The Assessment of Outcomes in Depression: Measures of Social Functioning

David Healy

North Wales Department of Psychological Medicine, Hergest Unit, Bangor, Gwynedd LL57 2PW, Wales, UK

SUMMARY — The methods of evaluating antidepressant efficacy have remained essentially unchanged since the late 1950s. They involve an almost exclusive reliance on observer-based disease-specific instruments, such as the Hamilton rating scales for depression. These function well for drug registration purposes, but arguably do little to inform clinical practice. Progress will require a greater range of instruments and, in particular, instruments which tap into a non-core symptom domain of functioning, e.g., social functioning or quality of life. Two recent studies comparing reboxetine and fluoxetine indicated differences on an instrument designed to tap into the domain of social functioning, and have given some pointers toward a way forward. Current economic constraints will probably put a premium on the development of this domain. A fresh look at this area is also of considerable interest for psychopathology. **Rev Contemp Pharmacother 2000; 11: 295–301.**

INTRODUCTION

Current methods of evaluating antidepressant effects emerged shortly after the introduction of the antidepressants in 1958. The introduction of the earliest antipsychotics in 1954 to the USA had led to a meeting in 1956, convened by the Psychopharmacology Service Centre branch of the NIMH, to determine what could be said about the evaluation of the new agents. The possibility of using rating scales to map clinical change was extensively discussed, as was the need for randomized placebo controlled trials. An alternative was the use of large simple trials with global assessments of functioning. The main proponent of this latter option, Nathan Kline, argued that the use of randomized controlled trials and rating scales risked producing a version of the rabbit out of the hat trick, which involved putting a rabbit in the hat in the first instance (Kline, 1959). Kline's preference was for large simple trials with clear-cut endpoints, such as rates of suicide or discharge from hospital or return to work – broadly speaking, improved social functioning.

Historical events overtook the argument. With the arrival of the antidepressants, the appearance of rating scales on which the antidepressants had demonstrable effects tipped the balance toward short trials using rating scales. Shortly after the introduction of the first monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), Hamilton (1960) published his now famous Hamilton Depression Rating Scale (HDRS, or HAM-D). This contained a set of items which were characteristically disturbed in cases of melancholic or vital depression, a condition on which ECT and the emerging TCAs in particular appeared to have significant effects. It is possible, however, that there was a too-ready acceptance amongst research workers and clinicians that these rating scale changes indicated changes in the underlying disorder exclusively. Another possibility was that they reflected, in part, the impact of symptomatic effects, such as improved sleep, improved appetite, and anxiolysis, that could have been demonstrated in healthy volunteers as well as in depressed patients.

In fact, the conjunction of randomized controlled trials and a single rating scale of this type is particularly open to potentially misleading effects. Randomized controlled trials demonstrate associations in a manner that may mask the underlying mechanism by which the associations are brought about. Such an approach takes the focus off the individual patient and off what is happening in that specific patient to produce a therapeutic response, and turns it instead onto rating scale scores, which are composite effects, demonstrated in an aggregate of patients.

However, clear changes in HAM-D scores in clinical trials that lasted for no more than 4 weeks on average proved an irresistible method for demonstrating treatment effects in a manner that convinced many, and this became the paradigm for the evaluation of antidepressant treatments. Subsequently, a number of other scales (Montgomery and Åsberg, 1979) – in particular the Montgomery Åsberg Depression Rating Scale (MADRS) – were added to the battery of instruments used, but these, as will become clear, have almost exclusively been instruments from the same domain of measurement as the HAM-D. As a consequence, it is reasonable to state that, in the past 40 years, the methods of evaluating outcomes have evolved substantially less than the drugs have done.

TREATMENT OUTCOMES

In antidepressant trials, a number of different treatment outcomes can potentially be demonstrated. These include: treatment effects; treatment efficacy; treatment effectiveness; and treatment efficiency. To date, standard clinical trials have been concerned almost exclusively with demonstrating treatment effects. This is particularly vulnerable evidence on which to base national campaigns to defeat depression, efforts to seek out and treat depressed employees in their work place, or other public policy initiatives aimed at reducing suicide rates or at the relief of depression-induced disability. There is no guarantee that demonstrations of short-term treatment effects will translate into long-term, more durable efficacy measures, such as reduced suicide rates or lowered disability rates.

