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Systematic Review and Guide to Selection of Selective Serotonin Reuptake Inhibitors

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Abstract

A meta-analysis of 20 short term comparative studies of 5 selective serotonin reuptake inhibitors (SSRIs; citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) has shown no difference in efficacy between individual compounds but a slower onset of action of fluoxetine. There were suggestions that fluoxetine caused more agitation, weight loss and dermatological reactions than the other SSRIs. More patients discontinued fluvoxamine and fewer patients stopped sertraline because of adverse effects than their comparator SSRIs.

The most common adverse reactions to the SSRIs were gastrointestinal (especially nausea) and neuropsychiatric (particularly headache and tremor). Data from the Committee on Safety of Medicines showed more reports of suspected reactions (including discontinuation reactions) to paroxetine, and of gastrointestinal reactions to fluvoxamine and paroxetine, than the other SSRIs during their first 2 years of marketing.

Prescription-event monitoring revealed a higher incidence of adverse events related to fluvoxamine than its comparators. There were higher incidences of gastrointestinal symptoms, malaise, sedation and tremor during treatment with fluvoxamine and of sedation, tremor, sweating, sexual dysfunction and discontinuation reactions with paroxetine. Fluoxetine was not associated with a higher incidence of suicidal, aggressive and related events than the other SSRIs.

Patients have survived large overdoses of each of the compounds, but concern has been expressed over 6 fatalities following overdoses of citalopram.

Drug interactions mediated by cytochrome P450 enzymes are theoretically less likely to occur during treatment with citalopram and sertraline, but there is a sparsity of clinical data to support this.

Methodological difficulties and price changes do not allow choice for recommendations on the choice of SSRI based on pharmacoeconomic data.

Taking into account the strengths and weaknesses of the methods used to compare drugs, guidelines to the selection of individual SSRIs in clinical practice are proposed. Citalopram should be avoided in patients likely to take overdoses. Fluoxetine may not be the drug of first choice for patients in whom a rapid antidepressant effect is important or for those who are agitated, but it may have advantages over other SSRIs in patients who are poorly compliant with treatment and those who have previously had troublesome discontinuation symptoms. Fluvoxamine, and possibly paroxetine, should not be used as first choice in patients especially prone to SSRI-related adverse reactions, while paroxetine should be avoided if previous discontinuation of treatment was troublesome. When in doubt about the risks of drug interactions, citalopram or sertraline should be considered given the lower theoretical risk of interactions.

Selective serotonin (5-hydroxytyptamine; 5-HT) reuptake inhibitors (SSRIs) have been used to treat depression for more than 15 years. Zimeldine, the first SSRI to be introduced into clinical practice (in 1982), was withdrawn from use shortly after its introduction because of the occurrence during treatment of the Guillain-Barré syndrome.[1,2] The currently marketed drugs are the subject of this paper. They include citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.

Clomipramine and venlafaxine will not be included because, in spite of their inhibitory effect on serotonin uptake, they and their major metabolites (desmethylclomipramine and o-demethylvenlafaxine) also inhibit noradrenaline uptake.[3,4] Nefazadone will not be reviewed as this drug and its primary metabolite, hydroxynefazadone, have potent antagonistic effects on 5-HT_{2A} receptor binding with only weak binding to the human serotonin transporter.[5,6]

There have been many comparisons of SSRIs with tricyclic antidepressants,[7-16] but there have been relatively few publications comparing individual SSRIs. In this paper we present the results of a systematic review of the comparative studies that have been carried out, assess the differences between SSRIs that have been reported, and offer guidelines for choosing individual compounds in clinical practice. As most of the comparisons that have been made relate to the use of SSRIs in the

treatment of depression, the emphasis in our paper will be on their role as antidepressants.

1. Methodology

1.1 Identification of Controlled Comparisons of SSRIs in the Treatment of Depression

Randomised controlled studies involving direct comparisons between the 5 SSRIs in the treatment of patients with major depressive illness were identified by contacting pharmaceutical companies, carrying out a Medline search up to December 1997, reviewing conference reports and manual cross referencing. For studies that did not provide all of the necessary information, the data were requested from the first author of the relevant publication. If there was no response from the author within one month a reminder was sent. 21 studies were identified[17-38] (see table I) with all but one[34] providing quantitative information.

Fourteen of the studies were published as peer reviewed articles, one as a peer reviewed article published in a journal supplement, and one as a paper in a non-peer reviewed journal supplement. We also identified 5 abstracts or posters. In the case of 5 studies further information was received from authors (table I). Most studies were short term trials of efficacy involving outpatients. Of the 21 studies, 16 involved comparison with fluoxetine, showing that it is widely used as the 'standard' comparator SSRI. It is noteworthy that 16 of the publications or reports acknowledged pharmaceutical company support, including 13 of the studies involving fluoxetine. All of these studies were supported by the company that marketed the comparator SSRI.

1.2 Meta-Analysis of Controlled Trials

Where possible the studies were examined quantitatively by meta-analytic pooling of individual results with the Arcus Quickstat Biomedical programme (Medical Computing; Research Solutions, 124 Cambridge Scientific Park, Cambridge CB4 4ZS, UK) using the methods of Hedges and Olkin[39] and Gardner and Altman.[40] Each SSRI was compared with the other SSRIs as a group and with other individual SSRIs where there were sufficient studies for a meaningful analysis.

The relative efficacy was calculated as an effect size (d)[39] defined as the difference in reduction in rating scale scores (initial score minus final mean score) for the 2 SSRIs being compared divided by the pooled final standard deviation. The Hamilton Depression Rating Scale[41] (HDRS) values were available for 16 studies and the Montgomery and Asberg Depression Rating Scale[42] (MADRS) values for 4 studies. For the 6 studies where the standard deviations of rating scale scores were not supplied, the effect size was calculated from the significance value (1 study) or, if that was not available, the pooled variance from studies with complete data using the same rating scale (5 studies). Heterogeneity was examined using Cochran's Q test and a summary variance-weighted effect size was then calculated using a fixed effects model for homogeneous data and a random effects model if it was heterogeneous.[43] An intention-to-treat, or last-observation-carried-forward, analysis was available in all but one study. A positive effect size indicates an advantage of the individual SSRI compared with the others.

Tolerability was assessed by calculating the relative risk (RR) of discontinuing treatment (total numbers of patients discontinuing treatment and numbers discontinuing treatment because of adverse effects) and of experiencing adverse effects (where at least one treatment-related effect or specific adverse effects was identified).[40] The RR of discontinuation due to treatment failure was also calculated. When there were significant results the absolute risk difference (RD) was calculated for clarification of their clinical significance. Variance-weighted pooling of individual results was carried out using a fixed effects model for homogeneous data and a random effects model if they were heterogeneous.[43] An RR of less than one indicates an advantage of an individual SSRI over its comparators.

Table I. Comparative randomised controlled trials of selective serotonin reuptake inhibitors (SSRIs)

Study	SSRI (N[a])	Dose (mg/day)	Patient characteristics[b]	Duration (weeks)	Efficacy/cost effectiveness	Tolerablity/quality of life
Aguglia et al.,[17] 1993	Fluoxetine (56) Sertraline (52)	28 72	Outpatients	8	Fx = S	Agitation Fx ≥ S Adverse effect dropouts Fx ≥ S
Ansseau et al.,[18] 1994	Fluvoxamine (64) Paroxetine (56)	152 25	In- and outpatients	6	Fv = P	Severe adverse effects Fv > P Adverse effect dropouts Fv > P Somnolence P > Fv
Bennie et al.,[19] 1995	Fluoxetine (144) Sertraline (142)	25 62	Outpatients including bipolar patients	6	Fx = S	Fx = S
Bisserbe et al.,[20]c,d 1996	Fluoxetine (120) Sertraline (122)	20-60 50-150	Outpatients with DSM-IV major depressive episode	26	Fx = S. More medical consultations and NS higher absence from work and overall costs with Fx	Adverse effects Fx = S
Bougerol et al.,[21] 1997	Citalopram (158) Fluoxetine (158)	40 20	Outpatients	8	Overall efficacy C = Fx. Severely depressed patients C > Fx	Gastrointestinal adverse effects C > Fx
De Wilde et al.,[22] 1993	Fluoxetine (50) Paroxetine (50)	42 31	Patients with DSM-III Major Depression - status not given	6	Patients responding at 3 weeks P > Fx Final efficacy Fx = P	Respiratory and skin-related adverse effects Fx > P
Gagiano[23] 1993	Fluoxetine (44) Paroxetine (44)	42 31	Outpatients	6	Fx = P	Significant weight loss on Fx, not P
Haffmans et al.,[24]d 1996	Citalopram (108) Fluvoxamine (109)	38 191	Outpatients	6	C = Fv	Gastrointestinal adverse effects Fv > C
Kiev & Feiger[25] 1997	Fluvoxamine (30) Paroxetine (30)	102 36	Outpatients	7	Fv = P	Sweating P > Fv
Latimer et al.,[26]c 1996	Fluoxetine (52) Sertraline (54)	20-60 50-150	Outpatients	24	Overall Fx = S Melancholic patients S > Fx	Dyspepsia S > Fx Skin-related adverse effects Fx > S Weight loss significant with Fx not S Quality of life measures Fx = S
Linden et al.,[27]c,d 1995	Fluoxetine (119) Sertraline (117)	30 75	Elderly (>60 years) outpatients	12	HDRS improvement at 2 weeks S > Fx Final efficacy Fx = S Improvement in some measures of cognitive function S > Fx	Fx = S
Nemeroff et al.,[28] 1995	Fluvoxamine (49) Sertraline (48)	124 137	Outpatients	7	Fv patients higher HDRS score at baseline. Efficacy Fv = S	Sexual dysfunction S > Fv Nausea Fv > S Adverse effect dropouts Fv > S
Ontiveros & Garcia-Barriga[29] 1997	Fluoxetine (61) Paroxetine (60)	20 20	Outpatients	7	Fx = P	Fx = P Observer and patient preference P > Fx

