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Changes in personality traits during treatment with sertraline or citalopram

LISA EKSELIUS and LARS VON KNORRING

Background Recent studies indicate that selective serotonin re-uptake inhibitors (SSRIs) reduce the symptoms accompanying personality disorders and modulate a normal personality.

Aims To examine the effect of two SSRIs, sertraline and citalopram, on personality traits in major depressed patients.

Method Personality traits were evaluated at baseline and after six months using the Karolinska Scales of Personality (KSP).

Results After treatment, significant changes in the direction of normalisation were seen in all scales. To determine whether the observed changes could be explained by improved depressive symptoms, multiple stepwise regressions with the separate KSP as dependent variables were performed. Improvements in depressive symptoms only accounted for 0–8.4% of the observed variance.

Conclusions In depressed patients treated with SSRIs significant effects are seen on personality traits measured by the KSP.

Declaration of interest The present study is a separate part of a large study financially supported by Pfizer AB.

Several studies have shown that individuals with a history of depression can be characterised by certain maladaptive personality traits, including lack of social confidence, neuroticism and introversion (Benhaminsen, 1981; Hirschfeld *et al*, 1989). In a recent study by Shea *et al* (1996), personality traits in subjects with a prospectively observed first depression were compared with subjects remaining well. There was no evidence of negative change from premorbid to postmorbid assessment, suggesting that such personality traits are a vulnerability factor for the development of depression. In an earlier study by Perris *et al* (1979), in-patients suffering from depressive syndromes completed a self-report questionnaire, the Karolinska Scales of Personality (KSP) (Schalling *et al*, 1987), during depression and when recovered after treatment with tricyclic antidepressants or electroconvulsive therapy. Twelve out of 15 scales remained stable. The only significant changes concerned components of anxiety and social desirability. Thus, the KSP are fairly independent of the state of the subject.

AIM

Recent studies indicate that selective serotonin re-uptake inhibitors (SSRIs) reduce the symptoms accompanying personality disorders (Fava *et al*, 1994; Coccaro & Kavoussi, 1997). It has also been reported that administration of an SSRI (paroxetine) modulates a normal personality by reducing negative affective experience and increasing affiliative behaviour (Knutson *et al*, 1998). The present study aimed to examine the effect of two SSRIs, sertraline and citalopram, on personality traits using the KSP in major depressed patients treated by general practitioners.

METHOD

Patient selection

Eligible subjects were depressed primary care patients participating in a randomised, double-blind, parallel group, multicentre study. The primary aim was to compare the efficacy and safety of sertraline and citalopram during 24 weeks of treatment (Ekselius *et al*, 1997), and the second aim, reported here, was to elucidate the effects of SSRIs on personality traits. Included patients were required to meet the DSM–III–R (American Psychiatric Association, 1987) criteria for a major depressive disorder and to have a minimum score of 21 on the Montgomery–Åsberg Depression Rating scale (MADRS) (Montgomery & Åsberg, 1979). The MADRS depression score should not decrease by more than 25% from the time of screening to inclusion. All patients recruited for the study were seen and treated by general practitioners who were trained and supervised by experienced psychiatrists. Altogether, there were 39 general practitioners who took part in the study as investigators. After complete description of the study to the subjects, written informed consent was obtained.

Exclusion criteria included: pregnancy or breast-feeding; severe depression of psychotic dimension; previous history of serious suicide attempt or suicide risk; therapy refractory depression; previous adequate treatment with sertraline or citalopram without significant effect; bipolar disorder; previous or present history of alcohol or drug misuse; history of epilepsy; known intolerance or allergic reactions to SSRIs; therapy with lithium within the preceding month; currently receiving and unable to discontinue any other psychotropic medication apart from a hypnotic for insomnia or a daytime anxiolytic (nitrazepam, 2.5–10 mg/day; flunitrazepam, 0.5–2 mg/day; or oxazepam, 15–25 mg/day); currently receiving treatment with cimetidine, warfarin or tryptophan; or significant concomitant hepatic or renal disease.

Of the 400 patients eligible for the clinical trial, 308 patients (77%) completed 24 weeks of treatment according to the study protocol. These 308 patients comprised the present study population. A total of 145 patients – 105 females and 40 males with a mean age of 47.3 years (s.d.=13.3) – comprised the sertraline group and the remaining 163 patients – 116 females and 47 males with a mean age of 48.1 years

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(s.d.=12.0) – comprised the citalopram group. The demographic data for the included patients are shown in Table 1.

