Does a Placebo Run-In or a Placebo Treatment Cell Affect the Efficacy of Antidepressant Medications?

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During the last decade, there has been an increasing use of a placebo run-in period prior to randomization to active treatments, or placebo in randomized controlled trials aimed at establishing acute phase antidepressant drug efficacy in patients with major depression. This procedure is thought to reduce response rates to placebo treatment after randomization, thereby increasing the drug–placebo difference. Metaanalyses of 101 studies reveal that a placebo run-in does not (1) lower the placebo response rate, (2) increase the drug-placebo difference, or (3) affect the drug response rate post-randomization in either inpatients or outpatients for any antidepressant drug group. If there is a post-randomization placebo treatment cell, drug response rates are unchanged or are slightly lower than if there is no placebo treatment cell for outpatients. These results suggest that a pill placebo run-in provides no advantage in acute phase efficacy trials. ***[Neuropsychopharmacology 11:33–43, 1994]***

KEY WORDS: *Depression; Placebo; Metaanalysis; Placebo run-in; Antidepressant medication*

The placebo run-in phase has become virtually standard practice in randomized controlled trials (RCTs) to test the efficacy of antidepressant medications in phase III and often phase IV studies. This single-blind phase usually lasts 3–14 days, followed by patients being randomized to treatment. However, if patients show a meaningful symptomatic reduction (usually defined as a 20% to 25% improvement on a symptom rating scale), subjects are excluded from study. The implications of this practice have rarely been empirically evaluated.

The rationale, based largely on intuition, is thought to reduce placebo responders post-randomization, thereby lowering post-randomization placebo response rates, and increasing differences between placebo and active treatments. Prien and Levine (1984) also suggested that the placebo run-in might eliminate rapid remitters, thereby reducing the need for post-randomization placebo control treatment in some circumstances.

The insufficient empirical data amassed to test these notions have not strongly supported the practice. Reimherr et al. (1989), in a retrospective reanalysis, discovered that the elimination of prerandomization placebo run-in "responders" reduced the drug-placebo difference from 30% to 25% in outpatients with major depression, and surprisingly, increased the placebo treatment response rates from 13% to 16%.

Additional circumstantial data to question the value of this practice is from adult trials that have attempted to clinically characterize placebo responders. Outpatients who "respond" *during* the placebo run-in tend to have longer episodes, a more chronic illness, a lower initial level of symptom severity, and are more likely nonendogenous. In comparison, patients who respond to placebo *after* randomization, tend to have shorter current episodes and higher symptom severity at randomization (Fairchild et al. 1986; Rabkin et al. 1986, 1987). These findings, albeit from different studies, hint that those who "respond" to a placebo run-in may not be isomorphic with those who ultimately respond to post-randomization placebo treatment.

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METHODS

Selection of Studies

This report is based on literature identified and tabulated for a larger review, commissioned by the Agency for Health Care Policy and Research (Depression Guideline Panel 1993). All relevant English language, peer-reviewed, randomized controlled acute phase treatment trials for inpatients and outpatients with major depression were included (see Depression Guideline Panel in press). The search, conducted by the National Library of Medicine, used MEDLINE and Psychological Abstracts. Key search words included generic names of all antidepressant medications. Abstracts were obtained and reviewed for all acute phase RCTs from 1975 to 1990 (except for monoamine oxidase inhibitors [MAOIs] from which literature from 1959 to 1990 was used).

Articles that met the following inclusion/exclusion criteria were selected: (1) written in English; (2) patients had major depressive or bipolar disorder; (3) the trial had to last three weeks; (4) a quantitative outcome measure was used; (5) a comparison was made between a known antidepressant drug and a placebo, another medication, or both; and (6) the study was blinded. A total of 141 eligible, placebo-controlled RCTs were identified, of which 101 could be metaanalyzed.

Evidence tables were created to summarize the author's report of either the percentage of responders in each cell or the percentage of responders between-cell differences. The numbers randomized, responding to, and completing each treatment cell were recorded (Depression Guideline Panel, in press).

Assessment of Outcome

For this report, we focused on studies providing dichotomous outcome measures. Categorical scoring was chosen because it addresses the question most patients want to know. How likely am I to get better if I follow treatment? In addition, categorical data was required for the metaanalytic procedures.