Patris et al.,[30]e 1996	Fluoxetine (184) Citalopram (173)	20 20	General practice patients	8	Patients responding at 2 weeks C > Fx Final efficacy Fx = C. Advantage to C in patients not taking hypnotics	Back pain C > Fx Weight loss and dry mouth Fx > C
Rapaport et al.,[31]d 1996	Fluoxetine (49) Fluvoxamine (51)	34 102	Outpatients	7	Fx = Fv	Nausea and vomiting Fx > Fv Agitation Fx ≥ Fv
Sechter et al.,[32]c,d 1996	Fluoxetine (119) Sertraline (117)	34 77	Outpatients	12	Fx = S	Adverse effects Fx = S Quality of life measure improvement S > Fx
Schone & Ludwig[33]f 1993	Fluoxetine (52) Paroxetine (54)	28 41	Elderly (>65 years) outpatients	6	HDRS improvement at 2 weeks P > Fx Patients responding at 6 weeks P > Fx	Adverse effects Fx = P Cognitive function improvement P > Fx
Shrivastava et al.,[34]c 1993	Fluoxetine (20) Paroxetine (19 Placebo (8)	10-50 20-80	Not stated	12	HDRS improvement at 2 weeks P > Fx Final efficacy Fx = P	Nausea, anorexia, tiredness Fx ≥ P
Tignol[35] 1993	Fluoxetine (87) Paroxetine (89)	20 20	Inpatients	6	Fx = P	Weight loss Fx > P Gastrointestinal adverse effects Fx ≥ P
Van Moffaert et al.,[36] 1995 – acute	Fluoxetine (82) Sertraline (83)	27 68	In- and outpatients	8	Fx = S	Agitation Fx > S
Van Moffaert et al.,[36] 1995 – continuation	Fluoxetine (56) Sertraline (49)	27 68	Treatment-responders in acute study	24	Fx = S	Fx = S
Zanardi et al.,[37]d 1996	Paroxetine (22) Sertraline (24)	50 150	In-patients (including bipolar patients taking lithium) with psychotic features	6	Response rate in intention-to-treat analysis S > P Response rate in completers S = P	Adverse effect dropouts P > S

a Intention to treat population. Efficacy analysis usually on smaller numbers of patients.

b Patients met criteria for unipolar DSM-III-R Major Depression unless otherwise stated.

c Reported in abstract/poster.

d Further information provided by author.

e Also reported in Bougerol et al.[21]

f Same study as reported by Geretsegger et al.[38]

C = citalopram; **Fv** = fluvoxamine; **Fx** = fluoxetine; **HDRS** = Hamilton Depression Rating Scale; **N** = number of patients in study; **NS** = nonsignificant; **P** = paroxetine; **S** = sertraline; **>** indicates significantly better than comparator SSRI for efficacy, quality of life, and preference indices; **>** indicates significantly more than comparator SSRI for adverse effect indices; ≥ indicates non-significantly (or significance not stated) better than comparator SSRI for efficacy, quality of life, and preference indices; ≥ indicates non-significantly (or significance not stated) more adverse effects than comparator SSRI for adverse effect indices; **=** indicates no difference between SSRIs.

1.3 Adverse Event Monitoring

Adverse drug reactions are reported in the literature as individual cases, publications of clinical drug trials and reports of drug safety monitoring. The voluntary reporting of isolated adverse effects depends on the awareness, vigilance and initiative of clinicians. Adverse events may be under diagnosed or not reported and, when they are reported, they usually serve as no more than a warning of a possible adverse reaction. The publication of isolated reports does not allow for a comparison of the incidence of adverse reactions and so such data will not be considered in this paper.

Reports of unwanted effects occurring during clinical trials also have their limitations such as deficiencies in reporting, relatively small numbers of patients and difficulty in establishing a causal relationship between the drug and the adverse effect. However, they are useful in providing clues as to the relative frequency of occurrence of effects during treatment, especially if they are based on double-blind, randomised, parallel-group comparisons. Such clues can serve as cues to the further investigation of these effects. It is therefore useful in the assessment of unwanted effects to review published data based on overviews of clinical trials and large databases.

We present data from 3 sources of information on adverse reactions to SSRIs: major published reviews of the 5 currently marketed SSRIs; data from the British Committee on Safety of Medicines (CSM) 'yellow card' system of monitoring; and the 'green form' system of prescription event monitoring (PEM) of the Southampton Drug Safety Research Unit (DSRU).

1.3.1 Committee on Safety of Medicines (CSM)

The CSM originated from the British Committee on the Safety of Drugs which was established by the Health Ministers in 1964 and financed by the Department of Health. It became reconstituted as the CSM in 1971 and suspected adverse drug reactions (ADRs) have since been monitored by the Committee.[44,45] Pharmacovigilance is carried out by the Medicines Control Agency and is based on multiple sources of information, including worldwide spontaneous reporting of ADRs, published reports, post-marketing safety studies, record-linkage databases, pharmaceutical companies and drug regulatory authorities (Personal communication with CSM-Medicines Control Agency 1998). Data from these sources are entered into a specialised computer system, Adverse Drug Reactions On-Line Information Tracking (ADROIT), to facilitate their rapid processing and analysis.[46]

1.3.2 Prescription Event Monitoring (PEM)

PEM is a non-interventional, non-experimental, observational cohort system of drug safety monitoring carried out in the DSRU in Southampton, England. No doctor is approached before the decision to treat a patient is made and the monitoring is independent of studies carried out by pharmaceutical companies. Cohorts comprising more than 10 000 patients treated by general practitioners with newly marketed drugs are studied. These cohorts provide approximately 10 times the amount of data on volunteers and patients that are available at the time of a marketing application.[47]

The evolution of the methodology of PEM[48-53] and its application to psychotropic drugs have been described in detail.[54-57] Patients receiving new drugs and the general practitioners who prescribe them are identified by the Prescription Pricing Authority. Copies of prescriptions are supplied in confidence and legible scripts (the overwhelming majority) are available for analysis. The names and addresses of the doctors who wrote the prescriptions are checked against the DSRU's register of general practitioners and patients who have received one or more prescriptions for a particular drug are identified.

Six to 12 months after the first prescription for each patient is written the practitioner is sent a 'green form' questionnaire on which he or she is asked to provide the following information:

- gender and age of patient
- indication for prescribing the drug
- dates of starting and stopping treatment
- reason for stopping
- drug(s) substituted

- effectiveness (or otherwise) of treatment
- dates and nature of any events that occurred during treatment (regardless of whether or not treatment was continued).

These data are linked with information from related prescriptions and processed by the DSRU's technical officers. Questionnaires are not sent to hospital doctors as practically all patients in Britain are assessed by general practitioners before referral to hospital, and the hospital sends a report to the practitioner on each patient seen.

In PEM, prescribers are asked to record all events and not just those suspected as being drug-related. An 'event' is defined as any:

- new diagnosis
- reason for referral to a hospital-based consultant or admission to hospital
- unexpected deterioration or improvement in a concurrent illness
- suspected drug reaction
- symptom, sign or non-medical event that is considered of sufficient importance to be entered into the patient's records.

Practitioners are not required to decide if there is a cause-and-effect relationship between any reported event and the drug treatment. Pre-existing diseases are not recorded as events unless an exacerbation occurs. Symptoms, signs and the results of laboratory tests are accepted as events only if the underlying disorder or disease responsible is not reported. Wherever possible each event is matched with those in an 'event dictionary'[58] and then categorised into 'event groups' based on the physiological system they predominantly effect.

Different methods of assessment have been used to compare individual SSRIs. In earlier studies events occurring at a rate of one or more per 1000 patients (number of events/number of patients × 1000) during the first month following the start of treatment (T1) were analysed by 2 methods. In the first of these a rate ratio T1/T2 was calculated, with T1 being the event rate per 1000 patients during the first month of treatment and T2 the mean event rate per 1000 patients during the second to sixth month of treatment. PEM studies of 42 drugs carried out in the DSRU had suggested that a rate ratio (T1/T2) of 3 or more signals an association with the drug being investigated. Statistical support for the validity of this suggestion was provided by Andrew et al.[52] The second test used a Poisson model to calculate the 99% confidence intervals for the difference between the event rate in month 1 (T1) and the mean event rate in months 2 to 6.[59]

Apparent associations between drug exposure and particular events reported during the 6-month period following the start of treatment are assessed with the help of information provided on the green forms. The outcome of each pregnancy reported as an event is determined by sending a further questionnaire to the patient's medical practitioner. Death with no specific cause is followed up by obtaining copies of the death certificates from the Office of National Statistics.

