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Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability

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Abstract

Objective—To examine the evidence for using selective serotonin reuptake inhibitors instead of tricyclic antidepressants in the first line treatment of depression.

Design—Meta-analysis of 63 randomised controlled trials comparing the efficacy and acceptability of selective serotonin reuptake inhibitors with those of tricyclic and related antidepressants.

Main outcome measures—Improvement in mean scores on Hamilton depression rating scale for 53 randomised controlled trials. Pooled drop out rates from the 58 trials which reported drop out by treatment group.

Results—Among the 20 studies reporting standard deviation for the Hamilton score no difference was found in efficacy between serotonin reuptake inhibitors and tricyclic and related antidepressants (standardised mean difference 0.004, 95% confidence interval -0.096 to 0.105). The difference remained insignificant when the remaining 33 studies that used the 17 item and 21 item Hamilton score were included by ascribing weighted standard deviations. The odds ratio for drop out rate in patients receiving serotonin reuptake inhibitors compared with those receiving tricyclic antidepressants was 0.95 (0.86 to 1.07). Similar proportions in both groups cited lack of efficacy as the reason for dropping out but slightly more patients in the tricyclic group cited side effects (18.8% v 15.4% in serotonin reuptake group).

Conclusions—Routine use of selective serotonin reuptake inhibitors as the first line treatment of depressive illness may greatly increase cost with only questionable benefit.

Introduction

Selective serotonin reuptake inhibitors are a relatively new class of antidepressants that have been heavily promoted for use as first line treatment in depression. They are the most commonly prescribed antidepressant in the United States,¹ but their routine use in Britain is controversial.^{2,4}

The high specificity of serotonin reuptake inhibitors, without antagonism of neurotransmitter receptors or direct cardiac effects, has led to the expectation that they have the same antidepressant activity as tricyclic

and related antidepressants but do not produce many of the common side effects.⁵ Thus it is claimed that they have two important advantages over tricyclic and related antidepressants—they are better tolerated and are less toxic in overdose.⁴ However, disagreement exists about the role of serotonin reuptake inhibitors in treating major depression.^{2,3}

One reason for these differences of opinion is that the claims made for serotonin reuptake inhibitors are often based on the results of individual trials.² Many of the studies are not large enough to detect or exclude with certainty clinically relevant differences in the effects of serotonin reuptake inhibitors and tricyclic and related drugs. We reviewed the evidence for the efficacy and acceptability of serotonin reuptake inhibitors compared with the tricyclic and related antidepressants by meta-analysis. We included data from all comparable randomised controlled trials, which enables smaller effects to be detected or excluded with confidence. The large number of studies also gives the findings potentially greater generalisability.

Methods

We conducted a meta-analysis of the results of efficacy studies and of the drop out rates. We identified 64 randomised controlled trials comparing serotonin reuptake inhibitors with tricyclic or related antidepressants by searching Medline and *Index Medicus*, manual cross referencing, and discussion with experts (table I).⁶⁻⁹ One study did not use a double-blind design and was therefore excluded from the analysis.¹¹ Some multicentre studies have been published in aggregate and separately, and we took great care to avoid including the same results more than once.⁷⁰

EFFICACY

The trials used various psychometric instruments to measure the efficacy of treatments. The most consistently used instrument, the Hamilton depression rating scale,^{71,72} was included in 61 of the trials. The Hamilton depression rating scale is a reliable instrument that is particularly weighted towards and sensitive to change in somatic symptoms rather than psychological and cognitive factors.⁷³ Most studies used either the 17 question or the 21 question instrument, although other versions were occasionally used. However, it is generally accepted that none of the items which supplement

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TABLE 1—Randomised clinical trials on the treatment of major depression with serotonin reuptake inhibitors and tricyclic and related antidepressants