Procedures

Following screening for eligibility, patients entered a one-week drug-free wash-out period. At the end of the wash-out period (referred to as baseline), patients were randomised to double-blind treatment with either sertraline (50–150 mg/day) or citalopram (20–60 mg/day) for 24 weeks. Patients participating in the study did not receive any other systematic treatment for depression.

Patients were assessed at baseline and during the study using the MADRS (Montgomery & Åsberg, 1979) and the Clinical Global Impression (CGI) scale (Guy, 1976). Interrater reliability for MADRS ratings was 0.89 (intraclass correlation coefficient).

Personality traits were assessed by means of the KSP at baseline and after 24 weeks (Schalling *et al*, 1987). The KSP have been developed with the purpose of operationalising and measuring constructs defining vulnerability for different forms of psychopathology. The inventory comprises 135 items grouped in 15 scales. Four scales concern anxiety proneness: *somatic anxiety* (autonomic disturbances, vague distress and panic attacks), *psychic anxiety* (cognitive, social anxiety, worrying, insecurity), *muscular tension* (subjective muscular tenseness and aches, difficulties in relaxing), and *psychasthenia* (low degree of mental energy, easily fatigued). Three scales are related to vulnerability for disinhibitory psychopathology: *impulsiveness* (non-planning, impulsive), *monotony avoidance* (need for change and action) and *socialisation* (positive childhood experiences, good school and family adjustment). Six scales are related to aggressivity and hostility: *verbal aggression* (aggressive feelings expressed in style and content of speech), *indirect aggression* (undirected expressive aggression), *irritability* (irritable, lacking patience), *suspicion* (distrusting people's motives), *guilt* (remorseful) and *inhibition of aggression* (non-assertive, sad rather than angry). Also included are: *detachment*, which is related to social withdrawal, and *social desirability*, which refers to conformity and control.

Most of the scales are based on hypotheses of biologically relevant temperament dimensions (Schalling *et al*, 1987). In most scales, the items were primarily selected on rational–theoretical grounds rather than by factor–analytical or empirical techniques. The scales have later been subjected to psychometric analyses. Personality traits, as assessed by the KSP in a non-patient sample, have been found to be stable after nine years, both with regard to absolute and relative stability (Gustavsson, 1997).

Although the KSP do not measure personality disorders, the anxiety scales, the aggressivity scales and the socialisation scale of the KSP seem to indicate personality pathology related to the general criteria of the personality disorders (Ekselius *et al*, 1994; Gustavsson, 1997).

Statistical methods

Responders were defined as those with at least a 50% MADRS score reduction at week 24 compared with baseline, a CGI severity score of 1–3 ('no mental illness' to 'mild severity') and a CGI improvement score rated as 'much' or 'very much improved'.

The KSP mean scores for the different scales were transformed into normative T-scores (mean=50, s.d.=10), based on a Swedish age and gender-stratified, non-patient sample. Changes in T-scores between baseline and week 24 assessments were tested by a two-tailed, paired *t*-test.

Multiple stepwise regressions were used to elucidate the possible importance of confounding factors, such as depressive symptoms, age, gender and type of drug, in personality changes during treatment. The different KSP scales were used as dependent variables and age, gender, type of drug and changes in total MADRS scores as independent variables.

The statistical analyses concerning changes in personality were carried out at the Department of Neuroscience, Psychiatry, Uppsala University on a Macintosh computer by means of Statview SE+Graphics (1988, Abacus Concepts, Inc.).

RESULTS

Of the 145 patients included in this study who were treated with sertraline, 130 (89.7%) were classified as responders with respect to the major depressive disorder. The corresponding figure in the citalopram group was 151 (92.6%) of 163 patients. (In the intention to treat analysis comprising all 400 patients, 75.5% *v.* 81.0% were classified as responders.) There was no statistically significant difference between the groups. Mean doses at week 24 were 82.4 mg of sertraline and 33.9 mg of citalopram.

At baseline, personality traits were characterised by increased anxiety and aggression and decreased social desirability and socialisation (Fig. 1).

After 24 weeks of treatment with sertraline or citalopram, small but statistically significant changes were seen in all the KSP except the impulsiveness scale. The changes (2.3–12.4%) were in the direction of normalisation, i.e. decreases in the anxiety and aggression-related scales and increases in social desirability and socialisation (Fig. 1 and Table 2). In this analysis, altogether, 45 *t*-tests were made. With regard to changes in the separate KSP, 30 *t*-tests were made. Thus, two significant changes might have occurred by chance but in fact 25 significant changes were found.

