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# Reboxetine: its effects as measured by the Social Adaptation Self-evaluation Scale

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The determination of the outcome of treatment for depression is important both for the symptoms of depression and social functioning. The aim of this review is to evaluate the outcome of two clinical trials comparing reboxetine and fluoxetine on depressive symptoms and social functioning. These studies used both conventional measures of outcome such as the Hamilton Rating Scale for Depression (HAM-D) and the Social Adaptation Self-evaluation Scale (SASS), a patient-centred, disease non-specific scale of social functioning, which was developed for measuring social functioning in depressed people. These findings, set against a background of all studies in which antidepressants have been compared using quality of life instruments, suggest that while some patients may appear to the clinician to have recovered, they may remain less than fully well and differences in selectivity for neurotransmitter systems may play a part in the degree of wellbeing that recovered patients might expect.

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## Introduction

A number of critics of the current psychotropic arena (1) have argued that, given the diversity in the preclinical pharmacology of agents conventionally labelled antidepressant, it is difficult to believe that these agents are equally beneficial in clinical settings. It has been suggested that the pharmaceutical industry, and perhaps clinical researchers, may have minimized the differences between agents in order to secure a large market share (1). Furthermore, it has been implied that clinical trials methods have not been designed to reveal differences that may exist between antidepressants.

Such critiques have a certain face validity. This is particularly the case with the selective serotonin reuptake inhibitors (SSRIs), which were developed because it was recognized that there were significant differences between the available tricyclic antidepressants (2). On the basis of global clinical impressions, Kielholz (3) characterized the available antidepressants as being variously drive-enhancing, variously sedative and having differential effects on something else, which seemed useful in terms of the treatment of mood disorders. Faced with schemas of the sort outlined by Kielholz (3), Carlsson (4) suggested that the drive-enhancing agents were more active on catecholamine systems while those that had another, as yet less clearly characterized action, had an effect on the serotonin (5-hydroxytryptamine; 5-HT) system (2, 4).

However, two developments supervened to create the impression that all antidepressants did essentially the same thing, regardless of the system on which they acted. One was the development of the monoamine hypotheses, which suggested a deficiency of central monoamines. More sophisticated versions of this posited a final common pathway or receptor lesion, in either catecholamine or serotonergic systems, to explain antidepressant efficacy (5, 6). These versions of the hypothesis were able, for a time, to accommodate the fact that there appeared to be antidepressants that were relatively selective either for the noradrenergic system or the serotonergic system.

In recent years this framework has been challenged for a number of reasons. First, the development of antidepressants such as bupropion and nomifensine, preferentially active on the dopamine

system, have been identified. Secondly, there is evidence that other agents such as isoniazid, which have no effects on dopamine, noradrenaline or serotonin, are antidepressant (7). Thirdly, there is evidence that reserpine, which depletes cerebral monoamines, has antidepressant properties (8). Finally, the SSRIs have demonstrated a clinical efficacy in a range of conditions such as obsessive–compulsive disorder (OCD), panic disorder and social phobia, when there is no depressive component. This suggests that these agents have a non-sedative anxiolytic or serenic action, which they do not share with other 'antidepressants'. This is an action that could conceivably account for their antidepressant properties (9). Furthermore, there has been an ongoing failure to find a lesion in any monoamine system.

The second development that led to the impression that all antidepressants were equivalent was the development of clinical trial methods that exclusively utilized disease-specific observer-based rating scales, such as the Hamilton Rating Scale for Depression (HAM-D) (10). On instruments such as these, all antidepressants show equivalent efficacy in mild to moderate depressive disorders. This appears to have led to a presumption that they were, therefore, all the same, despite earlier preclinical and clinical impressions. The efficacy of agents with actions on the serotonin system across a wide range of nervous conditions did not lead to this view being challenged, but more recent evidence that agents with an action on catecholamine systems appear to be more useful in severe depressive disorders may do so (9).

A second area of measurement is the domain of Clinical Global Impression instruments. These are observer-based instruments that are disease non-specific. There are two other domains of measurement, subject-based disease-specific measures and subject-based measures that are disease non-specific. Within the disease-specific domain, the best-known instruments are the Beck Depression Inventory (BDI) (11) and the Zung self-rating scale for depression (12). With these instruments, agents selective for the noradrenergic system have appeared to have advantages over agents selective for the serotonergic system (13). However, these results had little impact, in part because these instruments are used less frequently than the HAM-D in clinical trials.

