



## Treatment of depression with atypical features: A meta-analytic approach

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### Abstract

The present meta-analysis addressed the empirical evidence regarding the treatment of major depression with atypical features. The superiority of monoamine oxidase inhibitors (MAOIs) compared with other antidepressants in the treatment of major depression with atypical features has been frequently reported. According to the CONSORT Statement, studies included in our meta-analysis had to meet several criteria, especially a double-blind, controlled condition and an operational diagnosis according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-III or DSM-IV criteria, respectively. Four databases for research-based evidence were used in a systematic review: Medline, Embase, Psynex and PsycInfo. Only eight publications met inclusion/exclusion criteria, resulting in 11 comparisons. Our results contrast an effect size of 0.45 (95% confidence interval) for a comparison of MAOIs vs. placebo with an effect size of 0.02 (95% confidence interval:  $-0.10-0.14$ ) for a comparison of MAOIs vs. selective serotonin reuptake inhibitors. The effect size for MAOIs vs. tricyclic antidepressants was 0.27 (95% confidence interval:  $0.16-0.42$ ). MAOIs may be more effective for atypical major depressive disorder than tricyclic antidepressants. Most clinical research has been conducted on irreversible MAOIs. Additional studies testing more recently developed antidepressants (including reversible MAOIs) with an improved safety profile would be warranted. The available data are insufficient for a direct comparison between MAOIs and selective serotonin reuptake inhibitors.

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### 1. Introduction

Currently, depression is viewed as a single entity that varies in its severity and dimensional features. However, “atypical depression” is regarded by many clinicians as phenotypically, and perhaps also etiolo-

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gically, separate from other forms of depressive disorder. The concept of atypical major depression is characterized by a combination of unusual depressive symptoms and special personality features: It involves mood reactivity and “atypical” symptoms like reversal of vegetative symptoms (e.g., hyperphagia) rather than lack of appetite, as specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (American Psychiatric Association, 1994). The atypical character of these symptoms may lead physicians to exclude a diagnosis of depression for patients with substantial mood disorders. It must be emphasized that atypical depression may be a frequent form of depression in outpatients (Nierenberg et al., 1998) and that about 30% of unipolar depressive outpatients meet DSM-IV criteria for atypical major depression as suggested by Asnis et al. (1995). Accordingly, Angst et al. (2002) reported a high prevalence rate of DSM-IV atypical major depressive episodes in the community (4.8%).

The origin of the concept of atypical depression as a distinct subtype is based on a reported preferential response to one class of antidepressants: monoamine oxidase inhibitors (MAOIs) (West and Dally, 1959; e.g., see Liebowitz et al., 1988; Joyce and Paykel, 1989; Quitkin et al., 1993). Although the preferential response of atypical depression to MAOIs is now part of accepted wisdom in clinical psychiatry, the use of varying definitions of atypical depression before the inclusion of operational criteria in DSM-IV (American Psychiatric Association, 1994) makes it difficult to rely only on the above-mentioned findings and underlines the necessity of reviewing the evidence in a quantitative manner. The topic is of special interest as the use of MAOIs is considered germane to treatment-refractory depression (e.g., Birkenhager et al., 2004), one of the most common and vexing problems in the routine practice of psychiatry.

So far, only one study has addressed the question of whether MAOIs should be used as a first-line treatment in patients with atypical depression. In that study, Quitkin et al. (1993) used a quantitative (meta-analytic) approach instead of simply providing a narrative review of studies. The main result of this meta-analysis was that patients suffering from atypical depression were found to be characterized by a better response to MAOIs than to tricyclic antidepressants

(TCAs) or placebo. In view of newer randomized clinical trials considering the efficacy of MAOIs in atypical depression (e.g., Jarrett et al., 1999; Sogaard et al., 1999) and because the meta-analysis by Quitkin et al. (1993) preceded the current DSM-IV concept of atypical depression, we considered a new meta-analysis to be mandatory.

In this context, we were interested in the evidence for a concept of atypical depression as a depressive subtype that is preferentially responsive to MAOI treatment. Therefore, we conducted a meta-analysis, which is presented in this article.