This method has now been superceded by one in which incidence densities (IDs) of events are calculated.[57] IDs are calculated for events reported during the first month of treatment, the second to sixth month of treatment and the overall treatment period in patients for whom either the date of stopping the drug is known or in those who continue to take the drug. The densities are presented as the number of reports per 1000 patient-months of treatment and are calculated from the following formula: ID = number of events occurring during treatment period/patient-months of exposure to drug × 1000.

2. Controlled Comparisons of SSRIs

2.1 Results

2.1.1 Efficacy

A summary of the outcome of the 21 studies is presented in table II. Only 3 studies, each of them comparing fluoxetine with sertraline, investigated the outcome of treatment beyond 12 weeks. Sertraline was favoured on quality of life measures in one of these studies[33] and on economic grounds in another.[20]

Table II. Meta-analysis of efficacy of individual selective serotonin reuptake inhibitors (SSRIs) compared with all other SSRIs as a group

SSRI	Analysis	No. of studies (no. of patients)	Effect size (d)[a]	95% CI	p
Citalopram	End of study	3 (827)	0.08	–0.06 to 0.21	0.266
Fluoxetine	2 weeks[b]	15 (2542)	–0.11	–0.18 to 0.03	0.008
Fluoxetine	End of study	15 (2486)	–0.06	–0.14 to 0.01	0.108
Fluvoxamine	End of study	5 (553)	–0.07	–0.24 to 0.09	0.398
Paroxetine	End of study	8 (679)	0.03	–0.13 to 0.18	0.739
Sertraline	End of study	9 (1421)	0.08	–0.03 to 0.18	0.147

a Effect size, defined as the difference in reduction in rating scale scores (initial score minus final mean score) for the 2 SSRIs being compared divided by the pooled final standard deviation.

b Two studies reported results at 3 weeks.

There were no consistent differences reported in overall efficacy, although there were a few reported differences in the post-hoc analyses (see below). Fourteen studies involving 2464 patients reported figures for drop-outs due to treatment failure (overall rate 6.9%), with no difference between individual SSRIs (data not shown).

Fluoxetine

No difference was reported in the overall efficacy of fluoxetine compared with the other SSRIs at the study end-point, apart from in one study of elderly patients where paroxetine was considered significantly superior in terms of response (defined as a reduction of 50% or more in both HDRS and MADRS score) but not reduction in HDRS score.[32] A further 4 studies found an advantage to the comparator on post-hoc analyses; 3 of these reported greater efficacy and 1 an improvement in cognitive function (table I). In particular, citalopram was favoured in more severe depression[21] and sertraline in patients with a DSM-III-R diagnosis of melancholia.[26] Four studies reported a significant advantage to the comparator at week 2 (2 studies) or week 3 (2 studies), with a fifth reporting a trend in favour of the comparator between weeks 1 and 3. A quantitative analysis of the results at weeks 2 and 3 was therefore made in addition to the end-of-study results.

In the quantitative analysis, 15 comparative trials of fluoxetine (7 *vs* sertraline, 5 *vs* paroxetine, 2 *vs* citalopram and 1 *vs* fluvoxamine) provided data on overall efficacy at the end of the study. Eleven trials provided complete data (means and standard deviations or p value). There was a small advantage of the comparator SSRIs over fluoxetine which did not reach statistical significance (table II). There was a high degree of statistical homogeneity and the result was essentially the same when the analysis was confined to the studies with complete data (d = –0.08, 95% CI –0.17 to 0.01, p = 0.093) or the 6 large studies with over 200 patients (d = –0.05, 95% CI –0.15 to 0.05, p = 0.318). However, when the studies were analysed according to their duration, the 6 studies that only lasted 6 weeks showed a trend towards a greater efficacy of the comparators (d = –0.12, 95% CI –0.25 to 0.01, p = 0.073) which was not present when the 9 studies lasting 7 weeks or longer were analysed (d = –0.03, 95% CI –0.13 to 0.07, p = 0.525). This suggested that the duration of treatment might be a contributory factor.

This possibility was further supported by our analysis of data following 2 to 3 weeks of treatment. The same 15 studies provided figures for comparative efficacy at weeks 2 (13 studies) or 3 (2 studies). These early results showed the comparator SSRIs to be significantly more effective (table II). Similar effect sizes were obtained if the analysis was restricted to the 11 studies with complete data (d = –0.10, 95% CI –0.23 to 0.03, p = 0.134) or to the 6 largest studies, each of which included more than 200 patients (d = –0.10, 95% CI –0.20 to 0.00, p = 0.057). This result was consistent across comparator SSRIs, but only reached significance in comparison with paroxetine, where

the result was marked (d = –0.24, 95% CI –0.41 to –0.07, p = 0.005).

Other SSRIs

No significant differences in efficacy were found when the other individual SSRIs were compared with SSRIs as a group (table II).

2.1.2 Tolerability

The studies analysed demonstrated the typical adverse effect profile of SSRIs (see below), with gastrointestinal effects (particularly nausea) being most prominent, followed by headache and 'stimulant' adverse effects such as agitation, anxiety and insomnia. In general, there was a lack of sedation and anticholinergic adverse effects. The data provide different ways of quantitatively assessing tolerability, each with different strengths and weaknesses.

The total discontinuation rate is the most objective measure, but it only partially reflects tolerability as patients in trials stop treatment for a variety of reasons. Discontinuation attributable to adverse effects is a clinically relevant measure, but only reflects more severe effects and is prone to bias in reporting. The percentage of patients experiencing at least 1 treatment-emergent adverse effect is likely to be a sensitive measure, but many of the adverse effects are of minimal severity, clinically unimportant or unrelated to the drug. It is therefore prudent to examine all 3 measures in assessing overall tolerability.

The percentage of patients experiencing specific adverse effects can also be analysed, but such an analysis needs to be approached with caution because most of the studies only reported unwanted effects occurring above a certain frequency (typically 5 to 10%). For this reason analyses are unlikely to provide a true sample of the studies as a whole. The exception to this is nausea where figures are available from 17 studies.

The total discontinuation rate in the 19 trials providing data (2999 patients) was 25.6%. Nineteen studies (involving 3098 patients) reported discontinuations attributable to adverse effects with a rate of 10.8%. The figures compare favourably with approximately 30 and 15%, respectively, reported for SSRIs in comparative studies with tricyclic antidepressants.[60,61] The percentage of patients who experienced at least 1 treatment-emergent effect was 57.9% in 16 studies (2539 patients), while the percentage of patients who experienced nausea was 21.3% in 17 studies (2706 patients).

Citalopram

In the 3 large studies of citalopram there were no consistent differences in the adverse effect profile compared with the comparator SSRIs. The quantitative analyses also failed to show any differences (table III). The incidence of nausea in the 3 studies did not differ between citalopram and the comparators (RR = 1.02, 95% CI 0.75 to 1.38, p = 0.904).

Fluoxetine

None of the studies reported an overall difference in treatment dropouts between fluoxetine and its comparator SSRIs. However, in the quantitative analysis there was a nonsignificant greater risk of discontinuing treatment with fluoxetine than with the comparators (table III). The absolute increase in risk was 2.6% (95% CI –0.7 to 6.0% p = 0.123).

Table III. Meta-analysis of the tolerability of individual selective serotonin reuptake inhibitors (SSRIs) compared with other SSRIs as a group

SSRI	Total no. of drop-outs		Adverse effect drop-outs		Emergent adverse effects	
	no. of studies (no. of patients)	RR (95% CI)	no. of studies (no. of patients)	RR (95% CI)	no. of studies (no. of patients)	RR (95% CI)
Citalopram	3 (890)	1.00 (0.78-1.28)	3 (890)	1.04 (0.69-1.57)	2 (673)	1.06 (0.91-1.22)
Fluoxetine	14 (2459)	1.11 (0.97-1.27)	14 (2,558)	1.06 (0.85-1.34)	12 (2216)	1.00 (0.93-1.07)
Fluvoxamine	5 (594)	1.36 (1.02-1.80)*	5 (594)	1.89 (1.20-3.00)**	4 (377)	1.00 (0.91-1.09)
Paroxetine	8 (819)	0.84 (0.65-1.08)	7 (643)	0.96 (0.60-1.53)	7 (643)	0.98 (0.85-1.13)
Sertraline	8 (1236)	0.82 (0.64-1.05)	9 (1511)	0.73 (0.56-0.95)*	7 (1169)	1.00 (0.90-1.11)

CI = confidence interval; **RR** = relative risk; * $p < 0.05$; ** $p < 0.01$.

In the 5 studies (593 patients) comparing fluoxetine with paroxetine there was a significantly greater risk of discontinuation of fluoxetine (RR = 1.40, 95% CI 1.01 to 1.93, p = 0.042). There was, however, no increase in the risk of discontinuing treatment due to adverse effects (in all studies or in comparison with paroxetine alone) or of experiencing at least one adverse effect (table III). Thus, there was no consistent evidence that fluoxetine is less well tolerated than the other SSRIs.

Fluoxetine was noted to cause more agitation than the comparators in 3 studies, although this only reached statistical significance in one of the studies. Six studies (1001 patients) provided data for a quantitative analysis. While the overall rate of agitation was low (7.4%), there was an increased risk of agitation while on treatment with fluoxetine compared with comparator SSRIs (RR = 1.57, 95% CI 1.04 to 2.37, p = 0.031), and a higher absolute risk of 3.3% (95% CI 0.4 to 6.3%, p = 0.027). Examining other 'stimulatory' adverse effects, data from 10 studies (1971 patients) showed a slightly higher risk of anxiety/nervousness on fluoxetine, which was not statistically significant (RR = 1.23, 95% CI 0.88 to 1.71, p = 0.220). Similar results were obtained from 9 studies with regard to insomnia (1584 patients, RR = 1.29, 95% CI 0.93 to 1.79, p = 0.133).