The Social Adaptation Self-evaluation Scale (SASS) (14) measures aspects of the disease non-specific domain from a subject-based perspective. Other instruments in this area are Quality of Life (QoL) instruments (15–18), which have been used in trials of antidepressants but on which, to date, differential effects between antidepressants have not been reported. Until the use of the SASS in the recent reboxetine–fluoxetine studies, agents selective for the noradrenergic system have not been tested with such instruments. An emergence of differences between agents selective for the noradrenergic and serotonergic systems on alternative psychometric instruments such as the SASS would lend credence to the suggestion that the current range of antidepressants are not equivalent.

To illustrate some of these issues, this paper will review evidence from two clinical trials conducted using the SASS, along with all other studies that have used QoL instruments in which different antidepressants have been compared.

## Material and method

Patients aged 18–65 years, with a diagnosis of Major Depressive Episode (DSM-IIIR) (19), with a current episode present for 1–4 months and with a pretreatment total score on the 21-item HAM-D (10) of $\geqslant 22$ were enrolled into two studies. In the first study, 381 patients were admitted in 33 centres; 126, 127 and 128 were randomized to receive reboxetine, fluoxetine or placebo, respectively, for 8 weeks (20). In the second study, 168 patients were randomised to receive either fluoxetine or reboxetine in a 16-centre study (21).

Observer rating scales included the HAM-D (10), the Clinical Global Impression Scale (22) and the Montgomery–Åsberg Depression Rating Scale (MADRS) (23), while self-rating assessments included the patient Global Impression Scale (22) and the SASS (14). The SASS has 21 questions, exploring patient behaviour in four broad areas of social functioning: work, spare time, family and ability to cope with resources/finances. The SASS also assesses motivation, self-perception and satisfaction with a role. Each answer is scored from 0 to 3 giving a total range of 0–60. Normal scores fall within a band from 35 to 52 (14).

## Results

Of the 381 patients enrolled into the first study, 302 (103, 100 and 99 randomized to receive reboxetine, fluoxetine or placebo, respectively) provided SASS self-evaluation data at baseline and at last assessment. The mean values of the SASS total scores in the three treatment groups across the treatment period are shown in Fig. 1 (20).

At baseline there was no difference between the three groups. At the last assessment the three groups were significantly different (ANOVA; $P < 0.0001$) with mean SASS total scores of 35.3

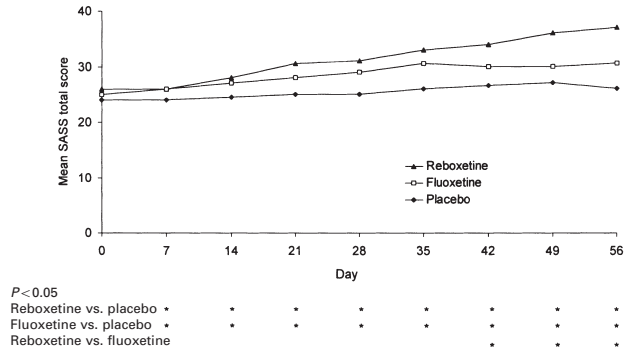


*Fig. 1.* Mean SASS total scores over time in patients in the reboxetine, fluoxetine and placebo groups.

(reboxetine), 31.9 (fluoxetine) and 27.2 (placebo), corresponding to an average improvement with respect to baseline of 41% in the reboxetine group, 31% in the fluoxetine group and 14% in the placebo group. At last assessment 46% of the fluoxetine group had returned to the normal range, while 55% of the reboxetine-treated group had done so.

A point–biserial correlation analysis was conducted for all items on the scale for the reboxetine, fluoxetine and placebo series to determine which items discriminated between treatments. In the case of comparisons between reboxetine and placebo, the correlation coefficient was positive and different from zero for all items except quality of spare time. The correlation was maximal for 12 items, including social attractiveness, external relationship appreciation, work enjoyment, social inquisitiveness, control of surroundings, family relationship quality, communication difficulties, interest in hobbies, external relationship quality, rejection sensitivity, intellectual interest and job interest.

In the case of comparisons between fluoxetine and placebo, the point–biserial correlation coefficient was positive and different from zero for 12 of the 21 items, with maximal correlations for seven items: family relationship quality, social attractiveness, work enjoyment, social inquisitiveness, external relationship appreciation, external relationship quality and job interest. However, for nine items no significant differences between fluoxetine and placebo were detected.

The results of the point–biserial correlation analysis comparing reboxetine and fluoxetine showed a correlation coefficient that differs from zero in favour of reboxetine for nine items. Values were maximal for six items: community involvement, interest in hobbies, social compliance, rejection sensitivity, control of surroundings and vainness. Among these items, community involvement and social compliance explore active social behaviour, while most of the others, i.e. rejection sensitivity, control of surroundings and vainness, investigate self-perception aspects.