## 2. Methods

### 2.1. Inclusion and exclusion criteria

Following the CONSORT Statement for reporting randomized trials (Moher, 1998; Altman et al., 2001), studies considered in our meta-analysis had to be randomized, controlled, double-blind clinical trials with eligibility criteria for participants, specific objectives, precise details of the interventions, clearly defined primary and secondary outcome measures for each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision. Furthermore, the studies had to compare monoamine oxidase inhibitors (MAOIs) with placebo or with selective serotonin reuptake inhibitors (SSRIs) or TCAs in the *acute* phase treatment (minimal treatment period: 6 weeks; maximal treatment period: 12 weeks) of adult patients suffering from depression with atypical features, as defined by the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (American Psychiatric Association, 1994) or DSM-III (American Psychiatric Association, 1980).

In these trials, atypical depression had to be the main diagnosis assessed in eligible patients. Moreover, only studies with samples not overlapping with others in studies reported elsewhere have been considered to avoid the repeated inclusion of the same subjects in our meta-analysis.

Our primary outcome criterion in the present meta-analysis was the efficacy of treatment in atypical depression, as measured by differences in the response rates between the compared treatments. Response has

been defined according to the original authors' definition (usually defined as at least 50% reduction in the severity of atypical depression). Clinical trials without a standardized indication of responder rates had to be excluded. Observer rating or self-report rating scales needed to have been used to assess the severity of depressive symptoms. Table 1 lists the psychometric instruments used in the studies included in our analysis.

## 2.2. Identification of clinical trials

We electronically searched for any trials testing the efficacy of MAOIs in atypical depression. The following databases have been considered: Medline (1966 onwards), Embase (1980 onwards), PsycInfo (1974 onwards) and Psynindex (1977 onwards). The search was performed using the following medical subject headings: "Atypical depression" and "treatment". It covered the years from 1966 through 2004. In addition, all reference lists of the identified articles were scrutinized for studies not indexed in the above-mentioned electronic databases. We reviewed the potential publications to see if the studies had a randomized and double-blind design comparing standard dosages of MAOIs with placebo or with stan-

dard dosages of other antidepressants (SSRIs and TCAs) in the indication "atypical depression" according to DSM-III or DSM-IV criteria, respectively. All identified articles were then reviewed if they met the above-mentioned eligibility criteria. As a result, eight relevant publications were identified (Liebowitz et al., 1988; Quitkin et al., 1988, 1990, 1991; Lonnqvist et al., 1994; Pande et al., 1996; Jarrett et al., 1999; Sogaard et al., 1999), resulting in 11 corresponding comparisons.

## 2.3. Statistical analysis

For each study, effect sizes were calculated according to the recommendations of Rosenthal (1991). Based on two-by-two cross-tables (verum–placebo/responders–non-responders), single effect sizes were determined by calculating the  $\phi$  coefficient. This coefficient can be interpreted as a response-rate difference and represents a common measure of effect size in the clinical literature with more intuitive clinical meaning than the odds ratio or relative risk reduction which are defined as quotients of two quotients and thus are not well suited for clinical interpretation. The absolute risk reduction does not allow integration of data in a satisfactory way; another disadvantage of this measure is

Table 1  
Characteristics of included studies (double-blind RCT)

Efficacy trials	N	Indication	Compounds	Psychometric instruments	Primary outcome criteria
Liebowitz et al. (1988)	119	atypical depression	phenelzine vs. imipramine vs. placebo	CGI, HAMD, SADS-C, SCL-90	CGI improvement score $\leq 2$
Quitkin et al. (1988)	60	atypical depression	phenelzine vs. imipramine vs. placebo	CGI, HAMD, SADS-C, SCL-90	CGI improvement score $\leq 2$
Quitkin et al. (1990)	90	atypical depression	phenelzine vs. imipramine vs. placebo	CGI, HAMD, SCL-90	CGI improvement score $\leq 2$
Quitkin et al. (1991)	64	atypical depression	phenelzine vs. imipramine	CGI, HAMD, SCL-90	CGI improvement score $\leq 2$
Lonnqvist et al. (1994)	53	atypical depression	moclobemide vs. fluoxetine	HAMD, MADRS, CGI	$\geq 50\%$ decrease in HAMD, CGI improvement score $\leq 2$
Pande et al. (1996)	40	atypical depression	phenelzine vs. fluoxetine	HAMD, CGI, PGI	$\geq 50\%$ decrease in HAMD, CGI improvement score $\leq 2$
Sogaard et al. (1999)	172	atypical depression	moclobemide vs. sertraline	HAMD, CGI, ADDS, HAMA	$\geq 50\%$ decrease in HAMD, CGI improvement score $\leq 2$
Jarrett et al. (1999)	72	atypical depression	phenelzine vs. placebo	HAMD, BDI, CGI	CGI improvement score $\leq 2$ , endpoint HAMD $\leq 9$

