Key messages

- Breast cancer is the commonest cancer in women throughout the world, and its incidence is increasing
- It has been suggested that smoking protects against breast cancer because of an antioestrogenic effect
- This study shows, however, that women who have smoked for more than 30 years have an increased risk of developing breast cancer
- Moreover, smokers with breast cancer were eight years younger than non-smokers with breast cancer

than those included in our model—for example, alcohol, diet, body size, and use of oral contraception—have been studied extensively.¹⁰⁻¹² The associations between these factors and breast cancer, however, are often weak and inconsistent. Although confounding cannot be ruled out as an explanation of our results, it is not likely that an inverse relation exists between smoking and breast cancer.

CONCLUSION

In conclusion, nothing in the present study suggests that smoking protects against breast cancer—rather, the opposite. Smoking seemed to increase the risk of developing cancer to a modest extent among women

who had smoked for more than 30 years. Moreover, breast cancer will occur eight years earlier in smokers than in non-smokers. This finding could support the hypothesis of a direct carcinogenic effect of tobacco.

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Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis

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Abstract

Objective—To assess treatment discontinuation rates with selective serotonin reuptake inhibitors compared with tricyclic antidepressants.

Design—Meta-analysis of 62 randomised controlled trials.

Subjects—6029 patients with major unipolar depression.

Main outcome measures—Pooled risk ratios for drop out rates with respect to all cases of discontinuation and those due to side effects and treatment failure.

Results—The total discontinuation rate was 10% lower with selective serotonin reuptake inhibitors than with tricyclic antidepressants (risk ratio 0.90; 95% confidence interval 0.84 to 0.97) and the drop out rate due to side effects was 25% lower (risk ratio 0.75; 0.66 to 0.84). There was no significant difference between drug classes in the drop out rates for treatment failure. The risk ratios for drop out did not differ significantly between individual selective serotonin reuptake inhibitors.

Conclusions—Selective serotonin reuptake inhibitors are better tolerated than tricyclic antidepressants as measured by total numbers of drop outs. The definite advantage to selective serotonin reuptake inhibitors is explained by fewer drop outs due to side effects. The overall difference, however, is comparatively small and may not be clinically relevant. Analyses of cost effectiveness should not overestimate the advantage to selective serotonin reuptake inhibitors.

Introduction

There is debate about the cost effectiveness of newer, more expensive antidepressants—especially

the selective serotonin reuptake inhibitors—compared with the cheaper, first generation tricyclic antidepressants.^{1,2} Both groups of drugs are of comparable efficacy,³⁻⁵ so that cost effectiveness hinges on tolerability and safety. Tricyclic antidepressants are much cheaper per tablet than selective serotonin reuptake inhibitors. But if compliance is poorer tricyclic antidepressants may prove more expensive overall because of costs incurred through treatment failure (for example, costs of extra treatment, time off work, sickness benefit, etc).⁶

One way of assessing relative tolerability is to measure discontinuation rates in randomised, double blind, parallel comparative trials. Though this is fairly crude,⁷ it provides an objective measure of the proportion of patients who persist with each treatment during the study. In an influential meta-analysis, Song *et al* found that efficacy and drop out rates did not differ between tricyclic antidepressants and selective serotonin reuptake inhibitors and concluded that the increasing use of the newer drugs as first line treatment was not warranted.⁴ Their analysis was weakened by the inclusion of non-tricyclic, second generation antidepressants in the tricyclic group (table I), accounting for about a quarter of the studies they analysed. These drugs generally have a better side effect profile than the tricyclic antidepressants⁸ but are infrequently used in practice.⁹ Hence the clinical relevance of their inclusion in the meta-analysis can be questioned.

Montgomery *et al* confined their meta-analysis to studies including tricyclic antidepressants and found that selective serotonin reuptake inhibitors caused significantly fewer drop outs due to side effects whereas there was no difference in drop outs due to inefficacy.⁷ Unfortunately, given that discontinuation due to side effects accounts for only 30-50% of drop outs,^{4,27} they failed to analyse total drop out rates.

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Possibly more prominent side effects could lead to a greater attribution of discontinuation to adverse effects without changing the number of patients who in fact stopped treatment. It is therefore very important to analyse both the total number of drop outs and the discontinuations that may be attributable to side effects or treatment failure.