Author (year)	Serotonin reuptake inhibitors (mg/day)	Tricyclic antidepressants (mg/day)	No of weeks' treatment	No of patients		Difference in mean Hamilton score* (SE)	No of drop outs		Odds ratio of drop outs (95% confidence interval)
				Serotonin reuptake inhibitors	Tricyclic antidepressants		Serotonin reuptake inhibitors	Tricyclic antidepressants	
Altamura <i>et al</i> ¹ (1989)	Fluoxetine (20)	Amitriptyline (75)	5	14	14	4.00 (2.38)†	2	4	0.42 (0.06 to 2.77)
Amore <i>et al</i> ² (1989)	Fluvoxamine (50-150)	Imipramine (50-150)	4	15	15	1.00 (NA)‡	0	5	
Bascara ³ (1989)	Paroxetine (20-30)	Amitriptyline (50-75)	6	27	23	NA	2	3	0.53 (0.08 to 3.51)
Bignamini and									
Rapisarda ⁴ (1992)	Paroxetine (20-30)	Amitriptyline (75-150)	6	156	153	1.00 (NA)‡	31	20	1.65 (0.89 to 3.04)
Bramanti <i>et al</i> ⁵ (1988)	Fluvoxamine (50-150)	Imipramine (50-150)	4	30	30	2.65 (1.21)‡	2	1	2.07 (0.18 to 24.15)
Bremner ⁶ (1984)	Fluoxetine (20-80)	Imipramine (75-300)	5	20	20	NA	4	3	1.42 (0.27 to 7.34)
Bressa <i>et al</i> ⁷ (1989)	Fluoxetine (20-60)	Imipramine (50-175)	5	15	15	4.00 (NA)‡	2	1	2.15 (0.17 to 26.67)
Chouinard ⁸ (1985)	Fluoxetine (20-80)	Amitriptyline (75-300)	5	25	28	4.80 (NA)‡	4	6	0.70 (0.17 to 2.83)
Cohn and Wilcox ⁹ (1985)	Fluoxetine (20-80)	Imipramine (100-300)	6	54	54	-1.15 (NA)‡	19	34	0.32 (0.15 to 0.70)
Cohn <i>et al</i> ¹⁰ (1990)	Sertraline (50-200)	Amitriptyline (50-150)	8	161	80	-0.60 (NA)†	79	41	0.92 (0.54 to 1.57)
Cohn <i>et al</i> ¹¹ (1990)	Paroxetine (10-50)	Imipramine (65-275)	6	NA	NA	2.00 (NA)†	NA	NA	
Corne and Hall ¹² (1989)	Fluoxetine (40)	Dothiepin (75)	6	49	51	2.20 (1.36)†	14	7	2.51 (0.92 to 6.90)
Danish University anti-depressant group ¹³ (1990)									
Debus <i>et al</i> ¹⁴ (1988)	Fluoxetine (20-60)	Clomipramine (150)	6	62	58	6.00 (NA)†	35	23	1.97 (0.95 to 4.08)
de Jonghe <i>et al</i> ¹⁵ (1991)	Fluvoxamine (50-300)	Trazadone (50-400)	6	22	21	2.00 (NA)†	8	10	0.63 (0.19 to 2.13)
de Jonghe <i>et al</i> ¹⁶ (1991)	Fluvoxamine (50-300)	Maprotiline (50-150)	6	24	24	-0.10 (2.16)†	4	6	0.60 (0.15 to 2.47)
De Wild <i>et al</i> ¹⁷ (1983)	Fluvoxamine (223-300)	Maprotiline (40-80)	6	30	35	2.60 (2.03)†	4	6	1.19 (0.49 to 2.89)
Dick and Ferrero ¹⁸ (1983)	Fluvoxamine (223-300)	Clomipramine (109-144)	6	21	23	1.30 (NA)†	0	0	
Dominguez <i>et al</i> ¹⁹ (1985)	Fluvoxamine (150)	Clomipramine (150)	4	17	15	1.80 (NA)§	4	3	1.23 (0.23 to 6.67)
Dorman ²⁰ (1992)	Fluvoxamine (50-300)	Imipramine (50-300)	4	35	35	-0.40 (NA)§	19	16	1.41 (0.55 to 3.61)
