Perel J M, Comes C, Jarrett D B, Masllinger A G, Thase M E, McEachran A B, Grochocinski V J (1990) Three year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatr *47*: 1093–1099

Gray J A (1982) The neuropsychology of anxiety. Oxford University Press, Oxford

Hamilton M (1960) A rating scale for depression. J Neuro Neurosurg Psych *23*: 56–62

Healy D (1987) The structure of psychopharmacological revolutions. Psych Dev *5*: 349–376

Healy D (1997) The antidepressant era. Harvard University Press, Boston

Healy D, Waterhouse J M (1991) Reactive rhythms and endogenous clocks: a shift work model of affective disorders. Psych Med *21*: 557–564

Healy D, Minors D S, Waterhouse J M (1993) Shiftwork, helplessness and depression. J Affect Dis *29*: 17–25

Hooley J M, Orley J, Teasdale J D (1986) Levels of expressed emotion and relapse in depressed patients. Br J Psychiatr *148*: 642–647

Jachuk S J, Brierley H, Jachuk S, Willcox P M (1982) The effect of hypotensive drugs on the quality of life. J Roy Coll Gen Pract *32*: 103–105

Kagan J (1994) Galen's prophecy. The role of temperament. Basic Books, New York

Kielholz P (1968) Die Behandlung endogener Depressionem mit Psychopharmaka. Deutsch Med Wochenschrft *93*: 701–710

Klerman G L, DiMascio A, Weissman M M, Prusoff B, Paykel E S (1974) Treatment of depression by drugs and psychotherapy. Am J Psychiatr *131*: 186–191

Kline N S (1959) Scales and checklists. In Cole J O, Gerard R W (eds), Psychopharmacology: problems in evaluation. National Academy of Sciences/National Research Council, Washington DC, pp. 485

Kramer P (1993). Listening to Prozac. Viking Penguin, New York

Lopez-Ibor J, Guelfi J, Pletan Y, Tournox A, Prost J F (1996) Milnacipram and selective serotonin reuptake inhibitors in major depression. Int Clin Psychopharmacol *11 (Suppl. 4)*: 41–46

Montgomery S A (1997) Is there a role for a pure noradrenergic drug in the treatment of depression? Eur Neuropsychopharmacol *7 (Suppl. 1)*: 3–9

Montgomery S A, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psych *134*: 382–389

Montgomery S A, James D, Montgomery D B (1987) Pharmacological specificity is not the same thing as clinical selectivity. J Psychopharmacol *3*: 179–183

Parker G, Hadzi-Pavlovic D (1996) Melancholia. A disorder of movement and mood. Cambridge University Press, Cambridge

Potter W Z, Manji H K (1994) Clinical onset of antidepressant action: implications for new drug development. In Langer S Z, Brunello N, Racagni G, Mendlewicz J (eds), Critical issues in the treatment of affective disorders. Karger, Basel, pp. 118–126

Sapolsky R M (1990) Adrenocortical function, social rank and personality among wild baboons. Biol Psychiatr *28*: 862–878

Sapolsky R M (1991) Testicular function, social rank and personality among wild baboons. Psychoneuroendocrinol *16*:281–293

Sapolsky R M (1992) Cortisol concentrations and the social significance of rank instability among wild baboons. Psychoneuroendocrinol *17*: 701–709

Sobin C, Sackheim H A (1997) Psychomotor symptoms of depression. Am J Psychiatr *154*: 4–17

Sotsky S, Glass D R, Shea M T, Pilkonis P A, Collins J F, Elkin I, Watkins J T, Imber S D, Leber W R, Moyer J, Oliveri M E (1991) Patient predictors of response to psychotherapy and pharmacotherapy: findings of the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatr *148*: 997–1008

van Praag H (1992) 'Make-believes' in psychiatry or the perils of progress. Brunner-Mazel, New York

Weissman M M (1997) Beyond symptoms: social functioning and new antidepressants. J Psychopharmacol *11(Suppl.)*: S5–S8

Weissman M M, Klerman G L, Paykel E S, Prusoff B A, Hanson B (1974) Treatment effects on the social adjustment of depressed patients. Arch Gen Psych *30*: 771–778

Weissman M M, Prusoff B, DiMascio A, Neu C, Goklaney, Klerman G L (1979) The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. Am J Psychother *136*: 555–558

Wheatley D, Kremer C (1997) A randomized double-blind comparison of mirtazapine and fluoxetine in patients with major depression. American Psychiatric Association, Annual Meeting, San Diego, May 1997 Abstract NR208

Zung W H K (1965) A self-rating depression scale. Arch Gene Psych *12*: 53–70

PX10393.00