Predictive value of pharmacological activity for the relative efficacy of antidepressant drugs

Meta-regression analysis

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Background There is uncertainty about the contribution of specific pharmacological properties to the efficacy of antidepressants.

Aims To assess whether specific pharmacological characteristics of alternative antidepressants resulted in altered efficacy compared to that of selective serotonin reuptake inhibitors in the treatment of major depression.

Method Meta-regression analysis of randomised trials that compare treatment with a selective serotonin reuptake inhibitor and an alternative antidepressant.

Results One-hundred-and-five randomised trials were included. None of the factors identified *a priori* predicted a statistically significant improvement in outcome across the trials.

Conclusions This analysis does not provide evidence that antidepressants acting at more than one pharmacological site differ in efficacy from drugs selective for serotonin reuptake in the treatment of major depression.

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About two-thirds of patients with a depressive disorder respond to antidepressant drugs. This proportion was described in the 1950s at the time it was discovered that monoamine oxidase inhibitors (MAOIs) and imipramine had antidepressant properties (Healy, 1997). In the four decades since, there has been enormous progress in neuroscience. The pharmacology of the first antidepressants is now known in greater detail and we have seen increasing development of new antidepressants with specific, designed pharmacological properties. In spite of these advances, there has been no convincing demonstration that an antidepressant has any greater efficacy than the first serendipitously discovered drugs, although progress has been made in improving side-effects and safety. However, for over a decade it has been recognised that combinations of drugs may be more effective than a single drug: the best combination established is the augmentation of antidepressants with lithium (Austin *et al*, 1991). This suggests that it should be possible to design a drug with more than one pharmacological action, which would be more effective than the selective, single-action drugs. Clinical belief in the greater effectiveness of clomipramine, and recent claims that some drugs, such as venlafaxine (Clerc *et al*, 1994), may be more effective than the selective serotonin reuptake inhibitor (SSRI) fluoxetine, have raised the issue of whether a joint action in inhibiting the reuptake of both 5-hydroxytryptamine (serotonin, 5-HT) and noradrenaline may confer added benefit. This has also been suggested by open studies of combined treatment with an SSRI and a tricyclic antidepressant (TCA) (Nelson *et al*, 1991). Systematic reviews, using different methodologies, seeking to find out whether some antidepressants may be more effective than SSRIs, have reached differing conclusions. One overview of the effectiveness of various antidepressant drugs found statistical heterogeneity (systematic differences between studies) in treatment effects estimated in different studies, but not significant benefit for any one agent compared with others (Geddes *et al*, 2000). Other systematic reviews have suggested that SSRIs may be less effective than amitriptyline (Anderson, 2000), TCAs (in in-patients) (Anderson, 1998) and venlafaxine (Rudolph *et al*, 1998).

One way to address these discrepancies is to ask whether particular pharmacological properties or their combination might increase efficacy. We used an extension of traditional meta-analytic methods – meta-regression – which provides a robust new way of exploring the factors which could explain differences between treatments. In addition, other potentially confounding factors which may affect relative efficacy were investigated.

METHOD

Objective

Our primary objective was to examine the predictive value of different pharmacological action for antidepressant drugs, singly and in combination, on outcome. The factors studied were noradrenaline reuptake inhibition, serotonin (5-HT) reuptake inhibition and 5-HT_2 receptor antagonism. They were chosen because they have all, independently, been associated with antidepressant activity in specific drugs.

The important structural factors examined were: treatment setting (in-patient *v.* out-patient or family practice); dose of comparator (high *v.* low dose, based on the *British National Formulary* (British Medical Association & Royal Pharmaceutical Society of Great Britain, 1997), with a daily dose of <100 mg of most comparators defined as a low dose, apart from 75 mg for nortriptyline and venlafaxine, 45 mg for mianserin, 150 mg for trazodone, 200 mg for nefazodone); method of analysis (last observation carried forward *v.* end-point analysis); age of patients (defined as over 65 or of mixed age); measurement scale used (either Hamilton Rating Scale for Depression (Hamilton, 1960) or alternative scale); sponsor of the trial (where not stated, taken as SSRIs in comparisons with TCAs and older antidepressants, and the comparator in studies against drugs marketed since SSRIs).

Data-set and included trials

We analysed all available double-blind randomised trials which compared treatment of depression with an SSRI and with an alternative antidepressant drug that had a primary effect on 5-HT and/or noradrenaline reuptake and/or 5-HT_2 antagonism. This data-set was chosen because it provides a large group of studies of antidepressants with a well-defined single pharmacological action (5-HT reuptake inhibition). Eligible trials had to include adult or elderly patients with a major depressive episode for which relevant data were available. As SSRIs are a relatively homogeneous group in terms of pharmacological action, the planned comparisons enabled us to examine the relative efficacy of other antidepressants with different single and combined sites of action against a common standard. Given the increasing pre-eminence of SSRIs in first-line treatment of depressive illness, this is also relevant to current practice.

