Psychological Medicine, 2002, **32**, 517–524. © 2002 Cambridge University Press
DOI: 10.1017/S0033291701005086 Printed in the United Kingdom

Functional effects of agents differentially selective to noradrenergic or serotonergic systems

R. TRANTER,[1] H. HEALY, D. CATTELL AND D. HEALY

From the North Wales Department of Psychological Medicine, University of Wales, College of Medicine and Institute of Medical and Social Care Research, University of Wales, Bangor

ABSTRACT

Background. The diversity of pharmacological actions of antidepressants suggests that they may bring about their clinical effects by different functional means.

Methods. Twenty healthy volunteers were randomized in a cross-over design to receive 2 weeks of a clinical dose of both reboxetine and sertraline. Baseline assessments of personality were made using the Cloninger Tridimensional Personality Questionnaire and the Karolinska Scales of Personality. Daily and weekly ratings of mood (POMS and PANAS) and quality of life (SASS) were undertaken.

Results. Reboxetine and sertraline differed in their effects on the SASS as well as on measures of mood. Reboxetine appeared more likely to be energy enhancing; the effects of sertraline were more difficult to quantify. Personality factors, such as harm avoidance predicted the preference of subjects for these effects and the effect of being on a preferred drug had a significant impact on SASS, and ratings of moods as well as on self-assessments of personality.

Conclusions. The differences reported here are consistent with the original thinking that led to the development of the SSRIs. The findings point to the need for further research on possible differential functional effects of psychotropic agents selective to different brain systems. The findings also have implications for clinical practice, in particular for maintenance treatment with antidepressants.

INTRODUCTION

The selective serotonin reuptake inhibiting antidepressants (SSRIs) originated in clinical observations that not all antidepressants were the same (Kielholz, 1971). Some agents, Kielholz argued, made patients well by enhancing drive while others appeared to do something else, the nature of which was then unclear. Carlsson noted that the agents thought most likely to enhance drive had preferential actions on the catecholamine system, while those doing something else were more likely to act on the serotonergic system (Carlsson *et al.* 1969), leading him to suggest the synthesis of an SSRI, in part to establish how such an agent might effect clinical change (Carlsson, 1996).

However, concepts such as the beta-receptor down regulation hypothesis subsequently emerged, which essentially proposed that all antidepressants act through a final common pathway. A range of observations are at odds with the hypothesis of a final common pathway. First the SSRIs, in contrast to catecholamine selective tricyclic antidepressants (TCAs), are effective and have licences for the treatment of nervous conditions other than depression, such as obsessive–compulsive disorder, post-traumatic stress disorder and social phobia. Secondly, SSRIs appear less effective for melancholic or severe depressions than agents with significant actions on the catecholamine system. Thirdly,

[1] Address for correspondence: Dr Richard Tranter, North Wales Department of Psychological Medicine, University of Wales, College of Medicine, Hergest Unit, Bangor, Wales LL57 2PW.

https://doi.org/10.1017/S0033291701005086 Published online by Cambridge University Press

some studies (Joyce *et al*. 1994) have indicated that selective agents have differential effects according to personality type. Fourthly, in a recent study SSRIs were shown to have effects on personality, which it was claimed could be distinguished from their effects on mood (Ekselius & Von Knorring, 1999).

These observations provide a rationale for investigating the functional effects of antidepressants selective to different neurobiological systems. Clinical trials of antidepressants using conventional outcome measures, such as the HAM-D or the MADRS scales, have consistently failed to detect differences between agents with quite diverse pharmacological actions (Garattini, 1996). Two recent studies comparing reboxetine and fluoxetine, however, which showed similar results for the two drugs using the HAM-D, demonstrated quite different results on a Social Adaptation Self-Evaluation Scale (SASS) (Dubini *et al*. 1997; Massana *et al*. 1999). One means of exploring these findings is to see whether differences between selective agents emerge in a healthy volunteer population.