Thirteen studies (2267 patients) reported the incidence of nausea, with no difference found between fluoxetine and its comparators (RR = 1.03, 95% CI 0.87 to 1.22, p = 0.72). In 3 studies dermatological reactions, especially rashes, were reported more frequently during treatment with fluoxetine; the difference was statistically significant in two of these studies ($p < 0.05$). In three studies there was significantly more ($p < 0.05$) weight loss among fluoxetine-treated patients than those receiving comparator SSRIs, with one further study reporting significant weight loss on fluoxetine but not paroxetine (table I).

Fluvoxamine

Of the 5 studies involving fluvoxamine, 2 reported more treatment dropouts due to adverse effects during treatment with fluvoxamine than with the comparator SSRIs, while 3 reported more gastrointestinal effects or more severe adverse reactions (table I). Quantitative analysis showed that significantly more patients on fluvoxamine stopped treatment compared with other SSRIs (table III), with an absolute increase in risk of 7.6% (95% CI 0.7 to 14.5%, p = 0.03). There was also a significantly higher risk of treatment discontinuation due to adverse effects while on fluvoxamine (table III), with an absolute increase in risk of 6.5% (95% CI –1.5 to 14.6%, p = 0.112). However, there was no difference in the incidence of patients who experienced at least one adverse effect when comparisons were made with the other SSRIs (table III). This was in the context of a generally high rate of adverse effects in these patients (83%) compared with the mean rate for all studies (57.9%).

A high percentage of patients treated with fluvoxamine experienced nausea (28.6%), but the overall rate for fluvoxamine was no greater than for the comparator SSRIs (RR = 1.02, 95% CI 0.79 to 1.31, p = 0.908). There was a low correlation between the dose of fluvoxamine and the total discontinuation rate (rho = 0.23, p = 0.683), but a high significant correlation with the discontinuation rate attributed to adverse effects (rho = 0.98, $p < 0.001$). There was a lack of correlation between the dosage and the percentage of patients who experienced nausea (rho = –0.13, p = 0.95). This suggests that it is the severity of adverse effects rather than simply their occurrence that is related to dosage.

Paroxetine

There were no consistent differences in adverse effects in the 8 studies involving paroxetine, although 2 of the 5 studies that compared the drug with fluoxetine reported less weight loss on paroxetine (table I). One study had an extremely high treatment discontinuation rate among patients on paroxetine.[37] It differed from the other trials in that it was an inpatient study of patients with psychosis receiving a fixed upward dose escalation to 50mg of paroxetine by the beginning of the second week of treatment. Serotonergic adverse effects were said to be the reason for all discontinuations.

In our quantitative analysis there was a nonsignificant lower discontinuation rate among patients on paroxetine than the other SSRIs (table III). Statistically, much of the heterogeneity in the pooled results was due to the study by Zanardi et al.[37] Exclusion of this study gave a significantly lower risk of treatment discontinuation on paroxetine (RR = 0.74, 95% CI = 0.57 to 0.96, p = 0.024), with an absolute risk difference of -6.8% (95% CI –2.6% to –1.0%, p = 0.022). When discontinuations due to adverse effects from all studies were analysed, there was no advantage to paroxetine (table III), but exclusion of the Zanardi et al.[37] trial showed a nonsignificant advantage (RR = 0.67, 95% CI 0.40 to 1.12, p = 0.123). Adverse effects did not occur with a lower frequency on paroxetine whether the Zanardi et al.[37] study was included (table III) or excluded (RR = 0.95, 95% CI 0.81 to 1.11, p = 0.523). Seven studies (773 patients) reported the incidence of nausea with no overall difference between paroxetine and its comparators (RR = 1.04, 95% CI 0.83 to 1.30, p = 0.74).

Sertraline

There were 9 studies involving sertraline. Seven of these were comparisons with fluoxetine, in which some studies showed an advantage to sertraline with less agitation (2 studies), weight loss (2 studies) and dermatological adverse effects (2 studies). Two studies also reported fewer treatment discontinuations due to adverse effects during treatment with sertraline (table I).

In our quantitative analysis there were fewer (nonsignificant) total discontinuations on sertraline and significantly fewer discontinuations due to adverse effects, but no difference in the number of patients who experienced adverse effects (table III). The absolute reduction in risk of discontinuations due to adverse effects was –5.5% (95% CI –5.5% 10.9 to –0.01%, p = 0.045). Exclusion of the study carried out by Zanardi et al.,[37] did not greatly alter the results (total discontinuation RR = 0.86, 95% CI = 0.73 to 1.01, p = 0.074; adverse effect discontinuation RR = 0.80, 95% CI 0.61 to 1.04, p = 0.097). Confining the analysis to studies involving fluoxetine as the comparator drug gave similar relative risks, but the advantage to sertraline was not significant (total drop-out RR = 0.89, 95% CI 0.75 to 1.06, p = 0.195; adverse effect drop-out RR = 0.86 95% CI 0.65 to 1.13, p = 0.284).

The incidence of nausea, reported in 5 studies (998 patients) was not significantly different during treatment with sertraline compared with the other SSRIs (RR = 0.88, 95% CI 0.69 to 1.13, p = 0.327). The study by Nemeroff et al.[28] reported significantly more sexual dysfunction during treatment with sertraline than fluvoxamine (table I), but 4 other studies found no significant difference. Quantitative data were available from 4 studies (281 male patients). These data gave an overall rate of male sexual dysfunction of 9.6%, with no increased risk associated with sertraline (RR = 0.94, 95% CI 0.48 to 1.83, p = 0.855).

2.2 Discussion

2.2.1 Efficacy

Given the similar pharmacology of the SSRIs, it is not surprising that no consistent differences in overall efficacy were found. The isolated advantages noted in post-hoc analyses of individual studies are of uncertain significance and could have arisen by chance. However, there was one finding across a number of studies which was supported by the quantitative analysis; that was the slower onset of antidepressant action of fluoxetine at weeks 2 to 3 of treatment compared with the other SSRIs. The result showed statistical homogeneity and was robust to inclusion criteria, supporting the view that this is a real difference. There was also a suggestion that the therapeutic effect of fluoxetine had not completely caught up with that of its comparators by week 6, although there is less certainty about this. This finding has not previously been demonstrated in a systematic review and it warrants further investigation. The investigation should include checking study designs for blindness and assessing the possible role of sponsorship bias.

Fluoxetine has the lowest potency in inhibiting 5-HT reuptake of the SSRIs.[62] It also has the longest elimination half-life because of its active meta-

Table IV. Published incidences of selected symptoms occurring during treatment with selective serotonin reuptake inhibitors (SSRIs)[72-76]

Symptoms	Citalopram	Fluoxetine			Fluvoxamine	Paroxetine		Sertraline
	20-40 mg/day (n = 682)	20 mg/day (n = 682)	40 mg/day (n = 301)	60 mg/day (n = 209)	50-300 mg/day (n = 34587)	10-50 mg/day (n = 4126)		50-400 mg/day (n = 1902)
						<6/52	>6/52	
Gastrointestinal								
Constipation	13	-	-	-	3	4	8	-
Diarrhoea	7	13	15	16	2	-	3	16
Dry mouth	28	9	13	7	5	7	-	-
Dyspepsia	-	9	13	19	3	-	-	-
Nausea	19	11	21	27	16	12	3	21
Neuropsychiatric								
Agitation	6	-	-	-	2	-	3	11
Anxiety	-	15	16	21	1	-	-	-
Dizziness	9	9	6	11	4	4	3	15
Headache	15	20	19	16	5	-	15	18
Insomnia	18	13	15	22	4	6	8	15
Nervousness	-	19	15	19	3	-	-	-
Somnolence	14	6	14	14	6	11	6	-
Tremor	15	4	11	11	3	5	-	14
Other								
Asthenia	12	-	-	-	5	7	8	-
Sexual dysfunction	5	-	-	-	-	6	3	-
Sweating	20	7	9	8	2	9	12	-

n = number of patients; **-** = not specified in publication.

bolite, seproxetine (desmethylfluoxetine; norfluoxetine), which has a half-life of 1 week.[62,63] Steady state concentrations of fluoxetine plus seproxetine are not reached until 4 to 5 weeks after starting treatment, in contrast to those of the other SSRIs which are reached in less than 1 week. Therefore, it is conceivable that starting at a daily dose of fluoxetine of 20mg for the first week (as in all the studies we have reviewed) results in a delay in achieving a minimally effective plasma concentration of fluoxetine. Whether or not this is the explanation, it would appear that fluoxetine (at least administered in an initial daily dose of 20mg) may not be the SSRI of choice if a rapid onset of antidepressant action is required.

2.2.2 Tolerability

Caution is required in interpreting the results of the studies we have analysed because of the relatively small number of trials and potential biases arising from selective reporting, especially with regard to specific adverse effects. Drug company sponsorship could also have introduced a bias in reporting.[64,65] Nevertheless, some interesting tentative findings emerge. The most striking of these is the greater discontinuation rate among patients treated with fluvoxamine. This is probably of clinical importance as 1 extra patient in every 13 treated, discontinued fluvoxamine compared with the other SSRIs. The high fluvoxamine discontinuation rate may be related to higher dosages of fluvoxamine (150 mg/day or more), as the 2 studies with mean dosages of about 100 mg/day did not show high discontinuation rates. The incidence of adverse effects, particularly nausea, was not greater on fluvoxamine, suggesting that the poor tolerability was due to the severity rather than frequency of adverse effects.

