Research report

The clinical pharmacologic profile of reboxetine: does it involve the putative neurobiological substrates of wellbeing?

David Healy[a,*], Helen Healy[b]

[a]*North Wales Department of Psychological Medicine, Hergest Unit, Bangor LL57 2PW, UK*
[b]*Institute for Medical and Social Care Research, University of Wales, Bangor, UK*

Abstract

Following a review of the clinical trials of reboxetine, a new nonadrenegic reuptake inhibitor antidepressant, this paper presents a heuristic theoretical framework to better understand selective antidepressant action. For over three decades, the dominant views of antidepressant action have seen these agents active across all constitutional types and regardless of social setting. An increasing number of studies using quality of life methods are at odds with this view. This paper summarizes several of these studies, along with two studies of the effects of reboxetine on the quality of life, which reveal differential effects of selective agents that demand alternative explanations to the conventional monoamine theories. The authors submit that any revisions in our understanding of what is happening will have to pay attention to temperamental inputs that antedate affective episodes and to the sense of wellbeing and level of residual symptoms patients have on treatment after the acute phase of their illness has remitted. Obviously much more research needs to be done in this area. This invited paper sketches out, in very general terms, some provocative possibilities of how future understanding of antidepressants, temperament and their neurobiologic substrates could lead to better matching of specific antidepressants to specific temperament types. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Antidepressant; Reboxetine; Monoamine theories; Temperament; Quality of life

1. Introduction

In the mid 1960s, Paul Kielholz surveying the then available antidepressants, suggested that some depressed individuals get well by enhancing drive, while others help by doing something else which was either more mood enhancing or more anxiolytic (Kielholz, 1968; Healy, 1997). The implication was that the range of different antidepressants embodied a number of different therapeutic principles. Two important developments supervened which tended to obscure the recognition of possible differences. One was the emergence of the monoamine theories of depression (Schildkraut, 1965; Bunney and Davis, 1965), which posited a common catecholamine lesion in mood disorders, which all antidepressants,

*Corresponding author. Tel.: + 44-1248-384452; fax: + 44-1248-371397.

E-mail address: healy_hergest@compuserve.com (D. Healy)

regardless of their therapeutic class, acted to correct. The second was the adoption of rating scales such as the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory, reinforcing the impression that one was measuring the specific symptoms of a discrete disorder or disease entity (Healy, 1998a).

The catecholamine hypothesis was quickly complemented by an indoleamine hypothesis (Coppen, 1967 and 1972). This gave rise to the possibility that there might be catecholaminergic and serotonergic depressions. This issue was investigated extensively through the 1970s and early 1980s without a clearcut conclusion (Maas et al., 1984). Subsequent work with tryptophan-depletion and AMPT-challenge paradigms, however, has pointed to distinctive roles for the calecholamine and serotonin systems in mood disorders (Delgado et al., 1991 and 1993). This body of work has generally been interpreted in terms of discrete monoamine lesions, despite the fact that evidence of biochemical differences between subjects and differential responses to antidepressants might just as well stem from temperamental differences between subjects. Also consistent with a temperamental view of mood disorders, Delgado and colleagues have noted that their findings may speak primarily to a role for catecholamines or serotonin in the action of selective antidepressants rather than as evidence of a monoamine lesion.

Faced with Kielholz's schema, Arvid Carlsson suggested that those agents which were drive enhancing had preferential actions on catecholamine systems and those that were doing something else acted on the serotonin (5HT) system (Carlsson et al., 1969; Carlsson, 1996). This insight ultimately led to the creation of the 5HT Reuptake Inhibitors (SSRIs), of which zimelidine, in 1971, was the first patented and indalpine, in 1978, was the first released into clinical use. A subsequent generation of SSRIs came into clinical practice from about the mid-1980s. Despite the fact that the SSRIs were only developed because antidepressants differed in their functional effects and although they embodied a selective therapeutic principle, the dominant views of the day continued to see all antidepressants as somehow acting on some final common pathway. From 1975 through to 1985, this was beta adrenoceptor downregulation (Vetulani et al., 1996), while more recently the focus has been on 5HT-1a receptors (Artigas et al., 1994). Functional differences between the SSRIs and other antidepressants, on either a physiological or on a behavioral level, have been ignored in favour of views which emphasize crosstalk between monoamine systems (Manier et al., 1984).

Clinically, the SSRIs were quickly compared with the tricyclic antidepressants (TCAs) from the points of view of safety in overdose and freedom from side-effects, such as excess sedation and weight gain. This profile of effects made them more suitable for wider use in primary care depressive disorders than the TCAs had been. The area of primary care mood disorders, which almost certainly embraces a range of conditions, in which there are varying pharmacogenetic, temperamental and psychosocial inputs, provides possibilities for investigations with antidepressants of different pharmacological profiles. To date, these possibilities have not been addressed, owing in part to the side-effect profile of the older TCAs. The emergence of a selective norepinephrine reuptake inhibitor, reboxetine, which is neither sedative nor associated with weight gain and which is safe in overdose (Montgomery, 1997), might help us obviate some of these problems. It is now, in principle, possible to begin to examine the effects of different therapeutic interventions against a background of differing temperament types, different pharmacogenetic profiles and different comorbidities, in a way that has been impossible hitherto.