This healthy volunteer study therefore tested the following predictions. First, whether a noradrenergic selective agent, reboxetine, would have a differential effect on the SASS, compared with an SSRI, sertraline, in line with previously published findings in depressed patients. Secondly, whether this differential effect might stem from the drive-enhancing effects of a noradrenergic selective agent (Bosc *et al*. 1997). This possibility was explored further by analysing the effects of both agents on the POMS, which has subscales measuring vigour, fatigue, concentration, anxiety and depression. Thirdly, whether aspects of personality or temperament would be associated with preference for either a noradrenergic or serotonergic selective agent. Fourthly, whether aspects of personality as measured by the Karolinska Scales of Personality would show changes following treatment with an SSRI.

METHOD

Twenty healthy volunteers aged between 28 and 52, with a mean age of 37·8 years, were recruited to a study comparing reboxetine with sertraline on a range of personality, and self-report measures of mood and social adaptation. There were nine males and 11 females recruited from among the administrative, medical and nursing members of the North West Wales district general hospital psychiatric unit, as well as four others known to members of the unit. Ethical permission had been obtained from the North West Wales Ethical Committee. Written consent to inclusion was obtained from each subject. All volunteers were free of medical conditions. None were on concurrent drug treatment. None had a history of previous psychiatric service utilization – one had been treated 5 years previously for depression in primary care. One subject dropped out midway through the study owing to problematic personal circumstances.

All subjects entered the study at the same time. They were randomized to receive reboxetine, a selective noradrenaline reuptake inhibitor, or sertraline, an SSRI, in a crossover design so that half received reboxetine for 2 weeks followed by a 2 week drug-free period and thereafter sertraline for 2 weeks or alternatively sertraline followed by reboxetine. The medications were prepared to look identical. The dose of the drugs was either 4 mg of reboxetine for the first 5 days with an option to increase to 4 mg bd if tolerated or alternatively sertraline 50 mg for the first 5 days with an option to increase to 50 mg bd if tolerated. Of the 19 volunteers going onto reboxetine, 17 increased from 4 to 8 mg as per protocol with two reducing the dose to 4 mg at days 8 and 10. Of the 19 volunteers going onto sertraline, 17 increased from 50 to 100 mg as per protocol with four reducing the dose at days 8, 10, 12 and 13 respectively.

At baseline, subjects completed a Karolinska Scales of Personality (KSP) (Schalling *et al*. 1987), a Cloninger Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987), a Profile of Mood States (POMS) (McNair *et al*. 1988), a Positive and Negative Affect Scale (PANAS) (Watson *et al*. 1988), a Social Adaptation Self Evaluation Scale (SASS) (Bosc *et al*. 1997), a BIS-BAS scale (Carver & White 1994) and an Affect Intensity Measure (AIM) (Larsen & Diener 1985). The BIS-BAS scale, based on the work of Gray, was included as it has been hypothesized that it reflects the functioning of behavioural inhibitory and behavioural activation systems mediated by the serotonergic and catecholaminergic systems respectively. The

https://doi.org/10.1017/S0033291701005086 Published online by Cambridge University Press

AIM was included as a reduction of emotional reactivity has appeared to be one possible distinctive feature of SSRIs (Hoehn-Saric *et al*. 1991).

POMS, PANAS and SASS scales were completed on a daily basis and volunteers kept a daily diary of impressions of the functional and physical effects of each drug. The volunteers were actively encouraged to consult their partners or others as to any changes that these others noticed in them over each 2-week period. Modified versions of the BIS-BAS and AIM scales were completed weekly, along with the KSP.

Before the blind was broken all subjects completed a Likert scale asking them whether they could distinguish between the behavioural effects of the drugs and to mark their preference for each drug (−5, worse than normal; 0, no effect; 5, better than normal). An overall preference score was calculated by subtracting the score on reboxetine from the score on sertraline (−10, strongly preferred reboxetine; 10, strongly preferred sertraline). A side-effects questionnaire, aimed at eliciting the commonest side effects they might have had, was also completed. A focus group was conducted at the end of the study aimed at establishing whether there were effects characteristic of either drug. All ratings were done blind. The blind was only broken 2 weeks after the study was completed.