TABLE I—Papers included in meta-analysis of total drop outs by Song *et al*^a but excluded from this analysis for reasons stated

Study	Comparator antidepressant	Reason for exclusion
Debus <i>et al</i> , 1988 ¹⁰	Trazodone	Non-tricyclic antidepressant
de Jonghe <i>et al</i> , 1991 ¹¹	Maprotiline	Non-tricyclic antidepressant
de Jonghe <i>et al</i> , 1991 ¹²	Matroptiline	Non-tricyclic antidepressant
Dorman, 1992 ¹³	Mianserin	Non-tricyclic antidepressant
Falk <i>et al</i> , 1989 ¹⁴	Trazodone	Non-tricyclic antidepressant
Feighner <i>et al</i> , 1989 ¹⁵	Imipramine	Total drop outs not reported†
Feighner <i>et al</i> , 1991 ¹⁶	Bupropion	Non-tricyclic antidepressant
Ferreri, 1989 ¹⁷	Amineptine	Non-tricyclic antidepressant
Laakmann <i>et al</i> , 1988 ¹⁸	Amitriptyline	Conflicting numbers reported
Mertens and Pintens, 1988 ¹⁹	Mianserin	Non-tricyclic antidepressant
Muijen <i>et al</i> , 1988 ²⁰	Mianserin	Non-tricyclic antidepressant
Perez and Ashford, 1990 ²¹	Mianserin	Non-tricyclic antidepressant
Perry <i>et al</i> , 1989 ²²	Trazodone	Non-tricyclic antidepressant
Phanjoo <i>et al</i> , 1991 ²³	Mianserin	Non-tricyclic antidepressant
Poelinger and Haber, 1989 ²⁴	Maprotiline	Non-tricyclic antidepressant
Taneri and Kohler, 1989 ²⁵	Nomifensine	Non-tricyclic antidepressant

†Reported only drop outs due to side effects.

TABLE II—Discontinuation rates in double blind randomised studies in major depression comparing selective serotonin reuptake inhibitors with tricyclic antidepressants