2. Reboxetine: pharmacological profile

Reboxetine is a selective norepinephrine reuptake inhibitor derived from viloxazine. Unlike previous norepinephrine reuptake inhibitors, clesipramine, maprotiline and lofepramine, it has no significant effects on histaminic or cholinergic receptors or on adrenergic receptors other than the norepinephrine reuptake site (Brunello and Racagni, 1998).

In animal studies the potential antidepressant activity of reboxetine was first brought to light in the 1980s by its antagonism of reserpine-induced hypothermia and blepharospasm (Melloni et al., 1984), as well as antagonism of clonidine-induced hypothermia (Melloni et al., 1984). Indeed its antagonism of

clonidine-induced hypothermia was more rapid than that with available tricyclic antidepressants, suggesting that it might have a faster rate of onset than ether antidepressants; it prevented clonidine-induced hypothermia after a single dose, where chronic dosing was needed with the tricyclic antidepressants.

Reboxetine appears to be devoid of significant inhibitory effects on common cytochrome P450 enzyme systems (Dostert et al., 1997). In humans, its half life is approximately 13 h, permitting single daily dosage, although it has been studied in clinical trials in a b.i.d regime. Unlike the tricyclic antidepressants, the recommended dose 8 mg per day can be given on initiating therapy. The drug, therefore, appears suitable for use in primary care by virtue of its dose regimen and its low liability for drug–drug interactions. It is also potentially suitable for use in combination with other psychotropic agents, by virtue of its lack of 5HT-reuptake inhibiting properties as well as the lack of significant monoamine-oxidase inhibiting properties (Dostert et al., 1997; Brunello and Racagni, 1998)

2.1. Reboxetine: clinical trials

Short. term controlled clinical trials with reboxetine have been conducted against placebo, desipramine (150–200 mg/day), imipramine (150–200 mg/day) and fluoxetine (20–40 mg/day) (Montgomery, 1997). Inpatients or outpatients with a diagnosis of major depressive disorder according to DSM-III or DSM-IIIR (APA, 1980; 1987) have entered a total of eight randomised double-blind clinical trials with reboxetine (8–10 mg per day in adults or 4–6 mg per day in the elderly) versus other agents. The Hamilton Depression Rating Scale (Hamilton, 1960) was used as the primary measure of efficacy. Other measures included the Montgomery Asberg Depression Rating Scales (Montgomery and Asberg, 1979) and a Clinical Global Impression Scale (Guy, 1976), as well as a patient self-assessment measure of social functioning, the Social Adaptation Self-Evaluation Scale (SASS) (Bosc et al., 1997) which was used in the two fluoxetine-controlled studies.

The SASS is a 20-item questionnaire, taking 5 min to complete, which was developed on the basis that a drug active on catecholamine systems might show greater effects in areas of motivation than a drug active on 5HT systems (Dubini et al., 1997; Bosc et al., 1997). The SASS derives originally from assessments of social functioning by Myrna Weissman and Eugene Paykel in the mid-1970s, which led to the development of a social adjustment scale (SAS) (Weissman et al., 1974; Weissman, 1997). The original Weissman-Paykel approach involved observer-based assessments of social functioning. Assessing the area of social adjustment/social function through self-report produces a scale that overlaps heavily with many quality of life scales. This area is clearly of importance as there are indications that patient perceptions of well being as assessed by quality of life measurements may predict the stability of clinical response in the longer term (Thunedborg et al., 1995) The SASS was validated in French samples. While Danish, Finnish, English and Spanish versions now exist, it remains to be established that these translated versions possess the same psychometric properties and validity when applied to a range of populations of varying ethnic and cultural backgrounds.

Two short-term double blind studies compared reboxetine to placebo in acute depression in both inpatients and outpatients between the ages of 18 and 65 and in both instances reboxetine was clearly superior (Montgomery, 1997). A study comparing reboxetine and imipramine in adult patients found a significantly greater response rate with reboxetine than with imipramine with a significantly lower frequency of anticholinergic, sedative and cardiovascular adverse events in the reboxetine group (Berzewski et al., 1997). A study comparing reboxetine with imipramine in the elderly showed similar response rates with both active drugs and fewer adverse events with potentially serious consequences in the reboxetine group (Mucci, 1997).

Two short-term studies were conducted comparing reboxetine and fluoxetine, one of which contained a placebo arm. Using observer-rated disease specific instruments, such as the HDRS, both active drugs proved equivalent to each other and in the placebo controlled study, they both proved superior to placebo (Montgomery, 1997; Massana et al., in press; Healy, 1998a; 1998b). A further trial compared reboxetine with desipramine and placebo, in which reboxetine proved superior to placebo where

desipramine did not (Ban et al., 1998). In a long-term placebo-controlled study of 283 patients on either reboxetine or placebo, followed up over a 12-month period, it was found that there was a significantly lower rate of relapse on reboxetine compared to placebo (Montgomery, 1997).