Dunbar <i>et al</i> ²¹ (1991)	Paroxetine (15-30)	Amitriptyline (30-60)	6	29	28	-4.00 (NA)†	5	3	1.74 (0.37 to 8.08)
Dunner <i>et al</i> ²² (1992)	Paroxetine (20-50)	Imipramine (65-275)	6	240	240	0.00 (NA)†	102	127	0.66 (0.46 to 0.94)
Fabre <i>et al</i> ²³ (1991)	Fluoxetine (10-40)	Doxepin (<200)	6	136	135	-1.00 (NA)‡	45	39	1.22 (0.73 to 2.04)
Falk <i>et al</i> ²⁴ (1989)	Fluoxetine (20-60)	Nortriptyline (87)	5	103	102	0.00 (NA)§	39	45	0.77 (0.44 to 1.35)
Feighner <i>et al</i> ²⁵ (1991)	Fluoxetine (20-80)	Trazadone (50-400)	6	14	13	-0.07 (4.25)‡	3	10	0.08 (0.01 to 0.50)
Feighner <i>et al</i> ²⁶ (1989)	Fluoxetine (20-80)	Bupropion (225-450)	6	62	61	1.40 (NA)‡	18	16	1.15 (0.52 to 2.54)
Feighner and Cohn ²⁷ (1985)	Fluoxetine (20-80)	Imipramine (85-280)	6	31	36	-5.00 (NA)‡	10	9	1.43 (0.49 to 4.15)
Feighner <i>et al</i> ²⁸ (1985)	Fluoxetine (20-80)	Doxepin (50-250)	6	78	79	-0.29 (NA)‡	37	48	0.58 (0.31 to 1.10)
Ferretti ²⁹ (1989)	Fluoxetine (20)	Amitriptyline (75-300)	5	22	22	2.00 (NA)‡	5	12	0.25 (0.06 to 0.90)
Ginestet ³⁰ (1989)	Fluoxetine (58)	Amitriptyline (100)	6	31	32	-0.30 (NA)‡	4	7	0.53 (0.14 to 2.03)
Gonella <i>et al</i> ³¹ (1990)	Fluvoxamine (100-150)	Clomipramine (148)	8	NA	NA	0.20 (2.67)‡	NA	NA	
Guelfi <i>et al</i> ³² (1987)	Fluvoxamine (100-300)	Imipramine (100-150)	4	10	10	-1.90 (3.92)‡	1	0	
Guilbert <i>et al</i> ³³ (1989)	Fluvoxamine (100-300)	Imipramine (50-200)	4	77	81	-2.60 (1.86)‡	19	18	1.15 (0.55 to 2.40)
Guy <i>et al</i> ³⁴ (1984)	Fluvoxamine (150-225)	Clomipramine (25-75)	6	40	39	0.20 (NA)‡	9	12	0.65 (0.24 to 1.79)
Hutchinson <i>et al</i> ³⁵ (1992)	Paroxetine (20)	Imipramine (150-225)	6	17	19	NA	NA	NA	
Itil <i>et al</i> ³⁶ (1983)	Fluvoxamine (50-210)	Amitriptyline (100)	6	58	32	0.00 (NA)‡	12	11	0.50 (0.19 to 1.31)
Kuhs and Rudolf ³⁷ (1989)	Paroxetine (30)	Imipramine (50-210)	4	22	25	NA	12	12	1.30 (0.41 to 4.10)
Laakmann <i>et al</i> ³⁸ (1988)	Fluoxetine (20-60)	Amitriptyline (150)	6	20	20	0.40 (NA)‡	6	3	2.43 (0.51 to 11.51)
Lapierre <i>et al</i> ³⁹ (1987)	Fluoxetine (180)	Amitriptyline (50-150)	5	65	65	5.00 (2.45)†	29	22	1.57 (0.78 to 3.20)
Laursen <i>et al</i> ⁴⁰ (1985)	Fluoxetine (30)	Imipramine (173)	6	22	21	-5.00 (NA)†	7	12	0.35 (0.10 to 1.22)
Levine <i>et al</i> ⁴¹ (1987)	Fluoxetine (40-60)	Amitriptyline (50-150)	6	21	23	2.00 (NA)†	5	9	0.49 (0.13 to 1.80)
Loeb <i>et al</i> ⁴² (1989)	Fluoxetine (20)	Imipramine (75-150)	6	30	30	3.40 (NA)‡	8	2	5.09 (0.98 to 26.43)
Manna <i>et al</i> ⁴³ (1989)	Fluoxetine (20)	Imipramine (50-75)	5	15	15	-5.76 (NA)‡	NA	NA	