Table 1 Demographic characteristics and depressive history in patients treated with sertraline and citalopram

Characteristics	Sertraline (*n*=145)	Citalopram (*n*=163)
Mean age (years)	47.3	48.1
Age range (years)	22–71	19–70
Females	105 (72%)	116 (71%)
Males	40 (28%)	47 (29%)
Major depression, single episode	66 (46%)	64 (39%)
Major depression, recurrent episode	79 (54%)	99 (61%)
Mean number of previous episodes	5.7	6.3
Mean age of first depression	32	31
Age range of first depression	9–60	12–65

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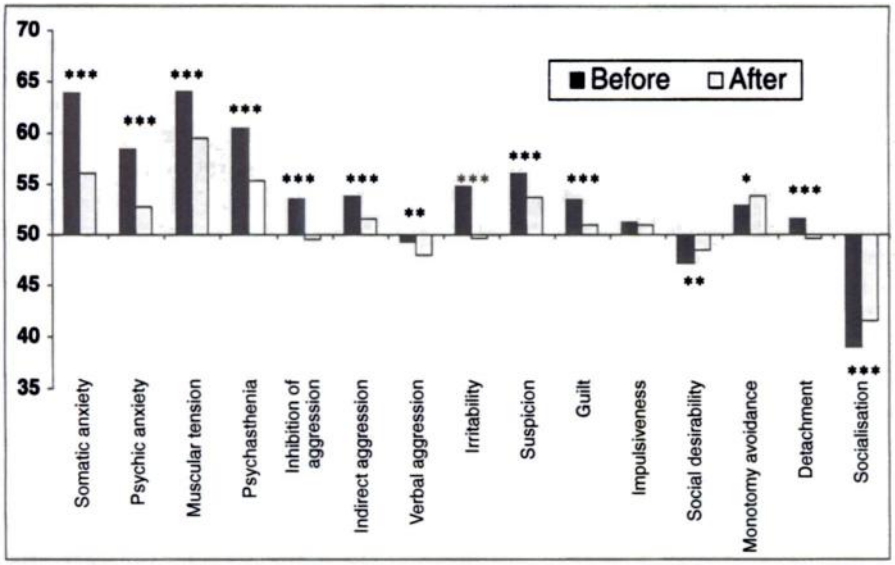

Fig. 1 The Karolinska Scales of Personality (KSP) traits in patients with major depressive disorder (n=308) treated with sertraline or citalopram for 24 weeks. Personality test scores are given as T-scores, which are standardised to have a mean of 50 (s.d.=10) in the KSP normative sample (*P<0.05, **P<0.01 and ***P<0.001).

Table 2 Changes in personality traits as determined by means of the Karolinska Scales of Personality (KSP) during 24 weeks of treatment with sertraline (n=145) or citalopram (n=163)

	Initial score for sertraline patients	Initial score for citalopram patients	Changes in sertraline patients	Changes in citalopram patients
Somatic anxiety	64.5 (11.1)	64.3 (13.1)	−7.6 (9.5)***	−8.0 (10.2)***
Psychic anxiety	57.9 (9.7)	58.8 (11.3)	−5.1 (7.4)***	−6.2 (8.0)***
Muscular tension	63.7 (13.2)	64.5 (13.8)	−4.1 (8.6)***	−5.1 (10.2)***
Psychasthenia	60.1 (10.3)	60.9 (11.4)	−4.7 (10.0)***	−5.6 (9.7)***
Impulsiveness	51.3 (9.4)	51.1 (10.0)	−0.3 (6.9)	−0.2 (6.3)
Monotony avoidance	52.8 (9.6)	53.1 (10.2)	0.5 (6.4)	1.2 (6.8)*
Socialisation	40.1 (12.1)	38.1 (12.1)	1.8 (6.1)***	3.1 (6.7)***
Detachment	51.9 (10.1)	51.2 (10.8)	−1.8 (6.6)**	−2.2 (8.3)**
Social desirability	47.1 (10.8)	47.2 (10.3)	1.1 (8.5)	1.6 (8.8)*
Indirect aggression	54.5 (9.4)	53.3 (9.7)	−2.7 (5.9)***	−1.8 (6.8)***
Verbal aggression	50.0 (10.0)	48.7 (9.7)	−1.5 (7.5)*	−1.1 (7.2)*
Irritability	54.6 (9.5)	55.1 (9.5)	−4.9 (9.0)***	−5.5 (9.9)***
Suspicion	54.1 (11.4)	57.8 (11.7)	−1.0 (9.0)	−3.5 (9.9)***
Guilt	52.7 (9.1)	54.2 (9.3)	−1.8 (8.8)*	−3.1 (8.5)***
Inhibition of aggression	53.3 (10.4)	53.8 (11.6)	−3.8 (7.3)***	−4.3 (8.2)***