Some understanding that this is the case has emerged in recent years with the growing acceptance that the demonstration of acute treatment effects in depressive disorders may have few implications for the longer term. In practice, however, this realisation has been confounded by a marketing of long-term treatment of depression on the basis of a small series of trials conducted over the course of a year or more, showing lower rates of relapse than on placebo. These trials may sometimes be compromised by a failure to recognise the possibility of treatment discontinuation effects or of other stress syndromes occurring in response to antidepressants or other psychotropic medicines, and in some cases, by the recruitment of patients who may be unrepresentative of those met in clinical practice.

Against this background, there stands the work of Klerman, Weissman, Paykel and colleagues, who, in the early 1970s, demonstrated that the symptomatic response of major depressive disorders to treatment with TCAs often failed to be accompanied by a rapid return to normal social functioning. Many patients spent several months, following an apparent treatment response, functioning at a lower social level than they had been before their hospitalization (Weissman et al., 1974). This observation led to the development of instruments to chart social functioning in depressed patients and, in particular, to the creation of the Social Adaptation Scale (SAS) (Weissman et al., 1974). It also added to the development of interpersonal therapy, which was aimed in the first instance at restoring the social functioning of the patient in a manner complementary to the symptomatic changes brought about by antidepressants (Weissman, 1997, 1998). This body of work, however, had little immediate impact on the evaluation of acute treatment effects of antidepressants in clinical trials designed for registration or marketing purposes.

QUALITY OF LIFE

The mid-1980s saw the emergence of the selective serotonin reuptake inhibitors (SSRIs). In general, these had smaller

treatment effects on hospitalized depression samples than were obtained with the older TCAs, but it was hoped that they might possess fewer adverse effects and be safer in overdose and hence more suitable for the treatment of primary care mood disorders. The market development of these agents coincided with a number of national campaigns to detect and treat depressive disorders; these campaigns were based on the hope that such treatment might reduce national rates of suicide, which it was believed stemmed, in part at least, from the effects of nondetection and non-treatment of major depressive disorders.

The clinical profile of the SSRIs encouraged a number of pharmaceutical companies to develop quality of life (QoL) scales as a means of measuring the overall impact of treatment (Stoker et al., 1992; Tuynman-Qua et al., 1992; Turner, 1994). The hope was that a combination of treatment effects in primary care depressions, together with a reduced burden of adverse effects, would demonstrate that treatment with SSRIs was preferable to treatment with TCAs. These instruments have subsequently been used in many clinical trials, but the results of relatively few such trials have so far been published.

Reports of some recent trials in which the QoL effects of two or more antidepressants have been compared, can be listed. Simon et al. (1996) compared fluoxetine, desipramine and imipramine using the HAM-D and the SF-36, finding no differences between the drugs on 3-month QoL outcomes. Souêtre et al. (1996), using the SF-36, compared amitriptyline, clomipramine and fluoxetine and found, broadly speaking, no differences between the drugs; when confounding factors were controlled for, there were benefits for fluoxetine in the domains of general health perception and social function. Wheatley et al. (1998) compared mirtazapine and fluoxetine using the HAM-D and the Quality of Life, Enjoyment and Satisfaction Questionnaire (QLESQ), the latter being a scale with a range of questions similar to those of the Social Adaptation Self-evaluation Scale (SASS) (Bosc et al., 1997); while mirtazapine was significantly more effective than fluoxetine when the HAM-D was used as an outcome measure, it was not stated whether the apparent improvements in QoL as assessed by scores on the QLESQ, were significantly different from baseline. Lydiard et al. (1998) compared sertraline with amitriptyline and placebo using the HAM-D and the QLESQ; both active drugs were associated with greater improvements than produced by placebo on QoL measurements, with sertraline showing a tendency to produce greater improvements. Kocsis et al. (1997), in a study involving 416 patients with a diagnosis of early-onset primary dysthymia, compared sertraline, imipramine, or placebo, using the QLESQ score as an outcome measure; they found both sertraline and imipramine to be significantly better than placebo in improving QLESQ scores from baseline, but no different from each other. Finally, Lonnqvist et al. (1994) compared moclobemide with fluoxetine using conventional outcome measures (HAM-D, MADRS and CGI) as well as scores on the SF-20 and found a significant change for the better in QoL in both treatment groups, even at week 2 but especially after 6 weeks of treatment. Significant improvements were seen after 2 weeks with moclobemide in all dimensions of the SF-20 scale, but fluoxetine failed to produce significant improvements at this time on the dimension of physical functioning and role functioning. By week 6, however, both treatments led to significant improvements on all dimensions of the SF-20: with moclobemide the greatest improvements by week 6 (percentage increases over baseline) occurred in role functioning and mental health, whilst with fluoxetine the greatest improvement at week 6 was (as with moclobemide) in role functioning.