When the analysis was confined to patients in core symptom remission (HAM-D $\leqslant$10) (Fig. 2), the differences in favour of reboxetine were even more marked with significantly better outcomes on 14 of the 21 items. The additional items were family-seeking behaviour, relationship-seeking behaviour, intellectual interest, work enjoyment and managing of resources and finances. In this case 63% of the fluoxetine patients had returned to normal, as defined by a SASS score within the normal range, while 37% of them had not, despite HAM-D scores indicative of remission ($\leqslant$). In the reboxetine-treated group 79% had returned to normal on the SASS, leaving 21% still outside the normal range.

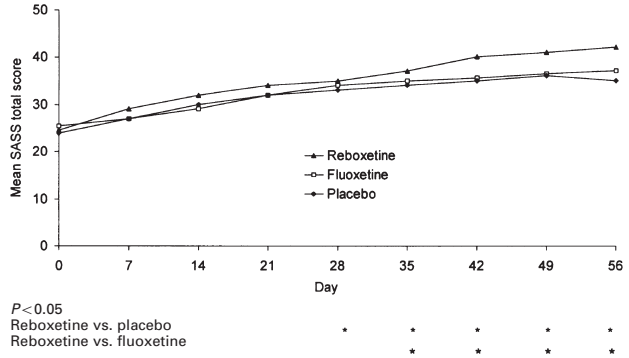


*Fig. 2.* Mean SASS total scores over time in patients in remission in the reboxetine, fluoxetine and placebo groups.

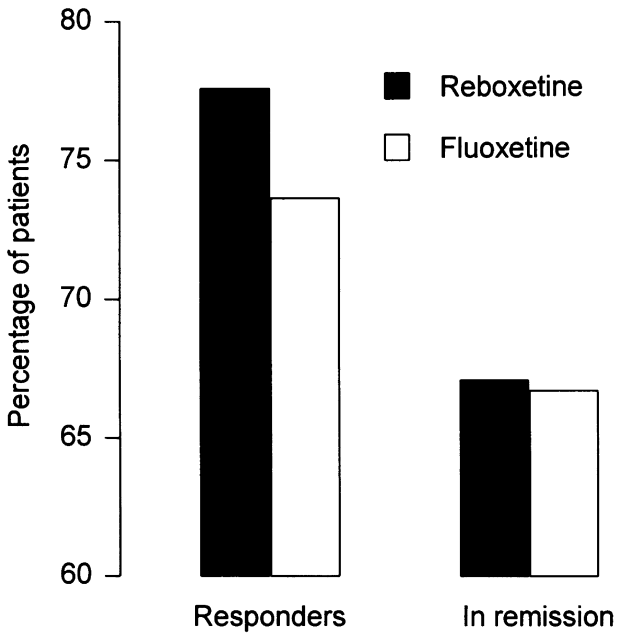


*Fig. 3.* Percentage of patients classified as responders or in remission after treatment with reboxetine or fluoxetine.

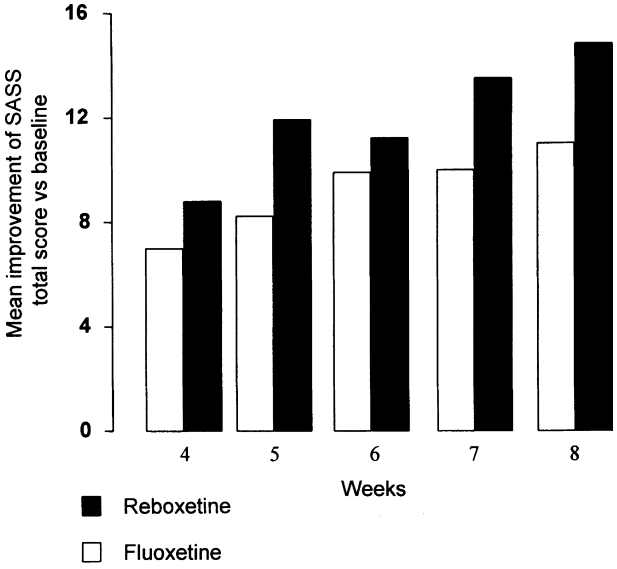


*Fig. 4.* Mean improvement in SASS total score after 4–8 weeks of treatment in patients in remission with SASS scores below 35 at baseline receiving reboxetine or fluoxetine.