Study	No of patients		Study length in weeks	Total drop outs		Risk ratio (95% confidence interval)	Drop outs due to side effects		Risk ratio (95% confidence interval)	Drop outs due to failure		Risk ratio (95% confidence interval)
	Serotonin reuptake inhibitors	Tricyclic antidepressants		Serotonin reuptake inhibitors	Tricyclic antidepressants		Serotonin reuptake inhibitors	Tricyclic antidepressants		Serotonin reuptake inhibitors	Tricyclic antidepressants	
Fluvoxamine:												
Amore <i>et al</i> , 1989 ^a	15	15	4	0	5	0	0	2	0	0	0	—
Bramanti <i>et al</i> , 1989 ^a	30	30	4	2	1	2.00 (0.19 to 20.90)	0	1	0	2	0	—
De Wilde and Doogan, 1982 ^a	15	15	4	0	0	0	0	0	0	0	0	—
De Wilde <i>et al</i> , 1983 ^a	21	23	6	0	0	0	0	0	0	0	0	—
Dick and Ferrero, 1983 ^a	17	15	4	4	3	1.18 (0.31 to 4.43)	0	0	0	1	1	0.88 (0.06 to 12.91)
Dominguez <i>et al</i> , 1985 ^a	35	35	4	19	16	1.19 (0.74 to 1.90)	10	8	1.25 (0.56 to 2.79)	1	0	—
Feighner <i>et al</i> , 1989 ^a	31	35	6	NA	NA	NA	7	13	0.61 (0.28 to 1.33)	NA	NA	NA
Gasperini <i>et al</i> , 1992 ^a	30	26	6	2	1	1.73 (0.17 to 18.04)	1	1	0.87 (0.06 to 13.81)	NA	NA	NA
Gonella <i>et al</i> 1990 ^a	10	10	4	1	0	—	NA	NA	NA	NA	NA	NA
Gueffi <i>et al</i> , 1987 ^a	77	81	4	19	18	1.11 (0.63 to 1.95)	2	5	0.42 (0.08 to 2.11)	0	3	0
Harris <i>et al</i> , 1991 ^a	35	34	6	12	10	1.17 (0.58 to 2.33)	5	6	0.81 (0.27 to 2.41)	0	2	0
Itil <i>et al</i> , 1983 ^a	22	25	4	12	12	1.14 (0.65 to 1.99)	9	7	1.46 (0.65 to 3.27)	0	1	0
Klok <i>et al</i> , 1981 ^a	18	18	4	5	3	1.67 (0.47 to 5.96)	2	1	2.00 (0.20 to 20.15)	1	0	—
Lapierre <i>et al</i> , 1987 ^a	22	21	6	7	12	0.56 (0.27 to 1.14)	1	1	0.95 (0.06 to 14.30)	2	6	0.32 (0.07 to 1.40)
Lydiard <i>et al</i> , 1989 ^a	18	18	6	NA	NA	NA	1	2	0.50 (0.05 to 5.04)	NA	NA	NA
March <i>et al</i> , 1990 ^a	18	18	6	5	3	1.67 (0.47 to 5.96)	4	3	1.33 (0.35 to 5.13)	1	0	—
Mullin <i>et al</i> , 1988 ^a	37	36	6	11	12	0.89 (0.45 to 1.76)	9	6	1.46 (0.58 to 3.68)	2	4	0.49 (0.09 to 2.49)
Nathan <i>et al</i> , 1990 ^a	17	20	4	0	2	0	0	2	0	0	0	—
Norton <i>et al</i> , 1984 ^a	35	31	4	4	1	3.54 (0.42 to 30.03)	2	0	—	1	0	—
Rahman <i>et al</i> , 1991 ^a	26	26	6	9	7	1.29 (0.56 to 2.93)	2	2	1.00 (0.15 to 6.57)	0	0	—
Roth <i>et al</i> , 1990 ^a	30	30	6	6	9	0.67 (0.27 to 1.64)	NA	NA	NA	NA	NA	NA
Fluoxetine:												
Altamura <i>et al</i> , 1989 ^a	13	15	5	2	4	0.58 (0.13 to 2.65)	NA	NA	NA	NA	NA	NA
Bremner, 1984 ^a	20	20	5	4	3	1.33 (0.34 to 5.21)	0	2	0	0	0	—
Bressa <i>et al</i> , 1989 ^a	15	15	5	2	1	2.00 (0.20 to 19.78)	0	0	0	0	0	—
Chouinard, 1985 ^a	25	28	5	4	6	0.77 (0.24 to 2.35)	0	4	0	1	0	—
Cohn and Wilcox, 1985 ^a	54	54	6	19	34	0.56 (0.37 to 0.85)	8	24	0.33 (0.16 to 0.68)	0	4	0
Corne and Hall, 1989 ^a	49	51	6	14	7	2.08 (0.92 to 4.72)	7	2	3.64 (0.80 to 16.69)	1	1	1.04 (0.07 to 16.18)
Fabre <i>et al</i> , 1991 ^a	103	102	5	39	45	0.86 (0.62 to 1.19)	17	29	0.58 (0.34 to 0.99)	2	5	0.40 (0.08 to 2.00)
Fawcett <i>et al</i> , 1989 ^a	20	20	6	8	11	0.73 (0.37 to 1.42)	4	10	0.40 (0.15 to 1.07)	2	0	—
Feighner, 1985 ^a	22	22	5	5	13	0.38 (0.17 to 0.90)	2	6	0.33 (0.08 to 1.48)	1	3	0.33 (0.04 to 2.96)
Feighner and Cohn, 1985 ^a	78	79	6	37	48	0.78 (0.58 to 1.05)	25	34	0.74 (0.49 to 1.12)	6	4	1.52 (0.45 to 5.18)
Feighner <i>et al</i> , 1989 ^a	61	58	6	31	28	1.05 (0.73 to 1.51)	13	18	0.69 (0.37 to 1.27)	13	7	1.77 (0.76 to 4.11)
