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REVIEW

MAOIs in the Contemporary Treatment of Depression

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We review the literature on the effectiveness of the monoamine oxidase inhibitors (MAOIs) and present metaanalyses of controlled trials comparing the FDA-approved MAOIs with both placebo and comparator tricyclic antidepressants. For outpatients, metaanalyses with intent-to-treat samples revealed generally comparable overall efficacy for phenelzine, isocarboxazid, and tranylcypromine. Drug–placebo differences were 29.5% (± 11.1%) (phenelzine; nine studies), 41.3% (±18.0%) (isocarboxazid; three studies), and 22.1% (± 25.4%) (tranylcypromine; three studies). For inpatients, phenelzine was 22.3% (± 30.7%) (five studies) more effective than placebo, whereas the isocarboxazid–placebo difference was lower (15.3%) (±12.6%). Both phenelzine and isocarboxazid were significantly less effective than comparator tricyclics for inpatients, whereas tranylcypromine has not been adequately studied. Both phenelzine and tranylcypromine appear to be more effective than tricyclics in depressed outpatients with atypical features. Monoamine oxidase inhibitors are also effective treatments for outpatients who have failed to respond to tricyclic antidepressants. Our review also suggests (1) the FDA-approved MAOIs treat a somewhat different group of patients than tricyclics; (2) more severely depressed inpatients may not respond as well to MAOIs as to tricyclics; and (3) because of preferential MAOI responsivity, atypical or anergic depressions may be biologically different than classical depressions.
[Neuropsychopharmacology 12:185–219, 1995]

KEY WORDS: *Phenelzine; Tranylcypromine; Isocarboxazid; MAOIs; Depression; Antidepressant efficacy; Metaanalysis*

Monoamine oxidase inhibitor (MAOI) antidepressants have been in use for nearly 40 years (Ayd 1957; Crane 1957; Kline 1958; West and Dally 1959; Sargent 1961), during which time their popularity has waxed and waned (e.g., Quitkin et al. 1979; Paykel and White 1989). Recently, they have been largely viewed as second- or third-line antidepressant medications (Paykel and White 1989; Clary et al. 1990; Nierenberg 1991) for reasons of both efficacy and safety. In this report, we review the literature on the MAOIs currently approved for the treatment of depression in the United States by the Food and Drug Administration (FDA). Following a brief overview of the clinical pharmacology of the MAOIs, we examine their efficacy as acute and maintenance phase treatments using metaanalysis. Efficacy is determined with respect to placebo-control (PBO) and relative to standard tricyclic antidepressant (TCA) comparators. The relationship of response to degree of platelet MAO inhibition is considered, as are the side effects, tolerability, and safety of these agents. Finally, the literature on proposed MAOI-responsive subforms of depression is summarized.

CLINICAL PHARMACOLOGY OF MAOIs

There are currently four FDA-approved MAOIs available in the United States. They are phenelzine sulfate

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Received November 24, 1993; revised July 12, 1994; accepted July 15, 1994.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/95/$9.50
SSDI 0893-133X(94)00058-8

(PHZ) (Nardil), isocarboxazid (ISO) (Marplan), tranylcypromine sulfate (TRP) (Parnate), and selegiline hydrochloride (SEL) (Eldepryl). However, SEL's approval is limited to the treatment of Parkinson's disease, and a recent decision by the manufacturer of ISO may remove it from the market. A fifth MAOI, pargyline (Eutonyl), was approved for use in severe hypertension but is no longer being manufactured because of an unfavorable risk–benefit ratio in comparison with newer antihypertensive agents. Two additional MAOI antidepressants, moclobemide and brofaromine, are approved for use in Europe and/or Canada, but are not being studied for approval in the United States (Thase in press). Nevertheless, these drugs appear to be effective antidepressants when compared to either PBO or standard comparators (e.g., Norman et al. 1985; Lecrubier and Guelfi 1990; Larsen et al. 1991; Nolen et al. 1993; Volz et al. 1994). Another MAOI, clorgyline, also appears to have significant antidepressant activity (e.g., Potter et al. 1982). However, because of both proprietary and side-effect issues, clorgyline is not under active investigation at this time.

Monoamine oxidase inhibitors may be classified by their chemical structure (hydrazine versus nonhydrazine), by their relative selectivity for subforms of MAO (Type A, Type B, or mixed), or by the degree of affinity to enzyme inhibition sites (i.e., reversible versus functionally irreversible) (Klein and Davis 1969; Mann et al. 1984; Murphy et al. 1984). The type B MAO, found in brain, platelets, and elsewhere, has substrate specificity for phenethylamine and dopamine. Type A MAO, found in the brain, gut, and liver (but not platelets) is relatively substrate-specific for norepinephrine, serotonin, and tyramine (Mann et al. 1984; Murphy et al. 1984, 1987).

Pargyline was the first FDA-approved MAOI to be considered relatively selective for Type B MAO (Murphy et al. 1984). Type B enzymatic selectivity was originally considered desirable as a solution to the dietary restrictions necessitated by inhibition of tyramine metabolism. However, appropriately designed dose-response studies regarding pargyline's enzymatic selectivity were not performed in humans, and pargyline did not show much promise as an antidepressant (Murphy et al. 1987). Selegiline hydrochloride is also a selective inhibitor of Type B MAO at low doses (i.e., 5 to 10 mg/day) (Mann et al. 1984). However, there is little evidence to suggest that SEL is an effective antidepressant at these doses (e.g., Quitkin et al. 1984; Mann et al. 1989). In fact, SEL appears to lose its specificity for MAO-B inhibition at the very dosages at which it surpasses PBO as an effective antidepressant (Quitkin et al. 1984; Mann et al. 1989). This suggests that Type A MAO may be more critical in the pathophysiology of depression and/or more central to antidepressant activity than Type B. Clorgyline, moclobemide, and brofaromine are selective for Type A MAOI. The remaining three FDA-approved MAOIs are "mixed" inhibitors, because they inhibit both Type A and Type B enzymes even at lower dosages.

Clorgyline, pargyline, and the four FDA-approved MAOIs are relatively irreversible, meaning that the drugs bind tightly to the enzyme for the life of the enzyme. A minimum period of 7 to 14 days is needed to adequately "wash out" MAO inhibition caused by the irreversible MAOIs. Not surprisingly, the clinical effects of the irreversible MAOIs may persist for days or even several weeks after discontinuation (Murphy et al. 1987). By contrast, clinical effects that are plasma-level dependent (e.g., orthostasis) may reverse within hours to a few days of drug discontinuation (Murphy et al. 1987; Robinson and Kurtz 1987; Mallinger and Smith 1991). The newer Type-A selective MAOIs, moclobemide and brofaromine, are reversible and thus have a shorter duration of effects on enzyme inhibition (Möller et al. 1991; Roth and Guelfi 1992). Whereas drug plasma levels of both the reversible and irreversible MAOIs can be measured using methodology analogous to that for trace monoamines or amphetamines (e.g., Cooper et al. 1978; Karoum et al. 1982; Mallinger et al. 1990; Dingemanse et al. 1992), available evidence concerning plasma level–response relationships is scant. Plasma level monitoring of the irreversible MAOIs does not appear to be of clinical value, perhaps because of the short half-lives of these medications in relation to their pharmacodynamic effects (e.g., Mallinger et al. 1990). Available evidence suggests that plasma levels are also not useful for the prediction of response to either the irreversible (Mallinger et al. 1990) or reversible (Fritze et al. 1990; Danish University Antidepressant Group 1993) MAOIs.

All four FDA-approved MAOIs have some structural resemblance to amphetamine. However, they are neither habit forming or euphoriogenic for the vast majority of patients (Mallinger and Smith 1991; Thase in press). Nevertheless, metabolic pathways for two of the nonhydrazine MAOIs (SEL and TRP) may yield small amounts of amphetamine (Youdim et al. 1979; Karoum et al. 1982). The structure of TRP, which may be viewed as a cyclized form of amphetamine, probably precludes its metabolism to amphetamine except under unusual circumstances, such as following a massive overdose (Youdim et al. 1979). Moclobemide and brofaromine are also nonhydrazine MAOIs. Phenelzine sulfate and isocarboxazid differ from the other MAOIs in that they are hydrazine compounds; both drugs have a nitrogen-to-nitrogen bond in their side chain (Klein and Davis 1969; Murphy et al. 1984). Considerable clinical evidence indicates that the hydrazine MAOIs have greater hepatotoxicity than the nonhydrazines (Klein and Davis 1969; Timbrell 1979). The hepatotoxicity of the hydrazine MAOIs is best illustrated by earlier clini-

cal experience with iproniazid, which was removed from the market despite considerable antidepressant efficacy (Timbrell, 1979).

With respect to pharmacokinetics, all four FDA-approved MAOIs are rapidly absorbed and have elimination half-lives on the order of 1 to 4 hours (Murphy et al. 1987). All four drugs are tightly protein bound and are excreted after hepatic metabolism. With the possible exception of SEL's conversion to amphetamine (Karoum et al. 1982), none has clinically important metabolites (Murphy et al. 1987; Robinson and Kurtz 1987). Both moclobamide and brofaromine also have short half-lives (Thase in press). Moclobamide, but not brofaromine, has at least some active metabolites of clinical significance (Haefely et al. 1992; Thase in press).

It was initially believed that the antidepressant effectiveness of MAOIs was the *direct* result of MAO inhibition. This acute effect decreases degradation of monoamines (e.g., norepinephrine, serotonin, or dopamine) stored in presynaptic neurons, thereby resulting in an increased amount of these neurotransmitters available at the synapse (e.g., Schildkraut 1965; Klein and Davis 1969). More recent research indicates that this heuristic model does not fully explain the mechanism of MAOIs' efficacy (Mann et al. 1984; Murphy et al. 1987). For example, the positive (+) stero-isomer of TRP is a poor antidepressant despite inhibiting MAO (Escobar et al. 1974). The main pharmacologic difference between the negative (−) and + isomers of TRP is that the former has much weaker effects as a norepinephrine reuptake inhibitor in relation to its potency as an MAOI (Hendley and Snyder 1968). The other MAOIs may also block the reuptake of selected neurotransmitters (Murphy et al. 1987). However, like the nonMAOI uptake inhibitors, these acute effects often precede clinical antidepressant effects by weeks (Murphy et al. 1987). More consistent with the 2- to 4-week lag in therapeutic effect, chronic treatment with a diverse number of MAOIs has been shown to reduce the number of α_2- and β-adrenergic and serotonin (5-HT_2) post-synaptic binding sites in the brain (e.g., Murphy et al. 1987; de Montigny and Blier, 1988).

METHODS

Literature Review

This review identified all relevant literature, summarized the results in evidence tables, combined results across each study using metaanalysis, and compared the efficacy of alternative therapies. Each step in the process is discussed below.

The literature review was conducted by the National Library of Medicine using MEDLINE and Psychological Abstracts, targeting the key words: monoamine oxidase inhibitors, tranylcypromine, isocarboxazid, and phenelzine. All references published in English from 1959 through July 1992 were retrieved. Over 400 abstracts were identified. Articles selected were randomized controlled clinical trials (RCTs) against either PBO or another FDA-approved antidepressant that lasted at least 3 weeks, were peer-reviewed, and that focused on depressive disorders. Two studies (Hare et al. 1962; Overall et al. 1966) were excluded because the comparison drug was amphetamine, which is neither FDA-approved for depression nor so ineffective that it may be considered as a placebo intervention. Another study, by Hutchinson and Smedberg (1960), was excluded because it only lasted 2 weeks. Five additional studies were excluded because the principal diagnoses were not depressive disorders (Lascalles 1966; Solyon et al. 1973; Tyrer et al. 1973; Mountjoy et al. 1977; Sheehan et al. 1980). In one study (Lascalles 1966), patients suffered from facial pain; in the remaining four, the primary conditions were agoraphobia and/or panic disorder. Two other studies were excluded because TRP was compared to either brofaromine (Zapleták et al. 1990) or moclobemide (Gabelic and Kuhn 1990), which are not approved for use in the United States. We made three exceptions with respect to including the results of sequentially controlled trials. In one case, TRP was compared to 5-HTP *after* patients had failed to respond to adequate trials of approved antidepressants (Nolen et al. 1985). In the second case, TRP was compared to nomifensine (an FDA-approved antidepressant voluntarily withdrawn by its manufacturer) (Nolen et al. 1988). In the third case (Giller et al. 1984), the authors treated placebo nonresponders with open label ISO. We chose to exclude SEL, moclobemide, and brofaromine from the metaanalysis because these drugs have neither been approved by the FDA for the treatment of depression, nor is it likely that they will be in the forseeable future.

A total of 55 RCTs were available for review, including one study (McGrath et al. 1993) that was in press at the time of review. All cases involving the same authorial groups were excluded if there was obvious overlap of subjects included in the published reports. We also excluded preliminary reports if they were described in more detail in a subsequent publication. In one case, three groups (Davidson and Turnbull, 1983; Zisook 1983; Giller et al. 1984) published separate reports from their sites of a collaborative, multisite trial; subsequently, the overall findings were also reported (Davidson et al. 1988). We included only the three sites' reports in the metaanalysis. No controlled studies of children/adolescents were found, and only one controlled study of geriatric depression (Georgotas et al. 1986) was identified. The latter study was combined with the remaining 54 adult trials.

Evidence Tables

Each article meeting inclusion criteria was read, ab-

stracted by the first author, and tabulated onto evidence tables. Tables 1, 2, and 3 summarize the studies reporting categorical outcomes for each MAOI based on the number of responders in each cell, as well as the numbers of patients randomized to and completing each treatment cell and associated attrition rates. In 12 studies, the exact number of subjects lost to attrition was not specified. For simplicity's sake, we included these studies in the metaanalysis because there was no indication of differential attrition.

There are two kinds of comparisons reported: drug–PBO and drug–drug contrasts. A total of 36 MAOI versus PBO comparisons (17 PHZ, 12 ISO, and 7 TRP) and 44 MAOI versus standard medication comparisons (28 PHZ, 9 ISO, and 7 TRP) were found. Not all studies were subjected to metaanalysis because the outcome was not reported categorically (i.e., percent of responders). There were nine comparisons from eight studies excluded for this reason; these studies are summarized in Table 4.

In the current metaanalyses, we used categorical data for two pragmatic reasons: (1) they are of greatest interest to practitioners and patients, and (2) these data were available for a larger proportion of studies than were outcomes on continuous measures. We used the percentage of patients with a 50% reduction in Hamilton Rating Scale for Depression (HRS-D) (Hamilton 1960) *or* a Clinical Global Impression (CGI) (Guy 1976) response of 1 or 2 (markedly improved or very much improved) to define responders. These definitions were chosen because they are the most commonly reported methods to determine categorical outcome (Thase and Kupfer 1987; Prien et al. 1991; Angst et al. 1993). It should be noted that this method of determining categorical outcome may include a fair number of partially remitted cases (i.e., those with a high level of residual symptomatology). Although we accept that this level of improvement is clinically meaningful for the purposes of metaanalysis (Angst et al. 1993), we recognize that different results might emerge if a more stringent definition of outcome were to be utilized, such as complete remission (e.g., 17-item HRS-D ≤ 7 or ≤ 9) (Frank et al. 1991). When looking across acute phase studies with varying lengths (e.g., 4, 6, and 8 weeks), the 50% reduction rate also may underestimate the full response rate in the shorter studies.