Classification of drugs

Pharmacological classification of drugs was undertaken using the best available evidence. There are considerable difficulties in doing this, including availability of data in humans (species differences may be important), extrapolation from binding or *in vitro* data to activity *in vivo* (including the threshold at which an action becomes important) and the effect of metabolites. The classification used is described in Table 1 and is based, as far as possible, on recently available human binding data. Some generally accepted assumptions appeared less than well founded, from the available data, and there was uncertainty about the classification of some drugs. With regard to 5-HT reuptake inhibition, some drugs traditionally regarded, on the basis of studies in rats, as having minimal activity (especially dothiepin, but also nortriptyline and desipramine) may in fact have a significant degree of affinity for the human 5-HT transporter (Tatsumi *et al*, 1997). In the case of desipramine and nortriptyline, dynamic studies in transfected cells or human platelets found low activity (Lingjaerde, 1985; Barker & Blakely, 1995), but uncertainty remains about dothiepin. Trazodone and nefazodone are sometimes described as 5-HT reuptake inhibitors, but both animal and human data suggest low affinity for, and activity at, the 5-HT transporter (Richelson & Pfenning, 1984; Lingjaerde, 1985; Tatsumi *et al*, 1997). With regard to noradrenaline reuptake inhibition, the main uncertainty centred on venlafaxine, marketed as having both 5-HT and noradrenaline activity. However, the most comprehensive animal and human data indicate that it has low affinity for the noradrenaline transporter (Bolden-Watson & Richelson, 1993; Tatsumi *et al*, 1997) and human functional data suggest that inhibition of noradrenaline reuptake only occurs at higher doses (Abdelmawla *et al*, 1999). Concerning antagonism of human 5-HT_2 receptors, there is some uncertainty about the activity of clomipramine, which shows relatively low binding in animal studies (Pälvimäki *et al*, 1996), higher affinity in the human brain (Wander *et al*, 1986), but intermediate binding and activity in platelets (Ohsuka *et al*, 1995), raising uncertainty as to its effect *in vivo*, particularly at lower doses. The implication of this uncertainty was assessed in each case through a sensitivity analysis in which the initial classification excluded borderline properties, but separate analyses were performed in which they were included.

Table 1 Selected pharmacological action of antidepressants in humans

	5-HT reuptake	Noradrenaline reuptake	5-HT_2 antagonism
Tricyclic antidepressants			
Amitriptyline	+	+	+
Clomipramine	+	+	?
Desipramine	–	+	–
Dothiepin	?	+	–
Doxepin	–	+	+
Imipramine	+	+	–
Lofepramine	–	+	–
Nortriptyline	–	+	+
Selective serotonin reuptake inhibitors			
Citalopram	+	–	–
Fluoxetine	+	–	–
Fluvoxamine	+	–	–
Paroxetine	+	–	–
Sertraline	+	–	–
Others			
Amoxapine	–	+	+
Buproprion	–	–	–
Maprotiline	–	+	–
Mianserin	–	–	+
Nefazodone	–	–	+
Nomifensine	–	+	–
Trazodone	–	–	+
Venlafaxine	+	?	–

+, Likely to have significant action *in vivo*; –, unlikely to have significant action *in vivo*; ?, uncertain whether has significant action *in vivo* (see text for discussion of uncertainty for particular antidepressants).
Data based principally on Tatsumi *et al* (1997) (human transporter binding) and Cusack *et al* (1994) (human 5-HT_2 binding).

Search strategy

We undertook an optimally sensitive electronic search for randomised trials meeting our entry criteria. We searched Medline (1966–1997 via OVID) and EMBASE (1974–1997 via DIALOG) and reviewed the reference list of each identified study. Existing bibliographies and reviews for relevant studies were also examined.

Data abstraction

For each study located, data on main outcome were abstracted. The Hamilton Depression Rating Scale (Hamilton, 1960) was the preferred outcome scale, but where this was not available the Montgomery–Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979), or the Clinical Global Impression Scale (Guy, 1976) were

abstracted. Where data were not available in published reports, we routinely contacted the principal author and, where necessary, the sponsor of the study, to request data.

Data synthesis

Standardised effect sizes for each arm of included trials were estimated from the data, using the final rating scale score and the pooled estimate of study variance as described by Hedges & Olkin (1985). The use of an effect size has the advantage of standardising the scores from different studies, which may adopt differing approaches to assessing treatment effect, on a common and thus comparable scale.

We used a meta-regression technique to examine the extent to which the value of individual factors such as specific pharmacological properties predicted a positive outcome in the trials. We have taken a similar approach in other meta-regression analyses (Davis *et al*, 1999; Freemantle *et al*, 1999). BUGS software, described by Smith *et al* (1995), was used to specify the statistical model that attempted to explain variation in the results of different studies on the basis of a range of potentially important factors. This approach is analogous to standard regression analysis, but takes into account the fact that study results are *estimated* with measurement error (described by the confidence intervals), rather than known. The covariate terms for each factor applied to the model are multipliers which describe the positive or negative impact of different factors on the observed results. Where the estimated effect of a factor is not significantly different from zero, it does not contribute to an understanding of the differences in observed results, and so is not considered further in the analysis.

The statistical methods applied in this analysis have been developed relatively recently and are the subject of considerable interest. Further details of the general approach are available in the excellent introductory text by Gilks *et al* (1996) and details of the software are available from http://www.mrc-bsu.cam.ac.uk/bugs/.

RESULTS

In total, 105 trials comparing SSRIs with alternative antidepressant drugs were included. These trials looked at 11 537 patients – 5937 treated with an SSRI contrasted with 5600 treated with an alternative antidepressant drug. The most commonly used SSRI was fluoxetine, while the most commonly used alternative was amitriptyline. Trials of five SSRIs and 12 comparator drugs were identified. The major characteristics of each trial included are described in Table 2.