March <i>et al</i> ⁴⁴ (1990)	Fluvoxamine (50-300)	Clomipramine (75)	5	15	15	-1.00 (1.65)†	NA	NA	
Mertens and									
Pintors ⁴⁵ (1988)	Paroxetine (30)	Imipramine (50-300)	6	18	18	-2.00 (NA)†	5	3	1.92 (0.38 to 9.65)
Muijen <i>et al</i> ⁴⁶ (1988)	Fluoxetine (40-80)	Mianserin (60)	6	38	32	-6.00 (NA)‡	5	4	1.06 (0.26 to 4.34)
Mullin <i>et al</i> ⁴⁷ (1988)	Fluvoxamine (100-300)	Mianserin (40-80)	6	26	27	-4.00 (3.38)†	12	13	0.92 (0.31 to 2.72)
Nielsen <i>et al</i> ⁴⁸ (1991)	Paroxetine (20-40)	Dothiepin (75-225)	6	37	36	-0.20 (NA)†	11	12	0.85 (0.32 to 2.27)
Norton <i>et al</i> ⁴⁹ (1984)	Fluvoxamine (133)	Imipramine (100-200)	12	16	15	-2.00 (NA)†	4	1	0.52 (0.12 to 2.17)
Perez and Ashford ⁵⁰ (1990)	Fluvoxamine (100-600)	Imipramine (153)	4	35	31	0.30 (NA)†	4	1	3.87 (0.41 to 36.66)
Perry <i>et al</i> ⁵¹ (1989)	Fluoxetine (20-60)	Mianserin (60-360)	6	30	33	NA	9	9	1.14 (0.38 to 3.41)
Peselow <i>et al</i> ⁵² (1989)	Paroxetine (10-50)	Trazadone (50-400)	6	21	19	1.90 (2.64)§	4	4	0.88 (0.19 to 4.16)
Phanjo <i>et al</i> ⁵³ (1991)	Fluvoxamine (100-200)	Imipramine (65-275)	6	40	40	8.56 (NA)†	11	12	0.89 (0.34 to 2.33)
Poelinger and									
Haber ⁵⁴ (1989)	Fluoxetine (40)	Mianserin (40-80)	6	25	25	Did not use	9	10	0.84 (0.27 to 2.65)
Rahman <i>et al</i> ⁵⁵ (1991)	Fluvoxamine (50-200)	Maprotiline (75)	4	73	69	-1.00 (1.13)§	12	8	1.50 (0.57 to 3.93)
Reimherr <i>et al</i> ⁵⁶ (1990)	Sertraline (50-200)	Dothiepin (50-200)	6	26	26	Did not use	9	7	1.44 (0.44 to 4.70)
Ropert ⁵⁷ (1989)	Fluoxetine (20)	Amitriptyline (50-150)	8	126	122	1.72 (0.82)†	61	63	0.95 (0.60 to 1.50)
Roth <i>et al</i> ⁵⁸ (1990)	Fluvoxamine (100-300)	Clomipramine (75)	5	71	72	-1.40 (0.97)‡	16	24	0.58 (0.28 to 1.22)
South Wales Antidepressant Drug Trial Group ⁵⁹ (1988)	Fluoxetine (40-80)	Desipramine (100-300)	6	30	30	-1.20 (2.56)†	6	9	0.58 (0.18 to 1.91)
Stark and Hardison ⁶⁰ (1985)	Fluoxetine (20-80)	Imipramine (100-300)	6	185	186	-0.40 (1.72)†	15	7	2.81 (0.93 to 8.52)
Tamminen and									
Lehtinen ⁶¹ (1989)	Fluoxetine (40-80)	Dothiepin (50-225)	6	31	28	-0.40 (1.72)†	15	7	2.81 (0.93 to 8.52)
Taneri and Köhler ⁶² (1989)	Fluoxetine (40)	Imipramine (100-300)	6	185	186	0.30 (1.05)‡	87	87	1.01 (0.67 to 1.52)
Young <i>et al</i> ⁶³ (1987)	Fluoxetine (40-80)	Dothiepin (50-150)	5	26	25	-1.00 (NA)†	5	4	1.25 (0.29 to 5.31)
	Fluoxetine (40)	Nomifensine (150)	5	20	20	-2.50 (2.47)§	5	1	6.33 (0.67 to 60.17)
	Fluoxetine (40-80)	Amitriptyline (50-150)	6	32	32	NA	7	7	1.00 (0.31 to 3.27)