In nearly all studies, outcome was based either on the Hamilton Rating Scale for Depression (HRS-D) (Hamilton 1960) or the Clinical Global Impression (Guy 1976). Virtually every study that used the HRS-D counted a 50% reduction in the HRS-D score as a responder. If the HRS-D was not reported, then a CGI response of 1 or 2 (markedly improved, or very much improved) was counted.

Determination of Success Rates

The success of a treatment may be reported in three different ways. First, an "intent-to-treat" analysis, that utilizes all patients who improved (regardless if they remained in the study) as the numerator, and the number randomized to treatment as the denominator, addresses the question of how many patients randomized to the treatment improve. Second, an "adequate treatment" analysis includes only patients who received a predetermined minimum amount of treatment (typically 2–4 weeks for medication) as the denominator, and counts those that responded as the numerator. This approach answers the question of how many improve from receiving at least the minimal amount of treatment thought to be effective. Finally, a "completer" analysis includes only those who completed the full protocol. The numerator and denominator include only these patients.

These three methods produce different responses rates. Assume that 100 patients are randomized to treatment, 80 complete 3 weeks (defined a priori as "adequate treatment"), and 40 complete the treatment (e.g., 8 weeks). Assume an adequate course of treatment is 75% effective, a full course is 95% effective, and for simplicity, patients who withdraw from treatment do not improve. Completer response rate is 0.95 (40/40) or 95%. The adequate treatment response rate is 0.75 (40) plus 0.95 (40/80) or 78%. The intent-to-treat response rate is 0.95 (40/100) or 38%. Thus, success rates range from 38% to 95% depending on the sample chosen.

We used modified intent-to-treat analysis for this report. The denominator for this analysis was the number of patients randomized to each treatment cell. The numerator was the number of patients who improved while in treatment. This modification was required because very few studies followed patients after they left the trial. If some patients who left a study improved anyway (which is possible), the modified intent-to-treat response rates will be lower than a true intent-to-treat analysis. However, the between-treatment comparisons, based on the modified intent-to-treat analysis should generally be similar to those using a true intent-to-treat analysis because response rates in subjects leaving the study are not expected to differ across treatments.

Method of Metaanalysis

We conducted metaanalyses using the Confidence Profile Method (Eddy et al. 1990). This method uses a hierarchical Bayesian random-effects model and calculates the probability distribution that describes the results expected if a hypothetical additional study, similar to the ones included in the analysis, was performed. By taking into account the heterogeneity of study results, this type of analysis depicts the range of results practitioners could expect should they use the treatment in their own practice settings.

Whereas, the hierarchical random effects model is very robust, there are several potential threats to the