ADDS=Atypical Depression Diagnostic Scale (Stewart et al., 1993); BDI=Beck Depression Inventory (Beck et al., 1961); CGI=Clinical Global Impression Scale (Guy, 1976); HAMA=Hamilton Anxiety Scale (Hamilton, 1959); HAMD=Hamilton Depression Rating Scale (Hamilton, 1960); MADRS=Montgomery–Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979); N=number; PGI=Patient Global Impression (Improvement) Scale (Guy, 1976); SADS-C=Schedule for Affective Disorders and Schizophrenia-Change Version (Spitzer and Endicott, 1978); SCL-90=Hopkins Symptom Checklist (Derogatis et al., 1973).

Table 2  
 Studies with atypical depression not included ( $N=50$ ): exclusion criteria

Author (year)	Journal	Main exclusion criteria
$N=33$		
De Leo (1985)	Current Therapeutic Research	No MAOI
Davidson et al. (1988)	Archives of General Psychiatry	No MAOI
Magni et al. (1988)	Neuropsychobiology	No MAOI
McGrath et al. (1988)	Psychiatry Research	No MAOI
Goodnick and Extein (1989)	Annals of Clinical Psychiatry	No MAOI
Stewart et al. (1990)	Psychiatry Research	No MAOI
Cabras et al. (1991)	Minerva Psichiatriaca	No MAOI
Simpson and DePaulo (1991)	Journal of Clinical Psychopharmacology	No MAOI
Stratta et al. (1991)	International Clinical Psychopharmacology	No MAOI
Cironi et al. (1992)	Rivista di Psichiatria	No MAOI
Mercier et al. (1992)	Journal of Clinical Psychiatry	No MAOI
Stratta et al. (1992)	Rivista Sperimentale di Freniatria e Medicina Legale delle Alienazioni Mentali	No MAOI
Hayano et al. (1994)	Journal of the Wakayama Medical Society	No MAOI
McGrath et al. (1994b)	Journal of Clinical Psychopharmacology	No MAOI
Nierenberg et al. (1996)	Biological Psychiatry	No MAOI
Sovner and Fogelman (1996)	Journal of Clinical Psychiatry	No MAOI
Fava et al. (1997)	Psychopharmacology Bulletin	No MAOI
Salorio and DelPozo (1997)	Folia Neuropsiquiatria	No MAOI
Klein et al. (1998)	Depression and Anxiety	No MAOI
Stewart et al. (1998)	Journal of Clinical Psychopharmacology	No MAOI
Sotsky and Simmens (1999)	Journal of Affective Disorders	No MAOI
Avissar et al. (1999)	Archives of General Psychiatry	No MAOI
Gomes de Matos (2000)	Jornal Brasileiro de Psiquiatria	No MAOI
McGrath et al. (2000a)	American Journal of Psychiatry	No MAOI
McGrath et al. (2000b)	Journal of Clinical Psychiatry	No MAOI
Agosti and McGrath (2002)	Journal of Affective Disorders	No MAOI
Joyce et al. (2002)	Australian and New Zealand Journal of Psychiatry	No MAOI
Murck (2002)	Wiener Medizinische Wochenschrift	No MAOI
Davidson et al. (2003)	Biological Psychiatry	No MAOI
Ginsberg (2003)	Primary Psychiatry	No MAOI
Leppamaki et al. (2003)	European Neuropsychopharmacology	No MAOI
Mahajan et al. (2004)	European Journal of Endocrinology	No MAOI
Roose et al. (2004)	International Journal of Geriatric Psychiatry	No MAOI
$N=2$		
Robinson et al. (1973)	Archives of General Psychiatry	No diagnosis of AD according to DSM-III, DSM-III-R, DSM-IV or RDC
Quitkin et al. (1984)	Journal of Clinical Psychiatry	No diagnosis of AD according to DSM-III, DSM-III-R, DSM-IV or RDC
$N=3$		
Wager et al. (1988)	Human Psychopharmacology	Not double-blind
Thase et al. (1992)	Journal of Clinical Psychiatry	Not double-blind
McGrath et al. (1994a)	Journal of Clinical Psychiatry	Not double-blind
$N=3$		
Schweitzer et al. (1989)	International Journal of Clinical Pharmacology Research	No SSRI-, TCA- or placebo-controlled study
Tiller et al. (1989a)	Journal of Affective Disorders	No SSRI-, TCA- or placebo-controlled study
Tiller et al. (1989b)	British Journal of Psychiatry	No SSRI-, TCA- or placebo-controlled study