Judd <i>et al</i> , 1993 ^a	30	28	6	7	5	1.31 (0.47 to 3.64)	1	0	—	1	1	0.93 (0.06 to 14.22)
Keegan <i>et al</i> , 1991 ^a	20	22	6	2	3	0.73 (0.14 to 3.95)	1	0	—	0	3	0
Levine <i>et al</i> , 1987 ^a	30	30	6	8	2	4.00 (0.92 to 17.30)	2	0	—	2	1	2.00 (0.19 to 20.90)
Masco and Sheetz, 1985 ^a	20	21	6	1	5	0.21 (0.03 to 1.64)	0	2	0	1	1	1.05 (0.07 to 15.68)
Nielsen, <i>et al</i> 1993 ^a	29	30	8	8	8	1.03 (0.45 to 2.39)	4	4	1.03 (0.29 to 3.75)	1	1	1.03 (0.07 to 15.77)
Noguera <i>et al</i> , 1991 ^a	60	60	6	13	16	0.81 (0.43 to 1.54)	2	6	0.33 (0.07 to 1.59)	3	0	—
Ropert <i>et al</i> , 1989 ^a	71	72	6	16	24	0.68 (0.39 to 1.16)	4	12	0.34 (0.11 to 1.00)	NA	NA	NA
South Wales Antidepressant Drug Trial Group, 1988 ^a												
Stark and Hardison, 1985 ^a	31	28	6	15	7	1.94 (0.93 to 4.05)	8	0	0	5	4	1.13 (0.34 to 3.79)
Tamminen and Lehtinen, 1989 ^a	185	186	6	87	87	1.01 (0.81 to 1.25)	33	52	0.64 (0.43 to 0.94)	35	30	1.17 (0.75 to 1.83)
Young <i>et al</i> 1987 ^a	26	23	5	5	4	1.11 (0.34 to 3.63)	3	1	2.65 (0.30 to 23.77)	NA	NA	NA
	32	32	6	7	7	1.00 (0.40 to 2.52)	2	0	—	0	0	—
Paroxetine:												
Bascara, 1989 ^a	27	23	6	2	3	0.57 (0.10 to 3.11)	2	3	0.57 (0.10 to 3.11)	NA	NA	NA
Battegay <i>et al</i> , 1985 ^a	11	10	4	3	8	0.34 (0.12 to 0.94)	1	3	0.30 (0.04 to 2.46)	0	0	—
Bignamini and Rapisarda, 1992 ^a	156	153	6	31	20	1.52 (0.91 to 2.55)	8	5	1.57 (0.53 to 4.69)	9	8	1.10 (0.44 to 2.79)
Byrne, 1989 ^a	35	35	7	12	9	1.33 (0.64 to 2.76)	1	3	0.33 (0.04 to 3.05)	5	3	1.67 (0.43 to 6.45)
Danish University Antidepressant Group, 1990 ^a	62	58	6	12	19	0.59 (0.32 to 1.11)	1	10	0.09 (0.01 to 0.71)	9	7	1.20 (0.48 to 3.02)
Dunbar <i>et al</i> , 1991 ^a	241	241	6	102	127	0.80 (0.66 to 0.97)	55	85	0.65 (0.48 to 0.86)	25	17	1.47 (0.82 to 2.65)
Dunner <i>et al</i> , 1992 ^a	136	135	6	45	39	1.15 (0.80 to 1.64)	33	26	1.26 (0.80 to 1.99)	4	6	0.66 (0.19 to 2.29)
Guillibert <i>et al</i> , 1989 ^a	40	39	6	9	12	0.73 (0.35 to 1.54)	3	5	0.59 (0.15 to 2.28)	4	3	1.30 (0.31 to 5.44)
Hutchinson <i>et al</i> , 1991 ^a	58	32	6	12	11	0.60 (0.30 to 1.21)	8	6	0.74 (0.28 to 1.93)	0	1	0
Kihs and Rudolf, 1989 ^a	20	20	6	6	3	2.00 (0.58 to 6.91)	2	0	—	2	2	1.00 (0.16 to 6.42)
Lund Laursen <i>et al</i> , 1985 ^a	21	23	6	5	9	0.61 (0.24 to 1.53)	2	4	0.55 (0.11 to 2.69)	0	1	0
Moller <i>et al</i> , 1993 ^a	112	110	6	37	48	0.76 (0.54 to 1.06)	13	21	0.61 (0.32 to 1.15)	16	14	1.12 (0.58 to 2.19)
Nielsen <i>et al</i> , 1991 ^a	16	15	12	7	9	0.73 (0.36 to 1.46)	1	3	0.31 (0.04 to 2.69)	3	5	0.56 (0.16 to 1.96)
Ohrberg <i>et al</i> , 1992 ^a	79	80	6	13	19	0.69 (0.37 to 1.31)	10	14	0.72 (0.34 to 1.53)	2	2	1.01 (0.15 to 7.07)
Sertraline:												
Cohn <i>et al</i> , 1990 ^a	161	80	8	79	41	0.96 (0.73 to 1.25)	49	28	0.87 (0.60 to 1.27)	11	7	0.78 (0.31 to 1.94)
Fontaine, 1991 ^a	54	50	24	28	23	1.13 (0.76 to 1.67)	9	6	1.39 (0.53 to 3.62)	5	6	0.77 (0.25 to 2.37)
Reimherr <i>et al</i> , 1990 ^a	149	149	8	61	63	0.97 (0.74 to 1.27)	28	30	0.93 (0.59 to 1.48)	11	6	1.83 (0.70 to 4.83)
Thompson, 1991 ^a	88	93	6	9	13	0.73 (0.33 to 1.63)	NA	NA	NA	NA	NA	NA
Litalopram:												
Danish University Antidepressant Group, 1986 ^a	57	57	5	12	8	1.50 (0.66 to 3.39)	0	4	0	9	4	2.48 (0.72 to 8.59)
Gravem <i>et al</i> , 1987 ^a	27	24	6	4	4	0.89 (0.25 to 3.17)	1	1	0.89 (0.06 to 13.45)	0	0	—
Shaw, 1986 ^a	24	20	6	7	15	0.41 (0.21 to 0.79)	1	5	0.17 (0.02 to 1.31)	4	5	0.67 (0.21 to 2.16)