The predictive value of each factor was assessed in turn. None of the factors achieved a statistically significant predictive effect upon outcome and thus all coefficients reflect the predictive value of a factor alone in the model. As expected, 5-HT reuptake inhibition on its own did not predict any difference in efficacy; the coefficient was −0.003 (95% CI −0.064 to 0.048). For the presence of activity on noradrenaline reuptake, the coefficient was 0.006 (95% CI −0.042 to 0.082). The coefficients examining the predictive value of $5HT_2$ antagonism did not predict the outcome in the included trials (see Table 3 and Fig. 1).

We also examined the predictive value of the presence of dual action (5-HT and noradrenaline reuptake inhibition) and triple action (dual action plus 5-HT_2 antagonism) on the model. Neither predicted an increase in effectiveness.

None of the identified structural factors that may have confounded the results of the analyses had statistically significant predictive value and, perhaps surprisingly, the dose of the comparator had no influence, with the results being particularly precise (very narrow confidence interval). The most important structural predictor of outcome was trial sponsorship, which demonstrated a trend towards increased efficacy of the sponsor's drug, although this did not reach statistical significance.

DISCUSSION

We have shown that, in this data-set, there is no evidence to support the increased efficacy of specific combinations of actions at 5-HT and noradrenaline transporter and 5-HT_2 receptor sites, compared to a single action in inhibiting the reuptake of 5-HT. The results of our review suggest that great caution needs to be taken in ascribing any possible efficacy advantages of particular antidepressants over SSRIs to acute pharmacological properties.

Scope

We did not examine the efficacy of MAOIs, moclobemide or mirtazapine because their actions to increase 5-HT and noradrenaline function, while presynaptic, cannot be compared directly with single or dual action reuptake inhibition. Neither did we examine effects at other receptors, based on the principle of limiting the analysis to factors for which there is evidence of involvement in antidepressant efficacy. Our results indicate that the argument that a dual action (in inhibiting 5-HT and noradrenaline reuptake) could account for the results of selected trials in which superior efficacy is shown by one drug over another should be accepted with caution, and emphasise the difficulty in establishing the superiority of one antidepressant over another in studies such as these. The term 'dual action' has become a marketing concept for a number of antidepressants, and this study raises the question as to whether it has a legitimate scientific basis, in considering mechanisms behind antidepressant efficacy.

The role of 5-HT_2 receptor antagonism in antidepressant action is unclear, but is suggested because it is the principal pharmacological property of the antidepressants trazodone and nefazodone. The picture is further complicated by the differentiation of this receptor into 5-HT_{2A} and 5-HT_{2C} subtypes. Our analysis is based on antagonism of the 5-HT_{2A} subtype, and there is a lack of good data on the binding of antidepressants to the human 5-HT_{2C} receptor. Animal studies suggest that most, but not all, antidepressants bind with similar affinity to the two subtypes (Pälvimäki *et al*, 1996). However, this analysis has not made a specific examination of the role of 5-HT_{2C} receptor antagonism.

Issues in the analysis of the data

Our findings show that appropriate meta-regression techniques can be useful in examining the importance of different factors across a range of trials examining a common goal, but differing in potentially important characteristics. Standard ordinary least-squares regression is inadequate in an analysis such as this, as the method assumes that the observed outcomes in the trials (the estimate of the size of effect) are the true outcomes. It is important to recognise that the outcomes in clinical trials involve considerable uncertainty,

Table 2 Major characteristics of included trials (references are listed in the Appendix)

