HUMAN PSYCHOPHARMACOLOGY, VOL. 11, 365–372 (1996)

A Naturalistic Prospective Study of the Use of Fluoxetine in General Psychiatric Outpatients

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Two hundred and forty-eight consecutively recruited patients attending a general psychiatry clinic with a wide variety of psychiatric disorders were treated with fluoxetine for a minimum of 3 months. Fluoxetine was shown to be effective and well-tolerated in a number of conditions of which only 57 per cent were major depressive disorder. Specific conditions and/or the presence of co-morbid conditions believed to be due to underlying disturbances in *serotonin* metabolism were associated with a significantly enhanced response. In contrast, significantly more patients who did *not* have such morbidity or co-morbidity appeared to be made *worse* by treatment with fluoxetine. The implications of this for clinical practice are discussed.

KEY WORDS — naturalistic; fluoxetine; serotonin

INTRODUCTION

In the last few years a number of new antidepressants have appeared which have a preferential mode of action at specific monoamine receptor sites. Whereas all these drugs have been demonstrated in randomized controlled trials (RCTs) as having clinical efficacy as antidepressants (and in some cases other conditions as well) it is by no means clear whether there is any *clinical* advantage in using one drug over any other or for using a drug which is specific for serotonin, noradrenaline, or a combination of both. Comparison drug trials are few in number and, apart from the issue of side-effects and safety in overdose, clinical guidelines for selecting one class of antidepressant in preference to another are currently lacking.

Parallel with these pharmacological developments there has been a considerable advance in our understanding of the role of serotonin (5HT) in many psychiatric disorders. A number of these were reviewed by Lopez-Ibor in 1988 but since that time the list has grown. This has been matched by an increasing use by clinicians of SSRIs in conditions which lie outside of their current licensed indications. For example, in the case of fluoxetine, in addition to the treatment of depression there are now published trials and case reports indicating efficacy in obsessive compulsive disorder, depression with obsessional features, premenstrual syndrome, generalized anxiety disorder, panic disorder, bulimia nervosa, obese binge-eating, schizotypal and borderline personality disorder, deliberate self harm recidivism, treatment-resistant schizophrenia, aggression dyscontrol syndrome, anger attacks within depression, maintenance of amphetamine and cocaine dependency, management of nicotine withdrawal, alcoholism, seasonal affective disorder, attention-deficit disorder, sleep disorders, autistic behaviour and dysthymia to name but a few.

A clinician will find it hard to form a clear and informed opinion as to the real value of a particular drug unless he or she uses it frequently and preferably in a consecutive series of patients to avoid selection bias. The efficacy data concerning new antidepressants are derived from randomized controlled trials. Such trials, although the gold-standard for substantiating a drug's efficacy, are subject to design limitations which mean that drugs which perform well under trial conditions sometimes fail to impress once in the arena of clinical practice. There is therefore a need for additional, *naturalistic* studies in patients who are representative of those whom psychiatrists and GPs are

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CCC 0885–6222/96/050365–08

normally obliged to treat. Such studies generate further hypotheses which can be turned back into further RCTs. These arguments are discussed at length in a companion review article (Blacker and Mortimore, 1996).

STUDY AIMS

The purpose of this study was twofold: (1) to examine the clinical efficacy of the antidepressant fluoxetine in a naturalistic setting involving a large consecutive sample of patients, (2) to identify whether the presence or absence of clinical features belonging to conditions associated with disturbances in serotonin metabolism might predict a preferential response.