The response rate (treatment success) can be reported in three different ways. The question of how many patients randomized to the treatment got better is answered by an analysis of "intent-to-treat" (ITT) sample. An ITT analysis uses all patients who got better (regardless of whether they remained in the study) as the numerator, and the number randomized to treatment as the denominator. To answer the question of how many get better of those who received at least the minimal amount of treatment thought to be effective, an "adequate treatment" (AT) sample is used. Only those who received a predetermined minimum amount of treatment (typically 3 to 4 weeks for antidepressant studies) constitutes the denominator, whereas numerator counts those who responded while in treatment. Thirdly, a "completer" sample includes only those who received full treatment as the numerator (responders) and denominator (all completing treatment). These distinctions critically affect interpretation of study results, particularly when there is early attrition as a result of side effects. Accordingly, use of ITT samples is recommended for pharmacotherapy studies (Lavori 1992).

This report emphasizes use of modified ITT samples for metaanalysis. The denominator for the modified ITT was the number randomized to treatment, whereas the numerator was the number who stayed in treatment and got better. This modification was necessary because most studies did not follow-up patients once they exited the study. If some patients who left a study got better anyway (which is quite possible), the modified ITT response rates would be *lower* than those derived from a true intent-to-treat analysis. However, bias across treatment groups is not expected, so that between-treatment comparisons should still be valid. In general, AT samples often reveal 10 to 20% higher response rates than the ITT sample—especially with outpatients.

Overall, 981 cases began treatment with PHZ in controlled clinical trials reporting categorical outcomes, of which 799 completed an adequate treatment trials (i.e., $\geq$3 weeks of therapy) (Table 1). Table 2 reveals that a total of 434 patients began treatment in controlled studies of ISO, of which 373 cases received adequate trials. A total of 293 patients were randomly assigned to TRP in controlled clinical trials with categorical outcomes, of which 244 received adequate treatment trials (Table 3).

Metaanalysis

We used the Confidence Profile Method (CPM) of metaanalysis (Eddy et al. 1990) to calculate the response rates in each study and to provide summary statistics. This method employs a hierarchical Bayesian random-effects model and calculates the probability distribution to describe results expected if a hypothetical additional study (similar to the ones included in the analysis) were to be performed. By taking into account the heterogeneity of study results, the CPM depicts the expected range of results if pharmacotherapists were to use similar treatment protocols and patient samples in practice.

Each metaanalysis produces a probability distribution that depicts the likelihood that the parameter of interest falls within any particular range of values. For example, the metaanalysis result depicted in Figure 1 indicates that the mean (50th percentile) is .05% $\pm$ 6.6%,

Table 1. Acute Phase Trials of Phenelzine (PHZ) in Depression

Author	Diagnostic System, Diagnostic Method	Methods Duration (Weeks)	RX Cells (Dosages)	Randomized (*n*)/ Completers (*n*)	Responders Number (% ITT/% AT[a])	Attrition			Comments
						Side Effect	Lack of Efficacy	Administrative Dropouts	
Agnew et al. (1961)	DSM-I, CLIN	Random, DB (3 weeks)	PHZ (45 mg/d)	4/4	3 (75%/75%)	0	0	0	Inpatients; mixed depressive diagnoses; PHZ = IMI > PBO
			ISO	6/6	2 (33%/33%)	0	0	0	
			IMI (75 mg/d)	6/6	4 (67%/67%)	0	0	0	
			Placebo (PBO)	5/5	0 (0%/0%)	0	0	0	
Rees and Davies (1961)	"Diagnostic Criteria of Royal Bethlehem Hospital"	Random, DB (3 weeks)	PHZ (90 mg/d)	20/20	14 (70%/70%)	0	0	0	Inpatients; PHZ > PBO
			PBO	21/20	7 (33%/35%)	1	0	0	
Leitch and Seager (1963)	CLIN	Random, DB (4 weeks)	PHZ (45 mg/d)	24/22	11 (46%/50%)	NR	NR	NR	Inpatients; endogenous depression; PHZ = IMI
			IMI (150 mg/d)	26/25	15 (58%/60%)	NR	NR	NR	
Martin (1963)	No systematic criteria reported, CLIN	Random, DB (4 weeks)	PHZ (45–60 mg/d)	NR/47	27 (NR/57%)	0	6	2	In- (n = 79) and outpatients (n = 16); endogenous depression; IMI ⩾ PHZ
			IMI (150–200 mg/d)	NR/49	37 (NR/76%)	3	1	0	
Glick (1964)	Depression Rating scale and Global Rating, CLIN	Random, DB (4 weeks)	PHZ ($\bar{x}$ = 55 mg/d)	NR/4	2 (NR/50%)	0	0	0	Outpatients; PHZ = TRP > PBO
			TRP	NR/6	3 (NR/50%)	0	0	0	
			PBO	NR/6	1 (NR/17%)	0	0	0	
Greenblatt et al.[a] (1964)	DSM-I, CLIN	Random (Rx only), DB (3 weeks)	PHZ (60–75 mg/d)	NR/38	19 (NR/50%)	NR	NR	NR	Inpatients; mixed depressive diagnoses; 3 site collaborative study; PHZ = PBO ⩽ IMI < ECT
			IMI (200–250 mg/d)	NR/73	36 (NR/49%)	NR	NR	NR	
			ISO	NR/68	19 (NR/28%)	NR	NR	NR	
			PBO	NR/39	18 (NR/46%)	NR	NR	NR	
			ECT (> 9 treatments)	NR/63	48 (NR/76%)	NR	NR	NR	
Imiah et al. (1964)	No systematic criteria reported, CLIN	Random, single-blind (6 weeks)	PHZ (45 mg/d)	50/40	31 (62%/78%)	NR	NR	NR	Outpatients; PHZ = IMI
			IMI (150 mg/d)	50/41	34 (68%/83%)	NR	NR	NR	
Schildkraut et al. (1964)	DSM-I, CLIN	Random (3 weeks)	PHZ (45–60 mg/d)	6/6	5/6 (83%/83%)	0	0	0	Inpatients; PHZ = IMI > PBO
			IMI (100–200 mg/d)	6/6	5/6 (83%/83%)	0	0	0	
			PBO	5/5	0/5 (0%/0%)	0	0	0	
Brit. Med. Res. Coun. (1965)	No systematic criteria reported, CLIN	Random (Rx only), DB (4 weeks)	PHZ (60 mg/d)	65/50	19[b] (29%/38%)	1	10	4	Inpatients; predominantly endogenous; PHZ = PBO < IMI < ECT
			IMI (200 mg/d)	65/58	42[b] (65%/72%)	2	3	2	
			PBO	65/51	23[b] (35%/45%)	1	9	4	
			ECT (4–8 treatments)	65/58	49[b] (75%/84%)	2	5	9	

(continued)

Table 1. *(continued)*

Author	Diagnostic System, Diagnostic Method	Methods Duration (Weeks)	RX Cells (Dosages)	Randomized (*n*)/ Completers (*n*)	Responders Number (% ITT/% AT[b])	Attrition: Side Effect	Attrition: Lack of Efficacy	Attrition: Administrative Dropouts	Comments
Kay et al. (1973)	Newcastle Rating Scale, CLIN	Random, DB (4 weeks)	PHZ (45 mg/d)	31/27	18 (58%/67%)	0	2	2	Oupatients; non-endogenous depression; PHZ = IMI (intention to treat); PHZ ⩽ AMI completers only)
			AMI (150 mg/d)	31/18	15 (48%/83%)	5	5	3	
Robinson et al. (1973)	Structured Interview Depression, DSM-II	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 58.5 mg/d)	44/33	21 (47%/64%)	NR	NR	NR	Outpatients with nonendogenous depression; PHZ > PBO
			PBO	43/27	10 (23%/37%)	NR	NR	NR	
Raskin et al. (1974)	DSM-II, CLIN	Random, DB (4 weeks)	PHZ ($\bar{x}$ = 45.5 mg/d)	110/78	50[c] (45%/64%)	3	28	8	Inpatients; mixed diagnoses; 9 site collaborative study; PHZ = PBO
			PBO	111/81	49[c] (44%/60%)	0	32	11	
Ravaris et al. (1976)	Structured Diagnostic Interview, CLIN	Random, DB (6 weeks)	PHZ (total)	41/30	11 (27%)	0	2	9	Outpatients; predominantly nonendogenous; PHZ (60 mg) > PBO = PHZ (30 mg)
			60 mg/d	20/14	10 (50%)	0	1	5	
			30 mg/d	21/16	1 (5%)	0	1	4	
			AMI (150 mg/d)	21/19	4 (19%)	0	1	1	
Davidson et al. (1977)	Criteria of Feighner et al., CLIN	Random, DB (3 weeks)	PHZ (90 mg/d)	4/4	2 (50%)	0	0	0	Inpatients; PHZ = IMI
			IMI (150 mg/d)	6/6	3 (50%)	0	0	0	
Ravaris et al. (1980)	SDI, RDC	Random, DB (6 weeks)	PHZ (60 mg/d)	68/55	47 (69%/85%)	NR	NR	NR	Outpatients; predominantly nonendogenous; PHZ = AMI
			AMI (150 mg/d)	61/49	43 (70%/88%)	NR	NR	NR	
Hamilton (1982)	Criteria of Feighner et al., CLIN	Random (Rx only), open label	PHZ (45–90 mg/d)	NR/65	21 (NR/32%)	NR	NR	NR	Mixed in- and outpatients (majority of Rx cases are outpatients); melancholia; newly referred depressed; PHZ ⩽ IMI < ECT
			IMI (150–225 mg/d)	NR/65	28 (NR/43%)	NR	NR	NR	
			ECT (6–12 treatments)	NR/146	99 (NR/68%)	NR	NR	NR	

Rowan et al. (1982)	RDC, Newcastle Rating Scale, CLIN	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 75 mg/d)	58/42	35 (60%/83%)	4	2	10	Outpatients; non-endogenous; PHZ = AMI > PBO
			AMI ($\bar{x}$ = 188 mg/d)	62/44	41 (66%/93%)	3	4	11	
			PBO	56/45	33 (59%/73%)	1	3	7	
Kayser et al. (1985)	RDC, SDI	Random, DB (6 weeks)	PHZ (60 mg/d)	NR/23	20 (NR/58%)	NR	NR	NR	Outpatients; PHZ = AMI; In "hysteroid dysphoria," PHZ (9/9) > AMI (3/5)
			AMI (150 mg/d)	NR/24	18 (NR/75%)	NR	NR	NR	
Georgotas et al. (1986)	RDC, CLIN	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 54 mg/d)	30/20	13 (43%/57%)	2	0	8	Outpatients; age 55–75; PHZ = NTP > PBO
			NTP ($\bar{x}$ = 79 mg/d)	30/23	15 (43%/65%)	2	0	5	
			PBO	30/19	3 (10%/16%)	0	11	2	
Kayser et al. (1988)	DSM-III, SDI	Random, DB (6 weeks)	PHZ (60 mg/d)	NR/12	9 (NR/75%)	NR	NR	NR	Outpatients; DSM III melancholia; PHZ = AMI
			AMI (150 mg/d)	NR/12	8 (NR/67%)	NR	NR	NR	
Liebowitz et al. (1988)	RDC, CLIN	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 73 mg/d)	56/34	32[f] (57%/94%)	6	0	16	Outpatients; atypical major and minor depression; PHZ > IMI > PBO
			IMI ($\bar{x}$ = 255 mg/d)	52/38	22[f] (42%/58%)	5	0	9	
			PBO	55/47	13 (24%/28%)	5	0	3	
Quitkin et al. (1988)[e]	RDC, CLIN	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 72 mg/d)	24/17	12 (50%/74%)	NR	NR	NR	Outpatients; probable atypical major and minor depression; PHZ ≥ IMI = PBO; PHZ > PBO
			IMI ($\bar{x}$ = 267 mg/d)	23/19	9 (39%/47%)	NR	NR	NR	
			PBO	27/24	7 (26%/29%)	NR	NR	NR	
Quitkin et al. (1989)[e]	RDC, CLIN	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 71 mg/d)	26/20	18[f] (69%/90%)	2	0	4	Outpatients; mood reactive, major and minor depression; PHZ = IMI > PBO
			IMI ($\bar{x}$ = 259 mg/d)	27/19	15[f] (56%/79%)	4	0	4	
			PBO	27/20	5 (19%/25%)	0	0	6	

(continued)

Table 1. *(continued)*

Author	Diagnostic System, Diagnostic Method	Methods Duration (Weeks)	RX Cells (Dosages)	Randomized (*n*)/ Completers (*n*)	Responders Number (% ITT/% AT[h])	Attrition			Comments
						Side Effect	Lack of Efficacy	Administrative Dropouts	
Quitkin et al. (1990)[e]	RDC, CLIN	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 73 mg/d)	33/30	25 (76%/83%)	1	0	2	Outpatients; atypical major and minor depression; PHZ > IMI ⩾ PBO
			IMI ($\bar{x}$ = 270 mg/d)	37/34	17 (46%/50%)	0	0	3	
			PBO	34/26	5 (15%/19%)	2	0	6	
Quitkin et al. (1991)[e]	RDC, CLIN	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 69 mg/d)	43/35	22 (51%/63%)	NR	NR	NR	Outpatients; atypical major and minor depression patients who failed 6 weeks of placebo treatment; PHZ > IMI
			IMI ($\bar{x}$ = 276 mg/d)	37/29	10 (27%/34%)	NR	NR	NR	
McGrath et al. (1993)	RDC, CLIN	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 75 mg/d[g])	56/45	31 (55%/69%)	NR	NR	NR	Outpatients; probable or definite atypical major and minor depression patients who failed treatment with the other compound PHZ > IMI
			IMI ($\bar{x}$ = 274 mg/d[g])	33/22	9 (27%/41%)	NR	NR	NR	

Abbreviations: DB = double blind; PHZ = phenelzine; ISO = isocarboxazid; IMI = imipramine; PBO = placebo; TRP = tranylcypromine; ECT = electroconvulsive therapy; AMI = amitriptyline; NTP = nortriptyline; CMI = clomipramine; 5-HTP = 5-hydroxytryptamine; TRI = trimipramine; NR = not reported.

[a] Marked improvement only as employed in this study (the moderate improvement rating does not appear to correspond to the contemporary use of CGI score of 2).

[b] Number of responses calculated from author's reported percentages.

[c] Response rate estimated. Apparently, all nonresponders were removed from the study by week 4.

[d] SEM instead of SD.

[e] Patients completing >4 weeks are considered completers.

[f] Includes responders who could not tolerate ⩾4 tabs study Rx.

[g] Dosages reported only for nonresponders.

[h] ITT = intention to treat; AT = adequately treated or protocol completers.

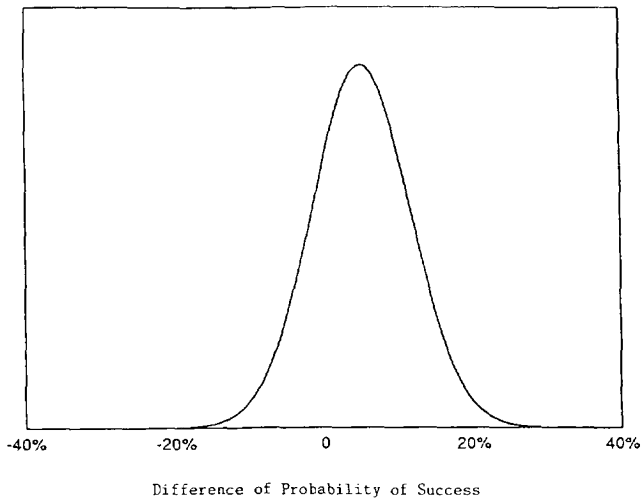

Figure 1. Graphic results representation of metaanalysis.

that 95% of the area of the curve (the Bayesian equivalent of a 95% confidence interval) lies between −8.0% and 17.7%, (i.e., there is a 22.5% chance that the actual value is less than zero). With this probability distribution, the reader can determine the probability that the true effect of treatment is greater than, less than, or equal to any selected value. Because space considerations preclude graphic presentations, the summary calculations report the number of studies used in the calculation, the mean, and the standard deviation. The latter variable serves as an indicator of the shape of the distribution. Distributions with smaller standard deviations relative to the mean are tall and narrow, indicating a higher degree of certainty of the result.