Statistical analysis

The results were analysed using SPSS to undertake repeated measures ANOVAs, Pearson product moment correlations and paired *t* tests. All data not conforming to normal distribution was log-transformed. The method for analysing a two-period cross-over study described by Fleiss (1986) was employed. This technique allows the analysis not only of treatment effects but also differential carry-over effects that may bias the results of cross-over studies. The baselines presented are calculated according to condition.

Based on preference scores the sample was divided into three subgroups: strongly prefer reboxetine (−10 to −5); strongly prefer sertraline (5 to 10); and no strong preference (−5 to 5). For the two subgroups that displayed a strong preference, a comparison was made of first and second week mean SASS scores and PANAS scores on the preferred and the non-preferred drug. The null hypothesis was that drug preference would not affect these outcome measures at 1 or 2 weeks exposure. This was examined with paired samples *t* tests using SPSS.

RESULTS

In this study, the study monitors had a no better than 50% correct estimate as to which drug subjects were on; both drugs caused sleeplessness, nausea and sexual dysfunction in at least half of the subjects making it difficult to use these features as markers. The peripheral effects of the two drugs that provided the greatest distinctions were the presence of chilblains and cold sweats on reboxetine and jaw or throat dyskinesias or dystonias on sertraline. Neither of these side effects were expected by either the volunteers or the investigators, nor were they thought to be specific to one or other system. This overlap in side effects provides a justification for controlling each active agent with another active agent rather than with placebo.

SASS

The mean SASS scores for the end of week 1 and week 2 of treatment are shown in Table 1. Similar results are obtained if the SASS scores through week 1 or week 2 are averaged out or if the results are calculated on a daily basis.

A 2 (Drug: reboxetine, sertraline) × 3 (Time: baseline, week 1, week 2) repeated measures ANOVA was used to explore changes in SASS scores. A significant drug × time interaction was found ($F(2, 36) = 3{\cdot}22$, $P = 0{\cdot}05$). Paired *t* tests revealed a significant difference between SASS scores at week 2 ($t(18) = 2{\cdot}15$, $P = 0{\cdot}04$), with higher SASS scores in those taking reboxetine. There did not appear to be any significant cross-over effects. A similar trend was shown for week 1 ($t(18) = 1{\cdot}83$, $P = 0{\cdot}08$).

When the findings were analysed in comparison to baseline, there was a significant difference between sertraline scores and baseline at week 1 ($t(18) = 2{\cdot}35$, $P = 0{\cdot}03$) and at week 2 ($t(18) = 2{\cdot}33$, $P = 0{\cdot}03$) and significant differences between the difference between reboxetine and baseline and sertraline and baseline at week 1 ($t(18) = 2{\cdot}23$, $P = 0{\cdot}04$) and at week 2 ($t(18) = 2{\cdot}07$, $P = 0{\cdot}05$).

https://doi.org/10.1017/S0033291701005086 Published online by Cambridge University Press

Table 1. *Mean* (S.D.) *SASS and POMS scores on reboxetine and sertraline*

	Pre-reboxetine baseline	Reboxetine		Pre-sertraline baseline	Sertraline	
		Week 1	Week 2		Week 1	Week 2
SASS	41·21 (5·97)	41·73 (5·3)	41·47 (6·3)	41·63 (6·87)	39·26 (6·9)[a]	39·21 (6·8)[bc]
POMS						
Vigour	7·26 (3·62)	8·05 (6·53)	6·31 (3·80)	7·58 (3·53)	5·0 (4·16)[d]	5·74 (4·51)[e]
Fatigue	3·42 (4·48)	2·32 (2·47)	2·68 (3·38)	3·00 (3·46)	5·0 (4·76)[fg]	4·37 (5·02)
Concentration	1·89 (2·38)	0·8 (2·07)[h]	0·8 (1·9)[j]	1·68 (2·45)	2·42 (3·00)[k]	1·84 (2·96)
Anxiety	1·63 (2·54)	2·05 (3·00)	1·63 (2·5)	2·16 (2·57)	2·32 (3·65)	2·16 (3·77)
Depression	2·00 (2·45)	3·05 (4·03)	2·00 (3·00)	2·68 (3·58)	1·95 (3·27)	1·63 (3·26)