Table 2 (continued)

Author (year)	Journal	Main exclusion criteria
<i>N</i> = 2		
Stewart et al. (1997)	American Journal of Psychiatry	No acute treatment
Zubieta et al. (1999)	Journal of Psychiatric Research	No acute treatment
<i>N</i> = 4		
Liebowitz et al. (1984b)	Journal of Clinical Psychiatry	No response rates
Zisook et al. (1985)	Journal of Clinical Psychopharmacology	No response rates
Larsen et al. (1991)	Acta Psychiatrica Scandinavica	No response rates
McGrath et al. (1992)	Journal of Clinical Psychopharmacology	No response rates
<i>N</i> = 3		
Liebowitz et al. (1984a)	Archives of General Psychiatry	Partly same sample
Stewart et al. (1989)	Archives of General Psychiatry	Partly same sample
Stewart et al. (1993)	Journal of Clinical Psychopharmacology	Partly same sample

*N*=number; MAOI=monoamine oxidase inhibitor; AD=atypical depression; RDC=Research Diagnostic Criteria; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

that small differences in the marginal sections of response rates are less weighted than in the case of using the  $\varphi$  coefficient. Regarding the odds ratio, this frequently reported measure of effect size for categorical data has been shown to mislead when events (such as response rates in antidepressant trials) are common (Altman, 1998; Bracken, 1998). This is due to the dependency of the odds ratio on the base rate of the control group: If this reference response rate value is 3%, an odds ratio of 3 represents a response rate difference of 6%; if it is 30%, the same odds ratio is associated with a response rate difference of no less than 60%. For these reasons, the  $\varphi$  coefficient was selected as the measure of effect size in the present study. In a first step, it has been *z*-transformed according to the formula:  $z(r) = \arctan \text{hyp}(r)$ .

In a next step, weighted means of the above-mentioned *z*-transformed effect sizes have been computed, using the formula:

$$z(r) = \frac{\sum_i (N_i - 3) \cdot z(r)_i}{\sum_i (N_i - 3)}$$

( $z(r)$ =weighted means of *i* single *z*-transformed  $\varphi$  coefficients ( $z(r)_i$ );  $N_i$ =total (study- or comparison-specific) sample size).

Finally, this term has been retransformed by applying the formula:  $r = \tan \text{hyp}(z(r))$ .

This procedure gives more weight to trials with larger sample sizes. Positive values of *r* indicate the superiority of MAOIs.

To estimate the population effect size for each set of clinical studies, 95% confidence intervals have been constructed for the true value of the population effect size. If this interval contains a zero, then the two compared drugs do not significantly differ in their response rates. In accordance with the proposal by Cohen (1988), effect sizes below 0.25 are considered to be small, effect sizes between 0.25 and 0.40 are considered to be medium, and effect sizes above 0.40 are considered to be large.

Averaging of the single effect sizes has been preceded by examining their degree of heterogeneity. This has been performed by means of the  $\chi^2$  test for heterogeneity with *k* - 1 degrees of freedom, where *k* is the number of studies in the set. The formula is defined as follows:

$$\chi^2 = \sum_i^k \left( (r_i - \bar{r})^2 \cdot (N_i - 3) \right)$$

( $r_i$ =single effect size ( $\varphi$  coefficient);  $\bar{r}$ =arithmetical means of  $r_i$ ;  $N_i$ =total (study- or comparison-specific) sample size).

If this statistic was greater than the critical value at the 0.05 level, then the null hypothesis was rejected in support of the alternative that the effect sizes were heterogeneous. The studies were handled as fixed effects in the statistical model. To control for the existence of a publication bias, the dependency of the single effect