Undue significance should not be attached to small differences found by metaanalysis. Figure 2 depicts the results of two metaanalyses, one for treatment A, with a success rate of 34% (±12%), and one for treatment B, with a success rate of 28% (±11%). Although comparison of the means reveals that A is 6% better than B, there is about a 34% chance that B is actually better than A. Therefore, it is not certain that A was superior.

On the other hand, metaanalysis may show that several different treatments have similar response rates. This finding does not logically lead to the assertion that the two treatments are equivalent in actual practice unless it can be shown that the same patients respond to both treatments. The evidence suggesting biological heterogeneity among patients with major depressive disorder (e.g., Thase et al. 1985; Goodwin and Jamison 1990; Rush et al. 1991) is most compatible with the notion of differential response to medication. For example, some treatments may be effective earlier in the course of recurrent mood disorders, whereas others may be better in more chronic or recurrent cases (e.g., Post 1992). Further, basic pharmacology and clinical studies provide evidence that patients differ in the nature, likelihood, and severity of side effects experienced with a particular type of antidepressant medication. Heterogeneity with regard to side effects may make equivalently effective drugs based on trial data differently effective for a particular patient.

Limitations of Metaanalysis

There are several threats to the internal validity of metaanalysis. First, although the random effects model accounts for among-study variations and, in so doing, controls for random bias, it cannot account for systematic biases occurring across studies. Second, to be included in the metaanalysis, studies had to present sufficient data to permit calculation of the percent response for each treatment based on an ITT analysis. If studies without sufficient data fundamentally differed from those included, summary statistics may be biased. Similarly, a variety of publication biases (particularly the tendency to publish only those studies whose results reject the null hypothesis) could result in biased summary statistics. On the other hand, the hierarchical random effects model is very robust. Sensitivity analyses reveal that it would take a huge number of very large studies to change our results in any important way, if at least four studies are included in the metaanalysis and if the standard deviation is modest in relation to the mean difference between treatments.

Threats to the external validity of this metaanalysis are primarily related to the generalizability of patient groups studied. Although RCTs provide the best evidence for the efficacy of a treatment in a specific type of patient, stringent enrollment criteria, unique treatment settings, and unrepresentative clinical procedures may limit applicability to practice in general. Methods

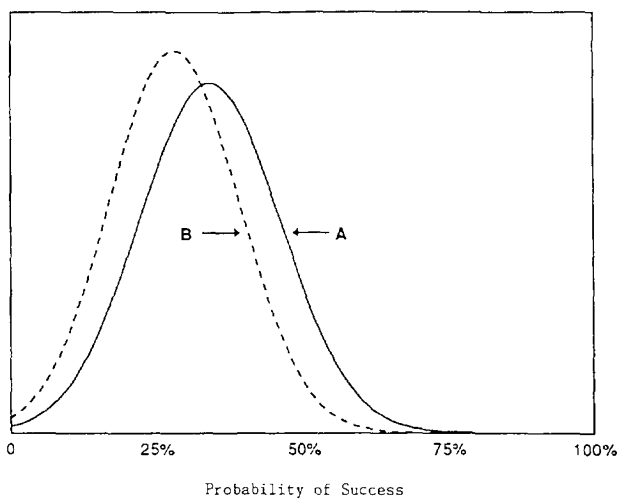

Figure 2. Comparison of metaanalysis results for treatments A and B.

Table 2. Acute Phase Trials of Isocarboxazid (ISO) in Depression

Author	Diagnostic System, Diagnostic Method	Method Duration (Weeks)	Rx Cells (Dosages)	Randomized (*n*)/ Completers (*n*)	Responders Number (% ITT/%AT[a])	Attrition			Comments
						Side Effects	Lack of Efficacy	Administrative Dropouts	
Ford et al. (1959)	No systematic method, CLIN	Random, DB (12 weeks)	ISO (20–30 mg/d)	15/12	12 (80%/100%)	1	0	3	Outpatients;
			PBO	9/8	1 (11%/13%)	0	0	1	ISO > PBO
Agnew et al. (1961)	DSM-I, CLIN	Random, DB (3 weeks)	ISO (20 mg/d)	6/6	2 (33%/33%)	0	0	0	Inpatients; mixed diagnoses with depressive features
			IMI (75 mg/d)	6/6	4 (67%/67%)	0	0	0	
			PHZ	4/4	3 (75%/75%)	0	0	0	
			PBO	5/5	0 (0%/0%)	0	0	0	
Joshi (1961)	No systematic method, CLIN	Random, DB (12 weeks)	ISO (30 mg/d)	26/22	13 (50%/59%)	2	2	0	Inpatients; mixed diagnoses with depressive features; ISO > PBO
			PBO	27/18	3 (11%/17%)	1	8	0	
Rothman et al. (1962)	DSM-I, CLIN	Random, DB	ISO (40 mg/d)	33/22	16 (48%/73%)	NR	NR	NR	Inpatients; mixed diagnoses with depressive features; ISO = IMI ⩾ PBO
			IMI (150 mg/d)	30/25	17 (57%/68%)	NR	NR	NR	
			PBO	26/17	10 (38%/59%)	NR	NR	NR	
Greenblatt et al. (1964)	DSM-I, CLIN	Random, DB (4 weeks)	ISO, (40–50 mg/d)	NR/68	19 (NR/28%)	NR	NR	NR	Inpatients; ISO ⩽ PBO ⩽ IMI = PHZ < ECT
			IMI (200–250 mg/d)	NR/73	36 (NR/49%)	NR	NR	NR	
			PHZ	NR/38	19 (NR/50%)	NR	NR	NR	
			PBO	NR/39	18 (NR/46%)	NR	NR	NR	
			ECT ⩾ 9 treatments	NR/63	48 (NR/76%)	NR	NR	NR	
Richmond and Roberts (1964)	No systematic method, CLIN	Random, DB (3 week trial)	ISO (40 mg/d)	NR/20	12 (NR/60%)	NR	NR	NR	Outpatients; ISO > pooled AMI + IMI
			TRP	38/20	12 (32%/60%)	NR	NR	NR	
			AMI (150 mg/d)	NR/20	6 (NR/30%)	NR	NR	NR	
			IMI (225 mg/d)	NR/20	6 (NR/30%)	NR	NR	NR	

Schorer et al. (1966)	DSM-I, CLIN	Random, DB (12 weeks)	ISO (60 mg/d) IMI (200 mg/d) PBO	NR/12 NR/11 NR/10	4 (NR/33%) 9 (NR/82%) 5 (NR/50%)	NR NR NR	NR NR NR	NR NR NR	Outpatients; ISO = PBO ⩽ IMI (48% attrition)
Kurland et al. (1967)	DSM-I, CLIN	Random, DB (3 weeks)	ISO (30 mg/d) PBO	75/65 70/59	53 (71%/82%) 47 (67%/80%)	0 0	7 2	3 9	Inpatients (2 site, state hospital study); ISO = PBO[b]
Hays and Steinert (1969)	No systematic criteria, CLIN	Random, DB (3 weeks)	ISO (30 mg/d) NTP (100 mg/d)	21/19 19/17	12 (57%/63%) 9 (49%/53%)	NR NR	NR NR	NR NR	Outpatients; ISO = NOR (not including cross-overs); ISO ⩾ NOR (including crossovers)
		Including crossover	ISO, NTP	25/23 23/21	14 (56%/61%) 9 (39%/43%)	NR NR	NR NR	NR NR	
Giller et al. (1984)	DSM-III RDC, CLIN	Unblinded crossover of PBO failures (4 weeks[c])	ISO (40 mg/d) PBO	16/16 30/22	11 (69%/69%) 4 (38%/18%)	0 NR	0 NR	0 NR	Outpatients; ISO > PBO
Davidson et al. (1988)[d]	RDC, DSM-III, CLIN	Random, DB (6 weeks[c])	ISO ($\bar{x}$ = 49 mg/d) PBO	87/68 87/62	45 (52%/66%) 20 (23%/32%)	10 3	1 11	8 11	Outpatients; 3 site multicentered trial; ISO > PBO at all 3 sites
Larsen et al. (1991)	DSM-III, Newcastle Rating Scale, CLIN	Random, DB (6 weeks)	ISO (30–40 mg/d) CMI (150–200 mg/d)	51/39 57/39	33 (65%/85%) 35 (61%/90%)	3 3	4 10	5 5	Outpatients; multicentered trial; ISO = CMI

Abbreviations: DB = double blind; PHZ = phenelzine; ISO = isocarboxazid; IMI = imipramine; PBO = placebo; TRP = tranylcypromine; ECT = electroconvulsive therapy; AMI = amitriptyline; NTP = nortriptyline; CMI = clomipramine; 5-HTP = 5-hydroxytryptamine; TRI = trimipramine; NR = not reported.

[a] ITT = intention to treat; AT = adequately treated or completed samples.

[b] Site interaction: Outcome at Crownsville site superior to Spring Grove site ($p < 0.0001$); outcome for ISO > PBO at Crownsville, but not Spring Grove. Categorical outcome not reported by site.

[c] 3 weeks treatment required to be considered as a completer.

[d] Includes the individual studies of Davidson and Turnbull (1983); Zisook (1983); and Giller et al. (1984).

Table 3. Acute Phase Trials of Tranylcypromine (TRP) in Depression

Author	Diagnostic System, Diagnostic Method	Method Duration (Weeks)	Rx Cells (Dosages)	Randomized (*n*)/ Completers (*n*)	Responders Number (%ITT/% AT[a])	Attrition			Comments
						Side Effects	Lack of Efficacy	Administrative Dropouts	
Bartholomew (1962)	No systematic diagnostic criteria, CLIN	Random, DB (6 weeks)	TRP ($\bar{x}$ = 43 mg/d)	51/42	27 (53%/64%)	4	1	4	Outpatients; TRP > PBO
			PBO	51/49	22 (43%/45%)	0	0	2	
Gottfries (1963)	No systematic method, CLIN	Random, DB (15 days)	TRP (30 mg/d)	NR/25	6 (NR/24%)	0	0	0	Inpatients; TRP = PBO
			PBO	NR/25	2 (NR/8%)	0	0	0	
Glick (1964)	Depression Rating Scale + Global Rating, CLIN	Random, DB (14 weeks)	TRP (37 mg/d)	NR/4	2 (NR/50%)	NR	NR	NR	Outpatients; sample too small to ascertain significance
			PHZ	NR/6	3 (NR/50%)	NR	NR	NR	
			PBO	NR/6	1 (NR/17%)	NR	NR	NR	
Richmond and Roberts (1964)	No systematic criteria, CLIN	Random, DB (3 weeks)	TRP (40 mg/d)	NR/20	10 (NR/50%)	NR	NR	NR	Outpatients; TRP > AMI + IMI
			ISO	38/20	12 (32%/60%)	NR	NR	NR	
			AMI (150 mg/d)	NR/20	6 (NR/30%)	NR	NR	NR	
			IMI (225 mg/d)	NR/20	6 (NR/30%)	NR	NR	NR	
Spear et al. (1964)	No systematic criteria, CLIN	Random, DB (3 weeks)	TRP (30 mg/d)	37/34	NR	0	3	0	Inpatients and outpatients (proportion not specified); TRP = IMI
			IMI (150 mg/d)	41/36	NR	0	5	0	
Himmelhoch et al. (1982)	RDC, SADS	Random, DB (6 weeks[b])	TRP (40 mg/d)	28/22	20 (71%/91%)	2	6	0	Outpatients; predominantly bipolar; anergic depression; TRP > PBO
			PBO	31/17	4 (13%/24%)	0	14	0	
Razani et al. (1983)	DSM-III, CLIN	Random, DB (4 weeks)	TRP (40 mg/d)	25/21	16 (64%/76%)	4	0	0	Inpatients (57%) and outpatients (43%); TRP = AMI
			AMI (293 mg/d)	28/20	15 (54%/75%)	8	0	0	
White et al. (1984)	RDC, CLIN	Random, DB (4 weeks)	TRP ($\bar{x}$ = 44 mg/d)	63/37	25 (40%/68%)	NR	NR	NR	Outpatients; TRP = NTP ⩾ PBO; TRP > PBO
			NTP (109 mg/d)	61/40	25 (41%/63%)	NR	NR	NR	
			PBO	59/45	19 (32%/42%)	NR	NR	NR	

Nolen et al. (1985)	DSM-III, CLIN	Random, open (4 weeks)	First phase					Inpatients; resistant to serial trials of tricyclics, oxaprotiline, fluvoxamine, and sleep deprivation; TRP > 5-HTP
			TRP ($\bar{x}$ = 82 mg/d)	14/14	8 (57%/57%)	0	0	0
			5-HTP ($\bar{x}$ = 182 mg/d)	12/12	0 (0%/0%)	0	0	0
			Crossover of failures					
			TRP	12/12	8 (67%/67%)	0	0	0
			5-HTP	5/5	0 (0%/0%)	0	0	0
			Pooled					
			TRP	26/26	16 (62%/62%)	0	0	0
			5-HTP	17/17	0 (0%/0%)	0	0	0
Nolen et al. (1988)	DSM-III, CLIN	Random, DB (4 weeks)	TRP ($\bar{x}$ = 78 mg/d)	11/11	5 (45%/45%)	0	0	0
			Nomifensine ($\bar{x}$ = 235 mg/d)	10/10	1 (10%/10%)	0	0	0
Himmelhoch et al. (1991)	DSM-III, RDC, CLIN	Random, DB (6 weeks[b])	TRP ($\bar{x}$ = 36.8 mg/d)	28/26	21 (32%/81%)	4[c]	0	1
			IMI (246 mg/d)	28/21	10 (36%/48%)	10[c]	0	2
Thase et al. (1992)	DSM-III, RDC, CLIN	Up to 6 weeks[b] DB for nonresponders of Himmelhoch et al. 1991	TRP ($\bar{x}$ = 39.2 mg/d)	12/10	9 (75%/90%)	0	0	0
			IMI ($\bar{x}$ = 150 mg/d)	4/3	1 (25%/33%)	3[c]	0	0

Abbreviations: DB = double blind; PHZ = phenelzine; ISO = isocarboxazid; IMI = imipramine; PBO = placebo; TRP = tranylcypromine; ECT = electroconvulsive therapy; AMI = amitriptyline; NTP = nortriptyline; CMI = clomipramine; 5-HTP = 5-hydroxytryptamine; TRI = trimipramine; NR = not reported.

[a] ITT = intention to treat; AT = adequately treated or protocol completers.

[b] 4 weeks of treatment required to be considered as a completer.

[c] Includes hypomanic and manic mood swings as adverse results.