Using placebo-controlled studies to define reboxetine's tolerability profile, the most common adverse events associated with its use have been dry mouth, constipation, sweating and insomnia. The occurrence

of some 'anticholinergic'-type side-effects may reflect reboxetine's central norad energic reuptake inhibition (Szabadi et al., 1998). Serotonergic-type side effects were no more common on reboxetine than on placebo. In clinical trials, reboxetine had minimal effects on the cardiovascular system and early clinical experience suggests a low toxicity in overdose (Baldwin et al., 1998).

In order to test for differential effects between norepinephrine selective and serotonin selective agents, the SASS was incorporated in the two short-term reboxetine-fluoxetine studies. In the placebo-controlled study, both active agents produced significantly greater improvements in social functioning than placebo on SASS scores (Fig. 1; Dubini et al., 1997). The reboxetine results at last assessment were in addition significantly better than the fluoxetine results both in the overall group (Fig. 2) and in those who were defined as responders (Fig. 3) according to a HDRS criterion (HDRS ≤ 10). In the overall group, reboxetine was significantly superior to placebo on all items of the scale and superior to fluoxetine on nine items of the scale. In those defined as responders, reboxetine was superior to fluoxetine on 14 of the 20 items on the scale. A second study, which directly compared reboxetine and fluoxetine
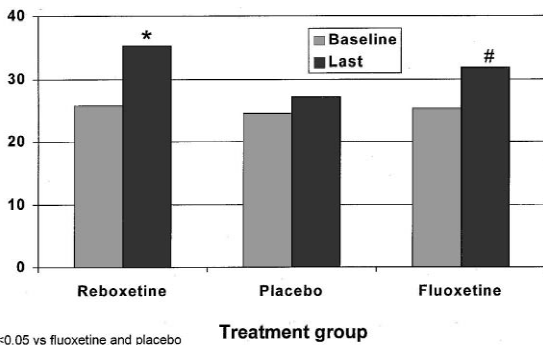
Fig. 1. SASS total score: mean values at baseline and at last assessment in the reboxetine, placebo and fluoxetine groups.
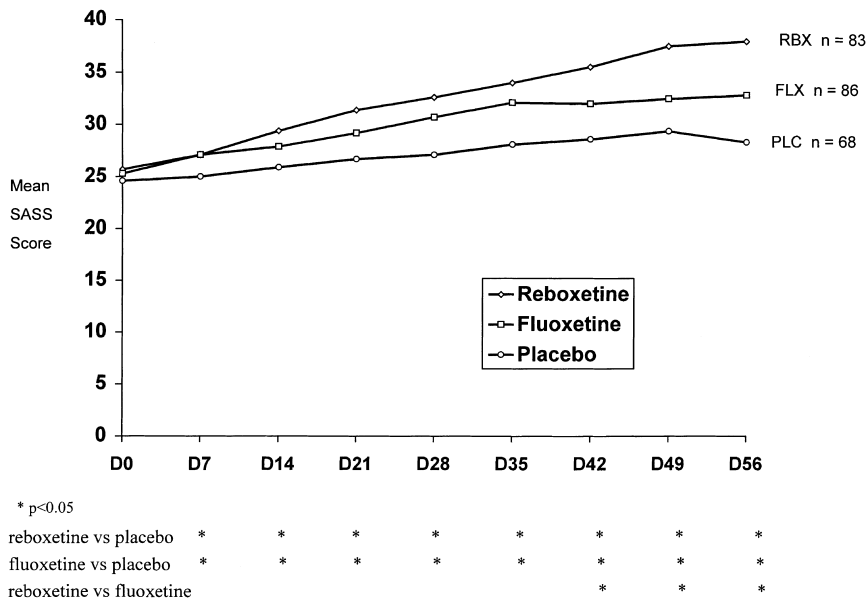

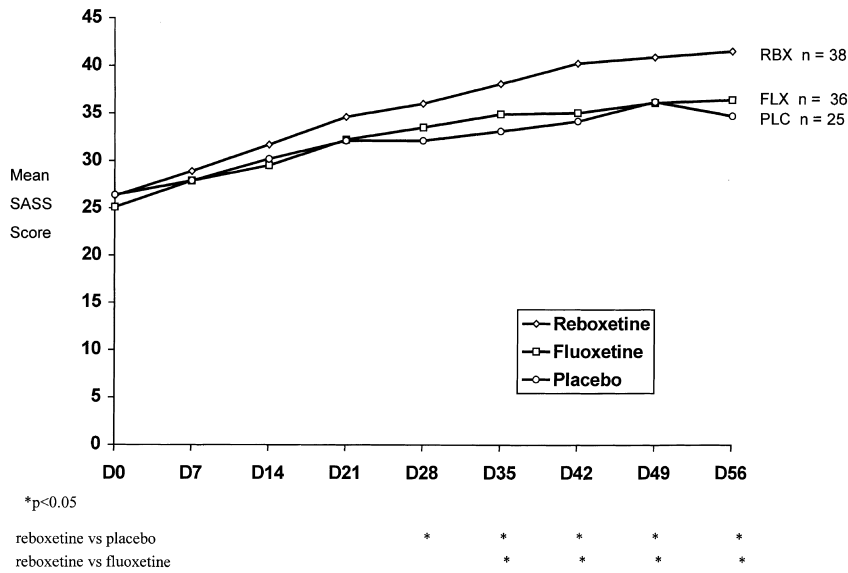Fig. 2. SASS scores: overall population.