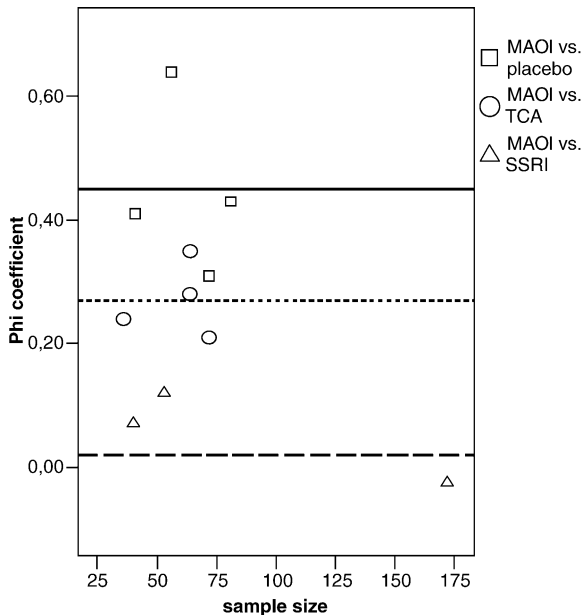


Fig. 1. Funnel plot illustrating the dependency of the single effect sizes (measured as  $\varphi$  coefficients) from the sample sizes for all comparisons of monoamine oxidase inhibitors (MAOIs) with placebo ( $\square$ ), tricyclic antidepressants (TCAs) ( $\circ$ ) and selective serotonin reuptake inhibitors (SSRIs) ( $\triangle$ ) in our meta-analysis. The continuous line represents the weighted arithmetical means of the effect sizes for the comparisons between MAOI and placebo; the dotted line represents the weighted arithmetical means of the effect sizes for the comparisons between MAOI and TCA and the dashed line the weighted arithmetical means of the effect sizes for the comparisons between MAOI and SSRI.

sizes from the sample size was graphically visualized using funnel plots (compare [Wilson and Henry, 1992](#)).

### 3. Results

The initial search turned up 165 publications regarding “treatment of atypical depression”. Of

these, 67 publications were selected to be examined in detail. Two of these articles were reviews ([Davidson and Pelton, 1986](#); [Heinze et al., 1989](#)), and another article was the aforementioned meta-analysis by [Quitkin et al. \(1993\)](#). Of 64 publications that presented the results of clinical trials, six had to be excluded because atypical depression did not represent the main diagnosis ([Larsen et al., 1984](#); [Cairoli et al., 1987](#); [McGrath et al., 1993](#); [Rothschild et al., 1994](#); [Partonen and Lonnqvist, 1996](#); [Joyce et al., 2004](#)). Of the remaining 58 studies, eight studies (13.8%) fulfilled the inclusion and exclusion criteria of our meta-analysis (see [Table 1](#)). [Table 2](#) summarizes the remaining 50 studies including citation and the main reasons for exclusion.

[Fig. 1](#) illustrates the association of single effect sizes and sample sizes for the comparisons between MAOIs and other drugs (TCAs, SSRIs and placebo). While the value distribution is rather symmetric for the comparisons between MAOIs and TCAs, quite asymmetrical distributions are found for the other comparisons. The asymmetrical distribution for comparisons between MAOIs and placebo is due to one study ([Quitkin et al., 1990](#)) that showed a very high response-rate difference between phenelzine and placebo (64%) in contrast to the lower response-rate differences in the other three studies comparing the efficacy of MAOIs and placebo in patients suffering from atypical depression ([Liebowitz et al., 1988](#); [Quitkin et al., 1988](#); [Jarrett et al., 1999](#)). However, it must be noted that the high response-rate difference in the randomized controlled trial published by [Quitkin et al. \(1990\)](#) does not go along with a relatively large sample size. The asymmetrical distribution for comparisons between MAOIs and SSRIs suggests a bias because the study with the highest sample size ( $N=172$ ; [Sogaard et al., 1999](#)) suggests a slight superiority of SSRIs; the two other studies with much

Table 3a  
Single effect sizes for clinical trials comparing the efficacy of MAO inhibitors and placebo in atypical depression

Efficacy trials	$N$	Effect size	CI (95%)	Verum	Response rate phenelzine	Response rate placebo
<a href="#">Liebowitz et al. (1988)</a>	81	0.43	0.262–0.697	Phenelzine	71% (24/34)	28% (13/47)
<a href="#">Quitkin et al. (1988)</a>	41	0.41	0.168–0.780	Phenelzine	71% (12/17)	29% (7/24)
<a href="#">Quitkin et al. (1990)</a>	56	0.64	0.477–0.997	Phenelzine	83% (25/30)	19% (5/26)
<a href="#">Jarrett et al. (1999)</a>	72	0.31	0.115–0.578	Phenelzine	58% (21/36)	28% (10/36)

$N$ =number; a positive effect size means that the MAOI is superior to placebo; CI=confidence interval; MAOI=monoamine oxidase inhibitor.