Table 4. Acute Phase Trials of Monoamine Oxidase Inhibitors in with Depression Reporting Only Continuous Outcomes

Author	Diagnostic System, Diagnostic Method	Methods Duration (Weeks)	RX Cells (Dosages)	Randomized (*n*)/ Completers (*n*)	Responders Number (%ITT/%AT[a])	Attrition			Comments
						Side Effects	Lack of Efficacy	Administrative Dropouts	
Overall et al. (1962)	DSM-I, CLIN	Random, DB (3 weeks)	ISO (30 mg/d)	~51/NR	NR	NR	NR	NR	Inpatients; predominately male; 32 multi-centered VA trial; PHZ = PBO < IMI
			IMI (225 mg/d)	~51/7	NR	NR	NR	NR	
			PBO	~51/7	NR	NR	NR	NR	
Khanna (1963)	No systematic method, CLIN	Random, DB (2 weeks)	TRP (30 mg/d)	15/15	NR	0	0	0	Inpatients (females); TRP > PBO (multivariate analysis)
			PBO	15/14	NR	1	0	0	
			Slow acetylators		Final HRSD				
Johnstone and Marsh (1973)	Newcastle Rating Scale, Standardized Interview of Goldberg et al.	Random, DB (3 weeks includes crossover phase)	PHZ (45–90 mg/d)	NR/16	2.2 (2.5)	NR	NR	NR	Outpatients; predominantly nonendogenous; PHZ > PBO in slow acetylators; PHZ = PBO in fast acetylators
			PBO	NR/23	8.4 (5.8)	NR	NR	NR	
			Fast acetylators						
			PHZ (45–90 mg/d)	NR/10	5.8 (4.6)	NR	NR	NR	
			PBO	NR/23	5.8 (4.4)	NR	NR	NR	
					Final Depression Score[b]				
Young et al. (1979)	Criteria not specified, CLIN	Random, DB (6 weeks)	PHZ ($\bar{x}$ = 45 mg/d), or ISO ($\bar{x}$ = 32 mg/d)	50/46	15.0 (NR)	NR	NR	NR	Outpatients; TRI > MAOI
			TRI ($\bar{x}$ = 106 mg/d)	34/30	11.8 (NR)	NR	NR	NR	

					Final				
Davidson et al. (1981)	Criteria of Feighner et al., New Castle Diagnostic, Rating, CLIN	Random, DB (3 weeks)	PHZ ($\bar{x}$ = 81 mg/d)	24/21	11.4 (2.1)[c]	0	0	3	Inpatients; PHZ = IMI
			IMI ($\bar{x}$ = 144 mg/d)	25/22	12.9 (2.5)[c]	0	0	3	
					Final HRSD				
Raft et al. (1981)	Criteria of Feighner et al., CLIN	Random, DB (5 weeks)	PHZ ($\bar{x}$ = 90 mg/d)	10/10	7.4 (4.6)	0	0	0	1 week inpatient followed by 4 weeks outpatient; patient recruited from a pain clinic; PHZ > AMI > PBO
			AMI ($\bar{x}$ = 235 mg/d)	12/7	19.8 (2.2)	5	0	0	
			PBO	7/6	25.3 (4.0)	1	0	0	
					Final HRSD				
Davidson et al. (1987)	RDC Newcastle Scale, CLIN	Random, DB (5 weeks)	PHZ (75–90) mg/d)	13/13	10.6 (6.7)	0	0	0	Outpatients; nonendogenous (95%) with anxious or atypical features; PHZ = IMI
			IMI (150 mg/d)	13/13	15.9 (9.8)	1	0	0	
				Melancholia	Final HRSD				
Vallejo et al. (1987)	DSM-III, CLIN	Random, DB (6 weeks)	PHZ (75 mg/d)	17/16	10.6 (7.1)	1	0	0	Outpatients, melancholic and dysthymic subgroups; melancholia: PHZ ≤ IMI; dysthymia: PHZ > IMI
			IMI (250 mg/d)	17/16	7.1 (5.5)	0	1	0	
				Dysthymia	Final HRSD				
			PHZ (75 mg/d)	19/16	7.3 (3.2)	3	0	0	
			IMI (250 mg/d)	20/16	10.4 (5.1)	4	0	0	

Abbreviations: DB = double blind; PHZ = phenelzine; ISO = isocarboxazid; IMI = imipramine; PBO = placebo; TRP = tranylcypromine; ECT = electroconvulsive therapy; AMI = amitriptyline; NTP = nortriptyline; CMI = clomipramine; 5-HTP = 5-hydroxytryptamine; TRI = trimipramine; NR = not reported.

[a] ITT = intention to treat; AT = adequately treated or protocol completers.

[b] Depression scale other than HRSD. Please refer to source.

[c] SEM rather than of SD.

to address this problem are under development (see Cross Design Synthesis: A New Strategy for Medical Effectiveness Research, U.S. Government Accounting Office, B244808 1992); however, the following three limitations should be kept in mind.

First, whereas most studies entered a well-characterized patient group (e.g., nonpsychotic outpatients with major depressive disorder), others included *unspecified* numbers of patients with psychotic subforms or bipolar disorder. Most studies did not specify whether more chronic or treatment refractory conditions were included or excluded. Without knowledge of the exact case mix in each study, some caution regarding generalizability is advisable.

Secondly, most trials were performed in academic psychiatric settings and enrolled patients *without* other significant psychiatric or serious general medical comorbidity. Such patients might be expected to be more treatment responsive than a more heterogeneous, truly representative sample in practice (i.e., patients enrolled in trials may not be fully representative of populations of interest).

Thirdly, although RCTs are conducted by prespecified protocols, these treatment procedures may differ substantially from routine practice. These differences consequently may affect outcome and generalizability to community practice.

RESULTS

Phenelzine (PHZ)

Outpatient Studies. A total of 23 RCTs of PHZ were identified, of which 14 were available for metaanalysis for the modified ITT analysis and 16 for the AT analysis (Table 5). The overall efficacy in outpatients was 57.9% (±4.0%) using the ITT sample, whereas it was 70.6% (±11.1%) with the AT sample.

A total of 11 RCTs in outpatients compared PHZ with PBO (Glick 1964; Johnstone and Marsh 1973; Robinson et al. 1973; Ravaris et al. 1976; Raft et al. 1981; Rowan et al. 1982; Georgotas et al. 1986; Liebowitz et al. 1988; Quitkin et al. 1988, 1989, 1990) (Table 1). The study by Ravaris et al. (1976) provided two contrasts (30 mg/day and 60 mg/day of PHZ) against PBO. For the metaanalysis, we chose only the 60 mg/day group. Virtually all of these studies concerned patients with nonpsychotic major depressive disorder, although only those studies published after 1982 consistently used prospectively determined, standardized diagnostic nomenclature, such as Research Diagnostic Criteria (RDC) (Spitzer et al. 1978) or the DSM-III (APA, 1980).

Based on the ITT sample, the overall efficacy for PHZ was 54.3% (±9.6%) in the 10 PHZ cells categorically reported in PBO-controlled studies. This response rate is comparable with those found in similar analyses

Table 5. CPM of Acute Phase Treatment Trials Reporting Categorical Outcomes for Phenelzine (PHZ) in Depressed Outpatients[a]

Study	(Drug Comparator)	Overall Efficacy		PHZ vs. PBO		PHZ vs. DRUG	
		ITT	AT	ITT	AT	ITT	AT
Glick 1964	(NA)	50.0 (17.7)	NA	28.6 (22.9)	NA	NA	NA
Imiah et al. 1964	(IMI)	61.8 (6.7)	76.8 (6.5)	NA	NA	−5.9 (9.4)	−5.3 (8.7)
Robinson et al. 1973	(NA)	47.8 (7.4)	63.2 (8.2)	23.9 (9.7)	25.7 (12.1)	NA	NA
Kay et al. 1973	(AMI)	57.8 (8.6)	66.1 (8.8)	NA	NA	9.4 (12.2)	−15.5 (12.4)
Ravaris et al. 1976[b]	(NA)	50.0 (10.7)	70.0 (11.5)	29.6 (13.6)	47.5 (14.6)	NA	NA
Ravaris et al. 1980	(AMI)	68.8 (5.5)	84.8 (4.8)	NA	NA	−1.3 (8.0)	−0.5 (6.8)
Rowan et al. 1982	(AMI)	60.2 (6.3)	82.6 (5.7)	1.4 (9.0)	9.7 (8.6)	−5.7 (8.7)	−9.7 (7.0)
Hamilton 1982	(NA)	NA	32.6 (5.7)	NA	NA	NA	−10.6 (8.3)
Liebowitz et al. 1984	(NA)	NA	65.6 (11.5)	NA	35.6 (14.6)	NA	22.4 (15.5)
Kayser et al. 1985	(NA)	NA	95.0 (6.6)	NA	NA	NA	36.7 (19.8)
Georgotas et al. 1986	(NT)	43.6 (8.8)	64.3 (10.2)	32.3 (10.4)	46.8 (13.2)	−6.4 (12.4)	−0.3 (14.0)
Kayser et al. 1988	(NA)	NA	73.1 (11.8)	NA	NA	NA	7.7 (17.4)
Liebowitz et al. 1988	(IMI)	57.0 (6.5)	70.0 (7.6)	32.9 (8.6)	41.9 (10.0)	14.6 (9.4)	20.0 (11.0)
Quitkin et al. 1988	(IMI)	50.0 (9.8)	69.4 (10.6)	23.2 (12.8)	39.4 (13.9)	10.4 (13.9)	21.9 (15.2)
Quitkin et al. 1989	(IMI)	68.5 (8.8)	88.1 (6.9)	48.9 (11.5)	61.9 (11.6)	13.2 (12.7)	10.6 (11.4)
Quitkin et al. 1990	(IMI)	75.0 (7.3)	82.3 (6.8)	59.3 (9.5)	61.9 (10.2)	29.0 (10.8)	32.3 (10.7)
Quitkin et al. 1991	(IMI)	51.1 (7.4)	70.8 (7.5)	NA	NA	23.5 (10.3)	27.5 (11.7)
McGrath et al. 1993	(IMI)	55.3 (6.5)	NA	NA	NA	27.3 (10.0)	NA
Total		57.9 (4.0) [14][c]	70.6 (11.1) [16]	29.5 (11.1) [9]	38.5 (13.1) [9]	8.8 (8.3) [11]	6.1 (1.9) [14]

Abbreviations: AMI = amitriptyline; IMI = imipramine; NT = nortriptyline; NA = no data available; PHZ = phenelzine; PBO = placebo; ITT = intention to treat; AT = adequate treatment.

[a] Figures are % responders; standard deviations are in parentheses.

[b] Includes only the 60 mg/d PHZ cell.

[c] Bracketed numbers represent the number of studies used in the calculation.

Table 6. CPM of Acute Phase Treatment Trials Reporting Categorical Outcomes for Phenelzine (PHZ) in Depressed Inpatients[a]

Study	(Drug Comparator)	Overall Efficacy		PHZ vs. PBO		PHZ vs. DRUG	
		ITT	AT	ITT	AT	ITT	AT
Agnew et al. 1961	(IMI)	90.0 (18.7)	NA	61.7 (21.4)	NA	5.7 (25.2)	NA
Rees and Davies 1961	(NA)	69.1 (9.9)	69.0 (9.8)	35.0 (14.0)	33.3 (14.2)	NA	NA
Leitch and Seager 1963	(IMI)	46.0 (9.8)	50.0 (10.2)	NA	NA	−11.4 (13.5)	−9.6 (13.9)
Martin 1963	(NA)	NA	57.3 (7.1)	NA	NA	NA	−17.7 (9.3)
Greenblatt et al. 1964	(NA)	NA	50.0 (7.9)	NA	3.8 (11.1)	NA	0.7 (9.8)
Schildkraut et al. 1964	(IMI)	78.6 (14.5)	NA	70.2 (17.9)	NA	0.0 (20.5)	NA
British Medical Research Council 1965	(IMI)	29.6 (5.6)	38.2 (6.7)	−6.1 (8.1)	−7.0 (9.6)	−34.9 (8.1)	−33.8 (8.9)
Raskin et al. 1974	(NA)	45.5 (4.7)	63.9 (5.4)	1.3 (6.6)	3.6 (7.6)	NA	NA
Davidson et al. 1977	(IMI)	50.0 (20.4)	NA	NA	NA	0.0 (27.0)	NA
Total		49.5 (14.0) [7]	54.5 (7.3) [6]	22.3 (30.7) [5]	5.2 (13.1) [14]	−21.0 (7.7) [5]	−15.8 (12.3) [4]

Abbreviations: IMI = imipramine; NA = no data available; PHZ = phenelzine; PBO = placebo; ITT = intention to treat; AT = adequate trial.

[a] Figures are % responders; standard deviations are in parentheses; number of studies used in calculations appears in brackets.

for TCAs (Depression Guideline Panel, 1993). Based on ITT metaanalysis, the PHZ-PBO difference was 29.5% (±11.1%). This was based on nine outpatient comparisons, after excluding the 30 mg/day group of Ravaris et al. (1976). Based on the AT sample (nine outpatient comparisons, again excluding the Ravaris et al. 30 mg/day group), the PHZ-PBO difference was 38.5% (±13.1%).

Two PBO-controlled outpatient trials of PHZ did not report categorical response rates (Johnstone and Marsh 1973; Raft et al. 1981). Both studies found significant improvements in standard depression ratings favoring PHZ over PBO (see Table 4).

Twenty contrasts from 18 reports compared response to PHZ against standard TCAs in controlled outpatient trials (see Table 1; Imiah et al. 1964; Kay et al. 1973; Young et al. 1979; Ravaris et al. 1980; Raft et al. 1981; Hamilton 1982; Rowan et al. 1982; Kayser et al. 1985, 1988; Georgotas et al. 1986; Davidson et al. 1987; Vallejo et al. 1987; Liebowitz et al. 1988; Quitkin et al. 1988, 1989, 1990, 1991; McGrath et al. 1993). The vast majority of patients in these studies appeared to have met current criteria for major depressive disorder, whereas most of the remaining patients would have met criteria for dysthymic disorder using the current nomenclature. PHZ doses ranged from 45 to 90 mg/day. Among these 20 contrasts, one each was with nortriptyline (NOR) and trimipramine (TRI), 11 were with imipramine (IMI), and seven were with amitriptyline (AMI).

Comparisons of PHZ against these standard TCAs was possible on 11 of 20 available contrasts for the ITT sample and on 14 of 20 available contrasts for the AT sample. Overall, there was a modest but reliable advantage (8.8 ± 8.3%) favoring PHZ over comparator antidepressants in outpatients using the ITT sample. However, many of these studies restricted enrollment to patients with features of atypical or nonendogenous depression (Kay et al. 1973; Ravaris et al. 1980; Raft et al. 1981; Rowan et al. 1982; Kayser et al. 1985; Davidson et al. 1987; Liebowitz et al. 1988; Quitkin et al. 1988, 1990, 1991; McGrath et al. 1993). In the eight studies of atypical or nonendogenous depression suitable for metaanalysis (Kay et al. 1973; Ravaris et al. 1980; Rowan et al. 1982; Liebowitz et al. 1988; Quitkin et al. 1988, 1990, 1991; McGrath et al. 1993), there was a significant advantage for PHZ over TCAs. The PHZ-TCA difference was 11.8% (±8.4%) based on the ITT sample. By contrast, when the studies of atypical depressions were excluded from the metaanalysis, the PHZ-TCA difference was −0.7% (±12.7%) in the remaining three contrasts (Imiah et al. 1964; Georgotas et al. 1986; Quitkin et al. 1989).