With regard to fluoxetine, it is notable that a number of studies found a higher incidence of weight loss, agitation and rashes. However, the incidence of these effects was low and only a minority of studies provided quantitative data on them.

Agitation was significantly more common with fluoxetine in the few studies reporting it, but there was less certainty about other 'stimulatory' effects. Selection bias in reporting agitation is possible but, even if the result is representative, only 3% more patients on fluoxetine experienced anxiety or agitation compared with other SSRIs. This is likely to be of minor importance clinically, although consistent with the view that it is reasonable to prescribe an alternative drug for patients who are already distressed by agitation. The studies we have reviewed support the opinion that fluoxetine is particularly liable to cause weight loss. This may be important in individual patients, but it should be noted that the level of evidence for weight loss is not high and its clinical relevance has been questioned.[66]

Some studies suggested that sertraline, and possibly paroxetine, may be better tolerated than other SSRIs, although the majority of these studies were comparisons with fluoxetine. The evidence was strongest for sertraline, with fewer discontinuations allegedly due to adverse effects. This may not be of clinical importance in the initial choice of SSRI, but it provides a rationale for trying sertraline in patients who have been intolerant of other SSRIs. This suggestion needs to be balanced against the results of an open study that investigated treatment with fluoxetine in patients who failed in treatment with sertraline.[67] In that study fluoxetine was effective and generally well tolerated. The uncontrolled nature of this study, though, means that no firm conclusion can be reached.

In the past it has been suggested that sertraline causes a high incidence of male sexual dysfunction,[68] but our results suggest that this effect does not occur more often with sertraline than other SSRIs. However, it is particularly difficult to com-

Table V. Reports to the British Committee on Safety of Medicines (CSM) of 'top ten' adverse events occurring during treatment with selective serotonin reuptake inhibitors (SSRIs). Total number of suspected adverse effects reported from the date the drugs was introduced on to the UK market to 25 September 1998 (rank order).

	Fluvoxamine (February 1987-)	Fluoxetine (March 1989-)	Sertraline (January 1991-)	Paroxetine (March 1991-)	Citalopram (June 1995-)
Abdominal pain	106 (10)	98 (>10)	26 (>10)	78 (>10)	7 (>10)
Agitation	140 (7)	309 (5)	49 (10)	236 (>10)	14 (8=)
Anxiety/nervousness	65 (>10)	277 (7)	59 (>10)	304 (9)	17 (5=)
Diarrhoea	273 (3)	239 (9)	182 (2)	279 (10)	26 (6)
Dizziness	181 (5)	211 (>10)	106 (4)	754 (3)	36 (3=)
Dry mouth	22 (>10)	42 (>10)	39 (>10)	132 (>10)	13 (9=)
Fatigue	76 (>10)	120 (>10)	21 (>10)	189 (>10)	17 (5=)
Headache	151 (6)	451 (2)	108 (3)	447 (5)	40 (2)
Insomnia	120 (9)	261 (8)	76 (6)	321 (8)	13 (9=)
Nausea	726 (1)	661 (1)	203 (1)	1113 (1)	65 (1)
Pruritus	38 (>10)	207 (>10)	50 (>10)	96 (>10)	14 (8=)
Rash, unspecified	28 (>10)	366(4)	64 (10)	137 (>10)	17 (5=)
Sedation	133 (8)	146 (>10)	35 (>10)	296 (>10)	12 (10)
Sweating	46 (>10)	187 (>10)	67 (8)	411 (6)	25 (4)
Tremor	182 (4)	297 (6)	100 (5)	548 (4)	36 (3=)
Urticaria	15 (>10)	416 (3)	34 (>10)	96 (>10)	15 (7)
Vomiting	301 (2)	221 (10)	66 (9)	319 (7)	16 (6=)
Withdrawal reaction	13 (>10)	75 (>10)	67 (7)	1026 (2)	16 (6=)
Total reactions	**4598**	**11 984**	**3526**	**14 958**	**936**
Total reports	**2440**	**6785**	**1848**	**6839**	**478**

Table VI. Number of reports of suspected adverse drug reactions received by the British Committee on Safety of Medicines (CSM) during first 2 years of marketing of selective serotonin reuptake inhibitors (SSRIs) listed under system order class (shown in bold) and 'high level terms' (i.e. individual events). The values presented for system order class are the total number of reactions reported, while those under 'high level terms' are those of particular relevance to antidepressant drugs

System	Fluvoxamine February 1987-89	Fluoxetine March 1989-91	Sertraline January 1991-93	Paroxetine March 1991-93	Citalopram June 1995-97
No. of prescriptions written during first 2 years[a]	110 000	361 000	138 000	380 000	237 000
Cardiovascular	107	89	44	185	27
Metabolism/nutrition	59	78	26	100	23
Anorexia	46	30	7	22	2
Weight loss	4	20	1	5	2
Gastrointestinal	1049	516	271	969	117
Abdominal pain	66	40	20	39	5
Constipation	19	2	3	22	1
Diarrhoea	162	61	72	114	19
Dry mouth	18	13	15	64	12
Dyspepsia	30	31	12	13	1
Nausea	512	240	91	498	50
Vomiting	195	79	32	150	11
General	619	409	178	1050	99
Dizziness	125	73	34	150	22
Fatigue	51	46	6	72	9
Insomnia	65	80	22	122	7
Irritability	4	9	2	10	1
Malaise	85	22	14	51	4
Sedation	88	47	21	161	7
Withdrawal reaction	2	0	4	133	7
Haemopoietic	10	12	5	27	5
Hepato-biliary	22	17	13	51	9
Jaundice	2	5	0	12	4
Musculoskeletal	30	42	16	76	15
Neurological	338	418	146	783	127
Convulsions, unspecified	11	30	7	21	4
Convulsions, grand mal	15	14	3	8	2
Myoclonic seizures	1	7	2	6	1
Extrapyramidal disorders, all forms	12	25	4	57	11
Headache, unspecified	92	159	43	193	25
Paraesthesia	34	25	12	65	7
Tremor, unspecified	110	73	33	228	24
Psychiatric	244	348	92	434	46
Aggression	6	30	5	16	2
Agitation	75	91	12	82	10
Anxiety	34	42	9	51	7
Confusion	29	22	9	29	3
Mania	11	19	7	11	0
Suicide, accomplished	3	8	1	8	0
Suicide, attempt	1	25	1	4	0
Nervousness	3	11	7	42	7
Reproductive	14	54	39	269	26
Male sexual disorder	6	14	13	134	10

Table VI. Contd

System	Fluvoxamine	Fluoxetine	Sertraline	Paroxetine	Citalopram
	February 1987-89	March 1989-91	January 1991-93	March 1991-93	June 1995-97
No. of prescriptions written during first 2 years[a]	110 000	361 000	138 000	380 000	237 000
Skin and subcutaneous tissues	112	345	109	422	75
Alopecia	3	9	2	13	6
Pruritus	13	54	12	44	9
Rash,type specified	15	34	16	38	7
Rash, unspecified	10	89	16	56	8
Sweating	29	32	30	153	16
Urticaria	6	48	7	23	10
Total reactions	**2707**	**2478**	**993**	**4620**	**606**
Total reports	**1537**	**1404**	**522**	**2297**	**304**
Fatal	**15**	**22**	**4**	**22**	**5**

a Number of prescriptions based on data from IMS UK and Ireland (1997); figures presented are to nearest 1000 prescriptions.

pare sexual adverse effects of drugs, as they are under-reported and inadequately assessed in clinical trials.[69-71]

3. Adverse Event Monitoring

3.1 Published Reviews

Data on the incidence of common suspected adverse effects reported in at least 2 of the 5 major overviews of adverse reactions to the SSRIs[72-76] have been extracted and are shown in table IV.

Major difficulties with the data prevent definitive conclusions on the relative incidence of adverse effects being drawn. These include variability in diagnoses, treatment settings, trial design, dosage regimens, treatment durations, and symptom reporting thresholds.

For these reasons it is difficult to make meaningful comparisons from the reviews and we therefore attach less importance to them than to the other results reported in our paper.

3.2 CSM Data

A cause-and-effect relationship between a suspected adverse event reported to the CSM and the drug received by the patient cannot be assumed. Furthermore, it is not possible to assess the incidence of events, as neither the number of reactions (the numerator) nor the number of patients who received (and actually took) the drug (the denominator) are known. For these reasons only the 'top ten' events for each of the 5 SSRIs, with comparable figures for their SSRI comparators, are presented as they are more likely than other events to be related to the drugs (see table V).

It will be noted from the table that gastrointestinal events (especially nausea) and neuropsychiatric events (notably headache and tremor) have the highest ranks. It is not possible to make accurate statistical comparisons from the relative rank orders but a high rate of reporting of events can serve as a signal that they are drug-related and require further investigation. Examples of these include discontinuation reactions (which rank second for paroxetine) and urticaria (which ranks third for fluoxetine and seventh for citalopram).