Table 3b

Single effect sizes for clinical trials comparing the efficacy of MAO inhibitors and tricyclics in atypical depression

Efficacy trials	N	Effect size	CI (95%)	Compounds	Response rate phenelzine	Response rate imipramine
Liebowitz et al. (1988)	72	0.21	0.003–0.466	Phenelzine vs. imipramine	71% (24/34)	50% (19/38)
Quitkin et al. (1988)	36	0.24	–0.050–0.606	Phenelzine vs. imipramine	71% (12/17)	47% (9/19)
Quitkin et al. (1990)	64	0.35	0.149–0.639	Phenelzine vs. imipramine	83% (25/30)	50% (17/34)
Quitkin et al. (1991)	64	0.28	0.069–0.560	Phenelzine vs. imipramine	63% (22/35)	35% (10/29)

N=number; a positive effect size means that the MAOI is superior to tricyclic antidepressants; CI=confidence interval; MAOI=monoamine oxidase inhibitor.

smaller samples suggest a slight superiority of MAOIs (Lonnqvist et al., 1994; Pande et al., 1996). However, in all three studies, the effect sizes were very low, thus not suggesting a pronounced publication bias.

Data from four randomized controlled trials (RCTs) in patients suffering from atypical depressive disorder all consistently showed phenelzine to be superior to placebo in terms of the proportion of responders and the effect sizes (summarized in Table 3a). The effect sizes are medium to large with rather wide individual confidence limits reflecting the small sample sizes.

Data from three RCTs in patients with atypical depressive disorder (Liebowitz et al., 1988; Quitkin et al., 1990, 1991) all indicated phenelzine to be superior to the TCA imipramine in terms of the response rates and effect sizes, which were in the medium range (summarized in Table 3b). However, the 95% confidence interval (CI) computed for the medium effect size (0.24) in one RCT published by Quitkin et al. (1988) suggests that phenelzine is not statistically superior to imipramine.

Data from three other RCTs in patients with atypical depressive symptoms showed phenelzine or moclobemide, respectively, was not superior to a SSRI in terms of the response rates and the effect sizes, which were very low (summarized in Table 3c).

In summary, our results contrast a mean large effect size of 0.45 (95% CI: 0.35–0.60) for a comparison of MAOIs vs. placebo with a very low effect size of 0.02 (95% CI: –0.10–0.14) for a comparison of MAOIs vs. the SSRIs. These results indicate that MAOIs are significantly superior to placebo, but not to the SSRIs. The effect size for MAOIs vs. the TCA imipramine was in the medium range (0.27; 95% CI: 0.16–0.42), reflecting a superiority of MAOIs over imipramine (these results are summarized in Table 4). With respect to the drug comparisons (MAOIs vs. placebo; MAOIs vs. TCAs; MAOIs vs. SSRIs), homogeneity of the averaged effect sizes was given despite rather pronounced spreading of effect sizes regarding the comparison between MAOIs and placebo.

#### 4. Discussion

Our main purpose was to examine the validity of the widely accepted assumption of a preferential response to MAOI therapy in depressed patients with atypical features. The studies included in our analysis suggest that MAOIs are consistently superior to placebo in atypical depression. The average effect size was in the large range ( $\varphi=0.45$ ), and the corresponding 95% CI with a lower limit of 0.35 also

Table 3c

Single effect sizes for clinical trials comparing the efficacy of MAO inhibitors and SSRI in atypical depression

Efficacy trials	N	Effect size	CI (95%)	Compounds	Response rate MAOI	Response rate SSRI
Lonnqvist et al. (1994)	53	0.12	–0.134–0.406	Moclobemide vs. fluoxetine	67% (16/24)	55% (16/29)
Pande et al. (1996)	40	0.07	–0.231–0.392	Phenelzine vs. fluoxetine	85% (17/20)	80% (16/20)
Sogaard et al. (1999)	172	–0.03	–0.178–0.122	Moclobemide vs. sertraline	63% (52/83)	65% (58/89)

N=number; a positive effect size means that the MAOI is superior to SSRI; CI=confidence interval; MAOI=monoamine oxidase inhibitor; SSRI=selective serotonin reuptake inhibitor.

Table 4

Mean effect sizes for clinical trials comparing the efficacy of MAO inhibitors and other compounds in atypical depression

Compounds	<i>N</i> , comparisons	<i>N</i> , patients	Effect size	CI (95%)	$\chi^2$ (heterogeneity)
Phenelzine vs. placebo	4	250	0.45	0.352–0.605	3.35 (n.s.)
Phenelzine vs. imipramine	4	236	0.27	0.161–0.421	0.67 (n.s.)
Phenelzine/moclobemide vs. SSRI	3	265	0.02	–0.104–0.139	0.95 (n.s.)