Table 1. Studies Available for Intent-to-Treat Metaanalyis

Drug	No. of Studies	Reference by Author(s)
Tricyclics		
Amitriptyline	12	Feighner et al. 1979; Goldberg and Finnerty 1980; Reimherr et al. 1990; Rickels and Case 1982; Rowen et al. 1982; Claghorn et al. 1983; Hormazabal et al. 1985; Imlah 1985; Rickels et al. 1985; Amsterdam et al. 1986; Kleiser and Lehmann 1988; Spiker and Kupfer 1988
Desipramine	3	Stewart et al. 1981, 1983, 1985
Doxepin	3	Veith et al. 1982; Jarvik et al. 1983; Rickels et al. 1985
Imipramine	48	Agnew et al. 1961; Rothman et al. 1962; Greenblatt et al. 1964; Schildkraut et al. 1964; British Medical Research Council 1965; Raskin et al. 1978; Kellams et al. 1979; Escobar et al. 1980; Feighner 1980; Gerner et al. 1980; Mann et al. 1981; Rickels et al. 1981; van der Velde 1981; Rickels et al. 1982a,b; Veith et al. 1982; Feighner et al. 1983a,b; Itil et al. 1983; Jarvik et al. 1983; Meredith and Feighner 1983a; Meredith et al. 1984; Reimherr et al. 1984; Liebowitz et al. 1984a,b; Cohn and Wilcox 1985; Dominguez et al. 1985; Kocsis et al. 1985; Stark and Hardison 1985; Lipman et al. 1986; Mendels and Schless 1986; Wakelin 1986; Lapierre et al. 1987; Rickels et al. 1987; Byerley et al. 1988; Liebowitz et al. 1988; Quitkin et al. 1988; Cohn et al. 1989; Conti and dell'Osso 1989; Elkin et al. 1989; Feighner and Boyer 1989; Kocsis et al. 1989; Lydiard et al. 1989; Peselow et al. 1989; Quitkin et al. 1989; Stewart et al. 1989; Versiani et al. 1989; Quitkin et al. 1990
Nortriptyline	3	White et al. 1984; Georgotas et al. 1986; Katz et al, 1990
Heterocyclics		
Amoxapine	1	Rickels et al. 1981
Bupropion	4	Fabre et al. 1983; Meredith and Feighner 1983b; Feighner et al. 1984; Lineberry et al. 1990
Maprotiline	2	van der Velde 1981; Edwards and Goldie 1983
Trazodone	7	Kellams et al. 1979; Escobar et al. 1980; Feighner 1980; Goldberg and Finnerty 1980; Mann et al. 1981; Rickels and Case 1982; Klieser and Lehmann 1988
SSRIs		
Fluoxetine	11	Reimherr et al. 1984; Cohn and Wilcox 1985; Stark and Hardison 1985; Fieve et al. 1986; Goodnick et al. 1987; Wernicke et al. 1987[a]; Fabre and Putnam 1987[a]; Byerley et al. 1988; Muijen et al. 1988; Cohn et al. 1989; Dunlop et al. 1990[a]
Fluvoxamine	6	Itil et al. 1983; Dominguez et al. 1985; Wakelin 1986; Lapierre et al. 1987; Conti and dell'Osso 1989; Lydiard et al. 1989
Sertraline	2	Peselow et al. 1986; Reimherr et al. 1990
Paroxetine	2	Feighner and Boyer 1989; Peselow et al. 1989
MAOIs		
Isocarboxacid	8	Ford et al. 1959; Agnew et al. 1961; Joshi 1961; Rothman et al. 1962; Kurland et al. 1967; Davidson and Turnbull 1983; Giller et al. 1984; Davidson et al. 1988
Phenelzine	16	Agnew et al. 1961; Rees and Davies 1961; Schildkraut et al. 1964; British Medical Research Council 1965; Robinson et al. 1973; Raskin et al. 1974; Ravaris et al. 1976; Rowan et al. 1982; Liebowitz et al. 1984a,b; Georgotas et al. 1986; Quitkin et al. 1988, 1989, 1990; Stewart et al. 1989; Georgotas et al. 1986
Tranylcypromine	3	Bartholemew 1962; Himmelhoch et al. 1982; White et al. 1984

[a] Included 20 mg, 40 mg and 60 mg treatment cells.
SSRIs = selective serotonin reuptake inhibitors; MAOIs = monoamine oxidase inhibitors.

internal validity of the metaanalyses. The random effects model accounts for among-study variations and, therefore, accounts for random bias; however, it cannot account for any systematic biases that occurred in all studies. Secondly, for inclusion in the metaanalysis, studies had to present sufficient data to permit calculation of the percentage of the response for each treatment, based on the intent-to-treat sample. If studies without sufficient data were fundamentally different from those that were included, summary statistics may be biased. Similarly, a variety of publication biases (e.g., the preferential publication of those studies disproving the null hypothesis) could result in biased summary statistics.

Table 2. Number of Randomized Placebo Controlled Studies[a]

	Outpatient	Inpatient
Placebo run-in	53 (41)	14 (9)
No placebo run-in	54 (33)	20 (18)
Total	107 (74)	34 (27)

[a] The numbers in parentheses are the number of trials subjected to metaanalysis.

Tabulation of Findings

We report findings for inpatients and outpatients separately, because attrition rates, as well as placebo and drug response rates, may differ for these two groups. We combined, however, adult and geriatric studies because (1) there is no evidence of differential responses to drug or placebo in published studies to date (Depression Guideline Panel 1993); and, (2) the number of geriatric studies was too few for meaningful independent analyses.