[a] $P \leqslant 0{\cdot}05$ SASS scores for week 1 differ between sertraline and baseline.
[b] $P \leqslant 0{\cdot}05$ SASS scores for week 2 differ between sertraline and baseline.
[c] $P \leqslant 0{\cdot}05$ SASS scores differ between reboxetine and sertraline.
[d] $P \leqslant 0{\cdot}05$ Vigour scores differ between sertraline week 1 and baseline.
[e] $P \leqslant 0{\cdot}05$ Vigour scores differ between sertraline week 2 and baseline.
[f] $P \leqslant 0{\cdot}05$ Fatigue scores differ between sertraline and reboxetine at week 1.
[g] $P \leqslant 0{\cdot}05$ Fatigue scores differ between sertraline and baseline at week 1.
[h] $P \leqslant 0{\cdot}05$ Concentration scores differ between reboxetine and baseline at week 1.
[j] $P \leqslant 0{\cdot}05$ Concentration scores differ between reboxetine and baseline at week 2.
[k] $P \leqslant 0{\cdot}05$ Concentration scores differ between reboxetine and sertraline at week 1.

POMS

The end of week 1 and end of week 2 values of the Profile of Mood States (POMS) are reported in Table 1. There are similar results if the data are calculated through week 1 or week 2 or if the results are calculated on a daily basis. A series of repeated measures 2 (Drug: reboxetine, sertraline) × 3 (Time: baseline, week 1, week 2) ANOVA were performed on all subscales of the POMS. Both time and drug were within subject factors since all participants had both reboxetine and sertraline. There were no significant main effects of either time or drug for the depression, anger or vigour subscales, ($F < 1$) in all cases.

There were main effects for drug ($F(1, 18) = 51{\cdot}70$, $P = 0{\cdot}001$) and time ($F(1, 18) = 29{\cdot}81$, $P = 0{\cdot}001$) on the concentration subscale and a significant drug × time interaction ($F(2, 36) = 10{\cdot}82$, $P = 0{\cdot}001$). While scores on sertraline increased compared to baseline, indicating increased level of difficulty concentrating, these were not significant. Scores for reboxetine decreased compared to baseline and were significant at week 1 ($t(18) = -3{\cdot}88$, $P = 0{\cdot}001$) and at week 2 ($t(18) = -4{\cdot}60$, $P = 0{\cdot}001$). At week 1 there was a significant difference between reboxetine and sertraline ($t(18) = -3{\cdot}04$, $P = 0{\cdot}007$). There was a similar trend at week 2 ($P = 0{\cdot}07$).

There was a trend toward a main effect of drug for fatigue ratings ($F(1, 18) = 3{\cdot}485$, $P = 0{\cdot}078$). Paired t tests revealed a significant difference in fatigue ratings at the end of week 1 between the two drugs ($t(18) = -2{\cdot}32$, $P = 0{\cdot}03$). Fatigue ratings on sertraline were significantly higher than those on reboxetine. Paired t tests revealed a significant difference between pre-sertraline fatigue levels and week 1 scores ($t(18) = 2{\cdot}52$, $P = 0{\cdot}02$). Consistent with these findings on fatigue, differences were found on the vigour subscale of the POMS for sertraline; week 1 and week 2 values to baseline were significantly different ($t(18) = -2{\cdot}46$, $P = 0{\cdot}02$ for week 1 and $t(18) = -2{\cdot}10$, $P = 0{\cdot}05$ for week 2).

PANAS

There were no significant differences between the drugs on the positive or negative subscales of the PANAS.

Preference index

The distribution of preference scores, along with the division into strong reboxetine preference, no preference and strong sertraline preference is shown in Fig. 1. There were 12 subjects who showed a strong preference for one or other drug (seven for sertraline and five for reboxetine).