It is important to note that the differences between reboxetine and fluoxetine cannot be explained in terms of differential responses, at least as assessed by conventional measures such as the HAM-D or the MADRS, where both drugs performed similarly. In both cases, therefore, there had been a comparable response across what are usually thought of as the core symptoms of the disorder (Fig. 3).

In the second study (21) 168 patients were recruited, of whom 79 were randomized to receive reboxetine and 89 were randomized to receive fluoxetine. Of these, 153 patients were evaluable and 45 patients in the reboxetine group and 55 in the fluoxetine group achieved remission. The overall SASS scores in both groups did not differ significantly. When remitted patients in the reboxetine and fluoxetine groups were compared using the SASS, reboxetine-treated patients tended to do better than those treated with fluoxetine ($P=0.07$). When patients who, on entry into the study, had social functioning levels in the normal range (35–52) were excluded, improvement in the SASS total scores tended to be better (although not significantly) ($P=0.075$) for patients in the reboxetine group (Fig. 4).

There were significant differences ($P\leqslant 0.05$) in favour of reboxetine for four items including interest in leisure activities, extra-family relationships, management of resources and organization of environment. When an index of improvement was constructed by comparing remitters and non-remitters in each group, there was a significantly better outcome for remitters in the reboxetine group compared with those in the fluoxetine group ($P=0.04$).

## Discussion

There clearly needs to be some caution when considering results from just two clinical trials (20, 21). The SASS is a psychometric instrument that is not specific to a particular disease. It is self-rated by patients, covering areas of social and personal functioning that are traditionally covered by quality of life instruments (24, 25). A number of companies have produced similar scales (26) and used them in clinical trials; however, the data, for the most part, have not been reported in the literature. Therefore, a good case can be made for the fact that the current findings with reboxetine on the SASS do not stand in isolation.

In fact, so few QoL results have been reported, where two antidepressants have been compared directly, that these results comparing reboxetine and fluoxetine achieve considerable significance. Simon and co-workers (27) compared fluoxetine, desipramine and imipramine using the HAM-D and the SF-36, and found no differences between the drugs on 3-month QoL outcomes. Souetre and co-workers (28) compared amitriptyline, clomipramine and fluoxetine, using the SF-36 questionnaire and found, in general, no differences between the drugs. When confounding factors were taken into account, there were benefits for fluoxetine in the domains of general health perception and social function. Wheatley and co-workers (29) compared mirtazapine and fluoxetine using the HAM-D and Quality of Life

Enjoyment and Satisfaction Questionnaire (QLESQ) (a scale with a very similar range of questions to the SASS). While mirtazapine was significantly more effective than fluoxetine using the HAM-D as an outcome measure, interestingly both treatments did comparatively poorly on the QLESQ with little change from baseline (29). Lydiard and co-workers (30) compared sertraline with amitriptyline and placebo using the HAM-D and the QLESQ. Both active drugs were associated with greater improvements than placebo on QoL measurements, with sertraline showing a predisposition for greater improvements. Furthermore, Kocsis and colleagues (31) used the QLESQ to compare 416 patients with a diagnosis of early onset primary dysthymia, treated with sertraline, imipramine or placebo. They found that while both sertraline and imipramine were significantly better than placebo in improving QLESQ scores from baseline, no significant difference was observed between the active drugs.

Finally, Lonnqvist and colleagues (32) compared moclobemide with fluoxetine using conventional outcome measures along with the SF-20. A significant change for the better in QoL was found in both treatment groups, even at week 2, but especially after 6 weeks of treatment. Improvement was seen in all dimensions of the scale. For moclobemide there were comparatively greater increases in scores in the domains of social and role functioning, while for fluoxetine the greatest improvements were in the domain of perceptions of physical health.

What do these findings mean? One possibility is that the SASS or other QoL instruments in some sense measure treatment efficacy and may reflect nuances of efficacy that traditional observer-based, disease-specific rating scales such as the HAM-D miss, other than in severely depressed populations.

Another possibility is that the SASS gives some assessment of the overall impact of treatment. As with the antihypertensives, the overall impact of treatment, from the point of view of the patient, is a complex mixture of treatment efficacy as regards the index disorder together with the impact of side-effects on the individual's lifestyle and social functioning. To date, there has been no means of comparing the burden of side-effects stemming from agents active on one system with those stemming from agents active on another. However, in the case of the antihypertensives, it is clear that the angiotensin-converting enzyme inhibitors are preferred by patients to the beta-blockers, even though in terms of observer-based measures of efficacy these treatments are equivalent. This must, in part, be caused by the impact of differing sets of side-effects on the QoL. Similarly, the SASS may give some indication as to the overall impact of treatment on the patient. The role of side-effects on the overall impact of treatment may play a greater part in the early rather than later weeks of treatment.