*The difference in mean Hamilton score was calculated from data reported at the last week of the trial: difference in mean score=mean score in serotonin reuptake inhibitor group—mean score in tricyclic group. †17 Item Hamilton scale. ‡21 Item Hamilton scale. §Other items or unknown items of Hamilton scale. NA=not available.

the basic 17 questions provide additional information of value.

The mean difference in Hamilton scores between patients treated with serotonin reuptake inhibitors and those treated with tricyclic or related antidepressants (treatment difference) was calculated for each trial. A pooled estimate of the treatment difference was calculated by averaging all the treatment differences, weighting each by the inverse of the individual squared standard errors.⁷⁴ This gave larger studies, with tighter confidence intervals, more influence in the pooled estimate of difference in efficacy than smaller ones.

Only 20 trials presented the standard deviation of Hamilton scores needed to calculate the weights. A test for heterogeneity (non-random differences) of standardised treatment difference between the studies, with

a χ^2 statistic, showed no significant heterogeneity ($Q=23.58$, $df=19$; $p=0.213$),⁷⁵ so a fixed effects method was used to estimate the pooled difference in efficacy.⁷⁶

To avoid the potential bias from using only 20 trials, we ascribed a standard deviation to the remaining 33 studies which used the 17 or 21 item Hamilton scale. Since the standard deviations of the scores from the 16 trials using the 17 or 21 item scale were similar, for each scale a weighted average of these standard deviations was used to calculate a standard error for each of the 33 studies. Pooled estimates of treatment differences were calculated for all 49 studies and compared with the estimate derived from the 16 studies that presented standard deviations for either the 17 or 21 item Hamilton scale.

ACCEPTABILITY

Acceptability to patients is an important element in a treatment's effectiveness.⁷⁷ Drop out, which is a useful measure of acceptability,⁷⁸ was reported in 58 trials. We compared drop out rates in the two arms of the trials and analysed the main subjective reasons given by patients for discontinuing therapy (inefficacy and side effects) when available.

The ratio of drop out rate of patients in the serotonin reuptake inhibitor group to that in the tricyclic and related antidepressant group (odds ratio) was calculated for each study. A pooled estimate of the overall odds ratio of drop out was calculated by weighting each odds ratio by the inverse of the variance; thus studies with more subjects were given more weight. The odds ratio was heterogeneous among studies ($Q=78.79$, $df=57$; $p=0.03$) and so the pooled odds ratio was calculated by a random effects method.^{75 79}

Results

EFFICACY

Of the 20 trials which presented the mean Hamilton score and its standard deviations, six used the 21 item Hamilton scale, 10 the 17 point scale and four other versions. Pooled results are presented separately for the 17 and 21 item version of the scale and then all 20 trials were combined by using the standardised difference between mean Hamilton scores for the serotonin reuptake inhibitor and tricyclic and related antidepressant groups: Standardised difference = difference between means/standard deviation.