Personality measures

Significant correlations were found between liking for either reboxetine or sertraline and TPQ measures. Harm avoidance on the TPQ

https://doi.org/10.1017/S0033291701005086 Published online by Cambridge University Press

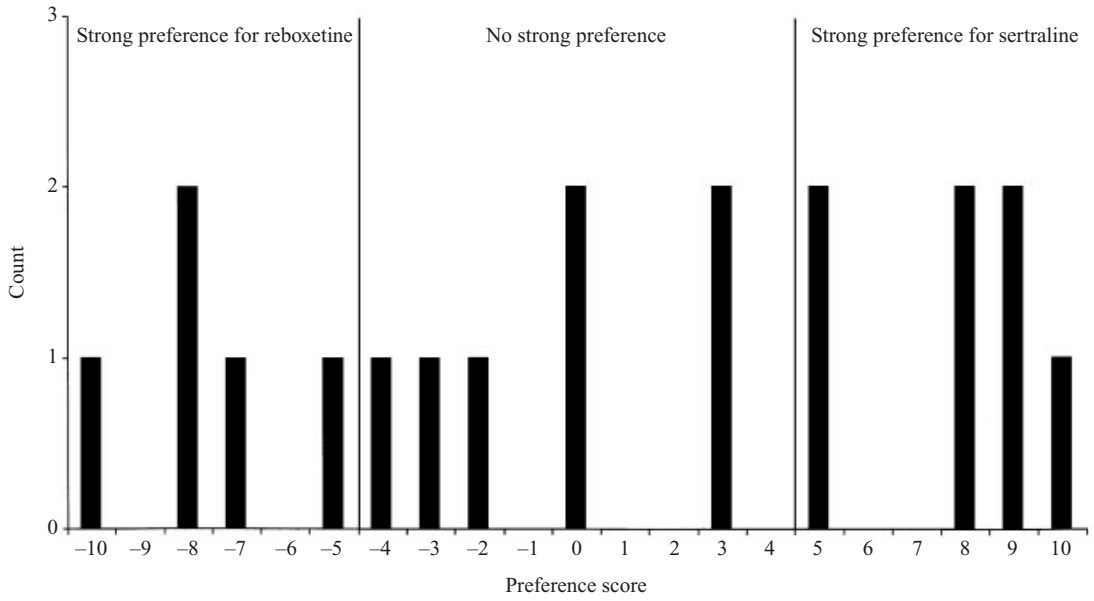


FIG. 1. Antidepressant preference scores: −10, strong reboxetine preference; 10, strong sertraline preference.

Table 2. *Effect of preference on SASS and PANAS scores*

	Mean SASS		Mean PANAS			
			Positive subscale		Negative subscale	
Outcome	Week 1	Week 2*	Week 1**	Week 2**	Week 1**	Week 2*
Preferred	39·5 (5·1)	39·4 (5·1)	23 (5·8)	22·3 (4·9)	11 (2·1)	11 (1·9)
Non-preferred	38·4 (5·3)	35·9 (7·0)	18 (6·4)	17·1 (4·8)	13·4 (3·5)	14·6 (5·0)

Standard deviations are shown in parentheses.
* $P < 0{\cdot}05$; ** $P < 0{\cdot}005$.

correlated positively with reboxetine appreciation ($r(19) = 0{\cdot}46$, $P = 0{\cdot}057$) and negatively with sertraline appreciation ($r(19) = -0{\cdot}66$, $P = 0{\cdot}003$). Within the harm avoidance subscale, HA1 (anticipatory worry) correlated positively with reboxetine appreciation ($r(19) = 0{\cdot}495$, $P = 0{\cdot}037$) and negatively with sertraline appreciation ($r(19) = -0{\cdot}721$, $P \leqslant 0{\cdot}001$). The novelty seeking and reward dependence dimensions of the TPQ did not correlate significantly with appreciation for either drug but on the preference index novelty seeking 2 (impulsiveness) correlated with preference for reboxetine ($r(19) = 0{\cdot}46$, $P = 0{\cdot}048$).

There was also a negative correlation between socialization on the KSP and preference for reboxetine ($r(19) = -0{\cdot}492$, $P = 0{\cdot}032$) and a positive correlation with preference for sertraline ($r(19) = 0{\cdot}464$, $P = 0{\cdot}046$), but no correlation between social desirability and drug preference. Socialization in turn correlated negatively with harm avoidance on the TPQ ($r(19) = -0{\cdot}472$, $P = 0{\cdot}041$), while social desirability correlated with reward dependence ($r(19) = 0{\cdot}55$, $P = 0{\cdot}015$). There was no correlation between baseline SASS measures and either socialization or social desirability scores.