DOMAINS OF MEASUREMENT

It is clear that there are a number of possible domains of measurement in which antidepressant effects can be judged. These include a disease-specific physician-rated domain, where effects may be assessed on instruments such as the HAM-D or the MADRS. A second domain is a disease-specific and patient-rated: in the case of depression, the best known instruments are the Beck Depression Inventory or the Zung Self Rating Scale. A third area is the domain of physician-rated global functioning where effects may be measured using global functioning assessment scales (Guy, 1976) or, alternatively, by structured instruments such as the SAS (Weissman et al., 1974). Finally, there is the patient-rated domain of global or social functioning, in which social functioning self rating scales and/or QoL scales are the main instruments.

If rating scales are to be used as surrogate measures of antidepressant efficacy in short-term treatment trials, a convincing demonstration of treatment efficacy is more likely in cases where a treatment effect can be shown to occur across a range of domains of measurement. At present, this has not convincingly been demonstrated for any TCA or SSRI.

CLINICAL OUTCOME AND UNDERLYING MECHANISMS

There is a further hazard to proceeding in the manner that has been customary in clinical trials to date. As mentioned above, the demonstration of a treatment effect on an instrument such as the HAM-D in a randomized controlled trial may provide evidence of an association between treatment and a particular effect, but it may provide little or no information about, or may even mask, the mechanism by which this effect is brought about. Conventional clinical trials have led to a general clinical impression that antidepressants are all much the same, differing only in their adverse effect profile and their toxicity in overdose. Although the SSRIs were designed to have quite different clinical profiles from those exhibited by the TCAs (Healy, 1999), clinical trials which emphasize only changes in HAM-D scores as an endpoint fail to demonstrate such differences, particularly in the manner in which the different drugs bring about their therapeutic effects. Prior to the adoption of such standard end-point indices, there had been a clear recognition that antidepressants differed in the mechanisms underlying their clinical actions. Some were thought to produce improvements in depressive disorders by enhancing drive while others did something else (Healy,

1999): those that were thought to enhance drive were more active on the catecholamine system, while the agents doing something else had preferential effects on the 5-HT system.

THE SOCIAL ADAPTATION SELF-EVALUATION SCALE

The view that an agent acting on catecholamine systems would enhance drive, led to the development of the Social Adaptation Self-evaluation Scale (SASS). The hope was that this instrument might tap into the distinctive profile of effects of a selective catecholamine reuptake inhibitor, such as reboxetine (Bosc et al., 1997; Dubini, personal communication). It was thought that the somewhat energizing effects of such an agent would translate into beneficial social functioning effects. This led to the use of the scale in two clinical trials in which reboxetine was compared to fluoxetine.