Trial	Effect size	Number in comparator group	Number in treatment group	SSRI	Comparator	Setting	Age	Methods	Scale	Active treatment (weeks)	Dose of SSRI	Dose of comparator
Ahlfors *et al*, 1988	0.63	34	37	Citalopram	Mianserin	Out-patients/family practice	Adult	End-point	MADRS	4	38.6	61.1
Amin *et al*, 1984	−0.11	106	105	Fluvoxamine	Imipramine	Out-patients/family practice	Adult	LOCF	HAM–D	6	155	156
Arminen *et al*, 1982	−0.30	29	21	Paroxetine	Imipramine	In-patients	Adult	End-point	HAM–D	12	20–40	100–200
Baker *et al*, 1997	0.01	19	20	Fluoxetine	Doxepin	Out-patients	Adult	End-point	HAM–D	6	97	169
Baldwin *et al*, 1996	−0.08	100	95	Paroxetine	Nefazodone	Out-patients	Adult	LOCF	HAM–D	8	32.7	472
Battegay *et al*, 1985	0.10	6	8	Paroxetine	Amitriptyline	Out-patients	Adult	LOCF	HAM–D	6	30	75
Beasley *et al*, 1991	0.11	57	63	Fluoxetine	Trazodone	Out-patients	Adult	LOCF	HAM–D	6	20.9	244.1
Beasley *et al*, 1993a	0.47	60	54	Fluoxetine	Imipramine	In-patients	Adult	LOCF	HAM–D	6	72	192
Beasley *et al*, 1993b	−0.08	71	65	Fluoxetine	Amitriptyline	Out-patients	Adult	LOCF	HAM–D	5	65.2	201.4
Berlanga *et al*, 1997	−0.17	36	37	Fluoxetine	Nefazodone	Out-patients	Adult	LOCF	HAM–D	8	24.0	400.0
Bersani *et al*, 1994	0.00	30	31	Sertraline	Amitriptyline	Out-patients	Adult	End-point	HAM–D	8	88	84
Besançon *et al*, 1993	0.63	32	33	Fluoxetine	Mianserin	Out-patients	Adult	End-point	MADRS	8	26.7	72
Bouchard *et al*, 1987	0.01	34	39	Citalopram	Maprotiline	In-patients	Adult	End-point	MADRS	4	46	101
Bramanti *et al*, 1988	0.58	29	28	Fluvoxamine	Imipramine	Not clear	Adult	LOCF	HAM–D	4	100–120	100–135
Bremner, 1984	−1.32	19	16	Fluoxetine	Imipramine	Out-patients	Adult	End-point	CGI	5	60	175–200
Byerley *et al*, 1988	−0.11	24	20	Fluoxetine	Imipramine	Out-patients	Adult	End-point	HAM–D	6	40–80	150–300
Christiansen *et al*, 1996	0.20	57	56	Paroxetine	Amitriptyline	Family practice	Adult	End-point	HAM–D	8	28.1	112.7
Clerc *et al*, 1994	0.58	33	34	Fluoxetine	Venlafaxine	In-patients	Adult	LOCF	HAM–D	6	40	200
Cohn & Wilcox, 1984	0.02	31	35	Fluoxetine	Imipramine	Out-patients	Adult	End-point	HAM–D	6		
Cohn, C. K. *et al*, 1990	−0.07	64	121	Sertraline	Amitriptyline	Out-patients	Elderly	End-point	HAM–D	8	116.2	88.3
Cohn, J. B. *et al*, 1990	0.24	31	35	Paroxetine	Imipramine	Out-patients	Adult	End-point	HAM–D	6	65	275
Corne & Hall, 1989	0.42	44	34	Fluoxetine	Dothiepin	Family practice	Adult	End-pont	HAM–D	8	40±	75±
Dalery *et al*, 1992	0.09	68	73	Fluoxetine	Amineptine	Out-patients	Adult	End-point	MADRS	13	20	200
Danish University, 1990	0.65	36	34	Paroxetine	Clomipramine	In-patients	Adult	End-point	HAM–D	6	30	150
de Jonghe *et al*, 1991*a*	0.33	34	28	Fluoxetine	Maprotiline	In-patients	Adult	End-point	HAM–D	6	40–80	50–150
de Jonghe *et al*, 1991*b*	−0.01	21	21	Fluvoxamine	Maprotiline	Out-patients	Adult	End-point	HAM–D	6	100–300	50–150
De Mendonça Lima, 1997	−0.02	20	20	Fluvoxamine	Maprotiline	In-patients	Adult	End-point	MADRS	4	100	75
De Wilde *et al*, 1983	−0.42	15	15	Fluvoxamine	Clomipramine	Out-patients	Adult	End-point	HAM–D	4	259	231
De Wilde *et al*, 1985	−0.44	29	29	Citalopram	Mianserin	In-patients	Adult	LOCF	CGI	6	53.1	94.1
Dick & Ferro, 1983	0.30	13	13	Fluvoxamine	Clomipramine	In-patients	Adult	End-point	HAM–D	4	130.9	132.8
Dominguez *et al*, 1985	−0.26	19	16	Fluvoxamine	Imipramine	Out-patients	Adult	End-point	CGI	4	100–300	100–300
Dorman, 1992	−0.68	25	24	Paroxetine	Mianserin	Out-patients	Elderly	End-point	HAM–D	6	15–30	30–60
Fabre, 1996	−0.62	48	46	Fluvoxamine	Imipramine	Out-patients	Adult	LOCF	HAM–D	6	117	180
Falk *et al*, 1989	−0.75	12	13	Fluoxetine	Trazodone	Out-patients	Elderly	LOCF	HAM–D	6	48	350

(continued)