The theoretical basis for this hypothesis is that there appear to be psychopathological *dimensions* which cross existing diagnostic boundaries and which are related to functional disturbances in monoamine metabolism (Van Praag *et al.*, 1990). We recognize that apparent responsiveness to SSRIs does not *in itself* imply serotonergic dysfunction; however, research has demonstrated deficiencies in serotonergic systems in individuals exhibiting dysfunctional maladaptive control of goal-directed behaviours including impulsive and aggressive individuals (Asberg *et al.*, 1976; Winchel and Stanley, 1991; Hollander *et al.*, 1994), disorders of eating such as bulimia nervosa and subsyndromal binge-eating (Jimerson *et al.*, 1992; Brewerton *et al.*, 1992; Wurtman *et al.*, 1993; Wallin and Rissanen, 1994), binge-related alcohol abuse (Virkkunen and Linnoila, 1990; Tollefson, 1991), obsessive compulsive disorder and compulsive addictive behaviours (Hollander *et al.*, 1988; Bastini *et al.*, 1991). Synthesis and metabolism of serotonin varies with menstrual (Rapkin *et al.*, 1987; Ashby *et al.*, 1988; Halbreich and Tworek, 1993) and seasonal rhythms (Asberg *et al.*, 1984; Sarrias *et al.*, 1989; Malmgren *et al.*, 1989) and so may have a role in the genesis of psychological symptoms which emerge in relation to these cycles such as premenstrual dysphoric disorder and seasonal affective disorder. Abnormalities in serotonin have also been found in pain syndromes such as migraine (Ferrari and Saxena, 1993).

These studies support a role for serotonin in inhibiting response to many stimuli across a wide variety of behaviours including regulation of sexual, aggressive and feeding behaviours, both in normal individuals and those with mood and anxiety disorders, with subjective aversive experiences of anxiety, frustration and pain acting as mediators in this process.

METHOD

Two hundred and forty-eight consecutive patients referred to a single psychiatrist (CVRB) and deemed to require treatment with antidepressant or equivalent pharmacotherapy were prescribed fluoxetine in standard doses. Patients were eligible if they were on no antidepressant medication or had failed to respond to previous prescriptions. All eligible patients were entered into the study regardless of age, social circumstances, severity of disorder, aetiology or physical health. Patients were reviewed by the consultant (CVRB) and all received a minimum of 3 months therapy. Those who withdrew early because of non-response or side-effects are included in the analysis. Twenty-five patients who failed to return after the first visit were not included as no outcome data was available even after contacting the GP.

Diagnoses were made according to DSM IV criteria. The only exception to this rule was chronic fatigue syndrome for which we used the Oxford Consensus Criteria (Sharpe *et al.*, 1991). Each diagnosis was recorded only once. In cases where the patient had significant symptoms of obsessional thoughts, panic attacks and/or binge-eating episodes not sufficient to meet diagnostic criteria for the *disorder* in question they were rated as having subsyndromal conditions.

Careful attention was paid to the presence or absence of disorders associated with disturbances in serotonin metabolism. The choice of what constituted a 'serotonergic' disorder was determined by whether there was research evidence of an accompanying abnormality in serotonin systems from animal, post mortem, neuroendocrine or other biological research (see above). Panic disorder was not rated as a specifically 5HT disorder as we feel the court is still out on whether this is predominantly a 5HT or noradrenergic disorder or a combination of both.

The disorders that were rated as 'serotonergic' were thus: (i) impulse control disorders including aggression dyscontrol, impulsive deliberate self harm, borderline personality disorder and compulsive addictive behaviours such as pathological gambling; (ii) bulimia nervosa, and obese binge eating with carbohydrate craving; (iii) obsessive compulsive disorder and subsyndromal obsessional thoughts; (iv) binge-related alcohol abuse;

(v) seasonal affective disorder and atypical depression; (vi) premenstrual dysphoric disorder; (vii) migraine.

For the purposes of subsequent analysis the presence of any *one* of these disorders (either as the principal or co-morbid diagnosis) was taken as indicative of 'serotonergic' status; patients in whom *no* such conditions were found were rated as 'non-serotonergic'.

Tolerance to fluoxetine was assessed using a three-point scale: 1 = no side effects; 2 = side-effects present but tolerable; 3 = intolerable side-effects leading to treatment discontinuation.

The side-effects themselves were assessed and recorded at each appointment.