Of the 381 patients enrolled into the first study, 302 (103, 100 and 99 randomized to reboxetine, fluoxetine and placebo, respectively) provided SASS self-evaluation data at baseline and at last assessment. The following account of the results of this study is based mainly upon the report of Dubini et al. (1997) but also includes information not presented in the published report (Pharmacia and Upjohn, 1999). The mean values of the SASS total scores in the three treatment groups across the treatment period are shown in Figure 1 (Dubini et al., 1997). At baseline, there was no difference between the three groups, but at the last assessment the three groups were significantly different (ANOVA; $p < 0.0001$), with mean SASS total scores of 35.3 on reboxetine, 31.9 on fluoxetine, and 27.2 on placebo, corresponding to an average improvement with respect to baseline of 41% on reboxetine, 31% on fluoxetine and 14% on placebo. On the last assessment 46% of the fluoxetine group showed SASS scores that had returned to the normal range; in the reboxetine treated group 54% of patients showed this.

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 were detected between fluoxetine and placebo.

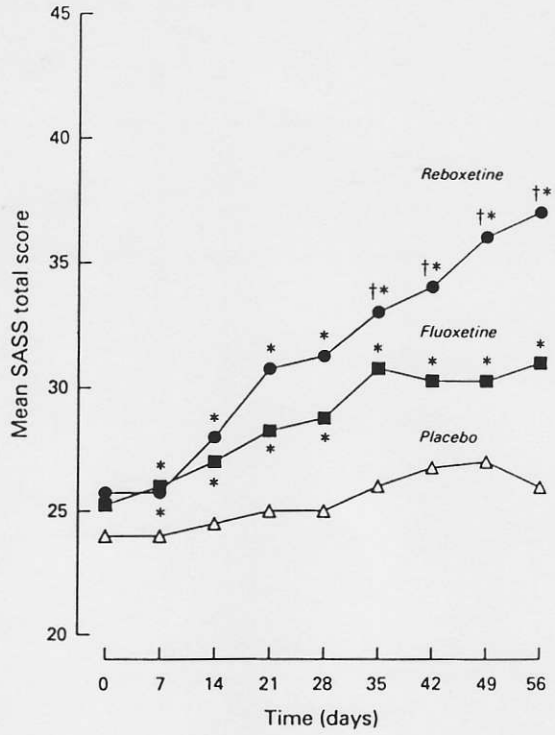

Figure 1. Mean SASS total scores over time in patients treated with reboxetine, fluoxetine or placebo. *In comparison with the corresponding value for placebo, $p < 0.05$; †in comparison with the corresponding value for fluoxetine, $p < 0.05$. After Dubini et al. (1997).

The results of the point-biserial correlation analysis comparing reboxetine and fluoxetine showed a correlation coefficient that differed 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 scores <10) (Figure 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 an SASS score within the normal range (a total score of ≥ 35), while 37% of them had not, despite HAM-D scores indicative of remission. In the reboxetine-treated group, 79% had returned to normal on the SASS, leaving 21% still not within the normal range.

These 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.

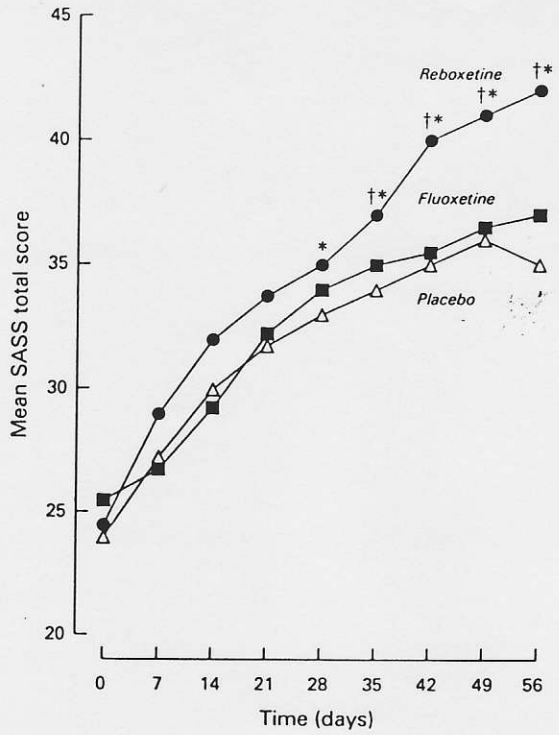

Figure 2. Mean SASS total scores over time in patients treated with reboxetine, fluoxetine or placebo groups, and in core symptom remission. After Dubini et al. (1997).