NA = data not available.

The main objective of this meta-analysis was to discover whether the overall discontinuation rate with selective serotonin reuptake inhibitors is different from that with tricyclic antidepressants. Drop outs due to side effects and treatment failure were also analysed.

Methods

Potential studies testing five selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) against a tricyclic antidepressant in patients with the equivalent of major unipolar depressive illness were identified from previous meta-analyses and reviews and by manual cross referencing and a Medline search in June 1993. We identified 81 reports of double blind randomised controlled trials in depressed patients. We were careful to avoid duplication and whenever possible for multi-centre studies used the combined multicentre report; in two exceptions there was lack of information about drop outs.^{28 29} This left 71 studies, of which 62 provided adequate information on the total number of drop outs and a further two reported only drop outs due to side

TABLE III—Excluded studies comparing selective serotonin reuptake inhibitors with tricyclic antidepressants, and reasons for exclusion

Study	Serotonin reuptake inhibitor	Reason for exclusion
Amin <i>et al</i> , 1984 ²⁹	Fluvoxamine	Multicentre study, drop outs not reported
Byerley <i>et al</i> , 1988 ³¹	Fluoxetine	In Stark and Hardison multicentre study ²⁹
Cohn <i>et al</i> , 1990 ³⁴	Paroxetine	Drop outs not reported
Coleman and Block, 1982 ²⁸	Fluvoxamine	Summary of three studies
Feighner, 1992 ²⁵	Paroxetine	Same study as Dunbar <i>et al</i> ²⁷
Feighner and Boyer, 1989 ³⁶	Paroxetine	In Dunbar <i>et al</i> multicentre study ²⁷
Feighner <i>et al</i> , 1993 ²⁷	Paroxetine	Same study as Dunbar <i>et al</i> ²⁷
Gagliano <i>et al</i> , 1989 ³⁸	Paroxetine	Insufficient information on drop outs
Ginestet <i>et al</i> , 1989 ³⁹	Fluoxetine	Drop outs not reported
Guy <i>et al</i> , 1984 ¹⁰⁰	Fluvoxamine	Drop outs not reported
Hutchinson and Vince, 1992 ¹⁰¹	Paroxetine	Same study as Hutchinson <i>et al</i> ³⁰
Judd, 1991 ¹⁰²	Fluoxetine	Interim report of Judd <i>et al</i> ⁸¹
Laakmann <i>et al</i> , 1988 ¹⁸	Fluoxetine	Conflicting numbers reported
Levine <i>et al</i> , 1989 ¹⁰³	Fluoxetine	Same study as Levine <i>et al</i> ⁸³
Loeb <i>et al</i> , 1989 ¹⁰⁴	Fluoxetine	Drop outs not reported
Manna <i>et al</i> , 1989 ¹⁰⁵	Fluoxetine	Drop outs not reported
Peselow <i>et al</i> , 1989 ¹⁰⁶	Paroxetine	In Dunbar <i>et al</i> multicentre study ²⁷

TABLE IV—Drop out rates for selective serotonin reuptake inhibitors compared with tricyclic antidepressants