Table 2 *(continued)*

Trial	Effect size	Number in comparator group	Number in treatment group	SSRI	Comparator	Setting	Age	Methods	Scale	Active treatment (weeks)	Dose of SSRI	Dose of comparator
Feighner *et al*, 1989	0.18	45	52	Fluoxetine	Imipramine	Out-patients	Adult	End-point	HAM–D	6	NA	NA
Fudge *et al*, 1990	0.26	15	17	Fluoxetine	Trazodone	Out-patients	Adult	End-point	HAM–D	6	20–60	50–400
Geretsegger *et al*, 1995	−0.19	31	28	Paroxetine	Amitriptyline	In-patients	Elderly	End-point	HAM–D	6	22.7	109.6
Ginestet, 1989	0.89	26	28	Fluoxetine	Clomipramine	In-patients	Elderly	Not clear	HAM–D	8	58	148
Gonella *et al*, 1990	−0.22	20	20	Fluvoxamine	Imipramine	Out-patients	Adult	LOCF	HAM–D	4	140	130
Gravem *et al*, 1987	−0.27	14	12	Citalopram	Amitriptyline	Out-patients/Family practice	Adult	End-point	CGI	6	36.1905	161.84211
Guelfi *et al*, 1983	−0.24	68	59	Fluvoxamine	Imipramine	In-patients	Not clear	End-point	HAM–D	4	221	112
Guillibert *et al*, 1989	0.03	39	40	Paroxetine	Clomipramine	Out-patients	Elderly	Not clear	HAM–D	6	30	75
Harris *et al*, 1991	0.63	26	24	Fluvoxamine	Amitriptyline	Out-patients	Adult	Not Clear	HAM–D	6	100–150	100–150
Hutchinson, 1992	0.00	21	46	Paroxetine	Amitriptyline	Family practice	Elderly	End-point	HAM–D	6	30	100
Itil *et al*, 1983	0.31	14	9	Fluvoxamine	Imipramine	Out-patients	Adult	End-point	HAM–D	4	101	127
Judd *et al*, 1993	−0.33	23	23	Fluoxetine	Amitriptyline	Out-patients/Family practice	Adult	End-point	HAM–D	6	20	176
Kasper *et al*, 1990	0.05	20	21	Fluvoxamine	Maprotiline	In-patients	Adult	LOCF	HAM–D	4	229	236
Kasper *et al*, 1995	−0.11	106	105	Fluvoxamine	Imipramine	Out-patients/Family practice	Adult	End-point	HAM–D	4	50–300	50–300
Kerkhofs *et al*, 1990	−0.25	10	9	Fluoxetine	Amitriptyline	In-patients	Adult	End-point	HAM–D	6	60	150
Klok *et al*, 1981	0.36	15	13	Fluvoxamine	Clomipramine	In-patients	Adult	End-point	HAM–D	4	150	150
Kuhs & Rudolf, 1989	0.08	17	14	Paroxetine	Amitriptyline	In-patients	Adult	End-point	HAM–D	6	30	150
La Pia *et al*, 1992	−0.31	16	19	Fluoxetine	Mianserin	Out-patients/Family practice	Elderly	End-point	HAM–D	6	20	40
Laakmann *et al*, 1988	0.53	46	39	Fluoxetine	Amitriptyline	Out-patients	Adult	End-point	HAM–D	5	20–60	50–150
Laakmann, 1991	0.02	62	62	Fluoxetine	Amitriptyline	In-patients	Adult	End-point	HAM–D	6	40	100
Lapierre *et al*, 1987	−1.17	2	7	Fluvoxamine	Imipramine	In-patients	Adult	End-point	HAM–D	6	207.1	191.7
Laursen *et al*, 1985	0.07	14	16	Paroxetine	Amitriptyline	In-patients	Adult	End-point	HAM–D	6	38.75	160.71429
Lydiard *et al*, 1989	0.31	15	17	Fluvoxamine	Imipramine	Out-patients	Adult	End-point	HAM–D	6	240	180
Lydiard *et al*, 1997	0.16	104	119	Sertraline	Amitriptyline	Out-patients	Adult	LOCF	HAM–D	8	90.8	91.3
Manna *et al*, 1989	−0.30	15	15	Fluoxetine	Clomipramine	In-patients	Adult	LOCF	HAM–D	6	20	75
Mertens & Pintens, 1988	−0.39	31	36	Paroxetine	Mianserin	In-patients	Adult	LOCF	HAM–D	6	30	60
Moller *et al*, 1993	0.30	68	72	Paroxetine	Amitriptyline	In-patients	Not clear	End-point	HAM–D	6	30	150
Muijen *et al*, 1988	−0.45	14	14	Fluoxetine	Mianserin	Out-patients	Adult	End-point	HAM–D	6	60–80	60–80
Mullin *et al*, 1988	−0.04	24	26	Fluvoxamine	Dothiepin	Out-patients	Adult	End-point	HAM–D	6	100–300	75–225
Nathan *et al*, 1990	−0.08	18	17	Fluvoxamine	Desipramine	In-patients	Adult	Not clear	HAM–D	4	203	206
Nielsen *et al*, 1991	0.00	12	11	Paroxetine	Imipramine	Not clear	Adult	End-point	HAM–D	4	30	150
Noguera *et al*, 1991	−0.35	60	60	Fluoxetine	Clomipramine	Out-patients	Adult	LOCF	HAM–D	6	40	100
Norton *et al*, 1984	0.02	30	33	Fluvoxamine	Imipramine	Out-patients	Adult	End-point	HAM–D	4	132.8	153.3
Ohrberg *et al*, 1992	−0.07	59	61	Paroxetine	Imipramine	Out-patients	Adult	End-point	HAM–D	6	32.2973	166.88312
Ottevanger, 1995	0.12	20	20	Fluvoxamine	Clomipramine	In-patients	Adult	LOCF	HAM–D	4	204	106

(continued)