Values are means with standard deviations in parentheses.
Significant changes during treatment (paired t-test, two-tailed): *P<0.05, **P<0.01 and ***P<0.001.

There were small differences between the effects induced by sertraline or citalopram, significant only with regard to the suspicion scale: sertraline group, −1.0 (9.0) (mean (s.d.)); citalopram group, −3.5 (9.9) (t=2.30, P<0.05).

In a series of multiple stepwise regressions with the separate KSP as dependent variables, the percentage variance explained by the changes in the separate KSP never exceeded 8.4% (Table 3).

There were no differences between men and women with regard to changes in the specific personality scales. In the multiple stepwise regressions, gender was included as an independent variable but was never entered in the final models (Table 3).

DISCUSSION

Over the past few years, a number of studies have indicated that SSRIs may be beneficial in the treatment of certain personality disturbances (Fava *et al*, 1994; Coccaro & Kavoussi, 1997). The results of the present study indicate that treatment with sertraline or citalopram for 24 weeks in patients with major depressive disorders influences separate personality traits measured by the KSP. In general, most personality traits studied were normalised, i.e. significant decreases in the anxiety and aggressivity-related scales and significant increases in the scales measuring social desirability and socialisation. Of course, it is a risk that the changes in the personality scales seen in the present study reflect regression towards the mean. However, the results are completely in line with recent studies indicating that SSRIs reduce the symptomatology accompanying personality disorders (Fava *et al*, 1994; Coccaro & Kavoussi, 1997) and that administration of an SSRI (paroxetine) modulates a normal personality by reducing negative affective experience and increasing affiliative behaviour (Knutson *et al*, 1998).

Relative effect of changes in depressive symptoms

One acknowledged source of error is that the state of the subject has influenced the results of the self-rating of the personality traits (von Zerssen, 1977). Furthermore, absence of a control (placebo) group makes it difficult to judge whether the changes in personality characteristics were created by the antidepressants. However, in an earlier study where the KSP were used (Perris *et al*, 1979), in-patients suffering from moderate to severe depressive episodes completed the KSP shortly after admission to hospital when they were depressed, and a few months later when they were at home having recovered from the depressive illness. The results verified that most of the scales in the inventory measure traits that are fairly independent of the state of the subject, except the scales measuring psychic anxiety, somatic anxiety and social desirability. Furthermore, in the present study, improvement in depressive symptoms, age, gender and type of drug explained no more than 0–8.4% of the

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Table 3 Stepwise multiple regressions, with changes in the different Karolinska Scales of Personality (KSP) as dependent variables and age, gender, type of drug and changes in total Montgomery–Åsberg Depression Rating Scale (MADRS) scores as independent variables (n=308)

	Entered variables	Multiple r	r^2 % of variance explained	F	P
Somatic anxiety	MADRS change	0.27	7.3%	23.79	<0.01
Psychic anxiety	MADRS change	0.27	7.3%	24.23	<0.01
Muscular tension	MADRS change	0.21	4.4%	13.86	<0.01
Psychasthenia	MADRS change	0.27	7.3%	23.90	<0.01
Impulsiveness	–	–	–	–	–
Monotony avoidance	–	–	–	–	–
Socialisation	MADRS change	0.29	8.4%	27.22	<0.01
Detachment	MADRS change	0.18	3.2%	10.72	<0.01
Social desirability	MADRS change	0.15	2.3%	6.95	<0.01
Indirect aggression	Age	0.14	2.0%	6.40	0.05
Verbal aggression	–	–	–	–	–
Irritability	MADRS change	0.29	8.4%	27.21	<0.01
Suspicion	MADRS change	0.21	4.4%	8.09	<0.01
	Type of drug			5.33	
Guilt	–	–	–	–	–
Inhibition of aggression	MADRS change	0.16	2.6%	7.86	<0.01

variance in any separate personality scale. The poor fit of the models found indicates that factors other than the included variables must explain the observed changes in the personality scales. Thus, it seems reasonable to believe that the changes seen in the personality scales might be an effect of the SSRIs.