Five comparisons between PHZ and TCAs were available from four outpatient trials reporting only continuous outcome measures (see Table 4). In three trials comparing treatments in atypical or dysthymic samples, PHZ was more effective than either IMI (Davidson et al. 1987; Vallejo et al. 1987) or AMI (Raft et al. 1981). In two comparisons of major depressive cases, PHZ was less effective than either IMI (Vallejo et al. 1987) or TRI (Young et al. 1979).

Inpatient Studies. There were seven PBO-controlled inpatient studies available for metaanalysis of overall efficacy (49.5% ± 14.0%) with the ITT sample, and six inpatient studies for the AT sample (54.5% ± 7.3%). The five available PBO contrasts for inpatients resulted in a PHZ-PBO difference of 22.3% (±30.7%). Metaanalysis of the four studies with AT samples revealed a PHZ-PBO difference of 5.2% (±13.2%). Variability of response is notable in these studies.

A total of eight RCTs on inpatients contrasted PHZ with another standard TCA (see Table 1; Agnew et al. 1961; Leitch and Seager 1963; Martin 1963; Greenblatt et al. 1964; Schildkraut et al. 1964; British Medical Research Council, 1965; Davidson et al. 1977, 1981). All of these inpatient trials contrasted PHZ with IMI. For the ITT sample, PHZ had a 21.0% (±7.7%) *lower* response rate than IMI. For the AT group, PHZ also fared significantly worse (−15.8%) (±12.3%) than IMI. Similarly, electroconvulsive therapy (ECT) was clearly superior to PHZ in the three studies (Greenblatt et al. 1964; British Medical Research Council 1965; Hamilton 1982) providing such a comparison. By contrast, in the single trial reporting only continuous outcome measures, Davidson et al. (1981) found that high dose PHZ (mean: 81 mg/day) and modest dose IMI (mean: 144 mg/day) were comparably effective.

Isocarboxazid (ISO)

Outpatient Studies. Based on ITT samples, metaanalysis revealed ISO efficacy rates of 60.1% (±7.1%) (five studies), and 68.2% (±11.2%) (eight studies) for the AT samples.

Eight comparisons from seven PBO-controlled, outpatient RCTs with ISO were identified (see Table 2; Ford et al. 1959; Schorer et al. 1966; Hays and Steinert 1969; Young et al. 1979; Davidson and Turnbull 1983; Zisook 1983; Giller et al. 1984; Davidson et al. 1988) with five comparisons suitable for metaanalysis with ITT samples. Using ITT samples, there was an average difference of 41.3% (±18.0%) between ISO and PBO. This is not statistically significantly higher than the PHZ-PBO difference in outpatients. Based on the eight AT comparisons, the ISO-PBO difference was 32.9% (±21.7%). In addition, Giller et al. (1984) reported a 69% response rate in PBO nonresponders "crossed-over" to active ISO treatment.

Five outpatient RCTs (see Table 2; Richmond and Roberts 1964; Schorer et al. 1966; Hays and Steinert 1969; Young et al. 1979; Larsen et al. 1991) contrasted ISO with TCAs (one study used either AMI or IMI, one used IMI alone, and one each used NOR, TRI and clomipramine [CLO] as the contrast drug). Richmond and Roberts (1964) also concurrently studied TRP, whereas Young et al. (1979) also studied PHZ. ISO dosages ranged from 20 to 60 mg/day. Metaanalysis of two studies appropriate for ITT revealed an ISO-TCA difference of only 1.9% (±10.0%). For the four AT samples, ISO and the contrast TCA were equally effective for outpatients with an ISO-TCA difference of 4.8% (±19.4%).

Inpatient Studies. Metaanalysis of four ITT samples showed an overall response for ISO of 56.7% (±10.5%). For the three AT samples, the ISO response rate was 50.5% (±18.1%).

Table 7. CPM of Acute Phase Treatment Trials Reporting Categorical Outcomes for Isocarboxazid (ISO) in Depressed Outpatients[a]

Study	(Drug Comparator)	Overall Efficacy		ISO vs. PBO		ISO vs. DRUG	
		ITT	AT	ITT	AT	ITT	AT
Ford et al. 1959	(NA)	78.1 (10.0)	96.2 (5.1)	63.1 (12.7)	79.5 (12.9)	NA	NA
Richmond and Roberts 1964	(AMI/IMI)	NA	59.5 (10.5)	NA	NA	NA	28.6 (14.4)
Schorer et al. 1966	(IMI)	NA	34.6 (12.7)	NA	−15.4 (19.2)	NA	−44.6 (17.0)
Hays and Steinert 1969	(NT)	56.8 (10.3)	62.5 (10.6)	NA	NA	0.8 (8.3)	9.7 (15.6)
Davidson and Turnbull 1983	(NA)	NA	71.9 (10.9)	NA	48.5 (15.2)	NA	NA
Giller et al. 1984	(NA)	67.7 (11.0)	80.4 (7.4)	53.1 (12.7)	34.7 (12.6)	NA	NA
Davidson et al. 1988	(NA)	51.7 (5.3)	65.9 (5.7)	28.2 (6.9)	33.4 (8.1)	NA	NA
Larsen et al. 1991	(CMI)	64.4 (6.6)	83.8 (5.8)	NA	NA	3.2 (9.1)	−5.0 (7.6)
Total[b]		60.1 (7.1) [5]	68.2 (11.2) [8]	41.3 (18.0) [3]	32.9 (21.7) [5]	1.9 (10.0) [2]	4.8 (19.4) [4]

Abbreviations: AMI = amitriptyline; IMI = imipramine; NTP = nortriptyline; CMI = clomipramine; NA = no data available; ITT = intention to treat; AT = adequate treatment; ISO = isocarboxazid; PBO = placebo.

[a] Figures are % responders; standard deviations are in parentheses; number of studies used in calculations appears in brackets.

[b] PBO controls from Giller et al. (1984) overlap with Davidson et al. (1988). They are not tallied twice in total.

Table 8. CPM of Acute Phase Treatment Trials Reporting Categorical Outcomes for Isocarboxazid (ISO) in Depressed Inpatients[a]

Study	(Drug Comparator)	Overall Efficacy		ISO vs. PBO		ISO vs. DRUG	
		ITT	AT	ITT	AT	ITT	AT
Agnew et al. 1961	(IMI)	35.7 (16.9)	NA	27.4 (19.9)	NA	−28.6 (24.0)	NA
Joshi 1961	(NA)	50.0 (9.4)	58.7 (10.0)	37.5 (11.3)	40.3 (13.3)	NA	NA
Rothman et al. 1962	(IMI)	48.5 (8.4)	71.7 (9.2)	9.6 (12.5)	13.4 (14.6)	−7.9 (12.2)	4.4 (12.9)
Greenblatt et al. 1964	(IMI)	NA	28.3 (5.4)	NA	−18.0 (9.5)	NA	−21.1 (7.9)
Kurland et al. 1967	(NA)	70.4 (5.2)	NA	3.5 (7.6)	NA	NA	NA
Total		56.7 (10.5) [4]	50.5 (18.1) [3]	15.3 (12.6) [4]	9.1 (26.4) [3]	−14.1 (27.5) [2]	−10.0 (21.8) [2]

Abbreviations: ISO = isocarboxazid; PBO = placebo; IMI = imipramine; AMI = amitriptyline; NA = no data available; ITT = intention to treat; AT = adequate treatment.

[a] Figures are % responders; standard deviations are in parentheses; number of studies used in calculations appears in brackets.

Six RCTs compared ISO and PBO in depressed inpatients (Tables 2 and 4) (Agnew et al. 1961; Joshi 1961; Overall et al. 1962; Rothman et al. 1962; Greenblatt et al. 1964; Kurland et al. 1967). All of these studies were conducted prior to 1970. Doses ranged from 20 to 60 mg/day. Of the six inpatient contrasts, only one revealed a significant ISO-PBO difference (Joshi 1961) based on the authors' report. In a second study involving two inpatient sites (Kurland et al. 1967), ISO was more effective than PBO at one site but no more effective than PBO at the other. Greenblatt et al. (1964) found ISO to be significantly less effective than PBO. Overall et al. (1962), reporting results on a continuous outcome measure extracted from several rating scales, found that ISO and PBO were not significantly different.

Four inpatient studies were eligible for metaanalysis with ITT samples (Rothman et al. 1962; Kurland et al. 1967; Agnew et al. 1961; Joshi 1961). The ISO-PBO difference for inpatients was 15.3% (±12.6%). For the AT sample, the ISO-PBO difference was 9.1% (±26.4%) (three studies). Thus, ISO *has not* been shown to be more effective than PBO for inpatients in doses studied.

A total of four inpatient RCTs were found contrasting ISO with TCAs (Agnew et al. 1961; Overall et al. 1962; Rothman et al. 1962; Greenblatt et al. 1964). Based on the authors' report, IMI appeared more effective than ISO in doses from 20 to 50 mg/day. Of these four reports, two were available for metaanalysis using the ITT samples (Rothman et al. 1962; Greenblatt et al. 1964). An overall ISO-TCA difference of −14.1% (±27.5%) was found favoring the TCA over ISO. Similarly, for two AT samples, the ISO-TCA difference was −10.0% (±21.8). Overall et al. (1962) also found ISO to be less effective than IMI on a continuous outcome composite measure. In the Greenblatt et al. (1964) study, ISO also was significantly less effective than ECT. Thus, ISO, like PHZ, appears to be a less effective inpatient treatment than both the TCAs and ECT.

Tranylcypromine (TRP)

Outpatient Studies. Based on five outpatient studies subjected to metaanalysis using ITT samples, TRP had an overall efficacy rate of 52.6% (±12.4%). For the six studies available for AT metaanalysis, an overall efficacy rate of 67.7% (±9.2%) was found.

Four PBO-controlled outpatient trials with TRP were identified (see Table 3; Bartholomew 1962; Glick 1964; Himmelhoch et al. 1982; White et al. 1984). The Glick (1964) report was previously reviewed because it also included a PHZ cell. The sample of Himmelhoch et al. (1982) was predominantly bipolar, whereas the remaining studies enrolled either predominantly or exclusively unipolar depressions. In these four studies, TRP doses ranged from 30 to 60 mg/day. Based on the authors' report, TRP's efficacy exceeded that of PBO in all four trials.

Among the four outpatient, PBO-controlled trials, only the study of Glick (1964) was not suitable for metaanalysis. In the remaining three studies, the TRP-PBO difference was 22.1% (±25.4%). This drug-PBO difference is lower than that of the other MAOIs in outpatients, but not significantly so. For the three AT samples, the TRP-PBO difference was 32.1% (±23.4%).

Six reports compared TRP and various TCAs (see Table 3). TRP was compared to NOR (White et al. 1984) and either AMI or IMI (Richmond and Roberts 1964) in unipolar depressed outpatients. Himmelhoch et al. (1991) used IMI as the comparator in an outpatient study of anergic bipolar depression, with Thase et al. (1992a) reporting results of a double-blind crossover protocol for nonresponders from that study. In two other trials, TRP was compared to either IMI (Spear et al. 1964) or AMI (Razani et al. 1983) in samples that included both in- and outpatients. TRP dosages approximated 40 mg/day across all studies.

The authors reported that TRP exceeded the efficacy

Table 9. CPM of Acute Phase Treatment Trials Reporting Categorical Outcomes for Tranylcypromine (TRP) in Depressed Outpatients[a]

Study	(Drug Comparator)	Overall Efficacy		TRP vs. PBO		TRP vs. DRUG	
		ITT	AT	ITT	AT	ITT	AT
Bartholomew 1962	(NA)	52.9 (6.9)	64.0 (7.2)	9.6 (9.7)	19.0 (10.0)	NA	NA
Glick 1964	(NA)	NA	NA	NA	NA	NA	NA
Richmond and Roberts 1964	(AMI/IMI)	41.8 (7.0)	50.0 (10.7)	NA	NA	24.2 (8.3)	19.0 (14.5)
Himmelhoch et al. 1982	(NA)	70.7 (8.3)	89.1 (6.4)	56.6 (10.3)	64.1 (11.8)	NA	NA
White et al. 1984	(NT)	39.8 (6.1)	67.1 (7.5)	7.3 (8.5)	24.7 (10.4)	−1.3 (8.7)	4.9 (10.6)
Himmelhoch et al. 1991[b]	(IMI)	NA	79.6 (7.6)	NA	NA	26.4 (13.1)	31.9 (12.9)
Thase et al. 1992a[b]	(IMI)	73.1 (11.9)	NA	NA	NA	38.1 (21.3)	NA
Total		52.6 (12.4) [5]	68.6 (10.8) [5]	22.1 (25.4) [3]	32.1 (23.4) [3]	16.8 (13.3) [4]	17.3 (11.6) [3]

Abbreviations: AMI = amitriptyline; IMI = imipramine; NT = nortriptyline; NA = no data available; ITT = intention to treat; AT = adequate treatment.
[a] Figures are % responders; standard deviations are in parentheses; number of studies used in calculations appears in brackets.
[b] Samples include only bipolar, depressed phase patients.

of the comparison TCA in three outpatient studies (Richmond and Roberts 1964; Himmelhoch et al. 1991; Thase et al. 1992a), including both studies of anergic bipolar depression. In the remaining three studies, TRP and standard TCAs (IMI: Spear et al. 1964; AMI: Razani et al. 1983; NOR: White et al. 1984) did not differ in efficacy.

Four of five outpatient RCTs contrasting TRP and a standard TCA were available for metaanalysis (Richmond and Roberts 1964; Himmelhoch et al. 1991; Thase et al. 1992a; White et al. 1984). The overall TRP-TCA difference was 16.8% (±13.3%), indicating a modest advantage for TRP. For the AT sample, the TRP-TCA difference was 17.3% (±11.6%). These differences favoring TRP were basically attributable to the Pittsburgh studies of anergic bipolar depression (Himmelhoch et al. 1991; Thase et al. 1992a).

Inpatient Studies. Four controlled clinical trials (see Table 3; Gottfries 1963; Razani et al. 1983; Nolen et al. 1985, 1988) reported categorical outcomes in comparisons involving TRP. In the case of Nolen et al. (1985), TRP was significantly more effective than 5-HTP. No TCA-controlled study of TRP was found in a sample exclusively comprised of inpatients. The study of Razani et al. (1983), which included a majority of inpatients (57%), found TRP and NOR to be equally effective. In Nolen et al.'s (1988) second study, a double-blind comparison of TRP and nomifensine in refractory depression, TRP was significantly more effective than

Table 10. CPM of Acute Phase Treatment Trials Reporting Categorical Outcomes for Tranylcypromine (TRP) in Depressed Inpatients[a]

Study	(Drug Comparator)	Overall Efficacy		TRP vs. PBO		TRP vs. DRUG	
		ITT	AT	ITT	AT	ITT	AT
Gottfries 1963	(PBO)	NA	25.0 (8.3)	NA	15.4 (10.1)	NA	NA
Razani et al. 1983[b]	(AMI)	63.5 (9.3)	63.5 (9.3)	NA	NA	10.0 (13.0)	−10.4 (13.2)
Nolen et al. 1985[c]	(5-HTP)	61.1 (9.2)	61.1 (9.2)	NA	NA	58.3 (10.0)	58.3 (10.0)
Nolen et al. 1988	(NOM)	45.8 (13.8)	45.8 (13.8)	NA	NA	32.2 (17.0)	32.2 (17.0)
Total		58.6 (10.8) [3]	49.5 (14.0) [4]	NA	15.4 (10.1) [1]	18.7 (23.1) [3]	8.2 (32.2) [2][d]

Abbreviations: AMI = amitriptyline; NOM = nomifensine; 5-HTP = 5-hydroxytryptamine; PBO = placebo; NA = no data available; ITT = intention to treat; AT = adequate treatment.
[a] Figures are % responders; standard deviations are in parentheses; number of studies used in calculations appears in brackets.
[b] Includes both inpatients (57%) and outpatients (43%).
[c] 5-hydroxytryptamine used as comparator.
[d] Total excludes 5-HTP contrast.

nomifensine. The importance of this finding is underscored by the fact that all patients had previously failed to respond to adequate trials of TCAs, fluvoxamine, and oxaprotiline.