Fig. 3. SASS scores: patients in remission.

gave similar results (Massana et al., in press). Reboxetine was associated with a return to SASS scores in the normal range (35–52), whereas fluoxetine was not (Figs. 2 and 3). Taking the responder group only, the mean figures translate as follows: over three-quarters of those defined as well by the HDRS defined themselves as well on the SASS, whereas less than two-thirds of those taking fluoxetine and defined as well on the HDRS defined themselves as well on the SASS (Fig. 3). These differences between the drugs do not appear to stem from a differential efficacy, at least as conventionally defined, as HDRS scores were similar for both groups (Fig. 4).

2.2. Discussion

These results from clinical trials, in conjunction with the results of preclinical studies, strongly suggest that reboxetine is an agent possessing antidepressant properties with a treatment effect size in the range of standard antidepressants and a favorable pharmacogenetic and tolerability profile. The differential effects of reboxetine and fluoxetine on the SASS have a particular significance for the management of primary care mood disorders as reboxetine's comparative tolerability and safety means that, like
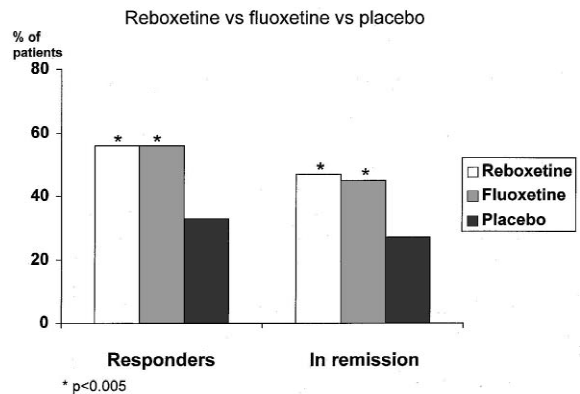

Fig. 4. Reboxetine versus fluoxetine: response to treatment.

fluoxetine, it is likely to be deployed most extensively in primary care settings.

The effects of reboxetine have implications for our notions of what antidepressants 'treat' in patients with mood disorders. They also yield indications for effects these agents have on how well patients feel when they have been restored to 'normal' that may have consequences for the longer-term management of these conditions. The discussion section of this paper will focus on what current data support on the issue of what antidepressants treat in patients with mood disorders. An additional more speculative

commentary section will tackle the second issue of wellbeing in the maintenance phase of treatment.

The demonstration that both selective norepinephrine uptake inhibitors and selective serotonergic reuptake inhibitors get primary care depressed patients well has implications for our notions of what antidepressants do. While there are some indications that drugs active on norepinephrine systems are more likely to benefit patients with classic melancholic features, such as loss of energy and loss of interest and to benefit more severely depressed patients (Nelson et al., 1984; Nelson and Mazure, 1990), the majority of mild to moderate primary care depressions, in the light of these results with reboxetine, a priori would appear to stand a roughly equal chance of having the core features of their disturbance ameliorated by a variety of different therapeutic agents. This is an argument against any common mechanism of action of the antidepressants. By extension, it suggests that whatever lesion or lesions there may be in depressive disorders, these do not lie in the monoamine systems on which the majority of antidepressants act.

There are a number of other features of antidepressant actions, which support such an interpretation. One is the fact that the SSRIs in particular have effects across a variety of conditions such as social phobia, obsessive compulsive disorder, panic disorder, body dysmorphic disorder and posttraumatic stress disorder (PTSD) in addition to mood disorders (Goodnick and Goldstein, 1998). Indeed their treatment effect sizes for these other conditions may be greater than the effect size in severe mood disorders. In contrast, while norepinephrine reuptake inhibitors are useful for depressive disorders and possibly panic disorder, they are likely to be useful for a different spectrum of disorders, including attention deficit hyperactivity disorder and pain syndromes (Leonard and Healy, 1998), than the SSRIs. A differential efficacy across a range of conditions suggests that these differing therapeutic principles produce distinctive functional changes. These functional changes have a modest therapeutic benefit across a range of quite different psychopathological syndromes rather than a large and specific therapeutic benefit for particular conditions (Healy, 1998b).