The average baseline Hamilton score was about 26 on the 21 item scale and 24 on the 17 item scale. No significant difference was found in mean Hamilton score in the 21 item scale for serotonin reuptake inhibitors compared with tricyclic and related anti-

TABLE II—Drop out rate in patients treated with serotonin reuptake inhibitors and tricyclic and related antidepressants

	No (%) receiving serotonin reuptake inhibitors	No (%) receiving tricyclic antidepressants
Total drop outs (58 studies)	2817 (32.3)	2701 (33.2)
Reason for drop out:		
Side effects (51 studies)	2556 (15.4)	2445 (18.8)
Inefficacy (39 studies)	2155 (7.0)	2042 (6.8)

TABLE III—Odds ratio of drop out in patients treated with serotonin reuptake inhibitors compared with tricyclic and related antidepressants

Drop outs	Odds ratio	95% Confidence interval
Fluoxetine	0.921	0.699 to 1.215
Fluvoxamine	1.013	0.756 to 1.358
Paroxetine	0.973	0.779 to 1.216
All serotonin reuptake inhibitors	0.950	0.816 to 1.107*
Due to side effects	0.805	0.648 to 1.001
Due to inefficacy	1.022	0.801 to 1.304

* $Q=78.79$, $df=57$; $p=0.0295$.

depressants, after up to eight weeks of treatment (mean difference 0.13; 95% confidence interval -1.01 to 1.28) (fig 1). Tricyclic and related antidepressants were significantly more effective than the serotonin reuptake inhibitors in trials using the 17 item scale (mean difference 1.29, 0.28 to 2.30) (fig 1) but the difference was not clinically important.

Overall, in the 20 trials which presented the standard deviation of the Hamilton score the tricyclic and related antidepressants showed a small but non-significant benefit in efficacy when compared with the serotonin reuptake inhibitors (standardised difference 0.004, 95% confidence interval -0.096 to 0.105).

We ascribed weighted average standard deviations to the remaining 33 studies that used the 17 or 21 item Hamilton score as an end point so that the results for all 49 studies could be pooled. A standard deviation of 8.27 was ascribed to studies using the 21 item scale and 6.81 to those using the 17 item scale. Again, there were no differences in trials using either the 21 item scale (mean difference 0.147; -0.597 to 0.891) or the 17 item scale (0.727, 0.083 to 1.370). This strengthens the inference that there is no significant difference in efficacy between serotonin reuptake inhibitors and tricyclic and related drugs.

ACCEPTABILITY TO PATIENTS

Fifty eight studies reported drop out rates during the treatment phase. The pooled drop out rate was 32.3% in patients receiving serotonin reuptake inhibitors and 33.2% among those receiving tricyclic and related antidepressants (table II). The odds ratio for drop out for serotonin reuptake inhibitors compared with tricyclic and related antidepressants was estimated to be 0.95, which was not significantly different from 1 (95% confidence interval 0.816 to 1.107) (table III, fig 2).

Several trials reported the reason given by patients for dropping out from treatment. The two most commonly cited reasons were lack of efficacy and side effects. There was no difference in the drop out rate attributed to lack of efficacy among the two groups but drop out because of side effects was slightly more common among patients taking tricyclic antidepressants (tables II and III).

Discussion

The results of this analysis are particularly important because the populations in the trials were generally similar to that found in primary or ambulatory care, where most first line treatment is undertaken. Our most important finding was that there was no statistically or clinically significant difference in the accept-