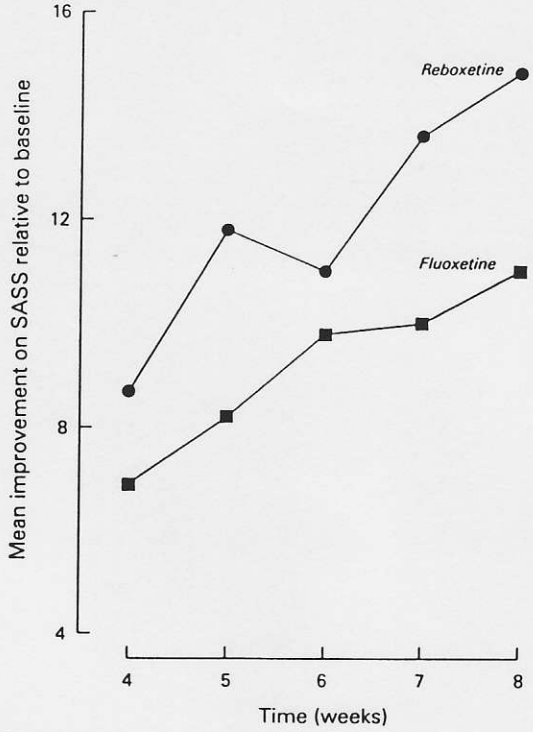

Figure 3. Mean improvement in SASS total score after 4–8 weeks of treatment in patients in remission with SASS scores below 35 at baseline and receiving treatment with either reboxetine or fluoxetine. Based on unpublished data obtained during the course of the study reported by Massana et al. (1999) (Pharmacia and Upjohn, 1999).

In the second study (Massana et al., 1999), 168 patients were recruited, of whom 79 were randomized to reboxetine and 89 to fluoxetine. Of these, 153 continued through the study and contributed evaluable data at the end, when 45 patients on reboxetine and 55 on fluoxetine achieved remission. Again, the following account for the findings, though drawn mainly from the published report (Massana et al., 1999), also contains information acquired during the course of the study, but at present unpublished (Pharmacia and Upjohn, 1999). It was found that the overall SASS scores in the two treatment groups did not differ significantly; when remitted patients on reboxetine and fluoxetine were compared on the SASS, however, reboxetine did better than fluoxetine at a borderline significance level of $p = 0.07$ ($0.05 < p < 0.10$). When patients who had social functioning levels in the normal range (35–52) on entry into the study were excluded, there remained a consistently better result for reboxetine (see Figure 3), though the significance level remained borderline ($p = 0.075$). There were differences at a significance level of $p \leq 0.05$ in favour of reboxetine for four items, including: interest in leisure activities; extra-family relationships; management of resources; and organisation of environment. An index of improvement was constructed, defined as 100 (last score − baseline score)/baseline score; when this was applied to remitters and nonremitters on each drug, there was a significantly better outcome for remitters on reboxetine (57.9%) than for remitters on fluoxetine (37.2%) ($p < 0.05$).

Further discussion of the studies by Dubini et al. (1997) and Massana et al. (1999) is to be found in de Maio and Johnson (2000).

SOCIAL FUNCTIONING IN DEPRESSION

In interpreting what these results may mean, the first point to consider is that scores on the SASS do not necessarily translate directly into descriptions of social functioning. There is no information on whether the functioning of the patients in real-life social situations was any different following treatment with the two antidepressants, reboxetine and fluoxetine. Indeed, on a number of measures of social appropriateness fluoxetine might have been expected to produce favourable social outcomes: it is known that SSRIs can produce, in healthy volunteers and others, an apparent increase in social affiliation (Knutson et al., 1998) as well as a certain docility, probably through an action to reduce emotional reactivity. No information is currently available, however, regarding the effects of reboxetine on these dimensions of social functions. Different measures of social functioning may lead to different conclusions regarding the relative values of drugs in producing clinically desirable adjustments in everyday social behaviour.