The three inpatient studies available for metaanalysis of ITT samples revealed an overall efficacy of 58.6% (±10.8%) for TRP. The TRP-active drug comparison difference for the ITT samples was 18.7% (±23.1%) based on two studies (Razani et al. 1983; Nolen et al. 1988). For the AT inpatient samples, metaanalysis revealed an overall efficacy of 44.2% (±16.7%) (three studies), a TRP-PBO study difference of 15.4% (±10.1%) (one study; Gottfries 1963), and a TRP-comparator difference of 8.2% (±32.2%) (two studies; Razani et al. 1983; Nolen et al. 1988). A fourth study was identified after completion of the metaanalysis, comparing TRP (n = 26), amitriptyline (n = 28), and their combination (n = 25) in a hospitalized sample (O'Brien et al. 1993). Results indicated that the two monotherapies had roughly equal ITT response rates (54% and 50%, respectively). The combination of TRP and AMI was slightly, but not statistically, superior (64%) to the monotherapies.

In addition to these studies, four published reports were identified in which TRP was compared to either moclobemide (Gabelic and Kuhn 1990) or brofaromine (Zapleták et al. 1990; Nolen et al. 1993; Volz et al. 1994). Two studies were not included in the metaanalysis because of our *a priori* decision to require either PBO or an FDA-approved comparator (i.e., Gabelic and Kuhn 1990; Zapleták et al. 1990). The remaining two were published after the completion of the metaanalysis. Two of the trials studied tricyclic resistant depressions (Nolen et al. 1993; Volz et al. 1994) and one each studied endogenous (Gabelic and Kuhn 1990) and nonendogenous (Zapleták et al. 1990) depressive subforms. Response to TRP ranged from 29% to 79%, with the poorest showing in Nolen et al.'s (1993) study of tricyclic resistant inpatients. It should be noted that only the Nolen et al. (1993) study permitted doses of TRP in excess of 30 mg/day. In no study was the novel MAOI statistically more effective than TRP, although in three studies the reversible, selective MAOI was reported to be significantly better tolerated (Gabelic and Kuhn 1990; Nolen et al. 1993; Volz et al. 1994).

SUMMARY OF EFFICACY DATA

For outpatients using ITT samples, all three MAOIs appear to be equally effective (PHZ = 57.9% ± 4.0%; ISO = 60.1% ± 7.1%; TRP = 52.6% ± 12.4%). When compared to PBO in outpatients, ISO (41.3% ± 18.0%) had a larger relative advantage compared to either PHZ (29.5% ± 11.1%) or TRP (22.1% ± 25.4%) in the doses studied. However, the large intra-group variabilities in response rendered these differences nonsignificant.

For inpatients, PHZ was somewhat more effective (22.3% ± 30.7%) than PBO, whereas the ISO-PBO difference was smaller (15.3% ± 12.6%). Thus, the evidence for efficacy in relation to PBO for these two MAOIs in the treatment of hospitalized patients is not as robust as for TCAs. Tranylcypromine sulfate has simply not been studied in sufficient numbers of controlled inpatient trials to warrant comment. Nevertheless, the findings of Nolen and associates (1985, 1988, 1993) clearly demonstrate efficacy in treatment resistant cases. Moreover, in the recent study by O'Brien et al. (1993), TRP was as effective as AMI in hospitalized cases.

Only one geriatric study (Georgotas et al. 1986) met our criteria for inclusion in the metaanalysis, which precludes strong inferences about the efficacy of the MAOIs in older individuals. Similarly, only a pair of related outpatient studies specifically addressed treatment efficacy in bipolar depression (Himmelhoch et al. 1991; Thase et al. 1992a). Although both of these studies found TRP to be superior to IMI, the study groups were delimited bipolar depressions characterized by anergia, psychomotor retardation, and reversed neurovegetative symptoms. Thus, the generalizability of these findings to the full range of bipolar depressions is limited. Of note, however, is the fact that Himmelhoch et al. (1991) and Thase et al. (1992a) found TRP to be equally effective in bipolar I and bipolar II presentations.

No fully published comparisons were found between approved MAOIs and the newer, nonTCA antidepressants now available in the United States (e.g., trazodone, fluoxetine, sertraline, paroxetine, venlafaxine, nefazodone, or bupropion). Preliminary findings from a controlled trial comparing PHZ and fluoxetine have been published in abstract form (Pande et al. 1992), with no differences in outcome between the MAOI and the selective serotonin reuptake inhibitor (SSRI) observed. One other trial was found comparing the investigational MAOI moclobemide with the SSRI fluvoxamine (Bougerol et al. 1992) in which the MAOI and SSRI were comparably effective and generally well tolerated. Moreover, because the newer antidepressants are typically equal to the standard TCAs in efficacy in outpatients (Depression Guideline Panel 1993), it is reasonable to assume that the MAOIs and these newer drugs would be shown to be of comparable efficacy in comparisons of grouped data. Nevertheless, it is still conceivable that these different classes of medications may treat different subgroups of depressed patients. For example, Nolen et al. (1985, 1988) reported 40% to 60% response to TRP in patients previously resistant to fluvoxamine.

DOSING AND SAFETY ISSUES

What Are the Proper Dosages for Acute Phase MAOI Treatment? Although there are few MAOI dose-

response studies, the three that were identified found superior responses to higher doses when compared to lower dosages (Ravaris et al. 1976; Davidson et al. 1984; Tyrer et al. 1990). Extrapolation from the evidence tables and metaanalyses would indicate that there is *no* evidence to support the efficacy of available MAOIs at daily doses lower than 45 mg for PHZ, 30 mg for ISO, or 30 mg for TRP. Indeed, optimal responses appear to occur in those who can tolerate 75 to 90 mg/day of PHZ or 40 to 60 mg/day of ISO or TRP.

Of note is the study by Davidson et al. (1984) in which the value of higher doses of ISO was clear only for nonendogenous depression. This finding seems somewhat paradoxical because, traditionally, higher doses of antidepressant medication are generally utilized in the treatment of more severe depressive states (e.g., Klein and Davis 1969). Perhaps the higher dosages of ISO specifically enhanced anxiolytic effects in Davidson et al.'s (1984) nonendogenous patients.

Relationship of Acute Response to Percentage Platelet Inhibition and Dosage. Several groups have investigated whether the degree of platelet MAO (Type B) inhibition is related to antidepressant response. The principal positive findings include a large initial study of PHZ (Robinson et al. 1978) and three subsequent replications (Davidson et al. 1978b; Raft et al. 1981; Bresnahan et al. 1990). In each case, higher levels of platelet MAO inhibition were associated with higher PHZ response rates. Greatest efficacy was associated with values of ≥80% to 90% inhibition. However, this association rests on correlations on the order of 0.3 to 0.4, that is a moderate effect size that accounts for only 9% to 16% of the outcome variance.

A number of other studies have failed to find a significant relationship between the percent of platelet MAO inhibition and PHZ response (Dunlop et al. 1965; Beckmann and Murphy 1977; Georgotas et al. 1981, 1989; Lazarus et al. 1986; McGrath et al. 1993). In addition, in studies of treatment with ISO and TRP, platelet MAO inhibition has not been reliably associated with degree of improvement (Davidson and White 1983; Giller et al. 1984; Himmelhoch et al. 1991). However, most of the negative reports did not study a sufficiently large number of patients to preclude a Type II error. This is particularly true because of the relatively modest strength of the presumed relationship between platelet inhibition and treatment response.

Several other lines of evidence suggest that percent platelet inhibition may be, at best, an epiphenomenon of MAOI response. For example, in studies of SEL (a relatively selective Type B MAOI), it has been shown that virtually 100% inhibition of platelet enzymatic activity can be obtained at dosages that do not produce reliable antidepressant effects (Mendis et al. 1981; Quitkin et al. 1984; Mann et al. 1989). The platelet inhibition paradigm also does not account for drug effects on Type A enzyme in the brain, which may explain the lack of association in some studies, particularly those employing TRP (e.g., Himmelhoch et al. 1991). Finally, in a small series of four cases, Mann (1983) described relapse during MAOI therapy despite consistently high levels of platelet MAO inhibition. Thus, the routine clinical use of platelet MAO inhibition is not recommended given the current findings.

Safety and Tolerability. The most common side effects of acute therapy with the FDA-approved MAOIs include orthostatic hypotension, dizziness, mydriasis, piloerection, edema, tremor, anorgasmia, and insomnia (Klein and Davis 1969; Robinson and Kurtz 1987; Rabkin et al. 1988). Although the MAOIs have no prominent acute antihistaminic or anticholinergic effects at the receptor level, many patients experience a mild degree of dry mouth, blurred vision, and/or constipation. These side effects may be mediated through secondary, adaptational neurochemical processes, such as facilitation of noradrenergic neurotransmission (Robinson and Kurtz 1987). More recently, excessive daytime sleepiness has been reported (e.g., Joffe 1990). The latter side effect usually develops after at least several weeks of treatment. The significance of anorgasmia and other sexual dysfunctions during MAOI treatment also has been documented (Mitchell and Popkin 1983; Harrison et al. 1985). Similarly, weight gain and carbohydrate craving can become particularly troublesome during continuation and maintenance therapy (Evans et al. 1982; Robinson et al. 1991). Not infrequently, daytime sleepiness, sexual dysfunction, and weight gain are severe enough to lead to termination of an otherwise effective course of MAOI therapy (Agosti et al. 1988; Robinson et al. 1991).

Infrequent to rare side effects include allergies, hepatic dysfunction (with the hydrazine compounds, PHZ and ISO), and blood dyscrasias (Rabkin et al. 1988). Paresthesias related to vitamin B_6 deficiency has also been reported during treatment with PHZ (Stewart et al. 1984). All but the latter effect occur at rates comparable to TCAs (Klein and Davis 1969; Robinson and Kurtz 1987).

Contemporary studies comparing side effects and attrition resulting from side effects in patients treated with the FDA-approved MAOIs and TCAs generally document equivalent levels of total side-effect burden and attrition from acute treatment (Rabkin et al. 1984, 1985; Zisook 1984; Harrison et al. 1985; Agosti et al. 1988; Georgotas et al. 1989; Larsen et al. 1991). Thus, although the MAOIs and TCAs are distinctly different types of drugs, their overall tolerability seems equivalent in comparison of grouped data from acute phase trials. However, the different pharmacologic properties of TCAs and MAOIs provide a useful alternative

when patients are allergic or develop significant side effects to one or the other group. Extrapolating from comparisons of the side effects of TCAs and the newer antidepressants (e.g., Trivedi and Rush, submitted), the MAOIs would be expected, on average, to be less well tolerated than these newer agents. The earlier cited studies comparing TRP with RIMAs certainly are consistent with this notion (Gabelic and Kuhn 1990; Nolen et al. 1993; Volz et al. 1994).

Two possible subgroups of patients who may be relatively intolerant to tertiary TCAs may be younger depressed women (Raskin 1974; Thase et al. 1991) and anergically depressed bipolar patients of both sexes (Himmelhoch et al. 1982, 1991; Thase et al. 1992a). In such cases, the MAOIs have been reported to be both better tolerated and more effective (Himmelhoch et al. 1991; Thase et al. 1992a,b; McGrath et al. 1993).

The major safety concern during MAOI therapy with the currently approved agents is the so-called "cheese effect," a sudden episode of hypertension following ingestion of foodstuffs rich in tyramine, or sympathomimetic medications (Blackwell et al. 1967; Klein and Davis 1969; Robinson and Kurtz 1987). Hypertensive crises during MAOIs therapy occur in approximately five per 100 patients treated per year (Rabkin et al. 1988). The mechanism causing the "cheese effect" has been known for more than 25 years. At therapeutic dosages, PHZ, ISO, and TRP irreversibly bind to MAO in the gut and liver for days or even weeks. This impairs the oxidative degradation of tyramine and related vasoactive amines, as well as drugs such as cocaine and other psychostimulants, decongestants, large doses of caffeine (and probably other methylxanthine drugs), epinephrine (commonly combined with local anesthetics), and some antiasthmatic drugs (Klein and Davis 1969; Robinson and Kurtz 1987; Harrison et al. 1989). Although good data are lacking, in both our experience and that of others (Rabkin et al. 1988), MAOI-drug interactions are more common than MAOI-diet interactions.

The MAOI-related hypertensive crisis is readily reversible with appropriate medical treatment (e.g., Simpson and White, 1990). Nevertheless, it may cause a cerebrovascular accident or even death in vulnerable persons (e.g., patients with undetected berry aneurysms or arterio-venous malformations). The risk of hypertensive crises is, at least in theory, virtually eliminated by instructing patients to adhere to a diet low in tyramine and other vasoactive amines, and by forbidding the use of all sympathomimetic medications (e.g., Rabkin et al. 1985). Unfortunately, many patients learn that it is possible to "cheat" on such strict dietary prohibitions. Moreover, cases of apparent "autoinduction" or spontaneous hypertensive crises have been reported during treatment with TRP (Linet 1986; Fallon et al. 1988; Keck et al. 1989). It is probably fair to assume that prescription of the older MAOIs coveys a small but tangible risk of a hypertensive crisis despite explicit patient education (e.g., 5% risk/patient/year) (Robinson and Kurtz 1987). Should the newer, selective MAOIs ever be approved for use in the United States, their virtual freedom from the "cheese effect" will provide a welcome improvement over the older agents.

The need to prescribe a low tyramine diet and to depend upon responsible patient compliance are frequently cited factors inhibiting use of the older MAOIs as first- or even second-line agents (Clary et al. 1990). Psychiatrists who continue to use MAOIs often specialize in the treatment of mood disorders and, consequently, have greater contact with patients who have failed with other treatment modalities (Paykel and White 1989; Clary et al. 1990). Careful patient education, explicit information about dietary restrictions, and in case of emergencies, ready access to a p.r.n. fast-acting antihypertensive (such as sublingual nifedipine) greatly enhance confidence in the relative safety of these agents. Further, it should be recalled that MAOIs were used as front-line drugs for over eight years before the mechanism of the "cheese" reaction was clarified (Blackwell et al. 1967).

Other potentially problematic drug interactions include incompatibility of concurrent use with meperidine (and, possibly, other narcotics) (Meyer and Halfin 1981; Browne and Linter 1987) and SSRIs (e.g., sertraline, fluoxetine, and paroxetine) (Beasley et al. 1993). Both drug classes have been associated with delirious and/or fatal hyperpyrexic and hypertensive reactions. There also is some risk of these serious reactions when MAOIs are used in concert with or close proximity to TCAs (Klein and Davis 1969). Contemporary studies of combined TCA-MAOI therapy indicate that the latter risk is modest (Young et al. 1979; Razani et al. 1983; O'Brien et al. 1993). Tricyclic antidepressant-MAOI combinations are still used in refractory depressions when alternate therapies have failed (e.g., Feighner et al. 1985; Fawcett et al. 1991; Thase and Rush in press). Another combined treatment strategy, the addition of L-tryptophan to an ineffective MAOI, has also been associated with delirium and hyperthermic/hypertensive reactions (Pope et al. 1985), as well as a milder toxic state characterized by myoclonus, hyperreflexia, and diaphoresis (Levy et al. 1985). Although the FDA's withdrawal of L-tryptophan from the American marketplace makes this interaction somewhat moot, both the SSRI-MAOI and MAOI-L-tryptophan toxicities share a number of common features suggestive of a serotonin syndrome (Sternbach 1991).