Paired samples t tests examining whether subscales of the KSP change following treatment with reboxetine and sertraline found that both sertraline and reboxetine appear to increase monotony avoidance ($P < 0{\cdot}005$). Sertraline may cause an increase in socialization scores ($P < 0{\cdot}05$), with a trend for both drugs to do so, and reboxetine a reduction in hostility scores ($P < 0{\cdot}05$), with a trend for both drugs to do so,

https://doi.org/10.1017/S0033291701005086 Published online by Cambridge University Press

Table 3. *Effect of preference on KSP variables* (N = 12)

KSP subscale	Baseline Mean (S.D.)	Preferred Mean (S.D.)	Non-preferred Mean (S.D.)
Somatic anxiety	7·8 (5·3)	6·5 (6·0)	10·4 (6·3)*
Aggression	20·3 (6·6)	19·0 (6·6)	23·8 (7·7)*
Social desirability	15·1 (2·3)	14·7 (2·0)	13·6 (2·1)*
Agitation	13·6 (4·1)	11·8 (4·4)	12·8 (4·0)*
Hostility	12·9 (2·9)	10·2 (3·2)	12·3 (3·9)*
Psychaesthenia	13·5 (2·8)	12·5 (3·0)	15·6 (4·7)*

* Difference between preferred and non-preferred outcome significant at $P < 0{\cdot}05$.

although both these results should be interpreted with caution due to the multiple tests carried out.

A significant correlation was found between BIS-BAS reward and the reward dependence subscale of the TPQ ($r(19) = 0{\cdot}53$, $P = 0{\cdot}02$), consistent with Carver & White (1994), but BIS-BAS measures did not correlate with preference for either drug.

Effect of outcome on SASS & POMS scores

Comparisons of mean SASS scores over 2 weeks between the preferred and non-preferred drug exposure, for those 12 subjects who showed a strong preference for one or other drug, are shown in Table 2. In the second week of exposure the mean SASS score for the preferred drug was significantly higher than for the non-preferred drug. Similarly, the preferred drug produced significantly higher positive PANAS ratings, and lower negative PANAS ratings, for both weeks of exposure.

When an analysis of the effect on KSP scores was carried out on the 12 subjects who exhibited strong preference for one or other of the drugs, further significant differences emerged (Table 3). On their preferred drug, subjects scored lower on aggression, agitation, hostility, psychaesthenia and somatic anxiety, while scoring higher on social desirability, compared to the non-preferred drug.

AIM Scale

The AIM scale did not predict outcomes with either treatment and the modified AIM showed no differences between the two drugs after week 1 or week 2 of treatment.

DISCUSSION

In line with previously published findings (Dubini *et al.* 1997; Massana *et al.* 1999), reboxetine and sertraline appear to have differential effects on SASS scores. These changes, along with changes on the POMS subscales, occurring in a population of healthy volunteers not suffering from depression, are in line with the perceptions of Kielholz and Carlsson that noradrenergic selective drugs are energy enhancing and that there may be differential effects between selective agents.

It proved considerably more difficult to establish what the characteristic effect of serotonergic selective agents might be. In focus group settings, while still under the blind, half of the subjects volunteered that sertraline made them mellow, or less emotionally reactive and that these effects were either appreciated or not, while yet others described agitation. Effects consistent with a reduction in emotional reactivity were not described with reboxetine. However, none of the subscales or items of the POMS or PANAS or the Affect Intensity Measure (Larsen & Diener 1985) detected this or any other selective effect of sertraline.

Part of the problem in assessing this issue quantitatively lies in the variability of response that volunteers showed for each drug leading some, for instance, to feel calmer on sertraline while others were agitated (Healy 2000*a*, *b*). This issue poses methodological challenges that might be met using a repertory grid approach. Our findings that a preferred agent impacts on certain domains of functioning, as measured by the KSP, may contribute toward the development of such an approach.