In the case of the SSRIs there is good evidence that these agents can produce a reduction in emotional reactivity to stressors. The possible physiological underpinnings of this effect may involve a dampening action of 5HT on locus coeruleus reactivity to excitation. It has been shown that the excitatory effects of the main excitatory neurotransmitter, glutamate, on the locus coeruleus are blocked by 5HT (Aston–Jones et al., 1991; Svensson, 1997). This functional effect probably rather precisely underpins the role of SSRIs in dampening unwanted reactivity in PTSD. Behaviorally, such a physiological effect would be expressed in terms of increased sanguinity. This is the kind of effect that could be expected to have a modest utility across a range of conditions such as OCD, social phobia and panic disorder. An alternative is that the treatment effect size might be quite different in different personality types. Where an induction of sanguinity might be of benefit in all personality types in the case of PTSD, in the management of depression a dampening of responsiveness to the environment might be more welcome in some personality types, such as obsessives, than in others. The precise nature of the behavioral effect produced by norepinephrine reuptake inhibitors (NRI) remains to be specified clearly. A long tradition, stemming from Hess, of seeing the norepinephrine system as the 'ergotrophic' system suggests that NRIs act to facilitate behavioral output by enhancing social drive and motivation, as well as vigilance (Svensson, 1997; Healy and McMonagle, 1997).

Further clinical studies will be needed to tease apart some of the issues here. These will include studies of reboxetine across a range of other conditions such as OCD, social phobia and PTSD. Comparative studies of selective agents in depressions with comorbid personality disorders are also called for. Finally, it will be important to study reboxetine using a range of other quality of life arid social functioning instruments.

3. Toward a new theoretical framework of antidepressant action

In addition to the effect of reboxetine on conventional indicators of antidepressant efficacy, the findings of differential effects between it and fluoxetine on the SASS attract discussion and comment. These

findings are of interest as differential effects of this type are rarely reported and as such were unexpected. A number of cautions are in order. First, it remains to be seen if these findings can be replicated with better known instruments such as the SF-36, which has been far more extensively used and whose psychometric properties have been explored in greater detail. Second the database from which conclusions can be drawn remains very small. For example, it will be important in due course to establish what contribution a differential burden of side-effects may have contributed to the picture revealed by the SASS findings but the current database is too small to permit a convincing analysis of this question. It is also important to note the SASS is a self-report scale. As such it is by no means clear that anything to do with objective social functioning is actually being measured when this instrument is used. Finally in so far as differential effects have been demonstrated in this study it is not clear that the effect is not a temporal rather than an absolute effect With a longer observation period, there might be a closer approximation between the findings on both active drugs.

Despite these caveats, some speculation is called for, if only to enable the process of constructing experiments that might better exploit the opportunity opened up by these differential effects. These SASS results suggest that the HDRS failed to detect real differences between the two agents. In other words, while what are conventionally thought of as being core features of mood disorders, such as sleep and appetite disturbance, may improve on both drugs, other dimensions of the disturbances that are the affective disorders may not have returned to normal. Which dimensions?

One possibility takes us back to the way psychosyndromes and the effects of psychtropic drugs were viewed before the rise of the amine theories and the HDRS. This view is caught well in a quote from Horsley Gantt: ''It is quite likely that in psychiatric diseases, the action of the drug is determined more by the type or temperament of the individual than by a clinical diagnosis or the disease symptomatology'' (Gantt, 1967). In recent years, this alternative viewpoint has been most clearly expressed in the work of Akiskal (Akiskal, 1995; 1996). Current clinical trial methods, in contrast, have focused almost exclusive attention on the supposed core features of a mood disorder, which had been thought to derive from an underlying monoamine lesion. This approach has neglected for over two decades temperamental inputs to mood disorders and the possibility that differing therapeutic principles may accordingly be differentially effective in different affective syndromes. A great deal of work has been done to determine whether there are noradrenergic or serotonergic depressions, with investigators seeking MHPG or DHPG markers supposedly of a noradrenergic lesion or 5HIAA markers of a serotonergic lesion (Maas et al., 1984). Had these been found and had they predicted the response to norepinephrine selective agents or serotonergic selective agents, however, there is an alternative interpretation of the outcomes that has been neglected. This is that noradrenergic and serotonergic indices may be markers for temperamental types rather than for physiological lesions.

Some indicators of a new way forward in this area have come recently from work by Farde et al. (1997) who radiolabelled D2 receptors in healthy volunteers and found both considerable variation in D2 receptor density but more importantly that this variation correlated with aspects of personality. This result has already been replicated (Breier et al., 1998). If this is true for D2 receptors, it is likely to be true for noradrenergic and serotonergic receptors. And if this is the case, one might predict quite different responses to norepinephrine or serotonin selective agents as a consequence. On this basis, one might predict that different constitutionally-based personality types would respond to different pharmacological interventions. This has been predicted by Akiskal (Akiskal, 1996; 1997). This perspective has also found some empirical support in a study by Joyce et al. (1994) who investigated the influence of temperamental types on response to norepinephrine and serotonin preferring antidepressants. These researchers randomised a group of patients attending hospital clinics and emergency departments to either desipramine or clomipramine. They made no attempt to exclude individuals with marked personality variations. They found that asthenic personality types responded better to desipramine while individuals with borderline personality features showed a better response to clomipramine. In severe cases, tem-

peramental type predicted up to 50% of the variance in responsiveness to the different antidepressants (Joyce et al., 1994).