The MAOIs can be problematic in overdose, despite relatively modest direct effects on cardiac conduction (Robinson and Kurtz 1987; Simpson and White 1990). Specifically, the coupling of severe, dose-dependent,

hypotensive effects and marked vascular reactivity to sympathomimetic drugs results in a condition requiring rigorous monitoring in an intensive care setting (Linden et al. 1984). As noted earlier, metabolic conversion of SEL or TRP to amphetamine following overdose may complicate matters even further (Youdim et al. 1979; Karoum et al. 1982). Fortunately, the short elimination half-lives of all of the MAOIs enable a relatively rapid clearance of physiological effects, often within 72 to 96 hours of ingestion.

EFFICACY IN DEPRESSIVE SUBGROUPS

Interest in subgroups of patients especially responsive to MAOIs dates to initial reports by British investigators (e.g., West and Dally 1959; Sargant 1961), who described selected clinical features in patients who responded to MAOIs but who had previously responded poorly to TCAs or ECT. These symptoms, referred to as atypical because of their lower frequency in classic melancholia, included phobic or panic anxiety and reversed vegetative features (i.e,. overeating, oversleeping, or weight gain) (West and Dally 1959; Sargant 1961; Klein and Davis 1969). Himmelhoch et al. (1972) extended these observations by reporting on TRP treatment of TCA-resistant patients with anergic bipolar depression. Like atypical unipolar depressions, a number of bipolar patients manifest reversed neurovegetative features (e.g., Himmelhoch et al. 1972). Other investigations further established the efficacy of MAOIs in patients with primary anxiety syndromes (e.g., Solyom et al. 1973; Tyrer et al. 1973; Mountjoy et al. 1977; Sheehan et al. 1980). In close temporal proximity to these early observations, PHZ and ISO were found to be essentially ineffective in four large, multi-center, inpatient clinical trials (Overall et al. 1962; Greenblatt et al. 1964; British Medical Research Council 1965; Raskin et al. 1974). Thus, the impression was formed that MAOIs were preferentially effective in milder, atypical depressions and that MAOIs were less effective than TCAs in melancholic or endogenous unipolar depressions.

Endogenous Depression. The most compelling evidence that MAOIs are less effective in endogenous depressions comes from the aforementioned inpatient studies that were all published between 1962 and 1974. Some recent outpatient studies also favor this notion. For example, Vallejo et al. (1987) found a trend favoring IMI over PHZ in a study of 30 DSM-III melancholic outpatients. Similarly, Davidson et al. (1988) reported that ISO was significantly less effective in patients meeting diagnostic criteria for endogenous depression than it was in patients with nonendogenous depression. Consistent with these data, we found larger and more predictable MAOI-PBO differences in our metaanalysis in outpatient studies when compared to inpatient trials.

In contrast, however, are a number of controlled and open-label studies suggesting that MAOIs are effective treatments for many patients meeting contemporary criteria for endogenous depression (Davidson et al. 1981; Quitkin et al. 1981; Himmelhoch et al. 1982, 1991; McGrath et al. 1984, 1986; White et al. 1984; Nolen et al. 1985, 1988; Georgotas et al. 1986; Thase et al. 1991, 1992a; O'Brien et al. 1993). Thus, although TCAs may well be more efficacious first-line treatments than MAOIs in depressions characterized by melancholic or endogenous features, it is likely that the MAOIs are also effective treatments in such cases, particularly when used in larger doses and/or following an initial failure to respond to TCAs (e.g., Nolen et al. 1988; Thase et al. 1991).

The problem may be due in part to the heterogeneity within contemporary criteria for endogenous depression, such that the endogenous depression construct includes cases that are more (i.e., retarded and anergic depressions) and less (e.g., agitated unipolar melancholia) responsive to MAOI therapy. Nevertheless, there is no question about the efficacy of MAOIs in comparison to ECT. All four studies have found a significant advantage favoring ECT, whether MAOIs were given as monotherapies (Greenblatt et al. 1964; British Medical Research Council 1965; Hamilton 1982) or in combination with TCAs (Davidson et al. 1978a).

Psychotic Depression. The construct of psychotic (delusional) depression has evolved significantly over the past 30 years (Schatzberg and Rothschild 1992). As a result, it is not clear what proportion of the inpatient samples of the early negative studies of Overall et al. (1962), Greenblatt et al. (1964), the British Medical Research Council (1965), and Raskin et al. (1974) would meet contemporary criteria for psychotic depression. Subsequent work has clearly shown that psychotic depressions respond less favorably to antidepressant monotherapy with TCAs (e.g., Davidson et al. 1977; Spiker et al. 1985). If a high proportion of such patients were included in these older trials, it most likely helps to explain the relatively poor showing of MAOIs in the early inpatient studies. None of the contemporary controlled trials of MAOIs have included psychotically depressed patients. However, Janicak et al. (1988) evaluated the relative efficacy of PHZ in psychotic and nonpsychotic depressions in an open-label, inpatient study. They found PHZ to be significantly more effective in nonpsychotic than psychotic depressions (21/31 versus 3/14), a finding that parallels results from studies of TCAs (e.g., Davidson et al. 1977; Spiker et al. 1985). Thus, MAOI monotherapy, like TCA monotherapy, is not recommended for psychotic depressions. Publication of a series in which MAOIs were used in combination with neuroleptics in ECT-resistant, psychotic

depression would help to establish what role these agents have in the management of psychotic depression.

Atypical Symptom Features. It has been suggested that the atypical depression construct can be subdivided into anxious (Type "A") and reversed vegetative (Type "V") forms (Davidson et al. 1982; Himmelhoch and Thase 1989). Yet, it is oversimplistic to consider these subforms as mutually exclusive, because approximately one-third of atypically depressed outpatients meet criteria for both "A" and "V" subtypes (e.g., Davidson et al. 1982; Kayser et al. 1988).

With respect to the relative efficacy of PHZ and TCAs in anxious depression, several studies found modest, albeit statistically significant differences in favor of MAOIs, particularly on self-reported measures of psychic or somatic anxiety (e.g., Ravaris et al. 1980; Raft et al. 1981; Rowan et al. 1982). However, the outcome of patients treated with either PHZ or the comparator TCAs in these studies were generally more similar than different. The Columbia University research group subsequently reported PHZ to be more effective than imipramine in atypical depression with panic attacks (Liebowitz et al. 1984), an observation partially replicated by two other groups (Davidson et al. 1987; Kayser et al. 1988). However, the Columbia group was not able to replicate this finding in four subsequent reports (Liebowitz et al. 1988; Quitkin et al. 1989, 1990, 1993). Thus, the predictive value of anxiety or panic attacks for MAOI response is unlikely to be more than modest.

Several controlled studies have failed to document superior response to PHZ relative to TCAs in patients characterized by isolated reversed vegetative signs, such as hypersomnia and/or hyperphagia (Paykel et al. 1982; White and White 1986; Davidson et al. 1988; Kayser et al. 1988). However, these analyses were conducted post hoc in mixed samples of patients. Consequently, the results may be inconclusive either because of inadequate specification of the predictor variables or insufficient statistical power.

A series of prospective studies by the Columbia group (Liebowitz et al. 1984, 1988; McGrath et al. 1993; Quitkin et al. 1988, 1989, 1990, 1991) addressed these methodological problems. A "megaanalysis" summary of these results has also recently been published (Quitkin et al. 1993). Using an operational definition of atypical depression, consisting of preserved mood reactivity (at least 50% of normal maximum) and at least two associated symptom features (rejection sensitivity, leaden anergia, hypersomnia, and/or hyperphagia/weight gain), PHZ was superior to IMI in four separate trials (Liebowitz et al. 1988; Quitkin et al. 1990, 1991; McGrath et al. 1993). Phenelzine sulfate's superiority over IMI was apparent across the severity spectrum (Stewart et al. 1992). Two studies further delineated the specificity of this effect: PHZ was significantly more effective than IMI in patients with mood reactivity and only one associated atypical symptom (Quitkin et al. 1988), but not in depressions characterized only by mood reactivity (i.e., no atypical symptoms were present) (Quitkin et al. 1989). In the latter study, both PHZ *and* IMI were significantly more effective than PBO.

Although the Columbia University group's concepts of rejection sensitivity and hysteroid dysphoria (Klein and Davis 1969) have not yet been widely studied by others, some evidence supports the validity of this component of atypical depression. In a preliminary report, Kayser et al. (1985) found PHZ to be more effective than AMI in rejection sensitive patients, whereas the drugs were equally effective in "nonhysteroid" patients. This finding was apparently not sustained, however, in a subsequent report based on a larger sample (Kayser et al. 1988), although the method for reporting results is somewhat ambiguous. Davidson et al. (1988, 1989) found that the related construct of interpersonal sensitivity (as measured by a subscale derived from the self-report 90-item Hopkins Symptom Checklist) (Derogatis et al. 1973) was associated with more favorable response to ISO relative to PBO.

The relationship between "neurotic" forms of atypical depression, personality pathology, and MAOI response has been of interest to clinicians and clinical investigators for years (e.g., West and Dally 1959; Klein and Davis 1969). The overlap between the Columbia concept of rejection sensitivity, the more prototypic personality style of hysteroid dysphoria (Klein and Davis, 1969), and the categorical diagnosis of borderline personality disorder is considerable (Liebowitz and Klein 1981). It is of interest that results from two controlled trials have yielded strikingly opposite results (Parsons et al. 1989; Soloff et al. 1993). In an analysis of the Columbia dataset, atypical depression with associated borderline personality features was clearly more responsive to PHZ (20/22) than either IMI (13/34) or PBO (8/38) (Parsons et al. 1989). By contrast, in a prospective study of patients meeting DSM-III criteria for borderline personality disorder, PHZ was only somewhat more effective than PBO on a few dependent measures (Soloff et al. 1993), It seems likely that the advantage for PHZ reported by Parsons et al. (1989) was attributable to the fact that all patients were enrolled in the trial on the basis of atypical depression (i.e., personality pathology was secondary to the reason for study entry). By contrast, the study aims of Soloff et al. (1993) were just the opposite. Another difference between these studies was that Parsons et al.'s (1989) patients' entire treatment course was as an outpatient, whereas most of Soloff et al.'s (1993) patient cohort entered the study as inpatients, perhaps inflating the PBO responses.

A third study of MAOI treatment of borderline personality disorder was conducted in a sample of 16 treatment-resistant female outpatients referred to the National Institute of Mental Health (Cowdry and Gardner 1988). Patients who were not in major depressive episodes at the time of study entry participated in five sequential, double-blind, "cross-over" medication trials: PBO, alprazolam, carbamazepine, trifluoperazine, and TRP (mean = 40 mg/day). Tranylcypromine sulfate was significantly more effective than PBO, alprazolam and trifluoperazine and generally comparable to carbamazepine. This study is thus consistent with the report of Parsons et al. (1989) vis à vis the utility of MAOI treatment in dysphoric personality disordered patients.

The concept of Type V (reversed vegetative) depression has received less extensive study. Nevertheless, four reports from the University of Pittsburgh yield consistent findings with respect to differential efficacy of TRP and IMI in anergic depression. First, response to a standardized treatment protocol consisting of 16 weeks of IMI and interpersonal psychotherapy was significantly slower in anergic recurrent depression than in patients with more "typical" melancholic presentations (Thase et al. 1991). Second, efficacy of MAOIs in 42 cases of IMI-resistant recurrent depression was significantly related to the number and severity of anergic and reversed neurovegetative features (Thase et al. 1992b). Moreover, the degree of symptomatic improvement during TCA treatment was significantly *inversely* related to subsequent MAOI response (Thase et al. 1992b). Third, TRP was significantly more effective than IMI in a controlled trial of anergic bipolar depression (Himmelhoch et al. 1991). Finally, TRP was efficacious in a double-blind, cross-over of nonresponders from the parent study of anergic bipolar depression (Thase et al. 1992a).

One particular subform of Type V atypical depression is seasonal (winter) depression. To date, two published studies have reported on response to MAOIs in winter depression. In an open trial of 14 patients, Dilsaver and Jaeckle (1990) reported an 86% rate of full remission (n = 12) over four weeks of treatment with TRP (mean = 32 mg/day). By contrast, Lingjaerde et al. (1993) found no difference between moclobemide (9/16) and PBO (7/18) in a three week trial of winter depression. However, significant differences were found favoring moclobemide on a measure of reversed vegetative symptoms and among a subgroup of patients over the age of 45.

In summary, it does appear that MAOIs are significantly more effective than the TCAs in Type V or anergic depressive syndromes. The evidence does not, however, indicate that the MAOIs are preferentially effective in atypical depression when compared to their efficacy in other depressive states treated in ambulatory settings. Rather, it is likely that the tertiary amine TCAs that are significantly *less* effective (and/or poorly tolerated) in atypical *or* anergic depressive syndromes than in more typical depressive states (Liebowitz et al. 1988; Quitkin et al. 1989, 1993; Himmelhoch et al. 1991; Thase et al. 1991, 1992a,b; McGrath et al. 1993).

Chronic Depressions. A significant but often unspecified number of outpatients in studies by the research groups lead by Quitkin (e.g., Quitkin et al. 1993), Robinson (Robinson et al. 1973; Ravaris et al. 1976, 1980; Kayser et al. al. 1985, 1988), Paykel (Paykel et al. 1982; Rowan et al. 1982), and Davidson (Davidson et al. 1981, 1987; Raft et al. 1981; Davidson and Turnbull 1983; Davidson and Raft 1984) would meet DSM-III-R criteria for dysthymic disorder, chronic major depression, or acute major depression superimposed on dysthymic disorder (i.e., "double" depression). Thus, results of these studies are suggestive that MAOIs are more effective than PBO in chronic depressions.

Three reports address the question of efficacy in chronic depressions more specifically. Stewart et al. (1989) reported on a pooled sample of 194 predominantly atypical depressions (defined by Columbia University criteria) and found that PHZ and IMI were equally effective in "pure" dysthymia (i.e., dysthymia without major depression), whereas PHZ was significantly more effective than both IMI and PBO in "double" and chronic depressions. Imipramine was significantly more effective than PBO in "pure" dysthymia, whereas a trend (p = .09) favored PHZ over PBO. The relatively small number of cases of "pure" dysthymia in this report limited the power to detect drug-PBO differences. Atypicality, rather than chronicity, thus appeared to demarcate preferential PHZ response in the Columbia University group's experience.

Davidson et al. (1988) compared ISO (n = 68) and PBO (n = 62) in a pooled analysis of a three-site trial. Response in 35 cases of RDC minor depression was 58% (11/19) for ISO and 44% (7/16) for PBO. This difference was not significant in a *post-hoc* comparison. By contrast, there was a larger, highly significant ISO-PBO difference in the 95 patients meeting criteria for major depression [34/49 (69%) versus 13/46 (28%), χ^2 = 16.1, df = 1, p = .0001]. Chronicity *per se* (i.e., independent of the RDC major versus minor depression dichotomy) was not specified in this study, although the sample's average length of index depressive episode (28 months) would suggest that a majority of patients were chronically depressed.