In a recent study by Bagby *et al* (1998), self-report ratings and informant ratings of personalities of depressed out-patients were compared. From that study it was concluded that depressed mood may not influence the self-report of personality traits to the extent believed earlier. Similar results have also been reported by Shea *et al* (1996).

Biologically relevant temperament dimensions

The KSP were constructed to measure biologically relevant temperament dimensions. It has been suggested that the brain biogenic amine mechanisms contribute to the phenotypic expression of several important temperament dimensions (Cloninger, 1987; Zuckerman, 1995; Gustavsson, 1997). Thus, because the SSRIs change the activity in the brain serotonergic systems, changes in biologically relevant temperamental dimensions might be expected.

Serotonin, aggressive behaviour and impulsiveness

Evidence of an inverse relationship between central serotonergic (5-hydroxy-tryptamine) system function and impulsive aggressive behaviour has been accumulating for more than two decades (Coccaro & Favoussi, 1996). In the present study, all aggressivity and hostility scales showed a significant reduction during treatment with either sertraline or citalopram. This is in agreement with the results of earlier clinical trials, demonstrating that serotonin-enhancing agents reduce aggressive behaviour in patients with major depression (Fava *et al*, 1993), borderline personality disorder (Salzman *et al*, 1995) and personality disorder where there is a current history of impulsive–aggressive behaviour and irritability (Coccaro & Kavoussi, 1997). Furthermore, in healthy volunteers, Knutson *et al* (1998) demonstrated that, relative to placebo, SSRI administration reduced focal indices of hostility through a more general decrease in negative affect.

The only scale where no statistically significant change was observed was the impulsiveness scale. However, the patients in the present study tended to have normal impulsiveness scores at the beginning of the study. Thus, it seems as if non-normal (increased or decreased) scores of certain personality traits tend to be influenced towards normalisation by the SSRIs, whereas normal personality traits remain unchanged.

Socialisation as a measure of general dysfunction

Pretreatment socialisation scores in the present depressed population were low, roughly of the same magnitude as found earlier in patients with different forms of psychiatric disorders, for example affective and anxiety disorders (Gustavsson, 1997). After treatment, a significant increase in socialisation scores was demonstrated in both treatment groups. The KSP socialisation scale was originally constructed to assess psychopathic personality features (Schalling *et al*, 1987; Gustavsson, 1997). However, later studies suggest that a low score in socialisation characterises not only psychopathic personality but also personality pathology in general (Ekselius *et al*, 1994; Gustavsson, 1997). In addition, the socialisation scale manifests negative correlations with the Global Assessment of Functioning scale (Gustavsson, 1997) and all separate personality disorders in the DSM–III–R (Ekselius *et al*, 1994). In an earlier study, the socialisation scale was found to possess remarkable stability across nine years (Gustavsson, 1997). Furthermore, in the study of Perris *et al* (1979), no significant difference was found in the socialisation scale when patients were assessed during depression and after recovery.

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CLINICAL IMPLICATIONS

- The results indicate that in depressive disorders co-occurring with dysfunctional personality traits, SSRIs may influence both the depressive disorder and the personality.
- If the effect of SSRIs on personality traits seen in the present study is a direct effect, SSRIs may also be effective in the presence of dysfunctional personality traits even when there is no co-occurring depressive disorder.
- The observable effect of SSRIs on both depressive symptoms and personality traits might increase compliance during antidepressant treatment.

LIMITATIONS

- Although the personality inventory used has been demonstrated to be fairly independent of the clinical state of the investigated subjects, the improvement in depressive symptoms may have influenced the results.
- There are disadvantages as well as advantages when personality traits are determined only by means of self-rating.
- It is not known if the optimal doses of SSRIs and the optimal duration of the treatment are the same when SSRIs are used to influence personality traits as when the SSRIs are used to treat depressive disorders.

LISA EKSELIUS, PhD, LARS VON KNORRING, PhD, Department of Neuroscience, Psychiatry, University Hospital, Uppsala, Sweden

Correspondence: Lisa Ekselius, Department of Neuroscience, Psychiatry, University Hospital, S-751 85 Uppsala, Sweden. Tel: +46-18-66 52 27; Fax: +46-18-51 58 10

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