Efficacy was assessed using the Clinical Global Improvement scale (CGI; Guy, 1976) which was assessed cumulatively over time to represent the best overall response within the treatment episode. The CGI was selected on the basis of its proven reliability and validity. It also allows for a global assessment of outcome which accords best with clinical practice and allows for a comparison of outcome across a range of different conditions.

Statistical analysis of outcome was by means of chi squared tests; all comparisons were made across the full range of CGI points but in view of the smaller number of cases with CGI scores of 4, 5, 6 and 7, these were collapsed into a single category (CGI 4–7).

RESULTS

A total of 248 patients were recruited 65 per cent of whom were female. Their mean age was 40·5 years (range = 16–81) and the majority were aged between 20 and 49 years (69 per cent).

As expected, a wide range of diagnoses were obtained (Table 1). Co-morbidity and multiple diagnoses were a common phenomenon in this sample with an average of 2·4 DSM IV diagnoses per patient (Table 2).

Twenty-six patients (11 per cent) were unable to tolerate fluoxetine at a dose of 20 mg and had to withdraw from treatment. A further four patients were unable to tolerate *higher* doses and were also withdrawn. This gives a total withdrawal rate due to side-effects of *12 per cent*.

A further 50 patients (20 per cent) developed tolerable side-effects giving a total incidence of side-effects on 20 mg dose of 31 per cent. There was no relationship between tolerance and age.

When individual diagnoses (primary or secondary) are considered fluoxetine was found to be less well-tolerated in patients suffering from panic disorder, generalized anxiety disorder, obsessive compulsive disorder, bulimia nervosa, somatoform disorders and chronic fatigue syndrome (Table 3). Fluoxetine was tolerated better in those suffering from depressive disorders. The commoner side-effects leading to *withdrawal* were anxiety and agitation (4 per cent), headache (2 per cent), insomnia (2 per cent), aggression (1 per cent), nausea (1 per cent), and breathlessness (1 per cent). Less common side-effects leading to withdrawal included the emergence of severe panic attacks, fatigue, severe sweating, loss of libido, sexual dysfunction, rash, augmentation of obsessional symptoms, dizziness, suicidal thoughts, acute confusional state, loss of appetite, weight gain, tremor, hypertension and sedation.

The commonest *tolerated* side-effects were nausea (6 per cent), sedation (5 per cent), anxiety and agitation (3 per cent), insomnia (3 per cent), headache (3 per cent), sexual dysfunction and loss of libido (3 per cent), dry mouth (2 per cent), fatigue (2 per cent), tremor (2 per cent), aggression, diarrhoea, dizziness, suicidal thoughts, loss of appetite and blurred vision (all 1 per cent), and rash, augmentation of obsessional symptoms or

Table 1. Primary diagnoses

Major depressive disorder	123
Dysthymic disorder	17
Depressive disorder with seasonal pattern	7
Depressive disorder, not otherwise specified	3
Chronic fatigue syndrome	26
Obsessive compulsive disorder	12
Panic disorder	8
Generalized anxiety disorder	3
Post traumatic stress disorder	3
Bulimia nervosa	12
Eating disorder, not otherwise specified	1
Alcohol use disorders	6
Borderline personality disorder	6
Antisocial personality disorder	1
Impulse control disorders	5
Somatoform disorders	3
Schizoaffective disorder	2
Primary sleep disorders	2
Other disorders	8
Total	248

Table 2. All diagnoses and subsyndromal clinical features (primary and subsidiary)

Major depressive disorder	142
Depressive disorder with seasonal pattern	43
Dysthymic disorder	39
Depressive disorder, not otherwise specified	18
Bipolar disorder	2
Panic disorder	44
Panic attacks	20
Generalized anxiety disorder	33
Obsessive compulsive disorder	16
Obsessional thoughts	27
Social phobia	15
Specific phobia	9
Agoraphobia without history of panic disorder	9
Post traumatic stress disorder	4
Chronic fatigue syndrome	44
Premenstrual dysphoric disorder	43
Bulimia nervosa	17
Binge eating	37
Anorexia nervosa	1
Alcohol use disorders	25
Other substance related disorders	5
Borderline personality disorder	7
Other personality disorders	8
Impulse control disorders	29
Pathological gambling	1
Somatoform disorders	20
Migraine	18
Schizoaffective and other psychotic disorders	9
Mild mental retardation	4
Primary sleep disorders	3
Dementia	2
Other disorders	8

of irritable bowel syndrome, heartburn, flushes, hypomania, weight gain, myoclonic jerks, alcohol intolerance, haematuria and bruxism (all less than 1 per cent).