The findings on the SASS and the socialization item of the KSP indicate that although the term social appears in both metrics, the social domain is one that may comprise a number of subdomains and diverse agents may have differential effects on the perception or efficacy of social functioning, or in areas of affiliative rather than ergonomic behaviours. In the absence of objective measures, no inferences to actual social functioning should be drawn from these data.

Previous studies using SSRIs have reported difficulties in healthy volunteers. Saletu and colleagues reported that sertraline can produce a reduction in affective well-being, and a dose

https://doi.org/10.1017/S0033291701005086 Published online by Cambridge University Press

dependent increase in agitation (Saletu *et al*. 1986; Saletu & Grunberger 1988). Warrington and colleagues noting dropouts on paroxetine in a healthy volunteer population (Warrington *et al*. 1989) stated that 'antidepressants are poorly tolerated in volunteers'. Our results in contrast suggest that there is a right and a wrong agent for volunteers and that individuals on the correct agent may tolerate selective drugs very well, while finding agents selective to other systems difficult to tolerate. While many factors affect compliance, this observation maps onto findings that only 40% of depressed patients pursue a course of SSRIs beyond a month (Donohue & Taylor 2000).

Such preferences have significant effects on outcome as measured by the SASS and the PANAS, with less favoured agents leading to falls in SASS and positive PANAS scores and increases in negative affect scores on the PANAS. The findings on the KSP in contrast consisted of both positive and negative changes from baseline measures. These were consistent with unquantified changes reported by Knutson *et al*. (1998) in volunteers taking paroxetine.

The finding that personality factors are correlated with preference for selective agents replicates findings of Joyce *et al*. (1994). Further work into the role of the TPQ for predicting antidepressant preference is needed, particularly as no other factors have yet been shown to have a similar utility in such critical clinical decision-making.

Even though there was a substantially shorter exposure period (2 *versus* 24 weeks), our findings of KSP changes on socialization, monotony avoidance and hostility replicated the findings of Ekselius & Von Knorring (1999). In contrast, we did not find changes on the other variables they found changes on and both reboxetine and sertraline produced similar changes which is at odds with a selective serotonergic effect. However, the findings of change in a substantial number of domains of personality on the KSP in our healthy volunteers on a preferred agent suggests that there may indeed be some interaction between selective treatments, monoamine systems and domains of well-being captured in personality measurements. Indeed, one possibility is that SASS scores may reflect aspects of personality rather than objective social functioning.

Monoamine system changes have hitherto primarily been thought to reflect state rather than trait related changes in mood disorders, but a recently replicated study has tied monoamine receptor variation to aspects of personality as measured by the KSP (Farde *et al*. 1997; Breier *et al*. 1998). Changes of this sort would lead to predictions that responses to selective monoamine agents should vary by personality type or alternatively that functional outcomes should differ according to an individual's prior monoamine system configuration. A variation of functional outcome by personality type escapes a simple dichotomization into state or trait. This new domain would seem highly germane to the questions of well-being on antidepressants and the extent to which patients are left with residual symptoms, issues that have received considerable attention in the literature in recent years.

REFERENCES

Bosc, M., Dubini, A. & Polin, V. (1997). Development and validation of a social functioning scale, the Social Adaptation Self-evaluation Scale. *European Neuropsychopharmacology* **7** (suppl. 1), 57–70.

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. *American Journal of Psychiatry* **155**, 1440–1442.

Carlsson, A. (1996). The rise of neuropsychopharmacology: impact on basic and clinical neuroscience. In *The Psychopharmacologists* Vol. 1 (ed. D. Healy), pp. 51–80. Chapman & Hall: London.

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-metatyramine. *European Journal of Pharmacology* **5**, 357–366.

Carver, C. S. & White, T. L. (1994). Behavioral inhibition, behavioral activation and affective responses to impending reward and punishment: the BIS/BAS scales. *Journal of Personality and Social Psychology* **67**, 319–333.

Cloninger, C. R. (1987). A systematic method for clinical description and classification of personality variants: a proposal. *Archives of General Psychiatry* **44**, 573–588.