Finally, Vallejo et al. (1987) found PHZ to be more effective than IMI in a prospective trial of 30 dysthymic outpatients, whereas an opposite trend was observed in melancholia. Atypicality apparently was not assessed in this study. Taken together, these three reports suggest that although the MAOIs are efficacious treatments

of chronic depression, it is not clear that MAOIs have preferential efficacy over TCAs in chronic depression after the proportion of cases with atypical depression is taken into account.

Tricyclic Resistant Depression. More than 20 reports and clinical series have addressed the use of MAOIs in treatment resistant depression (Thase and Rush in press). However, only four of these studies met the criteria specified to be included in our metaanalysis (Nolen et al. 1985, 1988; Thase et al. 1992a; McGrath et al. 1993). In addition, the recent studies by Nolan et al. (1993) and Volz et al. (1994) were not included because TRP was compared with the experimental MAOI brofaromine.

Review of both controlled and uncontrolled studies reveals that approximately 50% of TCA-resistant patients respond to MAOIs, with response rates on the order of 70% reported in subsamples of atypical or anergic subforms of resistant depression (Thase et al. 1992a,b; McGrath et al. 1993). The poorest outcome observed to date in a study of TCA-resistant depression was the 29% (5/17) TRP response rate in the inpatient study by Nolen et al. (1993). This rate was based on a $\geq$ 50% reduction in HRS-D scores after 29 days of treatment. Using the apparently more generous CGI scale to classify outcome, 59% of patients responded. We note that Nolen et al.'s (1993) TRP response rate (29%) was nearly equal to that reported by Thase et al. (1992b) in their subset of patients with melancholic, *nonanergic,* TCA-resistant depression (33%). With an end-of-treatment mean TRP dose of 81 mg/day, the adequacy of the dosage regimen used in this trial cannot be questioned. In fact, because Mallinger et al. (1990) found a significant *inverse* relationship between TRP blood levels and clinical response in a protocol permitting upward dosing titration, it is conceivable that Nolen et al. (1993) used too high a dosage of TRP, inadvertently "overshooting" the optimal dosage.

There are no data from studies of resistant depression directly comparing response to the FDA-approved MAOIs with other popular treatment approaches, such as thyroid or lithium augmentation. Comparison of three studies (Thase et al. 1989a,b, 1992b) of somewhat overlapping study groups suggests that MAOI treatment (principally TRP) is more effective than thyroid augmentation and comparable with lithium augmentation. A recently published prospective study comparing treatment with brofaromine (n = 25) to lithium augmentation in an outpatient sample resistant to maprotiline reached a similar conclusion (Hoencamp et al. 1994), although neither strategy was particularly effective (brofaromine: 5/25; lithium: 6/26). As noted earlier, the published comparisons of MAOIs and ECT provide unequivocal support for ECT as the most effective option (Davidson et al. 1978a; Greenblatt et al. 1964; Hamilton 1982; British Medical Research Council 1965), although this conclusion would similarly apply to all other pharmacologic strategies for refractory depression (Thase and Rush in press).

Bipolar Disorder, Depressed Phase. The proportion of depressed patients in the early MAOI trials suffering from bipolar depression usually cannot be determined. As noted earlier, only a few contemporary studies have examined MAOI response in samples delimited to bipolar disorder. Himmelhoch et al. (1972) reported on the utility of TRP in an open-label study of TCA-resistant bipolar depressed patients in which most were receiving concurrent lithium. Sixteen of the 212 patients responded to treatment with TRP. Over the next 20 years, Himmelhoch and associates extended this finding in a series of double-blind outpatient studies relative to PBO (Himmelhoch et al. 1982) and IMI (Himmelhoch et al. 1991; Thase et al. 1992a). Although TRP has consistently performed well in these studies, replication by other groups would be reassuring, given the parochial nature of the Pittsburgh group's diagnosis of anergic depression.

The efficacy of other MAOIs in bipolar depression has not been established, nor has the value of MAOI treatment been evaluated in bipolar depressed patients characterized by melancholic features. With respect to the former issue, Larsen and Rafaelsen (1980) reported on favorable long-term treatment of TCA-resistant bipolar depression with ISO. With respect to the latter issue, Quitkin et al. (1981) described a series of five bipolar depressed patients with unequivocal endogenous features who responded to treatment with PHZ following unsuccessful treatment with TCAs. More recently, Angst and Stabl (1992) compared the outcome of 175 cases of bipolar depression treated with either moclobemide (n = 97) or active comparators (n = 78). Patients were pooled from a large number of clinical trials using sometimes differing methodologies. They found a 59% response rate to moclobemide and a 49% response rate to the other TCAs. Although a 10% between-group difference is not statistically significant in a study group of 175 patients, it is in the general direction of the findings reported by the Pittsburgh group.

Summary of Clinical Correlates of MAOI Response. Current evidence suggests that (1) the MAOIs PHZ and ISO may have a subtle anxiolytic advantage compared to TCAs; (2) PHZ is significantly more effective than IMI in atypical depression (as defined by Columbia University criteria); (3) TRP is similarly more effective than IMI both in unipolar and bipolar anergic depressions (as defined by University of Pittsburgh criteria); (4) MAOIs are probably less effective than tertiary TCAs as initial treatments of severe, hospitalized, and/or en-

dogenous depressions; (5) MAOIs are particularly useful in TCA refractory cases; and (6) when the MAOIs are directly compared to ECT (e.g., Greenblatt et al. 1964; British Medical Research Council 1965; Davidson et al. 1978a; Hamilton 1982), the latter clearly is superior in efficacy.

Continuation/Maintenance Treatment

Six controlled studies were identified concerning MAOIs during continuation (n = 4) or maintenance (n = 2) treatment (Davidson and Raft 1984; Harrison et al. 1986; Georgotas et al. 1988, 1989; Himmelhoch et al. 1991; Robinson et al. 1991). With respect to continuation treatment, two studies document clear efficacy when compared to PBO substitution (Davidson and Raft 1984; Harrison et al. 1986) and one study (Georgotas et al. 1988) found equivalence of PHZ and NOR as continuation treatments for depressed geriatric patients. In the study of Himmelhoch et al. (1991), sustained superiority during continuation therapy was found for TRP relative to IMI in anergic bipolar depression. Although the published literature on continuation phase treatment is meager, available results uniformly indicate that the benefit of MAOIs is sustained in 80% to 90% of patients for at least the first 3 to 6 months after responding to acute treatment.

Two controlled studies (Georgotas et al. 1989; Robinson et al. 1991) have examined longer term maintenance treatment with PHZ. The Georgotas et al. (1989) trial enrolled geriatric outpatients who had responded to acute treatment with either PHZ or NOR as randomly assigned. After 4 to 8 months of continuation therapy, patients were either maintained on study drug or randomly tapered to PBO in a one-year, double-blind maintenance phase. Results strongly favored PHZ; in fact, the value of NOR as a prophylactic treatment relative to PBO was not clearly established in this study. Robinson et al. (1991) studied long-term MAOI treatment in a younger sample of predominantly nonendogenously depressed outpatients. They found that PHZ was effective (relative to PBO) in either 45 or 60 mg/day maintenance dosages, with a trend favoring the higher dosage emerging during the second year of the trial. However, Robinson et al. (1991) also reported a very high number of drug drop outs during long-term treatment, which raises practical concerns about the feasibility of PHZ maintenance treatment.

It is surprising that so few controlled studies of long-term MAOI treatment are available. In this regard, a recent large, open-label study of prophylactic treatment with moclobemide indicated excellent tolerance and acceptable prophylaxis, with an approximately 25% cumulative one year relapse/recurrence rate among 153 patients (Moll et al. 1992). Similarly, in a 1-year open follow up of 82 brofaromine responders, Möller and Volz (1992) observed a 30% relapse/recurrence rate. These rates are comparable to the relapse rates observed during similar courses of TCA of SSRI therapy (e.g., Thase 1992). The problem of loss of therapeutic effect during long-term MAOI treatment is a not infrequent clinical problem that has eluded explanation (Mann 1983; Cohen and Baldessarini 1985). In some cases, noncompliance and pharmacokinetic factors have been excluded (e.g., Mann 1983), suggesting a state of pharmacologic tolerance. Although such "breakthrough" depressive episodes are not unique to the MAOIs (Cohen and Baldessarini 1985), it is our clinical impression that they occur more commonly during long-term treatment with the older MAOIs than with TCAs. We note, however, that this impression is not supported by the data of the only long-term study directly comparing an MAOI (PHZ) with a TCA (Georgotas et al. 1989). Dosage increase (Mann 1983; Cohen and Baldessarini 1985), lithium augmentation (Nolen et al. 1993), and drug discontinuation (Cohen and Baldessarini 1985; Thase 1992) are possible strategies to address the loss of drug effect during long-term treatment.

Are the MAOIs Interchangeable?

Each of the four FDA-approved MAOIs share a common organic ring, they inhibit both MAO-A and MAO-B at antidepressant doses, and their response rates, side-effects, and toxicities are much more similar than they are different. However, in spite of these commonalties, the interchangeability of the FDA-approved MAOIs has not been established.

Only five published RCTs have directly contrasted approved MAOIs. Two of these trials are essentially uninterpretable because of small numbers of patients (Agnew et al. 1961; Glick 1964). Richmond and Roberts (1964) found comparable response rates to TRP (50%) and ISO (60%). Greenblatt et al. (1964), on the other hand, found a strong trend favoring PHZ (50%) over ISO (28%). Young et al. (1979) apparently found no difference between PHZ and ISO, although outcomes were not explicitly reported. Thus, firm conclusions about the relative efficacy of the approved MAOIs simply cannot be made.

Logically, TRP (a nonhydrazine) differs sufficiently in its side-chain from PHZ and ISO (i.e., hydrazines) so that patients intolerant to one MAOI may do better on the other. This is particularly true for patients who develop hepatic dysfunction on hydrazine drugs and who may be switched to TRP following an appropriate washout (Robinson and Kurtz 1987). Clinical experience suggest that at least 7 if not 14 days should be allowed when switching from one MAOI to another in order to minimize the risk of hypertensive or hyperpyrexic crises (Rabkin et al. 1988). In our experience, TRP is more alerting than either PHZ or ISO, so that patients

who develop marked insomnia or hyperarousal on TRP may tolerate PHZ or ISO better (e.g., Himmelhoch and Thase 1989). Again, this clinical impression is not, however, supported by any empirical evidence.

MAOIs and the Newer Antidepressants

With the introduction of the Type A selective reversible MAOIs, moclobemide and brofaromine, clinicians in Europe and Canada are able to consider choosing an MAOI as a first-line treatment with much less concern about side effects and dietary interactions. Perhaps to help distinguish the newer agents from the older ones, a new acronym has been coined. RIMAs (*R*eversible *I*nhibitors of *M*onoamine oxidase type *A*). Moclobemide has received more extensive study than brofaromine (e.g., Möller et al. 1991; Angst and Stabl, 1992). A metaanalysis conducted by Angst and Stabl (1992) of the efficacy of moclobemide in over 700 patients found it to be significantly more effective than PBO and generally equivalent to TCAs. In this metaanalysis, moclobemide was more effective in retarded and endogenous depressions when compared to nonendogenous states (Angst and Stabl, 1992). However, Larsen et al. (1991) found both clomipramine and ISO to be significantly more effective than moclobemide in a study of nonendogenous patients. The findings of another recent multicenter trial similarly indicate that clomipramine is significantly more effective than moclobemide (Danish University Antidepressant Group 1993). Curiously, in contrast to studies of the older MAOIs, little evidence has emerged to suggest that moclobemide is a more effective treatment for atypical depression than are the TCAs (Larsen et al. 1991).

As reviewed earlier, five RCTs have compared Type A selective compounds with the older MAOIs. All five trials reported generally equal efficacy, but an advantage in tolerability during RIMA treatment (Gabelic and Kuhn 1990; Zapleták et al. 1990; Larsen et al. 1991; Nolen et al. 1993). These findings suggest both similarities and differences between the clinical profile and responsivity to the RIMAs and the older MAOIs. Should the RIMA compounds ever be approved for use in the United States, it is likely that their relative safety will eventually lead to their ascendancy over PHZ, ISO, and TRP. Nevertheless, the lingering clinical impression of some European investigators that the RIMAs are less potent antidepressants (e.g., Larsen et al. 1991; Danish University Antidepressant Group, 1993) suggests that the older MAOIs will remain in use for the treatment of refractory cases for the foreseeable future.

CONCLUSIONS

It is clear that PHZ, ISO, and TRP are effective treatments for outpatients with acute or chronic major depressive disorder. Among unselected groups of outpatients, all three FDA-approved MAOIs have response rates approximately equal to those for the TCAs. The major exception to their efficacy revealed in our metaanalysis are that ISO is no more effective than PBO for inpatients. In general, the MAOIs appear somewhat less effective than TCAs in more severely depressed, melancholic patients, although this conclusion may be biased by the results of older studies (e.g., Quitkin et al. 1979). By contrast, the MAOIs may have a modest advantage over TCAs in alleviating symptoms of generalized and phobic anxiety in depressed outpatients. The risk/benefit ratio of the currently available MAOIs is such that, despite their efficacy, they are likely to remain as second- or third-line treatments for most depressed patients.

The major indication for earlier use of the MAOIs in any contemporary treatment algorithm may be for depressive syndromes with atypical or anergic features (e.g., Himmelhoch et al. 1991; Thase et al. 1992b; Quitkin et al. 1993). Although further replication is needed, interpersonal rejection sensitivity may similarly help to differentiate a subgroup of depressions relatively less responsive to TCAs when compared to MAOIs (Davidson et al. 1989). However, it is conceivable that as evidence from studies of the SSRIs venlafaxine or bupropion in such patients emerges, this recommendation may be rendered obsolete (e.g., Reimherr et al. 1984; Goodnick and Extein 1989; Pande et al. 1992). The remaining important indication for the use of the MAOIs in the 1990s is for treatment of patients who have not responded to SSRIs, TCAs, and/or other newer generation agents (Nolen et al. 1988, 1993; Thase et al. 1991, 1992a,b; McGrath et al. 1993). Again, the MAOIs may be most effective in resistant depressions characterized by anergic or atypical features (Thase et al. 1992a,b; McGrath et al. 1993). For both indications, the sustained efficacy and tolerability of MAOIs as maintenance phase treatments warrants further study.

ACKNOWLEDGMENTS

This review was supported in part by the Depression Guideline Panel, Agency for Health Care Policy and Research (AHCPR) (Contract No. 282-91-0700). The views expressed are those solely of the authors. They do not represent the AHCPR, the Depression Guideline Panel, its consultants or its contributors. The review was also supported in part by NIMH Center Grants MH-41115 (Dallas) and MH-30915 (Pittsburgh), MH-41884 (M. Thase); and by the National Alliance for Research in Schizophrenia and Affective Disorders (Young Investigator Award) (M.H. Trivedi). The authors appreciate the secretarial support of Fast Word, Inc. of Dallas, Lisa Stupar and David Savage, and the administrative support of Kenneth Z. Altshuler, M.D., Stanton Sharp Professor and Chairman, Department of Psychiatry, UT Southwestern Medical Center and David J. Kupfer, M.D., Chairman, Department of Psychiatry, University of Pittsburgh Medical Center.

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