In the absence of other indicators of social performance it is difficult to tell exactly what the results mean. But what would the appropriate other indicators of performance be? The domains of social functioning, general wellbeing and QoL are overlapping. It may, indeed, be impossible to establish a single measure of social functioning in a manner that would permit a claim that a particular antidepressant benefits social functioning in a way that others do not.

The results of the studies comparing reboxetine with fluoxetine, using the SASS scores as outcome measures, require some explanation. There would certainly appear to be some sense in which patients taking reboxetine felt that their performance was improved, at least in the terms outlined by this instrument, and in which patients taking fluoxetine did not experience this improvement. One clue as to what may be involved is provided by looking more closely at the questions used on the SASS. These are very closely related to standard QoL questions. There is, in fact, a significant overlap between a number of the QoL scales, such as the Quality of Life in Depression Rating Scale (Endicott et al., 1993), and the SASS. It is possible that, in one sense, the SASS is more a QoL instrument than a measure of social functioning; if this is so, it may be that the results provide an index of subjective wellbeing rather than of conformity/social cohesion. This wellbeing may be influenced by positive effects of the drug (in terms of its action to increase energy and drive) and/or by the relative absence of adverse effects. Reboxetine does not appear to have the serenic effects of the SSRIs; accordingly, whilst it might be less likely to promote social affiliation and cohesion, it could be more likely to produce a subjective sense of social effectiveness.

How such an effect on social effectiveness might correlate with standard measures of social functioning as described by Weissman et al. (1974) cannot be answered at present in the absence of comparative data from the same study using both instruments. There is a striking discrepancy between the speed of social functioning improvement in trials with reboxetine and that reported in the studies by Weissman and colleagues in which other agents were used, though the studies conducted by Weissman et al. (1974) were primarily on hospitalized depressed patients, whereas the studies conducted in clinical trials with antidepressants today are, for the most part, on nonhospitalized samples. The social functioning deficit of current clinical trial samples will be much less marked than the problems afflicting individuals who have had to be hospitalized, and thus the delay in returning to normal social functioning following antidepressant treatment in primary care depressed samples is unlikely to be comparable to that found in hospitalized samples.

THE FUTURE

Whatever the precise effects of reboxetine on social functioning, the demonstration of a differential effect between it and fluoxetine on a measure of social functioning of some kind, will almost inevitably open up the domain of QoL and social functioning assessments in a manner that has not happened hitherto. Given a growing disenchantment with demonstrations of acute treatment effects in the absence of more convincing demonstrations of treatment effectiveness, this area is ripe for development.

There are also interesting issues for psychopathology in general. There is emerging evidence that there are variations in monoamine receptor densities across healthy volunteers and that these correlate with aspects of personality (Farde et al., 1997; Breier et al., 1998). If this is the case, it might be expected that agents selective for particular monoamine systems would have differential effects on different constitutional types. There is, in fact, clinical trial evidence that this is the case: Joyce et al. (1994), for example, demonstrated that personality variation can account for up to 50% of the variance of responsiveness to agents selective for the serotonergic or the catechoaminergic systems. Such findings indicate that it might be possible, through the targeting of an appropriate antidepressant to a particular constitutional type, to obtain enhanced social functioning.

The idea that certain agents might be preferential for particular constitutional types does not sit easily with current market development philosophies for antidepressants, which aim at treating depression as a unitary entity that should respond to antidepressant medication, regardless of the psychosocial setting or constitutional type of the patient. If constitutional types are indeed important in determining therapeutic outcome, this would suggest not only that certain agents would be beneficial in particular constitutional types but equally that others would be unhelpful. Current antidepressant trials are not designed to map out populations that are unresponsive or adversely affected by a selective antidepressant. Other outcome measures of the type first suggested by Kline in 1956, such as rates of suicide, rates of return to work, or discharge from hospital, might be more appropriate in this regard. Suicide is a clear-cut outcome measure: the challenge is, however, to devise response indices capable of detecting problems prior to suicide and which do not show up by the use of conventional instruments such as the HAM-D. The social functioning domain would seem a potentially fruitful area to explore in pursuit of such measures. The SASS may point a way forward.