	Serotonin reuptake inhibitors	Tricyclic antidepressants
Total dropouts:		
Total No of patients	3077	2952
No (%) of drop outs	948 (30.8)	986 (33.4)
Risk ratio (95% confidence interval)	0.90 (0.84 to 0.97)**	
Odds ratio (95% confidence interval)	0.87 (0.75 to 1.00)*	
Drop outs due to side effects:		
Total No of patients	2912	2782
No (%) of drop outs	419 (14.4)	522 (18.8)
Risk ratio (95% confidence interval)	0.75 (0.66 to 0.84)***	
Odds ratio (95% confidence interval)	0.68 (0.58 to 0.79)***	
Drop outs due to failure:		
Total No of patients	2786	2660
No (%) of drop outs	204 (7.3)	179 (6.8)
Risk ratio (95% confidence interval)	1.11 (0.91 to 1.36)	
Odds ratio (95% confidence interval)	1.13 (0.90 to 1.42)	

*P=0.065. **P=0.005. ***P<0.001.

effects (table II). The 17 excluded studies are listed in table III.

The ratio of the risks of patients stopping treatment with selective serotonin reuptake inhibitors (number of drop outs divided by number of patients) compared with those stopping tricyclic antidepressants (also referred to as relative risk)¹⁰⁷ was calculated for each group for total drop outs and for those due to side effects and treatment failures. In addition, the ratio of the odds (number of drop outs divided by number of patients completing) was calculated¹⁰⁷ to provide a comparison with results in previous meta-analyses.^{4,7} The complement of the risk ratio (1-risk ratio) gives the relative risk reduction comparing one treatment with another and allows implications to be drawn about drop out rates more easily than the odds ratio.¹⁰⁸ For example, a risk ratio of 0.75 indicates a 25% reduction in risk (1-0.75).

The heterogeneity of the studies was assessed by using Cochran's Q test.¹⁰⁹ No significant heterogeneity was found for total drop outs (Q=68.15; df=56; P=0.13) or for drop outs due to side effects (Q=46.38; df=41; P=0.26) or failure (Q=15.67; df=28; P=0.97), so the risk ratios were pooled by using a fixed effects model.¹⁰⁷ For the odds ratios there was significant heterogeneity for total drop outs (Q=74.60; df=56; P=0.049), so the individual results were pooled by using a random effects model.¹¹⁰ Odds ratios for drop outs due to side effects (Q=48.79; df=41; P=0.19) and failure (Q=15.91; df=28; P=0.97) were not significantly heterogeneous and were pooled by using the fixed effects model. The studies were examined for any significant differences between selective serotonin reuptake inhibitors by the method of Newman-Keuls.¹¹¹ Using this method, we calculated a pooled variance and carried out the possible pairwise comparisons of risk ratios for each type of drop out and adjusted the significance values for the fact that multiple non-independent tests were done. To avoid sampling bias we excluded sertraline and citalopram

from this analysis, as so few studies were available for these drugs.

The extent of publication bias was examined by means of a funnel plot,¹¹² in which sample size was plotted against the natural logarithm of the odds ratio. Large studies, which formed the apex, were less likely to be subject to publication bias than small studies (with a larger scatter of results), which formed the base. Publication bias is likely to cause asymmetry at the base.

Results

More patients taking tricyclic antidepressants dropped out than patients taking selective serotonin reuptake inhibitors, both overall and owing to side effects. In contrast, there was no significant difference in numbers of drop outs due to treatment failure (table IV). Results were similar for the risk and odds ratios, though for total drop outs the 95% confidence interval for the pooled odds ratio just encompassed 1. The pooled risk ratios indicated a 10% reduction in total drop outs (95% confidence interval 3% to 16%) and a 25% reduction in drop outs due to side effects (16% to 34%) when selective serotonin reuptake inhibitors were compared with tricyclic antidepressants. In other words, if we take the average dropout rates suggested by these studies (table IV) 30 of every 100 patients taking tricyclic antidepressants will drop out compared with 27 of every 100 taking selective serotonin reuptake inhibitors (a ratio of 10 to 9). Drop out attributable to side effects will amount to about 20 cases with tricyclic antidepressants compared with 15 with selective serotonin reuptake inhibitors (a ratio of 4 to 3).