More suspected ADRs are reported to the CSM during the first 2 years following the launch of a new product on to the market than at any other time.[77] For this reason we have listed in table VI the total number of reactions (recorded in their 'system organ class') and individual events (using 'high level terms') of particular relevance to antidepressants in general, and SSRIs in particular, that were reported during the first 2 years of marketing. It should be noted that there were more reports of gastrointestinal events than any others. The next highest frequency adverse events were 'general', neurological and psychiatric.

Table VII. Events with an incidence of 1 or more per 1000 patients occurring during the first month of treatment (T_1) with fluoxetine, fluvoxamine and paroxetine and a ratio of 3 or more for the incidence in month 1 to the mean incidence in months 2 to 6 (T_1/T_2)[a] [adapted from Edwards et al.[56], with permission]

Events	Fluoxetine (n = 12 692)			Fluvoxamine (n = 10 401)			Paroxetine (n = 13 734)		
	T_1	T_2	T_1/T_2	T_1	T_2	T_1/T_2	T_1	T_2	T_1/T_2
Neuropsychiatric									
Malaise	10.5	0.8	13	20.9	0.8	26	10.1	0.6	17
Headache	9.4	2.3	4	16.6	2.5	7	10.8	2.1	5
Insomnia	7.9	1.5	5	10.5	1.2	9	10.7	1.8	6
Anxiety	7.4	1.8	4	7.7	1.6	5	3.8	1.2	3
Drowsiness, sedation	6.7	0.7	10	15.0	1.0	15	16.7	1.1	15
Dizziness	5.4	1.3	4	17.5	1.3	13	9.5	1.6	6
Agitation	5.0	0.6	8	6.3	0.4	16	4.3	0.6	7
Tremor	4.7	0.9	5	9.0	0.5	18	10.2	0.6	17
Panic attacks	2.1	0.3	7	2.9	0.3	10	2.4	0.5	5
Peripheral sensory symptoms	1.7	0.5	3	3.3	0.6	6	1.0	0.5	2
Confusion	1.8	0.4	5	2.4	0.2	12	0.9	0.3	3
Unsteadiness	1.2	0.2	6	1.5	0.3	5	0.9	0.2	5
Gastrointestinal									
Nausea	16.2	1.6	10	64.0	2.0	32	35.3	2.1	17
Diarrhoea	5.8	1.5	4	15.7	1.6	10	6.6	2.0	3
Vomiting	5.4	1.1	5	20.7	1.4	15	7.9	1.0	8
Anorexia	2.0	0.5	4	4.2	0.4	11	1.5	0.2	8
Other									
Sweating	1.8	0.3	6	2.4	0.3	8	5.5	0.8	7
Palpitations	1.7	0.3	6	3.3	0.3	11	1.7	0.4	4
Dry mouth	1.4	0.1	14	2.6	0.2	13	3.5	0.3	12
Dysuria	1.1	0.3	4	1.1	0.3	4	0.9	0.2	5
Dyspnoea	1.0	0.3	3	1.0	0.3	3	0.9	0.3	3

a T_1 = event rate during first month after start of treatment; T_2 = event rate during second to sixth month after start of treatment.

Overall, more suspected reactions were reported during treatment with paroxetine (4620 individual reactions, 2297 patient reports) than the other SSRIs (fluvoxamine 2707 reactions, 1537 reports; fluoxetine 2478 reactions, 1404 reports; sertraline 993 reactions, 522 reports; and citalopram 606 reactions, 304 reports). More suspected gastrointestinal reactions were recorded during treatment with fluvoxamine and paroxetine than the other SSRIs: about twice as many as fluoxetine, 4 times as many as sertraline, and 8 to 9 times as many as citalopram. Paroxetine was associated with the highest number of general, psychiatric and neurological reactions. However, it is essential to interpret differences in the numbers of reports in relation to the numbers of patients treated. This is not known accurately, so numbers of prescriptions are provided instead as a rough measure of the extent of use of the individual drugs. These were obtained from the Medical Data Index.[78]

A notable difference among the general reactions were withdrawal (discontinuation) symptom reports recorded after cessation of treatment with paroxetine compared with the other SSRIs. During the first 2 years of marketing there were 133 reports with paroxetine, compared with 7 or less for the other drugs. The CSM drew attention to this suspected adverse reaction in 1993[79] and later investigated it in more detail.[80] These further investigations showed that there was a greater number of

discontinuation reactions reported after stopping treatment with paroxetine than fluvoxamine, fluoxetine and sertraline (5.1 *vs* 0.06 to 0.9%). Citalopram, which had not been marketed as long as the other SSRIs, was not included in the study. The number of reports of discontinuation reactions was compared with the number of prescriptions written for each of the 4 SSRIs in England, Wales and Northern Ireland obtained from the Prescription Pricing Authority. From these the number of reports per 1000 prescriptions (the 'reporting rate') was calculated.

The age and gender of patients who were prescribed SSRIs and the doses of paroxetine prescribed were obtained from the Medical Data Index. For patients on whom there had been reports of discontinuation reactions, data on their age, gender, most recent dosages of paroxetine before discontinuation, symptoms reported and outcome of the reaction were collated from the CSM reports. A follow-up questionnaire sent to doctors who had reported reactions 3 to 6 months after receipt of the report sought additional clinical information.

It was concluded that discontinuation reactions, although occurring more often on cessation of treatment with paroxetine than the other SSRIs, were rare. They were reported more often in younger patients. They occurred mostly 2 days after stopping treatment (within a week in 93% of cases) and the symptoms differed from those of a recurrence of depression.

3.3 PEM Data

Events occurring with an incidence of 1 or more per 1000 patients and a ratio of 3 or more for the ratio of the incidence in month 1 to the mean incidence during months 2 to 6 (T1/T2) in 12 692 patients treated with fluoxetine, 10 401 treated with fluvoxamine and 13 734 treated with paroxetine are shown in table VII.[56] The age and gender distribution of these patients, the indication for pre-

Table VIII. Aggression, suicide and related events occurring during treatment with selective serotonin reuptake inhibitors (SSRIs)[a] (reproduced from Edwards et al.,[56] with permission)

Events	Event rates per 1000 patients					
	fluoxetine		fluvoxamine		paroxetine	
	month 1 (N_1 = 10 102)	month 2 (N_2 = 6889)	month 1 (N_1 = 7179	month 2 (N_2 = 3590)	month 1 (N_1 = 11 046)	month 2 (N_2 = 7970)
Aggression	0.8	0.3	0.8	0.3	0.1	0.0
Agitation	5.9	1.6	9.3	2.0	5.0	1.9
Anxiety	8.3	3.6	9.1	2.9	4.3	1.5
Hyperactivity	1.1	0.0	0.1	0.0	0.5	0.1
Irritability	0.6	0.4	0.1	0.8	0.5	0.1
Mania/hypomania	0.2	0.9	0.1	0.6	0.5	0.4
Paranoid ideation	0.2	0.1	0.3	0.3	0.3	0.0
Suicide threat	1.0	0.7	1.0	0.6	0.0	0.0
Drug overdose	2.7	1.9	2.8	2.2	2.3	0.6
Drug overdose (accidental)	0.1	0.0	0.0	0.0	0.0	0.0
Drug overdose (fatal)	0.1	0.1	0.0	0.3	0.0	0.0
Self-injury	0.0	0.0	[a]	[a]	0.3	0.1
Suicide attempt[b]	0.7	0.3	0.6	0.3	0.5	0.0
Suicide[b]	0.2	0.0	0.0	0.0	0.3	0.1

a Event term not used in fluvoxamine study.

b Other than by overdose.

N_1 = average number of patients on treatment in month 1 for whom date of stopping drug is known or who continued treatment throughout period of observation; **N_2** = average number of patients on treatment in month 2 for whom date of stopping drug is known or who continued treatment throughout period of observation.

Table IX. Effects of selective serotonin reuptake inhibitors (SSRIs) on cytochrome P450 (CYP) at typical antidepressant dosages (adapted from Preskorn[92])

Enzyme	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
CYP1A2	-	-	+++	-	-
CYP2D6	+	+++	-	+++	+
CYP3A3/4	?	+[a]	++	-	-
CYP2C19	?	++	+++	?	-

a Seproxetine (norfluoxetine) has a greater effect.

? = no data; - indicates clinically insignificant (<20% increase in area under curve of substrate); + indicates mild effect (20 to 50% increase in area under curve of substrate); ++ indicates moderate effect (50 to 100% increase in area under curve of substrate); +++ indicates substantial effect (>150% increase in area under curve of substrate).

scribing the SSRIs and the concomitant medication received were similar, so the figures allow for valid comparisons.

It should be noted from the results that:

(i) gastrointestinal symptoms and malaise were reported more often during the first month of treatment with fluvoxamine than with the other 2 SSRIs;

(ii) drowsiness/sedation and tremor were reported more often during the first month of treatment with fluvoxamine and paroxetine than with fluoxetine; and

(iii) sweating was reported more often during the first month of treatment with paroxetine than with fluoxetine and fluvoxamine.

In view of the concern that had been expressed by Teicher et al.[81] and others[82-87] over the possibility of aggressive and suicidal thoughts and behaviour being caused by fluoxetine, the rates of these and related events occurring during treatment were analysed separately (table VIII).[56] Because the phenomena were said to have occurred within 2 months of the start of treatment with fluoxetine,[81] the data in the PEM analysis were limited to this period. The results show that the rate of aggressive, suicidal and related events during treatment with fluoxetine was not higher than with the other SSRIs. What differences there are appear disproportionately large because of the low rates of these events.