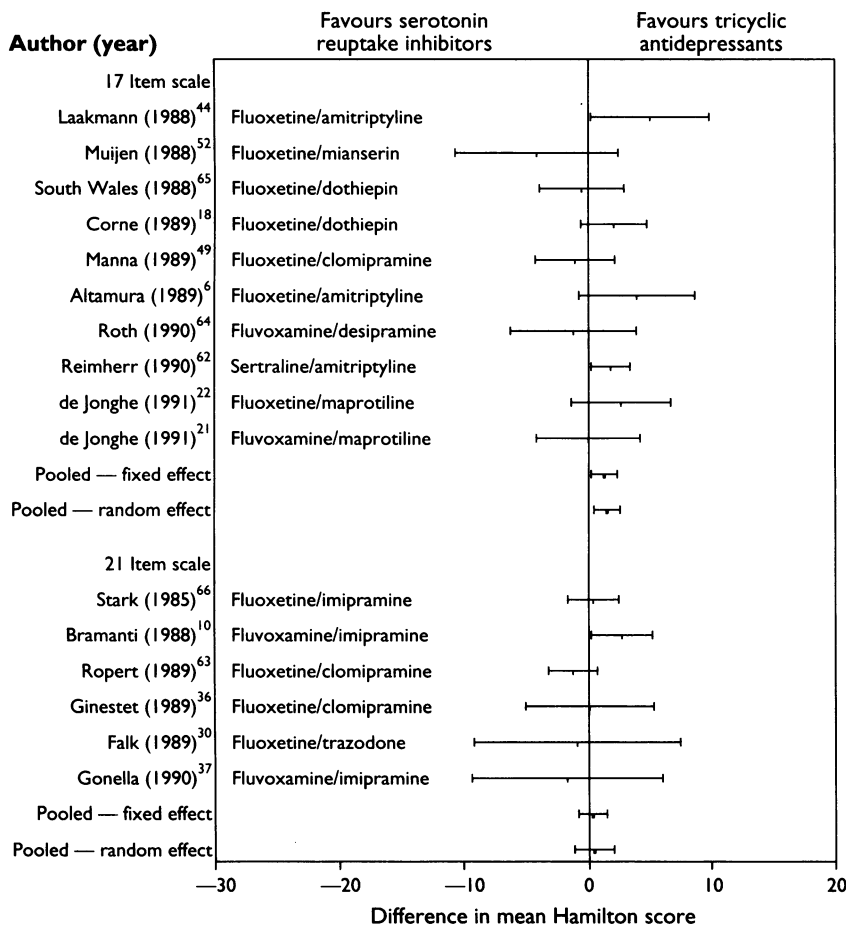


FIG 1—Difference (95% confidence interval) in mean Hamilton score in patients treated with serotonin reuptake inhibitors or tricyclic and related antidepressants (from data reported at last week of trial)

ability of serotonin reuptake inhibitors and tricyclic and related antidepressants in patients with major depression.

The serotonin reuptake inhibitors seem to have similar efficacy to the tricyclic and related antidepressants, but the analysis of efficacy is less reliable than that of acceptability because intention to treat analyses were not widely used, different Hamilton scales were

used, and reporting of standard deviation was inadequate. The length of follow up in all the studies (median six weeks) was short relative to the generally accepted desirable duration of treatment in this population.⁸⁰

In addition the study populations were heterogeneous despite all meeting the criteria for major depression. Some patients had a short lived mood disorder, which would be likely to resolve rapidly, perhaps without treatment. Others had a more persistent disorder, some of whom had already been treated unsuccessfully. Spontaneous resolution is likely to reduce the ability of any trial to show differences in the effect of treatment. On the other hand, the fact that some patients had already failed to respond to tricyclics before entering the trial might have introduced a bias against this class of drugs.

Better designed studies with more complete reporting of data would enable more reliable estimates of efficacy of treatment. This is essential for the translation of research findings into clinical practice and should be mandatory in reports in clinical journals.

The lack of evidence of greater efficacy and acceptability of serotonin reuptake inhibitors means that their adoption as the drugs of choice in major depression may be premature, although they may have a role in subgroups of patients in whom other treatments are contraindicated or have failed.

The other argument for prescribing serotonin reuptake inhibitors has been their reported lower toxicity in overdose compared with some antidepressants. However, more knowledge of the long term effects of these drugs is needed before they can be recommended as a safe alternative to tricyclic antidepressants, which are less expensive, equally effective, and well tolerated. It may be more effective to adopt alternative strategies for improving mental health and reducing suicides, as outlined in the recommendations of the Defeat Depression campaign of the Royal Colleges of Psychiatrists and General Practitioners.⁸⁰

In conclusion, our meta-analysis of randomised controlled trials indicates that selective serotonin reuptake inhibitors have no significant advantage in efficacy or acceptability over tricyclic and related antidepressants. This is at odds with some of the claims made in the promotion of serotonin reuptake inhibitors and does not support their increasing use as routine first line treatment for major depression.