We divided the medications into groups. The tricyclic medications included amitriptyline, desipramine, doxepin, imipramine, nortriptyline, and protriptyline. The heterocyclic group included maprotiline, amoxapine, trazodone, and bupropion. The selective serotonin reuptake inhibitors (SSRIs) included fluoxetine, paroxetine, and sertraline. The MAOIs included isocarboxacid, phenelzine, and tranylcypromine.

RESULTS

We posed four specific questions to be addressed by the metaanalyses: (1) Does a placebo run-in affect the post-randomization placebo treatment cell response rate?; (2) Does a placebo run-in affect the drug-placebo difference?; (3) Does a placebo run-in affect the drug response rate?; and, (4) Does a post-randomization placebo treatment cell affect drug response rates (with or without a placebo run-in)?

The number of studies available for intent-to-treat metaanalysis in placebo-controlled studies by individual drugs are listed in Table 1 and were as follows: for tricyclics, amitriptyline (n = 12), desipramine (n = 3), doxepin (n = 3), imipramine (n = 48), and nortriptyline (n = 3); for heterocyclics, amoxapine (n = 1), bupropion (n = 4), maprotiline (n = 2), and trazodone (n = 7); for the SSRIs, fluoxetine (n = 11) (with 17 cells), fluvoxamine (n = 6), sertraline (n = 2), and paroxetine (n = 2); and for the MAOIs, isocarboxacid (n = 8), phenelzine (n = 16), and tranylcypromine (n = 3). Table 2 summarizes the number of studies with and without a placebo run-in by patient status used in the metaanalysis.

Table 3 reveals that whether or not there is a placebo run-in, post-randomization placebo treatment cell response rates are identical. For example, the placebo treatment cell response rate for outpatients with a run-in was 27.8% ± 11.0% (39 studies), compared to 28.5% ± 8.5% (33 studies) without a run-in. These two rates are not different from each other. The placebo treatment cell response rates for inpatients were also not different between studies with and without a placebo run-in. Of additional note is the apparent fact that the placebo treatment cell response rates were similar for inpatients and outpatients. Thus, a placebo run-in does not affect the placebo cell response rates.

Table 4 addresses the question of whether or not a placebo run-in affects drug-placebo differences following randomization. For outpatients, the drug-placebo difference for tricyclics was 18.4% ± 5.9% (32 studies) with a placebo run-in, compared to 21.5% ± 8.3% (21 studies) without a run-in. Similarly for heterocyclics, it was 20.7% ± 18.9% (3 studies) with a placebo run-in and 14.8% ± 13.4% (5 studies) without a run-in. For the SSRIs, the drug-placebo difference with a placebo run-in was 20.8% ± 8.5% (23 studies) versus 27.0% ± 24.2% (2 studies) without a run-in. Finally, for the MAOIs with a placebo run-in, the difference in probability for drug-placebo was 31.1% ± 18.5% (6 studies) versus 29.9% ± 17.3% (8 studies) without a run-in. None of these drug-placebo differences in outpatients for individual drugs with and without a placebo run-in were different from each other. The total drug-placebo difference in outpatients for all drugs was 20.6% ± 6.2% (64 studies) *with* a placebo run-in versus 21.8% ± 7.7% (36 studies) *without* a run-in.

For inpatients, the drug-placebo difference for

Table 3. Placebo Treatment Cell Response Rate in RCTs with and without a Placebo Run-In[ab]

	Outpatient	Inpatient	Total
Placebo run-in	27.8% (11.0) [39]	26.2% (14.4) [9]	27.6% (11.4) [48]
No placebo run-in	28.5% (8.5) [33]	31.9% (14.8) [14]	29.5% (10.6) [47]
Total	28.0% (8.3) [72]	29.6% (14.7) [23]	28.2% (9.6) [95]

[a] Numbers in parentheses are standard deviations.
[b] Numbers in brackets are number of cells metaanalyzed.