A wide variety of other events occurring in all physiological systems were reported for each of the antidepressants, but the relatively small numbers do not allow for meaningful statistical comparisons to be made.

Using the most recently developed pharmacoepidemiological techniques, the PEM study of Mackay et al.[57] showed a similar range of events during treatment with fluoxetine, fluvoxamine, paroxetine and sertraline, but with the following differences between drugs during the first month of treatment:

(i) Nausea/vomiting reported more often during treatment with fluvoxamine (ID 127.2 per 1000 patient-months) than with fluoxetine, paroxetine and sertraline (IDs 26.3, 52.9 and 13.6, respectively).

(ii) Drowsiness reported more often during treatment with fluvoxamine and paroxetine (IDs 22.6 and 20.5, respectively) than with fluoxetine and sertraline (IDs 8.2 and 7.3, respectively).

(iii) Tremor reported more often during treatment with fluvoxamine and paroxetine (IDs 13.2 and 12.4, respectively) than with fluoxetine and sertraline (IDs 5.7 and 6.2, respectively).

(iv) Sweating and impotence or ejaculation failure reported more often during treatment with paroxetine than with the other 3 SSRIs (IDs not provided).

(v) Withdrawal (discontinuation) events reported more often following cessation of treatment with paroxetine (15 reports) than with the other SSRIs (2 reports for each).

The study failed to confirm an association between suicide and treatment with fluoxetine.

Overall, there was a considerably higher overall incidence of adverse effects (especially nausea/vomiting and malaise/lassitude) reported during

treatment with fluvoxamine compared with the other SSRIs. The fact that fluvoxamine was marketed before the comparator SSRIs had been considered as a possible explanation for the higher rate of gastrointestinal events with fluvoxamine. Its propensity to cause such events could have discouraged doctors from prescribing subsequently introduced SSRIs to patients prone to gastrointestinal symptoms. This possibility was investigated by Mackay et al.[57] who showed that the first NSAID, ACE inhibitor and proton pump inhibitor to be introduced into clinical practice in the UK

Table X. Interactions with selective serotonin reuptake inhibitors (SSRIs).[a] Bold type indicates interactions that are potentially hazardous

SSRIs	Interacting substance	Possible Result[b]
All	Alcohol	Possible enhanced effect
All	**Anticoagulant**	**Possible enhanced anticoagulant effect**
	acenocoumarol	
	warfarin	
All	**Antidepressant**	
	MAOIs[b]	**CNS toxicity[c]**
	tricyclics	**Increased plasma level of some tricyclics**
	trytophan	Agitation, nausea
	Antiarrythmic	
Fluoxetine	flecainide	**Increased plasma concentration of flecainide**
	Anticonvulsant	
Fluoxetine, fluvoxamine	carbamazepine	**Antagonism of anticonvulsant effect** (lowering of convulsive threshold)
	phenytoin	Increased plasma concentration of anticonvulsant
Paroxetine	phenytoin and possibly other anticonvulsants	Decreased plasma concentration of paroxetine
All	**Antihistamine**	
	terfenadine	**Increased risk of arrythmias**
All	**Antimanic**	
	lithium	**CNS toxicity[c]**
All	**Antimigraine**	
	sumatriptan	**CNS toxicity**
	Antipsychotic	
Fluoxetine, fluvoxamine	clozapine	**Possible increased plasma concentration of clozapine**
Fluoxetine	haloperidol	**Increased plasma concentration of haloperidol**
Fluoxetine, paroxetine	sertindole	**Increased plasma concentration of sertindole**
All	**Antiviral**	
	ritonavir	**Possible increased concentration of some SSRIs**
Fluvoxamine	**Anxiolytic/hypnotic**	
	benzodiazepines	Increased plasma concentration of some benzodiazepines
Fluvoxamine	**β-blocker**	
	propranolol	Increased plasma concentration of propranolol
Fluvoxamine	**Bronchodilator**	
	theophylline	**Increased plasma concentration of theophylline**
Fluoxetine	**Dopaminergic**	
	selegiline	**CNS excitation, hypertension**
All	**$5HT_1$ agonist**	
	sumatriptan	**CNS toxicity**
All	**Opioid analgesic**	
	tramadol	**Possible increased risk of convulsions**

a Based on British National Formulary[93] list of clinically important interactions.

b Interaction less likely to occur with newer reversible MAOIs.

c CNS toxicity is characterised by excitation, restlessness, sweating, flushing, pyrexia, fluctuating vital signs, tremor, rigidity, myoclonus, delirium, and rarely, coma and death.

5-HT = 5-hydroxytryptamine (serotonin); **MAOI** = monoamine oxidase inhibitor.

were, in each case, not the drugs which had the highest IDs of the most frequently reported events. Furthermore, there were no major differences between the drugs in the number of reports of respiratory tract infection, an event that has no apparent association with the indications for prescribing these drugs or with their adverse effect profiles, and can therefore be considered as purely 'background noise'. These observations militate against the possibility that the order in which the SSRIs were introduced into practice produced a bias in reporting.

4. Drug Interactions

Like other antidepressants, SSRIs interact with a wide variety of other drugs.[11,88-92] Some interactions have been demonstrated only in animals, while the evidence for others is based on isolated case reports or small scale controlled or uncontrolled studies. The capacity of individual SSRIs to cause interactions is influenced by their effects on cytochrome P-450 enzymes, and there is now considerable knowledge of the effects of SSRIs on CYP1A2, CYP2D6, CYP3A3/4 and CYP2C19. These effects are summarised in table IX. From the data presented it would appear that the potential for individual SSRIs to interact with other drugs is greatest for fluvoxamine, fluoxetine and paroxetine and least for sertraline and possibly citalopram (on which there are fewer data).

There is, however, a difference between interactions of theoretical concern and those shown to be important clinically. In general there are insufficient data available on the extent to which interactions occur in clinical practice. Drug interactions considered by the British National Formulary[93] to be of clinical relevance are summarised in table X. The most important of these are interactions with other drugs that affect serotonergic neurotransmission; these lead to the serotonin syndrome with the clinical features of CNS toxicity described in the table.

5. Lethality in Overdose

SSRIs, like other newer antidepressants, have a lower fatal toxicity index (number of deaths due to overdose per million prescriptions) than older antidepressants.[14,94] Despite the limitations of the methodology, especially uncertainty over the cause of death, the quantity of drugs and other substances taken, and the medical condition of the patients, the research has shown that SSRIs are relatively safe in overdose. This is consistent with their relative freedom from cardiotoxic effects in healthy adults,[95-100] although there is a paucity of data on the effects of overdose in the elderly and in patients with severe, pre-existing, cardiac and other physical illnesses.

There are no clinical data on the relative effects of individual SSRIs taken in overdose. Patients have survived overdoses of citalopram 5200mg,[101] fluoxetine 300mg,[102] fluvoxamine 9000mg,[103] paroxetine 850mg,[77] and sertraline 8400mg.[104] These quantities confirm the safety of overdoses of SSRIs in general, but say nothing about the relative toxicity of these drugs. Citalopram may be a possible exception to the safety profile of SSRIs in overdose. Six cases of suicide following overdoses of citalopram have been forensically investigated and reported.[106] Possible mechanisms of death that were considered by the authors of the report are cardiac arrhythmias and convulsive seizures.

The cause and mechanism of death in these cases have been questioned on the grounds that low citalopram : didemethylcitalopram ratios were found at post-mortem,[107] and because clinically significant cardiac arrhythmias occurred only rarely in 108 cases of overdose of citalopram taken alone reported to the Swedish Poisons Information Centre.[108] The suggestion that citalopram is more lethal in overdose than other SSRIs has also been questioned because only 1 of the 6 suicides followed an overdose of citalopram alone. The other patients had taken citalopram in combination with alcohol or anxiolytic-sedatives which could have potentiated the effects of the SSRI. The quantities of citalopram taken exceeded any dose seen among 234 cases of fluoxetine overdoses collected in 1 of

Table XI. Strengths and weaknesses of methods of identifying unwanted effects

	Strengths	Weaknesses
Case reports	May draw attention to hitherto unrecognised unwanted effects	Cause-and-effect relationship with drug cannot be established
Controlled clinical trials	Randomisation and blinding minimises bias Likely to identify more common unwanted effects Provides comparative data	Small sample sizes Unrepresentative patients Heterogeneity of patients Uncertainty over blinding Lack of information on compliance Difficulty relating less common effects to drug Lack of inter-rater reliability in multicentre studies
Meta-analysis of controlled trials	Attempts to identify all relevant trials by systematic review (although analysis limited to controlled trials) Pooling of data increases power Provides comparative data Provides a summary, quantified outcome measure	Same weaknesses as for individual controlled trials Cannot eliminate publication/reporting bias Pooling of data, which may be invalidated by heterogeneity of trials or requires simplication of outcome measures of individual trials Tendency to overinterpretation and sense of false certainty
CSM yellow card system	Nationwide system that monitors all drugs in use throughout their lives Has potential for all practitioners to |report suspected reactions all reactions in all patients to be reported Allows for monitoring in real world of general practice and hospital Provides a means of detecting rare adverse reactions Allows for comparisons of drugs with similar indications in similar patient populations during similar market lives Provides for research large subsamples of patients with uncommon or rare adverse reactions	Under-reporting of suspected adverse reactions[a] and reactions not clearly drug related Biases in reporting ease of recognition of reaction severity and seriousness of reaction novelty of drug extent of use of drug promotion of and publicity given to drug, adverse reaction and/or reporting of suspected ADRs Cause-and-effect relationship with drug cannot be established Does not allow for assessment of incidence because number of reactions and number of patients who received (and took) the drug is not known difficulties in relating reaction to drug
PEM	Non-interventional observational design reflecting practice in real world Nationwide in scope Provides large cohort within short time of drugs launch on to market Monitors events not just suspected adverse reactions Provides quantitative data on adverse events as seen from perspective of general practitioner Helps to identify events with incidence of 1 or more per 3000 patients Allows for identification of delayed adverse reactions Allows for comparisons of drugs with similar indications in similar patient populations Provides subsamples of patients who have had specific events (e.g. convulsions, pregnancy, death) for in-depth studies Provides pharmacoepidemiological data on prescribing practices	Relatively low response rate (return of "green forms")[b] Lack of data on patients of practitioners who do not return "green forms" Lack of information on compliance Confined to general practice; not yet fully implemented in hospitals

a Estimated at 10 to 15% of total.