The pooled odds ratios for the individual selective serotonin reuptake inhibitors fluvoxamine, fluoxetine, and paroxetine did not vary significantly for total drop outs or for drop outs due to side effects or treatment failure.

The funnel plot of sample size against the natural logarithm of the risk ratio was symmetrical (figure), suggesting that there was little publication bias in the selection of studies.

Discussion

The main finding of this meta-analysis was that tricyclic antidepressants are less well tolerated than selective serotonin reuptake inhibitors, certainly as measured by the fairly crude method of treatment discontinuations. The difference, however, is fairly small (about 10 patients taking tricyclic antidepressants dropping out for every nine taking selective serotonin reuptake inhibitors). The difference between tricyclic antidepressants and selective serotonin reuptake inhibitors was more noticeable for drop outs due to side effects than for total drop outs (about four

Funnel plot of natural logarithm of risk ratio plotted against numbers of patients in study

patients taking tricyclic agents dropping out for every three taking selective serotonin reuptake inhibitors). Though there may be a degree of "attributional" bias (that is, patients who drop out of treatment with tricyclic antidepressants may be more likely to attribute discontinuation to side effects because they are more prominent than with selective serotonin reuptake inhibitors),¹¹³ the difference in drop outs due to side effects seems to account for the overall difference in treatment discontinuations.

Our results fall somewhere between those of previous meta-analyses. In agreement with Montgomery *et al* we found that drop outs due to side effects were significantly fewer with selective serotonin reuptake inhibitors than with tricyclic antidepressants but that when we looked at the reduction in total drop outs the difference was less striking.⁷ Unlike Song *et al*⁴ we found a difference in the total drop out rate, which may be explained by our analysis of tricyclic antidepressants alone and in our larger dataset. The issue of the relative tolerability of second generation antidepressants (included by Song *et al*)⁴ should not be dismissed, particularly as many of these drugs share with the serotonin reuptake inhibitors the property of low toxicity in overdose. However, they are of minor importance clinically in terms of numbers of prescriptions⁹ and, with regard to cost effectiveness analyses, many (for example, lofepramine and trazodone) are nearly as expensive as the serotonin reuptake inhibitors.

RISKS OF BIAS

There are several possible methodological problems with this meta-analysis related to the quality of studies included and possible biases likely to influence outcome. The drop out rates differed widely between studies (from nil to 80% for individual drugs), probably influenced by factors such as patient selection, previous treatment, methodology, and study setting. Whether these biased the results in favour of one class of drug or another is difficult to determine, but arguably this was minimised by our including only double blind, randomised studies in patients with unipolar depression. Nine out of 71 studies did not provide adequate data on total drop outs, but these did not differ discernibly from the rest, so we believe that bias was unlikely from their exclusion. The large number of studies was likely to lessen the effect of random factors.

It could be argued that the total drop out rate in clinical trials is not relevant to everyday practice because of the study conditions and because a proportion of discontinuations are due to protocol violations. Extrapolating from the artificial setting of a trial to clinical practice is always difficult. However, the mean total drop out rate and the proportion of drop outs due to side effects in these studies (table IV) appear comparable to results in general practice, in which total drop out rates of between 30% and 70% have been reported by six weeks, some 30-40% of the drop outs being due to side effects.^{26 27} The results from these clinical trials are therefore arguably a guide to what happens in normal clinical prescribing, though this cannot be assumed.

COST EFFECTIVENESS

An important question is what the difference in drop out rates means for cost effectiveness. In their analysis, Jonsson and Bebbington⁶ used the results from a multicentre trial of paroxetine versus imipramine which found one of the larger differences in drop out rates between antidepressants (20% reduction).⁷⁷ On this basis, and making assumptions about the cost of treatment failure due to drop out and relapse and the cost of alternative treatment, they argued that the

Key messages

- There has been controversy about whether selective serotonin reuptake inhibitors are better tolerated than tricyclic antidepressants in depressive illness
- In a meta-analysis of randomised, short term clinical trials selective serotonin reuptake inhibitors were associated with 10% fewer overall drop outs than tricyclic antidepressants (nine drop outs for every 10 with tricyclic agents)
- This difference was accounted for by a lower rate of drop out related to side effects of selective serotonin reuptake inhibitors (25% reduction; three drop outs for every four with tricyclic agents)
- This comparatively small difference in drop out rate is of uncertain importance clinically and when cost effectiveness is considered
- Further studies of the tolerability of selective serotonin reuptake inhibitors compared with that of tricyclic antidepressants are required over a longer period in the setting of clinical practice rather than clinical trials

selective serotonin reuptake inhibitor cost about the same as imipramine for each patient treated and was cheaper per patient successfully treated.