In the majority of cases a dose of 20 mg was considered sufficient. However, a dose increase to 40 mg or 60 mg because of non- or partial response was thought necessary in 18 per cent. This led to a further clinical improvement in 47 per cent of cases (all diagnoses considered) and 45 per cent where the primary diagnosis was *depression*.

No differential in response was observed by age or sex. Response to fluoxetine, all diagnoses considered, is shown in Table 4.

The percentage response in the commoner conditions seen in this sample is shown in Table 5.

An important finding of this study was that a significant differential in response was seen between patients who did or did not have 'serotonergic' morbidity or co-morbidity (Chi^2; $3df = 11{\cdot}68$; $p = 0{\cdot}009$) (Table 6). The same finding was obtained with patients who were suffering from primary major depressive disorder (Chi^2; $3df = 8{\cdot}07$; $p = 0{\cdot}04$) (Table 7).

However, the differential in response between 'serotonergic' and 'non-serotonergic' cases was most marked in those patients who had no depressive symptoms. There were 46 such patients; 28 had serotonergic conditions (CGI 1 = 46 per cent, 2 = 21 per cent, 3 = 11 per cent, and 4–7 = 22 per cent) and 18 did not (CGI 1 = 6 per cent, 2 = 17 per cent, 3 = 11 per cent, 4–7 = 67 per cent). This indicates that even in the absence of depressive morbidity a significant proportion of patients with serotonergic features

Table 3. Treatment discontinuations in selected diagnostic groups (primary and subsidiary diagnoses) for fluoxetine 20 mg

Diagnosis	Total	Treatment discontinuation (%)	Odds ratio*
Major depressive disorder	140	12 (9)	0·60
Depressive disorder with seasonal pattern	41	4 (10)	0·88
Dysthymic disorder	37	2 (5)	0·43
Panic disorder	44	6 (14)	1·42
Generalized anxiety disorder	32	5 (16)	1·68
Obsessive compulsive disorder	15	3 (20)	2·20
Chronic fatigue syndrome	43	7 (16)	1·85
Premenstrual dysphoric disorder	41	6 (15)	1·56
Bulimia nervosa	17	3 (18)	1·88
Alcohol use and other substance related disorders	30	4 (13)	1·34
Somatoform disorders	19	3 (16)	1·63

*Odds ratio = ratio of discontinuations in those with diagnosis to those without diagnosis.

Table 4. All diagnoses (unselected patients): response to fluoxetine (optimal dose therapy) according to CGI score

CGI	Number (%)
1 = very much improved	107 (43)
2 = very improved	56 (22)
3 = minimally improved	27 (11)
4 = no change	37 (15)
5 = minimally worse	9 (4)
6 = much worse	12 (5)
7 = very much worse	0 —
Total	248

Table 6. Unselected patients. Serotonergic conditions present versus serotonergic conditions absent: response to fluoxetine (optimal dose therapy)

CGI	Serotonergic conditions present (%)	Serotonergic conditions absent (%)
1	66 (52)	41 (34)
2	22 (17)	34 (28)
3	16 (13)	11 (9)
4–7	23 (18)	35 (29)
Total	127	121

show an enhanced response whereas significantly more of the patients who did not have these features appeared to be worse following treatment with fluoxetine (Chi^2; $3df = 11{\cdot}87$; $p = 0{\cdot}009$).