Table 4. Drug-Placebo Differences in RCTs with and without a Placebo Run-In[ab]

	Outpatient		Inpatient	
	Placebo Run-In	No Placebo Run-In	Placebo Run-In	No Placebo Run-In
Tricyclics	18.4% (5.9) [32]	21.5% (8.3) [21]	25.6% (12.5) [8]	33.1% (7.9) [6]
Heterocyclics	20.7% (18.9) [3]	14.8% (13.4) [5]	32.2% (13.5) [4]	44.9% (10.8) [3]
SSRIs	20.8% (8.5) [23]	27.0% (24.2) [2]	25.5% (21.7) [2]	NA
MAOIs	31.3% (18.5) [6]	29.9% (17.3) [8]	NA	18.4% (22.6) [9]
Total	20.6% (6.2) [64]	21.8% (7.7) [36]	28.5% (10.3) [14]	35.6% (7.7) [18]

[a] Numbers in parentheses are standard deviations.
[b] Numbers in brackets are number of cells metaanalyzed.
SSRIs = selective serotonin reuptake inhibitors; NA = not available; MAOIs = monoamine oxidase inhibitors.

tricyclics was 25.6% ± 12.5% (8 studies) *with* a placebo run-in compared to 33.1% ± 7.9% (6 studies) *without* a run-in. For heterocyclics with a placebo run-in, the drug-placebo difference was 32.2% ± 13.5% (4 studies) compared to 44.9% ± 10.8% (3 studies) without a run-in. This finding indicates a tendency toward a higher drug-placebo difference in heterocyclics without a placebo run-in. Similar comparisons were not possible for SSRIs versus MAOIs because there were no inpatient studies of MAOIs with a placebo run-in, and no studies of SSRIs without a placebo run-in. Again, the total drug-placebo difference for all studies with a placebo run-in was 28.5% ± 10.3% (14 studies) versus 35.6% ± 7.7% (18 studies). In summary, Table 4 also reveals that the drug-placebo difference is only in the range of 21% to 35%, although the drug-placebo differences are consistently higher for inpatients than for outpatients. A placebo run-in does not affect drug-placebo differences in outpatients. For inpatients, a placebo run-in may actually reduce the drug-placebo difference.

Table 5 addresses the question of whether a placebo run-in affects the post-randomization drug cell response rates. The drug response rates for outpatients in studies with a placebo run-in are not different from drug response rates in studies without a placebo run-in. That is, the presence or absence of a placebo run-in does not affect drug response rates. This finding also appears to apply to inpatients.

Finally, Table 6 addresses the question of whether the presence of a post-randomization placebo treatment cell affects the drug cell response rates. For these analyses, all relevant studies were included whether or not they had a placebo run-in. For outpatients across all medication classes except the SSRIs, the drug response rate is unaffected by whether or not there is a post-randomization placebo treatment cell. Thus, the efficacy rates found in placebo-controlled trials would likely appear to generalize to trials without a placebo arm. For the SSRIs, however, it appears that when there was a placebo treatment arm, the drug response rate was lower than when there was no arm. With the inpatient studies, for each medication group, the presence or absence of a placebo treatment arm generally did not affect the drug response rate, except for the MAOIs, in which case, the inclusion of a placebo treatment arm was associated with a better overall response than when there was no such arm.

Thus, with few exceptions, the presence of a post-randomization placebo treatment cell does not appear to affect drug response rates. For the SSRIs, this finding

Table 5. Drug Response Rates in Studies with and without a Placebo Run-In[ab]

	Outpatient		Inpatient	
	Placebo Run-In	No Placebo Run-In	Placebo Run-In	No Placebo Run-In
Tricyclics	53.1% (6.4) [58]	48.9% (5.2) [58]	52.5% (11.6) [11]	59.7% (15.8) [21]
Heterocyclics	58.6% (6.6) [12]	58.6% (10.0) [22]	49.5% (19.8) [8]	51.4% (11.9) [8]
SSRIs	43.6% (5.7) [37]	54.9% (8.2) [6]	58.1% (9.2) [4]	53.6% (12.6) [7]
MAOIs	56.2% (6.4) [6]	57.8% (6.9) [16]	78.6% (14.5) [1]	54.2% (10.2) [14]
Total	52.4% (3.8) [103]	53.9% (4.4) [102]	58.1% (8.2) [24]	54.3% (7.3) [50]

[a] Numbers in parentheses are standard deviations.
[b] Numbers in brackets are number of cells metaanalyzed.
SSRIs = selective serotonin reuptake inhibitors; MAOIs = monamine oxidase inhibitors.