These findings can be explained in a variety of ways that may potentially be teased out further using highly selective agents, such as reboxetine and citalopram. One possibility is that a direct physiological input to temperament may mean that selective agents may act preferentially on the temperamental input to a psychosyndrome and they may act to bring about a resolution of the syndrome by modulating the 'disorder' in the personality. An alternative is that certain temperament types may react either favorably or adversely, for example, to the sanguinity inducing effects of an SSRI.

On this latter point, two possibilities present themselves. One is that certain temperamental types, by virtue of different physiological inputs, may be more liable than others to profound reductions in emotional reactivity in response to an SSRI for instance, amounting to emotional blunting. Effects of this nature could potentially account for the differential effects between reboxetine and fluoxetine on the SASS. A second possibility is that, given comparable reductions in emotional reactivity, some temperamental types may react adversely to the impact of this effect on their overall psychological make up. All individuals with PTSD may appreciate this effect regardless of temperamental type, but for other conditions, for example, clinically depressed individuals with marked obsessional features may welcome the relief conferred by sanguinity, whereas these same effects may be quite unwelcome for the restless, novelty-seeking temperament types (Akiskal, personal communication, August, 1998).

The view of antidepressant actions proposed above suggests that actions on different monoamine systems may bring about a resolution of depressive disorders indirectly. This view is in line with a view recently expressed by Angst and colleagues: "The therapeutic qualities of antidepressants do not lie in the suppression of symptoms but rather are related to their ability to elicit or maintain certain conditions which allow recovery in a subgroup of patients who would otherwise remain non-responsive" (Stassen et al., 1997).

But, if this is the mode of action of the antidepressants, one can expect treatment to continue to exert

these effects on formerly depressed individuals, in much the way that the drug might be expected to work on healthy volunteers. The question then arises as to how much the vigilance or drive-enhancing effects of norepinephrine reuptake inhibitors might be likely to impact on daily functioning or a sense of wellbeing. This point is of considerable relevance to questions of remission and relapse in the case of antidepressant therapy. To date, advice has focused almost exclusively upon getting depressed patients on to antidepressant therapy and keeping them on the treatment in order to forestall relapse, without any great deal of consideration of whether the individual is on the correct antidepressant or not. It is clear, however, that a large number of depressed subjects following the relief of the core disturbances may remain with low-grade symptoms despite ongoing treatment. Furthermore, there are indications that a lack of wellbeing, following the resolution of the acute phase of the disturbance, as measured by quality of life (QoL) instruments, may predispose to future relapses or earlier recurrences of the disorder (Souetre et al., 1996; Lonnquist et al., 1994; Thunedborg et al., 1995).

This area of wellbeing has been neglected in psychiatry/psychopharmacology to date. The neglect may stem in part from a fear that feeling well may herald a switch into mania. There are robust grounds to support a distinction between wellbeing and hypomania, however. The SASS, by virtue of its self-report character, has a great deal in common with QoL instruments and as such may best be interpreted as reflecting the sense of wellbeing subjects have while on treatment. The effects of reboxetine, as assessed by the SASS, may help shed further light on the interplay between temperament, pharmacogenetic and psychosocial factors in this area.

A recent study of social interactions in healthy volunteers taking paroxetine (Knutson et al., 1998) revealed a complex picture with volunteers reporting 'anxiolytic' effects but also appearing to observers to show more affiliative behavior. It is quite possible, therefore, that in certain individuals an SSRI may enhance aspects of social functioning, even though subjects record a reduced sense of wellbeing at the same time. In the populations studied with reboxetine, the most parsimonious interpretation at present

is that a greater proportion of subjects experienced a sense of wellbeing on reboxetine compared to those taking fluoxetine. Whether this translates into enhanced social functioning remains to be determined; bearing in mind that social functioning almost certainly has many different components which may vary independently. It, similarly, seems unlikely that feeling well on treatment is some unitary dimension that is produced equally by drugs with a particular pharmacological profile in all temperaments and social settings. The SASS data, however, suggests that there are some temperamental types who do feel better, or have a better quality of life, on norepinephrine selective agents. Further studies are needed to clarify this question. What is most crucial to the temperamental specificity question, is whether different antidepressants impact differentially on the range of social dysfunctions documented by Wells et al. (1989, 1992) generically for all common depressive subtypes.

We have offered here facts and speculations that pertain to the very nature of depression and its temperamental substrates. These are merely provocative possibilities for future research on the putative neurobiologic substrates of wellbeing. We submit that the recovery process in depression will be eventually much informed by such an approach.

References

Akiskal, H.S., 1995. Toward a temperament-based approach to depression: implications for neurobiologic research. Adv. Biochem. Pharmacol. 49, 99–112.

Akiskal, H.S., 1996. The temperamental foundations of affective disorders. in: Munct, C. et al. (Ed.), Interpersonal Factors in the Origin and Course of Affective Disorders, London Gaskell, pp. 3–30.

Akiskal, H.S., 1997. Toward an innovative classification of depression: temperament and pharmacological response. Drugs Today 33, 183–190.

Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, American Psychiatric Association, Washington D.C.

Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, American Psychiatric Association, Washington D.C.

Artigas, F., Perez, V., Alvarez, E., 1994. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. Arch. Gen. Psychiatry 51, 248–251.

Aston-Jones, G., Akaoka, H., Charlety, P., Chouvet, G., 1991. Serotonin selectively attenuates glutamate-evoked activation of noradrenergic locus coeruleus neurones. J. Neurosci. 11, 760–769.

Baldwin, D., Hawley, C., Szabi, E., 1998. Reboxetine in the treatment of depression: early clinical experience in the UK. Internat. J. Psychiatry Clin. Pract. 2, 195–201.

Ban, T.A., Gaszner, P., Aguglia, E., Batista, R., Castillo, A., Lipcsey, A., Macher, J.P., Torres-Ruiz, A., Vergara, L., 1998. Clinical efficacy of reboxetine: a comparative study with desipramine, with methodological considerations. Human Psychopharm. 13, S29–S39.

Berzewski, H., Van Moffaert, M., Gagiano, C.A., 1997. Efficacy arid tolerability of reboxetine compared with imipramine in a double-blind study in patients suffering from major depressive episodes. Eur. Neuropsychopharmacol. 7, 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, S57–S70.

Breier, A., Kestler, L., Adler, C., Elman, I., Wiesenfeld, N., Malhotra, A., Pickar, D., 1998. Dopamine D-2 receptor density and personal detachment in healthy subjects. Am. J. Psychiatry 155, 1440–1442.

Brunello, N., Racagni, G., 1998. Rationale for the development of noradrenaline reuptake inhibitors. Human Psychopharmacol. 13, S13–S19.

Bunney, W.E., Davis, J.M., 1965. Norepinephrine in depressive reactions. Arch. Gen. Psychiatry 13, 483–494.

Carlsson, A., 1996. The rise of neuropsychopharmacology: impact on basic and clinical neuroscience. in: Healy, D. (Ed.), The Psychopharmacologists, Chapman and Hall, London, pp. 51–80.

Carlsson, A., Corrodi, H., Fuxe, K., Hokfelt, T., 1969. Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-alpha-ethyl-meta-tyramine. Eur. J. Pharmacol. 5, 357–366.

Coppen, A., 1967. The biochemistry of affective disorders. Brit. J. Psychiatry 113, 1237–1264.

Coppen, A., 1972. Indoleamines and affective disorders. J. Psychiatr. Res. 9, 163–171.

Delgado, P.L., Price, L.H., Miller, H.L., Salomon, R.M., Licinio, J., Krystal, J.H., Heninger, G.R., Charney, D.S., 1991. Rapid serotonin depletion as a provocative challenge test for patients with major depression: relevance to antidepressant action and the neurobiology of depression. Psychopharmacol. Bull. 27, 321–330.

Delgado, P.L., Miller, H.L., Salomon, R.M., Licinio, J., Heninger, G.R., Gelenberg, A.J., Charney, D.S., 1993. Monoamines and the mechanism of antidepressant action effects of catecholamine depletion on mood of patients treated with antidepressants. Psychopharmacol. Bull. 29, 389–396.

Dostert, P., Benedetti, M.S., Poggesi, I., 1997. Review of the pharmacokinetics and metabolism of reboxetine, a selective noradrenaline reuptake inhibitor. Eur. Neuropsychopharmacol. 7, S23–S35.

Dubini, A., Bosc, M., Polin, V., 1997. Do noradrenaline and serotonin differentially affect social motivation and behavior? Eur. Neuropsychopharmacol. 7, S49–S56.

Farde, L., Gustavsson, J.P., Jonsson, E., 1997. D2 dopamine receptors and personality traits. Nature 380, 590.

Gantt, W.H., 1967. Role of drugs in conditioning. neuro-psychopharmacology. in: Brill, H., Cole, J.O., Deniker, P., Hippiis, H., Bradely, P.B. (Eds.), Proceedings of the Fifth International Congress of the CINP, Excerpta Medica, Amsterdam, pp. 811–814.

Goodnick, P.J., Goldstein, B.J., 1998. SSRIs in affective disorders: efficacy and quality of life. J. Psychopharmacol. 12, S21–S53.

Guy, V.I., 1976. Clinical global impressions. in: ECDEU Assessment Manual For Psychopharmacology, US Dept of Health, Education and Welfare, Rockville, pp. 217–222.

Hamilton, M., 1960. A rating scale for depression. J. Neurosurg. Psych. 23, 56–62.

Healy, D., McMonagle, T., 1997. The enhancement of social functioning as a therapeutic principle in the management of depression. J. Psychopharmacol. 11 (4), S25–S31.

Healy, D., 1997. The Antidepressant Era, Harvard University Press, Cambridge Mass.

Healy, D., 1998a. Reboxetine, fluoxetine and social functioning as an outcome measure in antidepressant trails: implications. Primary Care Psychiatry 4, 81–89.