Response to fluoxetine was particularly marked where *multiple* serotonergic conditions were present: a CGI score of 1 was obtained in 62 per cent of those with three or more such conditions (Chi^2; $3df = 13{\cdot}46$; $p < 0{\cdot}01$ when compared to non-serotonergic patients), 46 per cent of those with one or two 5HT conditions and 34 per cent of those with none.

Table 7. Primary diagnosis of major depressive disorder. Serotonergic conditions present versus serotonergic conditions absent: response to fluoxetine (optimal dose therapy)

CGI	Serotonergic features present (%)	Serotonergic features absent (%)
1	30 (64)	33 (43)
2	4 (8)	21 (28)
3	5 (11)	6 (8)
4–7	8 (17)	16 (21)
Total	47	76

Table 5. Selected diagnostic groups (primary and subsidiary): response to fluoxetine (optimal dose therapy)

Diagnosis	CGI score %				CGI mean value	Total number of cases	Chi^2 $3df$ (p)*
	1	2	3	4–7			
Major depressive disorder	48	23	9	20	2·12	142	3·90 (n.s.)
Depressive disorder with seasonal pattern	51	12	21	16	2·07	43	9·48 ($p < 0{\cdot}05$)
Dysthymic disorder	41	28	18	13	2·08	39	5·03 (n.s.)
Panic disorder	30	32	20	18	2·39	44	9·43 ($p < 0{\cdot}05$)
Generalized anxiety disorder	36·5	27·5	12	24	2·46	33	0·86 (n.s.)
Obsessional thoughts including obsessive compulsive disorder	54	16	14	16	2·02	43	5·73 (n.s.)
Chronic fatigue syndrome	30	18	14	38	3·00	44	8·44 ($p < 0{\cdot}05$)
Premenstrual dysphoric disorder	49	18·5	14	18·5	2·12	43	1·71 (n.s.)
Binge eating including bulimia nervosa	54	20	17	9	1·82	54	9·94 ($p < 0{\cdot}05$)
Alcohol use and other substance related disorders	33	25·5	17	26·5	2·40	30	1·98 (n.s.)
Borderline personality and impulse control disorder	61	17	11	11	1·64	36	6·52 (n.s.)
Somatoform disorder	25	15	10	50	3·10	20	10·27 ($p < 0{\cdot}02$)

*Comparison of outcome between patients with and without the diagnosis across a full range of CGI points with categories 4–7 collapsed.

DISCUSSION

Our aim in conducting this study was to *complement* the existing data from RCTs (Hall, 1988; Stokes, 1993) with respect to the use of SSRIs (in this case fluoxetine) in clinical practice by adopting a naturalistic approach largely neglected in the literature. The attraction of naturalistic data is that it is immediately applicable to the clinical situation and gives perhaps a more honest appraisal of how a particular treatment may be expected to work.

The assessment of outcome in this study was not blind and is therefore potentially subject to bias, a limitation which could not be avoided within the design. However the risk of rater bias should not, in itself, prevent studies such as this from taking place; one cannot conclude that all findings from such studies are due to bias and the observations may be true. These observations thus remain to be evaluated further under rigorous RCT design. We suggest that the current policy of exclusively developing drugs in highly selected trial patients and expecting the data to faithfully reflect how the drug will behave in actual clinical practice is suspect. RCTs have their own shortcomings and sources of bias and no one methodological approach is perfect. A combination of RCT and naturalistic studies is believed to be the optimum way forward for drug development.

The present study was the first of several naturalistic studies involving fluoxetine which were conducted by independent teams in a range of diagnoses and clinical situations but which follow the same or similar methodology (Bhaumik *et al.*, 1994; Daly *et al.*, 1994; McWilliam and Dover, 1994).