Jonsson and Bebbington found that their model was fairly robust when they considered a range of costs and drop out rates, but the relative drop out rate suggested by this analysis lies very close to the break even point. Our results indicate that for the 54% drop out rate with tricyclic antidepressants on which they based their analysis, 49% of patients would drop out with selective serotonin reuptake inhibitors. With these figures the tricyclic antidepressant would be a little cheaper per patient treated and a little more expensive per successfully treated patient compared with the selective serotonin reuptake inhibitor (about 5% in each case).⁶ It is not clear what the outcome would be if the lower average drop out rates suggested by our meta-analysis (about 30%) were used.

There was no significant difference between the risk ratios of drop outs for individual selective serotonin reuptake inhibitors when we used a conservative statistical test. The clinical impression of possible differences in tolerability between individual drugs is therefore not supported (but also not ruled out).

Conclusion

In conclusion, this meta-analysis shows that fewer patients discontinue treatment with selective serotonin reuptake inhibitors than with tricyclic antidepressants. This is due to a smaller drop out rate for side effects and probably reflects better tolerability. However, the difference is fairly small and, in purely economic terms in a cost effectiveness analysis, it is uncertain that this will offset the higher prescription costs of selective serotonin reuptake inhibitors. Furthermore, it must be borne in mind that these studies were over a relatively short period whereas the recommended duration of antidepressant treatment is at least four to six months,^{114 115} during which drop out rates may be much higher.^{87 116}

Though the degree of burden from side effects is reportedly associated with non-compliance,²⁷ it is not certain how important a poorer side effect profile is in determining discontinuation in longer term treatment.^{87 116} It must also be remembered that drop out

rates are a crude way to measure tolerability. The true relative side effect burden of the two classes of drugs, which includes quality of life, performance, and accidents,⁷ has not been addressed here.

The contentious issue of the relative cost effectiveness of newer versus older antidepressants remains unresolved, as the outcome of that analysis depends on the assumptions used; a main assumption concerns drop out rates. This meta-analysis should inform that debate. But the next step must be to investigate antidepressants prescribed in clinical practice rather than in clinical trials, with examination of a longer duration of treatment than four to eight weeks, using better measurements than crude drop out rates.

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A PATIENT WHO TAUGHT ME SOMETHING

Bizarre behaviour may not be hysteria

Over four decades ago when I was a senior medical student in Edinburgh we had a young woman with somewhat bizarre complaints on a medical ward. The clinical tutor, also a woman, discussed the patient with a group of us and, fearing that the nearby patient might overhear, said, "It's HYS." I was assigned to the patient and decided to prove that the transient visual symptoms and weakness were psychogenic.

I interviewed my patient at length as well as testing her with Carl Jung's word association list. Before long I was able to write up a psychopathological elucidation of the patient's problems. In brief, I showed that the single state and childlessness of this farm woman in her 30s could explain her symptoms. My write up was enough to impress the professor of medicine Stanley (later Sir Stanley) Davidson.

About six months later I saw the same patient sitting in a medical outpatient waiting room. We greeted each other and she told me why she was there. Recurrent and worsening symptoms had led her local doctor to send her back. This time the

neurological picture was clearly one of multiple sclerosis.

That experience helped me over a lengthy psychiatric career to maintain cautious scepticism when a young woman with vague and transient neurological symptoms was sent to me already diagnosed as "conversion hysteria." Often the apparently hysterical symptoms proved to be early warnings of the dreaded MS.

These memories were stirred up recently when I was asked to see the 31 year old wife of a doctor. In her 20s she had experienced "weird symptoms" with some motor weakness and a tendency to drop things plus inconsistent visual defects which were recurring after a recent pregnancy. Now, of course, we can "look into" the living brain tissue. Magnetic resonance imaging shows the presence of active demyelinating lesions as well as scarring. With her (and other patients since the first one in Edinburgh) my psychiatric task is not to treat hysteria but to help her deal with her emotional reactions to her illness.—JOHN A EWING is emeritus professor of psychiatry, University of North Carolina