Table 2 *(continued)*

Trial	Effect size	Number in comparator group	Number in treatment group	SSRI	Comparator	Setting	Age	Methods	Scale	Active treatment (weeks)	Dose of SSRI	Dose of comparator
Pakesch & Dossenbach, 1991	0.01	48	91	Fluoxetine	Clomipramine	Out-patients	Adult	LOCF	HAM–D	4	30.1	50
Peters *et al*, 1990	0.13	41	40	Fluoxetine	Amitriptyline	Out-patients	Adult	End-point	HAM–D	5	20	100
Phanjoo *et al*, 1991	0.35	15	16	Fluvoxamine	Mianserin	Out-patients/family practice	Elderly	End-point	MADRS	6	170	60
Poelinger & Haber, 1989	−0.25	69	73	Fluoxetine	Maprotiline	Out-patients/family practice	Adult	LOCF	HAM–D	4	NA	NA
Rahman *et al*, 1991	0.13	19	17	Fluvoxamine	Dothiepin	In-patients	Elderly	End-point	MADRS	6	157	159
Ravindran *et al*, 1995	0.16	30	34	Sertraline	Desipramine	Out-patients	Adult	End-point	HAM–D	8	50–200	50–225
Ravindran *et al*, 1997	−0.02	502	500	Paroxetine	Clomipramine	Family practice	Adult	LOCF	MADRS	8	28.2	99.75
Reimherr *et al*, 1990	0.13	144	142	Sertraline	Amitriptyline	Out-patients	Adult	LOCF	HAM–D	8	145	104
Remick *et al*, 1993	0.82	15	24	Fluoxetine	Desipramine	Out-patients/family practice	Adult	End-point	HAM–D	6		
Remick *et al*, 1994	−0.10	17	16	Fluvoxamine	Amitriptyline	Out-patients	Adult	LOCF	HAM–D	7	175	135
Robertson *et al*, 1994	0.13	77	76	Fluoxetine	Lofepramine	Out-patients/family practice	Adult	LOCF	HAM–D	6	20	140–210
Ropert, 1989	−0.29	48	55	Fluoxetine	Clomipramine	Out-patients	Adult	End-point	HAM–D	6	20	75
Rosenberg *et al*, 1994	−0.02	85	187	Citalopram	Imipramine	Family practice	Adult	LOCF	HAM–D	6	25	120
Rosenberg *et al*, 1994	0.00	85	193	Citalopram	Imipramine	Family practice	Adult	LOCF	HAM–D	6	48	120
Roth *et al*, 1990	−0.13	24	27	Fluvoxamine	Desipramine	Out-patients	Adult	End-point	HAM–D	6	218.2	224.6
Rush *et al*, 1998	0.03	62	60	Fluoxetine	Nefazodone	Out-patients	Adult	LOCF	HAM–D	8	20	200
Schnyder & Koller-Leiser, 1996	0.09	34	37	Paroxetine	Maprotiline	Out-patients/family practice	Adult	LOCF	HAM–D	4	32.2	107.4
Shaw *et al*, 1986	−0.08	20	24	Citalopram	Amitriptyline	Out-patients/family practice	Adult	LOCF	HAM–D	6	46	148
South Wales Antidepressant Drug Trial Group, 1988	−0.06	21	16	Fluoxetine	Dothiepin	Out-patients/family practice	Adult	End-point	HAM–D	6	67	172
Staner *et al*, 1995	0.72	19	21	Paroxetine	Amitriptyline	In-patients	Adult	LOCF	HAM–D	5	30	150
Stark & Hardison, 1985	0.03	186	185	Fluoxetine	Imipramine	Out-patients	Adult	LOCF	HAM–D	6	69.2	219.1
Stott *et al*, 1993	−0.01	262	243	Paroxetine	Amitriptyline	Family practice	Adult	Not clear	MADRS	8	20	75
Stratta *et al*, 1991	−0.04	9	14	Fluoxetine	Imipramine	Not clear	Adult	End-point	HAM–D	6	20	NA
Stuppaeck *et al*, 1994	−0.05	66	68	Paroxetine	Amitriptyline	In-patients	Adult	End-point	HAM–D	6	33.3	166
Szegedi *et al*, 1997	−0.01	260	257	Paroxetine	Maprotiline	Out-patients	Adult	LOCF	HAM–D	6	35.3	109.9
Timmerman *et al*, 1987	0.20	13	14	Citalopram	Maprotiline	In-patients	Adult	End-point	HAM–D	4	40–60	75–150
Tollefson *et al*, 1994	−0.08	62	62	Fluoxetine	Imipramine	Out-patients	Adult	LOCF	HAM–D	8	43	165
Tylée *et al*, 1997	−0.11	147	156	Fluoxetine	Venlafaxine	Family practice	Adult	LOCF	HAM–D	12	20	75
Unpublished, 1998*a*[1]	0.34	75	80	Paroxetine	Venlafaxine	Out-patients	Adult	LOCF	HAM–D	12	20	150
Unpublished, 1998*b*[1]	0.45	82	80	Paroxetine	Venlafaxine	Out-patients	Adult	LOCF	HAM–D	12	20	75
Unpublished, 1998*c*[1]	0.10	175	161	Paroxetine	Venlafaxine	Family practice	Adult	LOCF	HAM–D	12	20	75
Unpublished, 1998*d*[1]	0.20	44	52	Paroxetine	Venlafaxine	Out-patients/family practice	Adult	LOCF	HAM–D	6	36.3	269
Unpublished, 1998*e*[1]	0.02	196	186	Fluoxetine	Venlafaxine	Out-patients	Adult	LOCF	HAM–D	8	20–40	75–150
Unpublished, 1998*f*[1]	0.21	95	103	Fluoxetine	Venlafaxine	Out-patients	Adult	LOCF	HAM–D	8	20–40	75–150
Unpublished, 1998*g*[1]	0.06	122	119	Fluoxetine	Venlafaxine	Out-patients	Adult	LOCF	HAM–D	12	39.9	140.8
Young *et al*, 1987	0.11	25	25	Fluoxetine	Amitriptyline	Out-patients	Adult	End-point	HAM–D	6	73	122

1. Details available from the first author upon request.
SSRI, selective serotonin reuptake inhibitor; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; HAM–D, Hamilton Rating Scale for Depression; CGI, Clinical Global Impression scale.