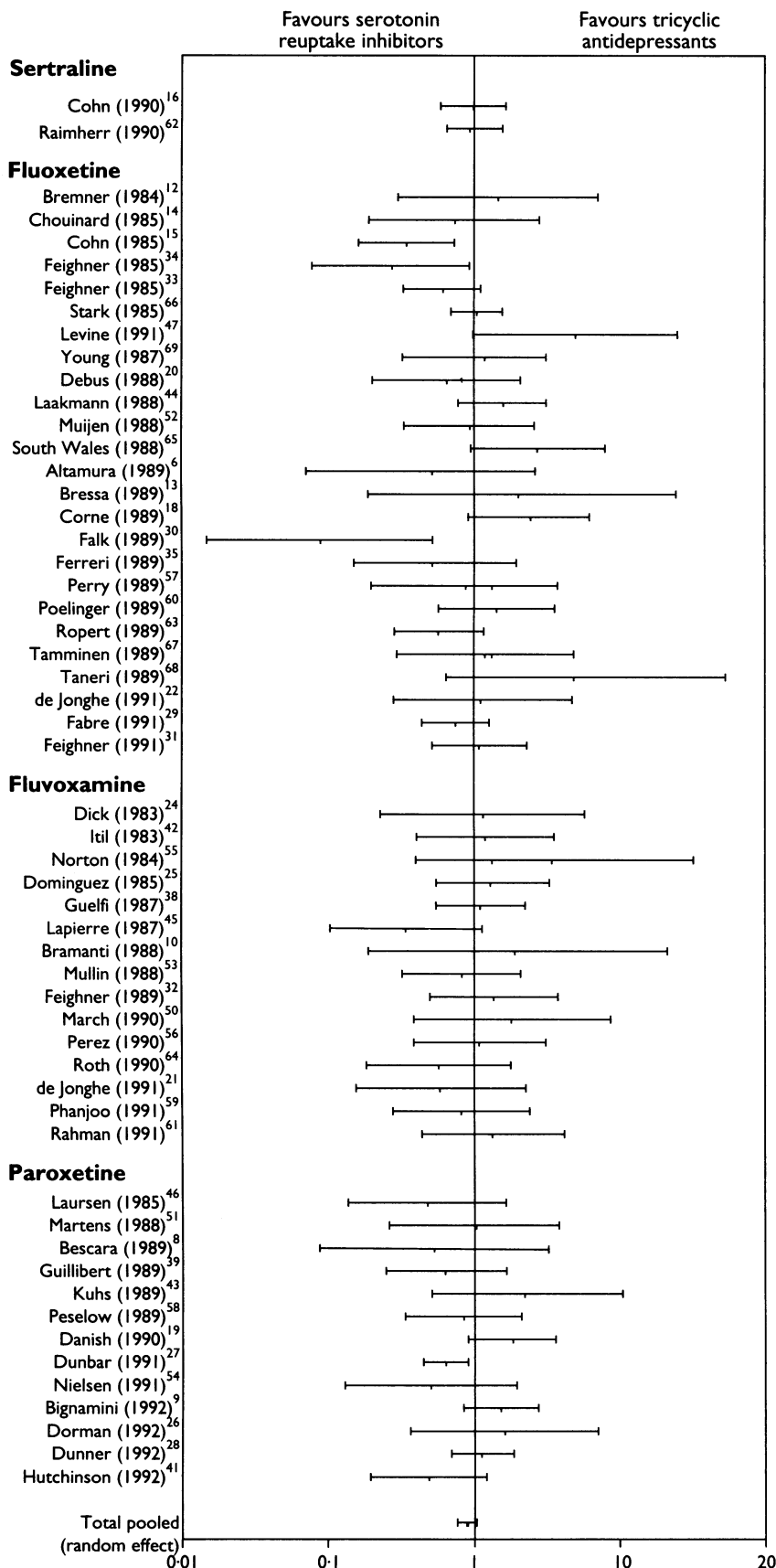


FIG 2—Odds ratio of drop out in patients treated with selective serotonin reuptake inhibitors and tricyclic and related antidepressants

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