Table 6. Drug Response Rates in Studies with and without a Post-Randomization Placebo Treatment Cell[a,b]

	Outpatient		Inpatient	
	With Placebo Treatment Cell	Without Placebo Treatment Cell	With Placebo Treatment Cell	Without Placebo Treatment Cell
Tricyclics	48.9% (4.9) [58]	53.6% (6.9) [58]	56.8% (16.9) [10]	55.0% (9.7) [22]
Heterocyclics	57.5% (5.3) [8]	61.7% (11.0) [26]	51.8% (9.6) [11]	50.8% (17.5) [5]
SSRIs	42.4% (4.6) [22]	55.3% (9.5) [21]	58.8% (9.2) [3]	55.2% (11.0) [8]
MAOIs	57.4% (7.1) [16]	61.2% (5.4) [6]	63.6% (17.1) [10]	54.7% (10.8) [5]
Total	50.6% (3.7) [104]	58.1% (4.6) [111]	56.9% (7.3) [34]	54.7% (6.8) [40]

[a] Numbers in parentheses are standard deviations.
[b] Numbers in brackets are number of cells metaanalyzed.
SSRIs = selective serotonin reuptake inhibitors; MAOIs = monoamine oxidase inhibitors.

was not accounted for by a different response within those studies without a placebo treatment cell that did 55.9% (± 17.0%) (15 studies) or did not 54.9% (± 8.2%) (6 studies) have a placebo run-in. One might speculate that the patient sample shifted between premarketing (more likely to include a placebo treatment cell) and post-marketing (less likely to have a placebo treatment cell) studies, or a shift on the rapidity with which dose escalation was recommended (i.e., more rapid escalation premarketing may have led to higher attrition and consequently lower response rates), or the initial symptom severity requirement may have been lowered in post-marketing studies. Alternatively, clinicians may have found that those with atypical features or more chronic forms of depression may preferentially tolerate and/or respond to the SSRIs, as suggested by Reimherr et al.'s (1984) retrospective analyses, that could have led to a more responsive sample with post-marketing studies.

DISCUSSION

In summary, the previous metaanalyses provide a somewhat surprising, but relatively solid set of findings. A placebo run-in, as compared to no placebo run-in, does not reduce (or increase) the post-randomization placebo response rate, drug response rate, or drug-placebo differences. One can ask, however, about the certainty of these findings. The metaanalyses used are based on a substantial number of studies. The certainty of the percent response rates is reflected in the standard deviations; thus, for the vast majority of analyses, the findings are robust.

We tested the stability of these findings using computer modeling for one part of the analysis. Table 3 shows that the placebo treatment cell response rate is 27.8% (±11.0%) for 39 studies of outpatients with a placebo run-in, and 28.5% (±8.5%) for 33 studies without a placebo run-in. In order to create a post-randomization placebo treatment cell response rate of 24.6% (±11.2%) in RCTs with a placebo run-in (i.e., 3.2% lower than the 27.8% estimated in the current 39 studies), an additional 39 similarly sized studies are needed that have a placebo response rate of only 20.0% (±10.9%).

Why might a placebo run-in generally fail to affect placebo response rates or drug-placebo differences post randomization? First, studies without a placebo run-in rarely enter patients immediately at the first visit. There is often a screening visit at which informed consent is obtained, and ratings, and laboratory screening tests are conducted. Patients, even on no medication, return 3 days to 10 days later, learn that their laboratory tests are normal, receive another severity rating, and are randomized. Sometimes a third visit, spaced only a few days after the screen visit, is needed. For example, patients on medications are discontinued, which may require an additional one to two visits. A nearly identical procedure is followed when there is a placebo run-in, as the pill placebo may be given between screen (first visit) and baseline (time of randomization). Furthermore, the intensity and/or nature of patient education/adherence counseling has generally increased over the years with or without a placebo run-in.