As regards side-effects, there are two points to note. One is that side-effect data are not collected systematically, and therefore the true frequency and impact of side-effects from all psychotropic drugs currently in use is not known. Secondly, a further issue with side-effects has been to devise a method of assessing which are worse than others. Since the release of the SSRIs, it has been commonly claimed that these agents produce less troublesome side-effects than the older tricyclic antidepressants. Whether dry mouth is a greater problem than severe nausea, sexual dysfunction and akathisia that may lead to suicide is, however, questionable. Arguably, only the patient is in a position to make this judgement. One benefit of the SASS or other quality of life measures is that they may perform just this function, since nausea, sexual dysfunction or akathisia are incompatible with self-ratings of normal social functioning.

Reviewing all the pertinent studies (including the SASS studies), in general the SSRIs fluoxetine and sertraline do not perform better than some of the older tricyclic antidepressants such as amitriptyline or clomipramine, which have traditionally been thought to have the heaviest burden of side-effects. It is also clear that there may be a considerable dissociation between observer-based, disease-specific ratings and QoL assessments. Finally, the SASS studies with reboxetine are the only studies employing QoL type measurements that demonstrate the effects of an agent selective for the noradrenergic system. The findings with reboxetine are consistent with findings for drugs which have some selectivity for the noradrenergic system using patient-based measures such as the BDI (11).

In later weeks of treatment, quite apart from responses of the index condition and the burden of side-effects, there may be an additional QoL contribution that a drug selective for the noradrenergic system may make in comparison to an SSRI. The SSRIs produce a non-sedative anxiolytic effect, reduce irritability (6) and take the edge off intrusive thoughts in OCD, social phobia and other conditions. This may be the means by which they exert their antidepressant effect. However, on occasions this anxiolytic effect can produce an over-unconcern, an excess sanguinity. There is no reason to suppose that taking the edge off intrusive thoughts will only happen to the intrusive thoughts associated with a depressive or obsessive disorder. It may well happen to thoughts which intrude and which are necessary for normal social functioning

such as worries about finances, etc. This point was illustrated in a recent study of healthy volunteers given paroxetine, where a sense of lessened concern and detachment was reported (33). An effect such as this could be expected to lead, in a proportion of individuals who had otherwise responded to treatment, to perceptions of altered social performance or QoL that would be consistent with the findings outlined for the SASS in those treated with fluoxetine.

As noted in the Results section the mean findings reported, rather than indicating effects across all the individuals in the clinical trial, are consistent with findings that a greater proportion of individuals feel normal on reboxetine compared with those on fluoxetine. The data suggest that a significant proportion of individuals respond to fluoxetine, become fully well and feel quite normal on this agent, but that over one-third of those who otherwise appear well are not as well as they may appear. One significant effect of SSRIs that may account for this is their sanguinity-inducing properties outlined above. In a proportion of individuals this may amount to a sense of detachment or emotional blunting. There have been Internet and extensive media reports of this phenomenon in recent years, but to date there have been few systematic studies of the issue. The findings on the SASS in this study, however, require explanation and are likely to bring this area into clearer focus.

Future studies will need to address whether there are any pharmacogenetic or personality-based predictors for these effects. Of interest is the report by Joyce and colleagues (34), which shows that personality may predict up to 50% of the variance in responsiveness to selective antidepressant agents. Recently, neuroimaging studies by Farde and colleagues (35), replicated by Breier and co-workers (36), which showed correlations between monoamine receptor densities and aspects of personality, may help explain the findings of clinical responsiveness. The availability of a selective noradrenergic agent such as reboxetine may allow these issues to be explored in greater detail.

## Conclusions

The results of these studies indicate that use of the SASS has opened up a new domain of measurement in the field of antidepressant assessment. The significance of such differences between antidepressants and the mechanisms mediating the differential effects on SASS between reboxetine and fluoxetine require further studies to establish the benefits of selective noradrenaline reuptake inhibitors on social functioning. Meanwhile, clinicians have strong indicators from the data that there is a right and a wrong antidepressant for the individual patient facing them. All antidepressants are not simply equivalent for all patients. This is particularly likely to be important during the post-recovery phase of treatment, where the level of wellbeing experienced by the patient on treatment may significantly affect their compliance with treatment and prospects for remaining well.

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