*N*=number; CI=confidence interval; a positive effect size means that the MAOI is superior to the other compound;  $\chi^2$  (heterogeneity)= $\chi^2$  for heterogeneity of single effect sizes; SSRI=selective serotonin reuptake inhibitor; n.s.=not significant.

suggests a large effect. Only one study (Jarrett et al., 1999) revealed a medium effect ( $\phi=0.31$ ) with a large 95% CI (0.12–0.58) due to a rather low sample size ( $N=72$ ).

The comparisons between MAOIs and TCAs showed in three of four cases superiority of MAOIs to TCAs in atypical depression, with the effect sizes being in the medium range (0.21–0.35). Only one study (Quitkin et al., 1988) did not confirm this superiority because the corresponding 95% CI included 0. This fact is caused by a large CI due to small sample size ( $N=36$ ); therefore, this finding should be interpreted with much caution.

At present, only three double-blind RCTs (Lonnqvist et al., 1994; Pande et al., 1996; Sogaard et al., 1999) provided a direct comparison of MAOIs and SSRIs regarding the therapeutic efficacy in atypical depression, and because of the rather small number of subjects, power was quite low and the confidence limits on the (small) pooled estimate of effect sizes were broad. Therefore, our meta-analytic finding that MAOIs and SSRIs did not significantly differ regarding clinical efficacy in atypical depression has to be interpreted cautiously. There are some other problems with the above-mentioned studies: The RCT presented by Lonnqvist et al. (1994) tested moclobemide, a reversible MAOI that may be less efficacious overall than the irreversible MAOIs (e.g., phenelzine). Another study (Pande et al., 1996) has considerably high response rates, suggesting high placebo response rates. Unfortunately, placebo arms were not part of the study design; the same is true for the RCT published by Sogaard et al. (1999). Therefore, placebo response rates could not be determined. One study not included in our analysis was a placebo-controlled, three-armed trial in 154 depressive patients with atypical features conducted by McGrath et al. (2000a). This study did not compare the efficacy of an MAOI and therefore was not in our primary focus and not included in our

meta-analysis. McGrath et al. (2000a) found the SSRI fluoxetine to be equal to the TCA imipramine, but both compounds were superior to placebo in treating atypical depression. Results of this study might also limit the above-mentioned findings of our meta-analysis.

Another limitation of our meta-analysis is the small number of studies included in the analysis. However, it has been reported that often less than 10% of studies meet the requirements for a meta-analysis (Bailar, 1997). Moreover, some studies included in our analysis had small sample sizes. On the other hand, there seemed to be no substantial variations in the methods applied and in the specific issues studied (as shown in Table 1). Of course, we cannot exclude that general problems of a meta-analysis occurred, e.g., there may be important unpublished work (especially unreported “negative” studies) that could not be considered, leading to a severe research bias (Steinbrook, 2004). We have addressed this issue by the application of funnel plots illustrating the effect size/sample size ratio for all comparisons of MAOIs with SSRIs, TCAs or placebo. These funnel plots revealed rather high straggling of the effect sizes, but no systematic dependency from the sample sizes, thus suggesting lack of a marked publication bias. Moreover, we asked an expert about unpublished studies in this field. He did not find any unpublished RCTs concerning the efficacy of MAOIs in atypical depression. Nevertheless, it may be the case that such studies were conducted and not published because of negative results.

Another issue should also be considered: Important studies may have been dropped because they did not meet our inclusion/exclusion criteria. In this context, three studies should be mentioned because they provide further information on the efficacy of psychotropic drugs in atypical depression and their methodological standard was quite high: In two of



them, Stewart et al. (1998) and Sotsky and Simmens (1999) published independent re-analyses of the results of the National Institute of Mental Health (NIMH) collaborative treatment of depression trial (compare Sotsky et al., 1991), which examined atypical depression (albeit identified post hoc with approximate diagnostic criteria) as a moderator of treatment effects (including imipramine vs. placebo), showing rather low response rates among patients with atypical depression and suggesting imipramine to be not better than placebo in this group. Both studies could *not* be considered in our meta-analysis because MAOIs were not applied. Another study (McGrath et al., 1993) revealed that non-responders to imipramine among outpatients with mood-reactive, nonmelancholic, mainly chronic depression had a significantly greater response rate to phenelzine than non-responders to phenelzine did to imipramine. Unfortunately, only 45 of the 89 patients included in this double-blind crossover trial suffered from definite atypical depression, and response rates for this subgroup were not given. Therefore, this interesting study could not be accounted for in our meta-analysis.