b Likely to be due to variables in practitioner behaviour rather than drug or event differences.[115]

ADRs = adverse drug reactions; **CSM** = British Committee on Safety of Medicines; **PEM** = prescription-event monitoring of the Southampton Drug Safety Research Unit.

Table XII. Advantages and disadvantages of individual selective serotonin reuptake inhibitors (SSRIs)

SSRI	Advantages	Disadvantages
Citalopram	Probable lower potential for drug interactions	Relatively new, therefore less chance of rare adverse reactions having been identified Case reports of lethality in overdose
Fluoxetine	Long half-life which may allow for less frequent administration in poorly compliant patients and less troublesome discontinuation effects	Possible slower onset of action Possible higher incidence of stimulant and dermatological effects, and of weight loss Longer delay required before switching to MAOI Potentially hazardous interactions[a] with antiepileptics (some), antipsychotics (some), flecainide, ritonavir, selegiline
Fluvoxamine		Higher incidence/severity of nausea and probably sedation and tremor leading to poor tolerability Potentially hazardous interactions[a] with antiepileptics (some); antipsychotics (some); theophylline
Paroxetine		Higher incidence of sedation, tremor, sweating, discontinuation reactions Potentially hazardous interactions[a] with ritonavir, sertindole
Sertraline	Probable lower potential for drug interactions[a]	

a See in conjunction with tables IX and X and section 4 of text.

MAOI = monoamine oxidase inhibitor.

4 US regional control centres. Furthermore, the post-mortem plasma drug concentration in the patient who died from an overdose of citalopram alone was similar to that in the only other well-documented death resulting from an overdose of an SSRI (fluoxetine) taken alone. To put this case in perspective, it was pointed out that the patient had taken 4000mg of citalopram (i.e. 200 tablets), the equivalent of more than 6 months supply at the normal dosage of 20 mg/day.[109]

6. Pharmacoeconomic Considerations

The pharmacoeconomics of prescribing antidepressants is complex and controversial. The acquisition costs of individual SSRIs are broadly similar, but differences in the way they are prescribed can influence the overall costs. For instance, in primary care there is evidence that the dose of fluoxetine is less likely than that of paroxetine and sertraline to be increased resulting in lower medication costs.[110,111]

In cost-effectiveness analyses there are major methodological difficulties related to the research design, populations studied and economic models applied. If different assumptions are made opposite conclusions can be drawn from the same randomised controlled trial.[112,113] In the trials referred to in our paper, one study found nonsignificantly greater costs of treatment with fluoxetine than with sertraline.[20] In contrast, a retrospective study in a health maintenance organisation found fluoxetine to be cheaper than paroxetine and sertraline.[114]

In view of these considerations we are of the opinion that published pharmacoeconomic data are at present not sufficiently valid to influence our choice of individual SSRIs. However, this situation is likely to change as a result of the forthcoming expiry of the patent on fluoxetine and recent price reduction of citalopram in the UK.

7. Practical Guidelines

There is no perfect way of comparing drugs. Each of the methods we have discussed (and others) has its strengths and weaknesses. These are summarised in table XI. The weaknesses and lack of uniformity in the methodology used in studying the different SSRIs make comparisons extremely difficult but, gleaning what we can from the studies reviewed, our overall view of the pros and cons of the 5 SSRIs are summarised in table XII.

The place of SSRIs in the pharmacotherapy of depression has been described elsewhere, so it will be discussed no further here. The guidelines we outline below and summarise in table XIII should be considered at the point where it is decided to use an SSRI as opposed to another class of antidepressant. The choice is not easy and no single SSRI has a significantly better safety and efficacy profile that the others. Each of the drugs has its advantages and disadvantages and many properties of the drug and patient-specific factors must be taken into account in determining choice. The final decision should be clinical rather than just pharmacological and should be based on the principle of tailoring treatment to an individual patient's needs.

No single SSRI is more effective than another; although fluoxetine appears to have a slower onset of action than other SSRIs. Rapidity of action is particularly important in the case of severely depressed and suicidal patients in whom it is desirable to obtain an antidepressant effect as soon as possible. For these reasons fluoxetine may not be the drug of first choice in such patients, with the possible exception of individual patients known from previous treatment to respond rapidly to fluoxetine. If fluoxetine is to be initiated in severely depressed patients, consideration should be given to using a higher starting dose than that usually recommended.

A rapid antidepressant effect is also important in women with post-partum depression, in whom we have to consider the safety of the newborn infant. However, an SSRI (or any other antidepressant) should only be administered to a nursing mother if there are compelling reasons to do so, with the benefits thought likely to outweigh the risks.

Fluoxetine may not be the best choice of SSRI in agitated patients since its stimulant effects could aggravate the agitation.

Suicidal patients require treatment with antidepressants that are safe in overdose. SSRIs (along with other newer antidepressants) are much less toxic than the tricyclic antidepressants and are therefore among the drugs recommended. In suicidal patients, and also in people with personality

Table XIII. Guidelines to choice of individual selective serotonin reuptake inhibitors (SSRIs): comments on factors determining choice

Type of patient	Comments
Severely depressed	When a rapid antidepressant effect is especially important, fluoxetine may not be the best choice because of a possible slower onset of action; in patients who have previously responded well to fluoxetine, and in whom it is again chosen, consideration should be given to using a higher starting dose
Agitated patients	Fluoxetine may not be the SSRI of choice as its stimulant effect could worsen the agitation
Suicidal patients and people prone to self-poisoning	Where there is a severe risk of self-poisoning citalopram may not be the best choice because of the possibility of higher lethality in overdose than other SSRIs
Depressed patients receiving concomitant medication	An SSRI that does not interact with the other drugs should be chosen; when in doubt citalopram and sertraline should be considered as there is theoretically less potential for, and there have been fewer reports of, interactions with these drugs. When combinations of drugs that may interact are prescribed extra care should be taken in monitoring patients; practitioners should keep up to date with interactions with SSRIs as new information becomes available
Patients who are poorly compliant with medication	Fluoxetine should be considered because of its (and its metabolite's) long half-life
Patients who are intolerant of an SSRIs adverse effects	A different SSRI to that previously given may be worth trying if not previously chosen
Patients who have had troublesome SSRI discontinuation symptoms	Paroxetine should be avoided; fluoxetine should be considered because of the long half-life; slow tapering of SSRI dose is advisable
Patients in whom an MAOI is likely be considered as the next therapeutic option	An SSRI other than fluoxetine should be considered because a longer drug-free interval to avoid the serotonin syndrome is required in the case of fluoxetine compared with other SSRIs (5 weeks versus 1-2 weeks)

MAOI = monoamine oxidase inhibitor.

disorders and others prone to incidents of self-poisoning, citalopram may not be the first line treatment in view of the reports of death resulting from overdose of this compound.

Reassuring statements are sometimes made about the tendency of individual SSRIs to cause fewer interactions than other antidepressants. These can give a false sense of security, so whenever a patient is receiving concomitant medication it is important to choose an SSRI that is least likely to cause a clinically important interaction. Furthermore, as increasing numbers of new drugs are launched on to the market it is essential to keep up to date on newly reported risks. The interactions with SSRIs that are currently of most concern are shown in table X. Particular attention should be paid to those re-listed in table XII when choosing an SSRI for a patient requiring treatment with other drugs.

The likelihood of a discontinuation reaction occurring on cessation of treatment with an SSRI can be reduced by tapering the dose prior to stopping the drug.[116-118] Alternatively, fluoxetine can be chosen for patients who have had particularly troublesome withdrawal symptoms in the past, since the long half-life of fluoxetine and its metabolite appears to lower the risk and decreases the severity of withdrawal symptoms.

8. Conclusion

The advantages and disadvantages of SSRIs that we have discussed should be taken into account when choosing a drug for an individual patient at any particular time. However, the antidepressant of choice may vary at different stages of patients' illnesses and with changes in any other treatment that he or she is receiving. As citalopram is the most recently introduced SSRI in the UK, less is known about it than the other SSRIs. To date it appears to have a relatively clean profile, although the shadow of possibly higher lethality in overdose than its competitors hangs over it and clearly calls for further investigation. In the light of existing knowledge the only SSRI that appears to have no apparent disadvantages in relation to its competitors is sertraline.

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