REFERENCES

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

Breier A, Kestler L, Adler C et al. Dopamine D-2 receptor density and personal detachment in healthy subjects. Am J Psychiatry 1998; 155: 1440–1442.

de Maio D, Johnson FN. The clinical efficacy of reboxetine in the treatment of depression. Rev Contemp Pharmacother 2000; 11: ~~000–000~~. 303–320.

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

Endicott J, Nee J, Harrison W, Blumenthal R. Quality of life enjoyment and satisfaction questionnaire. Psychopharmacol Bull 1993; 29: 321–327.

Farde L, Gustavsson JP, Jonsson E. D2 dopamine receptors and personality traits. Nature 1997; 380: 590.

Guy W. ECDEU assessment manual for psychopharmacology. Rockville, MD: US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, 1976.

Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56–62.

Healy D. The three faces of the antidepressants. A critical comment on the economic context of diagnosis. J Nerv Ment Dis 1999; 187: 174–180.

Joyce PR, Mulder RT, Cloninger CR. Temperament predicts clomipramine and desipramine response in major depression. J Affect Disord 1994; 30: 35–46.

Kline NS. Scales and checklists. In: Cole JO, Gerard RW, eds. Psychopharmacology: problems in evaluation. Washington, DC: National Academy of Sciences/National Research Council 1959: 475.

Kocsis JH, Zisook S, Davidson J et al. Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: psychosocial outcomes. Am J Psychiatry 1997; 154: 390–395.

Knutson B, Wolkowitz OM, Cole SW et al. Selective alteration of personality and social behaviour by serotonergic intervention. Am J Psychiatry 1998; 155: 373–379.

Lydiard RB, Stahl SM, Hertzman M, Harrison WM. A double-blind, placebo-controlled study comparing the effects of sertraline *versus* amitriptyline in the treatment of major depression. J Clin Psychiatry 1997; 58: 484–491.

Lonnqvist J, Sintonen H, Syvalahti E et al. Antidepressant efficacy and quality of life in depression: a double-blind study with moclobemide and fluoxetine. Acta Psychiatr Scand 1994; 89: 363–369.

Massana J, Möller H-J, Burrows GD, Montenegro RM. Reboxetine: a double-blind comparison with fluoxetine in major depressive disorder. Int Clin Psychopharmacol 1999; 14: 73–80.

Montgomery SA, Åsberg MA. New depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134: 382–389.

Pharmacia and Upjohn. Data on file, 1999.

Simon GE, VonKorff M, Heiligenstein JH et al. Initial antidepressant choice in primary care. Effectiveness and cost of fluoxetine *vs* tricyclic antidepressants. JAMA 1996; 275: 1897–1902.

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

Stoker MJ, Dunbar GC, Beaumont G. The SmithKline Beecham 'quality-of-life' scale: a validation and reliability study in patients with affective disorder. Qual Life Res 1992; 1: 385–395.

Turner R. Quality of life: experience with sertraline. Int Clin Psychopharmacol 1994; 9 (Suppl 3): 27–31.

Tuynman-Qua H, de Jonghe F, McKenna S, Hunt S. Quality of life in depression rating scale. Houten: Ibero, 1992.

Weissman MM. Beyond symptoms: social functioning and the new anti-depressants. J Psychopharmacol 1997; 11 (Suppl): S5–S8.

Weissman MM. Gerald Klerman and psychopharmacotherapy. In: Healy D, ed. The psychopharmacologists, Vol 2. London: Arnold, 1998: 000–000.

Weissman MM, Klerman GL, Paykel ES, Prusoff B, Hanson B. Treatment effects on the social adjustment of depressed patients. Arch Gen Psychiatry 1974; 30: 771–778.

Wheatley DP, van Moffaert M, Timmerman L et al. Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. J Clin Psychiatry 1998; 59: 306–312.

Å/

Please supply page numbers

521–542