Given the small number of applicable studies, perhaps we should have considered expanding the scope to include any RCT in which atypical depression was examined as a moderator of treatment effect. However, such an expansion would have led to inclusion of studies with marked methodological limitations and would have biased the results of our meta-analysis in a considerable amount. Therefore, we decided to select only studies that fulfilled rather restrictive inclusion as well as exclusion criteria for a meta-analytic investigation, as indicated above.

A general problem of clinical studies testing the efficacy of drugs in the indication “atypical depression” consists in the psychometric instruments. Most studies used the Hamilton Depression Rating Scale, which does not really fit the specific symptom profile in atypical depression. All studies we had considered in our meta-analysis did not indicate if the persons assessing outcome (the raters) were blinded to group assignment. Moreover, compliance of the patients had not been assessed by drug monitoring.

Apart from general concerns about the credibility of the findings of meta-analysis (Bailar, 1997) in view of the publication bias, i.e., the phenomenon in which,

for instance, clinical studies with negative findings are not published, our results do not conflict with findings of previous meta-analyses (Quitkin et al., 1993), nor with the American Psychiatric Association guidelines for atypical depression (Petersen et al., 2002). Quitkin et al. (1993) conducted a meta-analysis on a number of trials using the MAOI phenelzine with the conclusion that phenelzine was superior to the tricyclic compound imipramine. The American Psychiatric Association notes “. . . results of several studies suggest that SSRIs, MAOIs and possibly bupropion may be more effective treatments for atypical major depressive disorder. . .” than tricyclic antidepressants (American Psychiatric Association, 2000). In this context, it should be noticed that comparative studies in atypical depression using bupropion appear to be rare: We found only one small open trial suggesting that bupropion may be effective in treating major depressive disorder with atypical features (Goodnick and Extein-Irl, 1989).

Regarding biological and etiological aspects, patients with atypical depression seem to have a significantly different cortisol response to desipramine injection than patients with non-atypical depression. The cortisol response to intramuscular desipramine has been described as increased in atypical depression (Gold et al., 1995). It has been concluded that atypical depression might be associated with a less impaired norepinephrine system compared with non-atypical depression (Asnis et al., 1995; Nierenberg et al., 1998). This indication of less dysregulation of noradrenergic function in atypical depression would explain that patients suffering from this disorder respond less frequently to those compounds that have a predominantly noradrenergic mechanism of action. The strong effect of MAOIs on the serotonergic system compared with weaker effects of the tricyclics on the same system suggests that the pathophysiology of atypical depression may involve a primary abnormality in the indolamine system and only a minor or even no dysregulation of the noradrenergic system (McGrath et al., 1994a). A serotonin hypothesis for atypical depression has been suggested by Nierenberg et al. (1998). If this hypothesis is true, clinical efficacy of SSRIs in the indication of atypical depression can be expected. Unfortunately, the data at present are insufficient with respect to the clinical efficacy of SSRIs in patients with atypical depression

and more randomized controlled trials would be needed to address this question.

It seems noteworthy that most clinical research has been conducted on traditional MAOIs (e.g., phenelzine). Although more selective and less toxic MAOIs such as moclobemide have been developed and are approved by FDA and EMEA, there are only a few randomized controlled trials comparing the efficacy of moclobemide (or any other MAOI that selectively and reversibly inhibits monoamine oxidase type A) with the efficacy of another antidepressant (and/or placebo) in the indication of atypical depression. Since selectivity and reversibility of an MAOI promise lower toxicity and better tolerance, this generation of MAOIs may be a better alternative than the older MAOIs. Therefore, further comparative studies on the efficacy of these compounds might be useful in the indication atypical depression.

Treatments that appear promising in atypical depression, but had not been considered in our meta-analysis include above all cognitive behavioral therapy which might be effective in acute treatment (Mercier et al., 1992; Jarrett et al., 1999) as well as in maintenance therapy (Jarrett et al., 2000). Furthermore, it has been suggested that depressive patients with atypical features might benefit from gepirone (a 5-hydroxytryptamine partial agonist) (McGrath et al., 1994b) and from chromium picolinate (McLeod and Golden, 2000; Davidson et al., 2003).

Despite the high prevalence of atypical depression found in previous studies (e.g., Angst et al., 2002), studies testing the efficacy of the newer generation of antidepressants, such as venlafaxine, nefazodone or mirtazapine in this indication, are hard to find. More data about the efficacy of the newer generation of antidepressants in atypical depression would be warranted.

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