Donoghue, J. & Taylor, D. M. (2000). Suboptimal use of antidepressants in the treatment of depression. *CNS Drugs* **5**, 365–383.

Dubini, A., Bosc, M. & Polin, V. (1997). Do noradrenaline and serotonin differentially affect social motivation and behaviour? *European Neuropsychopharmacology* **7**, 49–56.

Ekselius, L. & von Knorring, L. (1999). Changes in personality traits during treatment with sertraline or citalopram. *British Journal of Psychiatry* **174**, 444–448.

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

Fleiss, J. L. (1986). *The Design and Analysis of Clinical Experiments*, pp. 263–270. J. Wiley & Sons: Chichester.

Garattini, S. (1996). Experimental and clinical activity of antidepressant drugs. In *Psychotropic Drug Development: Social, Economic and Pharmacological Aspects*. (ed. D. Healy and D. Doogan), pp. 1–16. Chapman & Hall: London.

Healy, D. (2000*a*). The assessment of outcome in depression.

https://doi.org/10.1017/S0033291701005086 Published online by Cambridge University Press

Measures of social functioning. *Reviews in Contemporary Pharmacotherapy* **11**, 295–301.
Healy, D. (2000*b*). Antidepressant induced suicidality. *Primary Care Psychiatry* **6**, 23–28.
Hoehn-Saric, R., Lipsey, J. R. & McLeod, D. R. (1990). Apathy and indifference in patients on fluvoxamine and fluoxetine. *Journal of Clinical Psychopharmacology* **10**, 343–345.
Joyce, P. R., Mulder, R. T. & Cloninger, C. R. (1994). Temperament predicts clomipramine and desipramine response in major depression. *Journal of Affective Disorders* **30**, 35–46.
Kielholz, P. (1971). *Diagnose und Therapie der Depressionen für Praktiker*. J. F. Lehmanns: München.
Knutson, B., Wolkowitz, O. M., Cole, S. W., Chan, T., Moore, E. A., Johnson, R. C., Terpstra, J., Turner, R. A. & Reus, V. I. (1998). Selective alteration of personality and social behaviour by serotonergic intervention. *American Journal of Psychiatry* **155**, 373–379.
Larsen, R. J. & Diener, E. (1985). A multitrait-multimethod examination of affect structure: hedonic level and emotional intensity. *Personality Individual Differences* **6**, 631–636.
McNair, D. M., Lorr, M. & Droppleman, L. F. (1988). *Manual for the Profile of Mood States*. Educational and Industrial Testing Services: San Diego, CA.
Massana, J., Moller, H.-J., Burrows, G. D. & Montenegro, R. M. (1999). Reboxetine: a double-blind comparison with fluoxetine in major depressive disorder. *International Clinical Psychopharmacology* **14**, 73–80.
Saletu, B. & Grunberger, J. (1988). Drug profiling by computed electroencephalography and brain maps with special consideration of sertraline and its psychometric effects. *Journal of Clinical Psychiatry* **49** 8 (suppl.), 59–71.
Saletu, B., Grunberger, J. & Linzmayer, L. (1986). On central effects of serotonin reuptake inhibitors: quantitative EEG and psychometric studies with Zoloft and zimelidine. *Journal of Neural Transmission* **67**, 241–266.
Schalling, D., Asberg, M., Edman, G. & Oreland, L. (1987). Temperament traits associated with platelet MAO activity. *Acta Psychiatrica Scandinavica* **76**, 172–182.
Warrington, S. J., Dana-Haeri, J. & Sinclair, A. J. (1989). Cardiovascular and psychomotor effects of repeated doses of paroxetine: a comparison with amitriptyline and placebo in healthy men. *Acta Psychiatrica Scandinavia* **80** (suppl. 350), 42–44.
Watson, D., Clark, L. A. & Tellegen, A. (1988). The development and validation of brief measures of positive and negative affect. The PANAS Scale. *Journal of Personality and Social Psychology* **54**, 1063–1070.

https://doi.org/10.1017/S0033291701005086 Published online by Cambridge University Press