Table 3 Predictive effects of pharmacological action and other study factors

Covariate	Coefficient	95% Credibility limits	
		Lower limit	Upper limit
Dual action	0.011	−0.025	0.096
Dual action (sensitivity)	−0.007	−0.086	0.034
Triple action	−0.05	−0.172	0.067
Triple action (sensitivity)	−0.040	−0.15	0.065
Noradrenaline reuptake	0.006	−0.042	0.082
Noradrenaline reuptake (sensitivity)	−0.016	−0.134	0.039
5HT reuptake	−0.003	−0.064	0.048
5HT reuptake (sensitivity)	−0.006	−0.070	0.033
$5HT_2$ antagonism	−0.001	−0.060	0.055
$5HT_2$ antagonism (sensitivity)	0.002	−0.042	0.057
Setting	−0.069	−0.176	0.041
Age	0.080	−0.113	0.28
Method	0.032	−0.065	0.13
Scale	−0.049	−0.175	0.088
Dose	0	>0.0010	<0.001
Funding	0.097	−0.03	0.23

See footnotes to Fig. 1 for explanation of the direction of effect of coefficients.

and that standard statistical techniques would fail to include an adequate estimate of measurement error.

Each of the factors was entered individually in the analysis, and only if a significant predictive effect had been found would its influence on other factors have been examined. A potential limitation of our study is that factors without a uniform influence on outcome could have been missed. For instance, the effect of in-patient treatment setting could be to favour one group of comparators but disadvantage others, giving no overall effect. Addressing this type of limitation requires strong *a priori* hypotheses, such as that for the category of 'dual action', and goes beyond this analysis.

The pharmacological classification of antidepressants we used needs comment. A difficulty permeating our analysis, and relatively unrecognised, is how limited our knowledge of even the acute pharmacology of antidepressants remains. Commonly held views about the pharmacology of antidepressants, at least *in vivo*, and in humans, probably go beyond the evidence. We are uncertain about whether many of the putative pharmacological properties of drugs are translated into effects in the human brain for many reasons, including continuing advances in our understanding of how neurotransmission may be modified, the lack of true selectivity of drugs (including the action of metabolites), lack of knowledge of the pharmacology of drugs in humans as opposed to other animals, and ignorance about neuronal concentrations of drugs and their metabolites at doses employed clinically. This suggests that the scientific question of whether particular putative actions or combinations of putative actions of drugs may relate to efficacy still awaits better understanding of what the actions really are. We have tried to use the best data available, including those obtained in experiments with human tissues, but these are relatively limited. Uncertainties about the classification of some drugs are inevitable, and for some there is evidence of a dose relationship across the doses used in the studies, which could not easily be accounted for in the analysis (for example, noradrenaline reuptake inhibition occurring only at a higher venlafaxine dose). A final important point is the recognition that the acute effects of antidepressants do not directly account for antidepressant action, which is believed to be due to secondary changes arising as a consequence of the primary effects. The acute pharmacology, even if it can be known, therefore stands as a crude proxy for as yet unknown changes that are crucial for antidepressant action. It is quite possible that it is not simply the presence or absence of an acute pharmacological effect but the balance between different ones that is important in determining later changes and, finally, response to antidepressants.

Quality of data

Our data-set is both large and systematically assembled, which means that the power to detect significant effects is high and that bias is minimised, although in interpreting our results it is important to recognise the limitations inherent in the data. The quality of the trials was variable and likely to have added 'noise' to the results. In addition, there is uncertainty about optimum doses for the comparators in relation to SSRIs, which will influence the analysis of dose; this may be particularly true for the comparator drugs in which there is uncertainty about pharmacological activity at specific sites, as discussed above. In our model there was strong evidence that the dose of comparator antidepressant had no effect on the relative effectiveness compared with that of an SSRI. Hence we believe it is unlikely that a major effect attributable to the chosen pharmacological actions, singly or in combination, has been obscured in the data, although we cannot exclude an effect of dose for some individual drugs or an interaction between factors. For example, as discussed above, drugs such as venlafaxine may cross from single to dual reuptake inhibition with increasing dose.

Most studies involved TCAs, and the lack of effect of dose on efficacy potentially adds to the debate about the supposed dangers of 'subtherapeutic' prescribing of TCAs, which has been seen as a factor influencing choice between antidepressants (Donaghue & Tylee, 1996). In clinical practice, it is not uncommon to see individual patients, often with more severe illness, whose depression only responds to higher doses of TCAs. The evidence that this is generally true is extremely limited (Blashki *et al*, 1971; Thompson & Thompson, 1989) and should not be accepted uncritically. The trials included in this analysis were not designed to look at the effect of dose, and differed as to whether a fixed or variable dose was employed. Nevertheless, not only was no effect of dose on relative efficacy detected, but the precision of the estimate was extremely high, making it very unlikely that a true effect was obscured, taking the cut-off between high and low dose that we employed. As nearly all 'low-dose' studies used TCA doses of 75 mg or above, this