There are three main conclusions from the present study. (1) The first is that fluoxetine has efficacy in a wide range of conditions (not just depressive disorder) in the naturalistic clinical setting. These include conditions which lie outside of the range of those for which the drug is currently licensed. A large proportion of patients did have depressive symptoms (81 per cent in all) but in only 59 per cent were they severe enough to meet diagnostic criteria for depressive *disorder*. It could be argued that the response seen in these sub-syndromally depressed patients was nonetheless an antidepressant one. On the other hand there is evidence that response to antidepressants is minimal in patients with mild, subdisorder depression (e.g. Hollyman *et al.*, 1988). The principal conclusion from this data is that it challenges psychiatrists to move away from narrow, stereotyped diagnostic views of what 'antidepressants' do and how they work to consider broader issues such as their applicability to treat a range of conditions which have as their core a behavioural disturbance of, say, compulsivity or retardation etc. There are a variety of ways in which an SSRI such as fluoxetine might benefit patients suffering from conditions with a high degree of co-morbidity (such as here). There are anti-compulsive, anti-impulsive and anxiolytic properties to consider as well as effects on satiety and aggression known to be related to serotonin deficiency. Our finding of a differential in response between serotonergic and non-serotonergic patients which was preserved even in cases with no depressive symptoms is therefore of great interest.

(2) The second conclusion from this study is that the discontinuation rate due to side-effects (12 per cent) was lower than that previously obtained in RCTs (Cohn and Willcox (1985) (15 per cent) and Stark and Hardison (1985) (18 per cent)) but similar to that obtained in other naturalistic surveys e.g. Linden *et al.* (1993) (12 per cent) and Corne and Hall (1989) (12 per cent). Naturalistic dropout rates are important because it is on these that the key issues of cost–benefit analyses, when comparing SSRIs with tricyclics, depend. At present, dropout rates for tricyclic antidepressants in naturalistic studies are approximately twice or even two-and-a-half times as high as those for SSRIs (Katon *et al.*, 1992). In addition, in a market saturated with new antidepressants practising clinicians need to have an idea of who *not* to give a particular drug to. The finding from the present study that it was the anxious, panicking, agitated, hypochrondriacal and body-watching patients who tolerated fluoxetine least well matches that reported in small-series case reports. Some of these patients were undoubtedly made worse by fluoxetine and deterioration included onset or increase in panic attacks, sleeplessness, worsening agitation, akathisia and in two cases suicidal ideation. We are aware that the debate concerning fluoxetine and suicidal ideation has been thoroughly dealt with in the literature, however the original finding by Teicher *et al.* (1990), albeit flawed and subject to alternative explanations, was nonetheless based on naturalistic data whilst the counter-arguments drew exclusively on RCT trial data. Fortunately none of our patients attempted suicide whilst taking fluoxetine and in the majority of cases in which suicidal thoughts were present fluoxetine

had a clear antidepressant, anti-suicidal, role. Serotonergic agonists are known to cause a marked transient increase in anxiety, obsessional symptoms and panic attacks (Zohar *et al.*, 1987; Westenberg and den Boer, 1989) with subsequent amelioration of symptoms over time. In the present study, in most of the cases in which deterioration occurred it was sustained and the improvement noted when the patient eventually stopped the drug, was at times quite marked.

The adverse event profile (in terms of type of event reported) was very similar to pooled data from clinical trials (Cooper, 1988) although we found a higher than expected incidence of sexual dysfunction and loss of libido. Nausea and sedation were less likely to lead to withdrawal than anxiety and agitation.

(3) The third conclusion is that there appeared to be a differential in response between patients who did and did not have serotonergic conditions either as their principal or subsidiary diagnosis. The significance of this effect is contributed to by the additional finding that a proportion of patients who *lacked* such serotonergic morbidity appeared to get *worse* on fluoxetine. Hitherto the research literature has failed to demonstrate any convincing evidence that there are different kinds of depression with preferential responses to different kinds of antidepressant yet clinical experience teaches otherwise: it is not uncommon for a patient to fail to respond to one class of antidepressant only to respond subsequently (in some cases repeatedly) to one from a different class. Clearly this finding needs to be examined further under more rigorous conditions using RCT design but if the observation concerning serotonergic loading and response to SSRIs turns out to be correct then clinical enquiry about such symptoms and disorders may be a useful clinical strategy when deciding which of the many drugs on offer one should select for treatment.

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