Healy, D., 1998b. Meta-analysis of trials comparing antidepressants with active placebos: commentary. Br. J. Psychiatry 172, 232–234.

Joyce, P.R., Mulder, R.T., Cloninger, C.R., 1994. Temperament predicts clomipramine and desipramine response in major depression. J. Affect. Disord. 30, 35–46.

Kielholz, P., 1968. Die Behandlung endogener Depressionem mit Psych pharmaka. Deutsch Med Wochenschrft 93, 701–710.

Knutson et al., 1998. Please supply reference.

Leonard, B.E., Healy, D., 1998. The Differential Effects of Antidepressants, Martin Dunitz & Co, London.

Lonnquist, J., Sintonen, H., Syvalahti, E., Appelberg, B., Koskinen, T., Mannikko, T., Mehtonen, O.-P., Naarala, M., Sihvo, S., Auvinen, J., Pitkanen, H., 1994. Antidepressant efficacy and quality of life in depression: a double..blind study with moclobemide and fluoxetine. Acta Psychiatr. Scand. 89, 363–369.

Maas, J., Koslow, J., Katz, M., Bowden, C., Gibbons, R., Stokes, P., Robins, E., Davis, J.M., 1984. Pine-treatment neurotransmitter levels and response to tricyclic antidepressant drugs. Am. J. Psychiatry 141, 1159–1171.

Manier, D.H., Gillespie, D.D., Steranka, L.R., Sulser, F., 1984. A pivotal role for serotonin (5-HT) in the regulation of beta adrenoceptors by antidepressants: Reversibility of the action parachlorophylalanine by 5-hydroxytroptophan. Experientia 40, 1223–1226.

Massana, J., Moller, H.-J., Burrows, D., Montenegro, R.M., in press. Reboxetine: a double-blind comparison with fluoxetine in major depressive disorders. Int. Clin. Psychopharmacol.

Melloni, P., Carniel, G., Della Toree, A., Bonsignori, A., Buonamici, M., Pozzi, O., Raccardi, S., Rossi, A.C., 1984. Potential antidepressant agents a-Aryloxybenzl derivatives of ethanolamine and morpholine. Eur. J. Med. Chem. Chim. Ther. 19, 235–242.

Montgomery, S., Asberg, M., 1979. A new depression rating scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Montgomery, S., 1997. Is there a role for a pure noradrenergic drug in the treatment of depression? Eur. Neuropsychopharmacol. 7, S3–S9.

Mucci, M., 1997. Reboxetine: a review of antidepressant tolerability. J. Psychopharmacol. 11 (4), S33–S37.

Nelson, J.C., Mazure, C., Quinlan, D.M., Jatlow, P., 1984. Drug responsive symptoms in melancholia. Arch. Gen. Psychiatry 41, 663–668.

Nelson, J.C., Mazure, C., 1990. A rating scale specific for tricyclic response in melancholia: the TRIM. J. Clin. Psychopharmacol. 10, 252–260.

Schildkraut, J.J., 1965. The catecholamine hypothesis of affective disorders. A review of supporting evidence. Am. J. Psychiatry 122, 509–522.

Souetre, E., Martin, P., Lozet, H., Monteban, H., 1996. Quality of life in depressed patients: comparison of fluoxetine and major tricyclic antidepressants. Int. Clin. Psychopharmacol. 11, 45–52.

Stassen, H., Angst, J., Delini-Stula, A., 1997. Delayed onset of action of antidepressant drugs. Eur. Psychiatry 12, 166–176.

Svensson, T., 1997. Electrophysiology of brain noradrenaline neurons and the mode of action of antidepressant drugs. in: Briley, M., Montgomery, S. (Eds.), Antidepressant Therapy at the Dawn of the Third Millenium, Martin Dunitz, London, pp. 19–35.

Szabadi, E., Bradshaw, C.M., Boston, P.F., Langley, R.W., 1998. The human pharmacology of reboxetine. Human Psychopharmacol. 13, S3–S12.

Thunedborg, K., Black, C.H., Bech, P., 1995. Beyond the Hamilton Depression Scores in Long-Term Treatment of Manic-Melancholic Patients: Prediction of Recurrence of Depression by Quality of Life Measurements. Psychother. Psychosom. 64, 131–140.

Vetulani, J., Stawarz, R., Pingell, J., Sulser, F., 1996. A possible common mechanism of action of antidepressant drug treatments. NS Arch. Pharmacol. 243, 109–114.

Weissman, M.M., 1997. Beyond symptoms: social functioning and the new antidepressants. J. Psychopharmacol. 11 (4), S5–S8.

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

Wells, K.B., Stewart, A., Hays, R., Buinnam, A., Rogers, W., Daniels, M., Berry, S., Greenfield, S., Ware, J., 1989. The functioning and wellbeing of depressed patients: results from the medical outcomes study. J. Am. Med. Assoc. 262, 914–919.

Wells, K.B., Buinnam, M.A., Rogers, W., Hays, R., Camp, P., 1992. The course of depression in adult outpatients: Results from the medical outcomes study. Arch Gen. Psychiatry 49, 788–794.