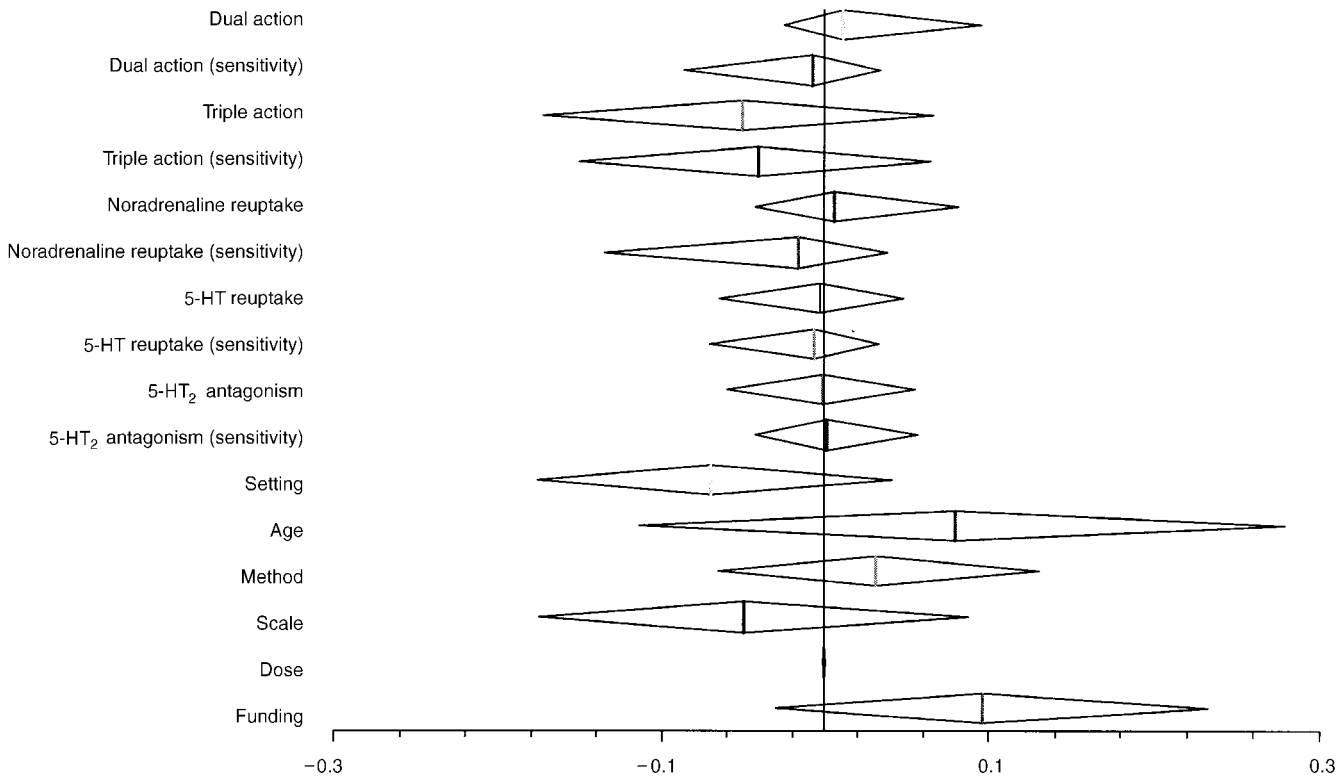

Fig. 1 Coefficient values for predictive value of receptor site activity.

For each coefficient described, the vertical line describes the point estimate of effect, and the diamond describes the limits of the 95% confidence intervals. The approach to estimation does not force assumptions of symmetry for confidence intervals. For pharmacological activity, a coefficient value less than zero implies an advantage for the presence of the factor described.

For the structural factors examined:

Setting: a positive value would suggest an increased efficacy for selective serotonin reuptake inhibitors (SSRIs) in in-patients

Age: a positive value would imply an increased efficacy for SSRIs where only those over 65 years are included

Method: a positive value would imply an increased efficacy for SSRIs in studies that used last observation carried forward instead of end-point analysis

Scale: a positive value would imply an advantage for SSRIs where the Hamilton Depression Rating Scale was used

Dose: a positive result would imply an advantage for SSRIs when a higher dose comparator was used

Funding: a positive result would imply an advantage for the sponsor's drug.

suggests that one needs to keep an open mind about whether the minimum therapeutic dose of TCAs may be 75 mg or below in populations such as these.

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APPENDIX – REPORTS OF TRIALS INCLUDED IN THE META-ANALYSIS

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CLINICAL IMPLICATIONS

- Currently, there is uncertainty about whether some antidepressants display superior efficacy.
- In our present state of knowledge of the pharmacology of individual drugs, there does not seem to be a simple relationship between acute pharmacological properties and efficacy.
- When choosing antidepressants on the basis of efficacy, clinicians should consider the properties of individual drugs rather than make assumptions about efficacy based on their acute pharmacological actions. Safety, tolerability and patients' preference are likely to be more important for most patients.

LIMITATIONS

- Differences in the reporting of outcomes between studies require standardisation of many outcomes, resulting in a reduction in interpretation of the practical importance of the results.
- Data on the relative effectiveness of different antidepressants remain limited for individual agents.
- Our knowledge of the acute pharmacology of individual antidepressants in humans is limited; this is even more true of the secondary effects believed to underlie the antidepressant action.

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