It is entirely reasonable to assume that the process of consenting, being educated, being screened for eligibility, and the subsequent post-screen visits even *without* a pill placebo are just as effective as a pill placebo in identifying placebo run-in "responders." That is, the pill placebo may add little except cost in identifying run-in "responders."

The findings in Table 4 deserve comment. There appears to be a slight difference between the effects of a placebo run-in versus no run-in on drug-placebo differences found with inpatients as opposed to outpatients. For inpatients, there is a tendency for studies without a run-in to be associated with a somewhat higher drug-placebo difference; however, the number of studies in each drug group is modest, so caution is warranted. On the other hand, one might speculate that for inpatients, the lack of a placebo run-in may induce investigators to enroll more acutely (severely) ill sub-

jects who in turn more specifically benefit from drug as opposed to placebo, thereby increasing drug–placebo differences.

In outpatients, the presence or absence of a placebo run-in generally appears to make no difference. With SSRIs, a 27.0% drug–placebo difference without a run-in, versus a 20.8% difference with a run-in is not meaningful given the high standard deviations and the availability of only two studies in the former group, although the difference is consistent with Reimherr et al. (1984).

Secondly, in outpatients, the metaanalyses suggest that the presence of a post-randomization placebo treatment arm generally does not significantly affect drug response rates, except for the SSRIs, in which case, the absence of a placebo arm is associated with a slight increase in the response rate. This finding could result from patients with greater Axis II or more chronic depressions who would decline a placebo-controlled study versus entering studies without a placebo arm, if the SSRIs were particularly beneficial for this patient group as compared to the other antidepressant classes. The latter notion is supported by Reimherr and colleagues (1984).

The overall slightly greater drug response rates in outpatients for all drugs (Table 6) in trials without,opposed to those with, a post-randomization placebo treatment cell, that are not robust, are seemingly consistent. This tendency could result from subject selection (i.e., less severely or chronically ill subjects being more likely included in post-marketing, nonplacebo controlled trials). Alternatively, it could result from investigator and participant knowledge of the lack of a placebo treatment cell, that leads to both expecting a greater response, thereby slightly inflating ratings in trials without a placebo arm, or conversely, slightly underestimating responses in placebo-controlled trials. However, because a similar pattern is *not* seen with inpatient trials, the case for patient/investigator bias is not strong.

For inpatients, the MAOIs with a placebo treatment cell were associated with greater efficacy than MAOIs without a placebo cell. This finding is consistent with the notions that MAOIs may be more effective in the less severely ill (e.g., outpatients versus inpatients) (Depression Guideline Panel 1993, pp. 50–51), combined with the idea that less severely ill inpatients may be more likely to agree to a placebo-controlled trial than the more severely ill may agree to.

Whether or not patients who drop their HRS-D score by a predetermined degree or percent should be excluded (whether with or without a placebo run-in) cannot be addressed by this report. Logic, clinical practice, and the need for clinical relevance and generalizability would argue that if there are sufficient symptoms at randomization to indicate drug treatment, the patient should be entered. That is, the raw HRS-D score at the time of randomization would seem to be the primary variable to dictate inclusion or exclusion. In addition, prior reports are consistent with the notion that patients who "respond" to a one-week placebo run-in are clinically dissimilar to those who respond to a multiweek post-randomization placebo treatment arm (Rabkin et al. 1987). Reimherr and coworkers (1989) suggest that the percent drop rule may not be valid and may even slightly reduce drug–placebo differences.

Finally, measurement itself may present a problem in some patients. For example, if a patient initially scores a 22 on the HRS-D, but at randomization drops to 17, a 20% drop has occurred, and the patient is excluded. However, the reliability even of the 17-item HRS-D is on the order of $\pm$ 2 in this range. Thus, a 22 is really a score of between 20 and 24. A 17 is really a score of between 15 and 19. Thus, at least in some patients, a clinically meaningless "drop" can lead to subject exclusion.

Conversely, Quitkin and coworkers (personal communication, June 1994) found in a retrospective analysis combining several trials that those with minimal severity reductions in the prerandomization pill–placebo run-in, had a higher response rate to either placebo or drug than those with a greater drop (although patients with a clinically significant drop were excluded). However, the drug–placebo differences in these two groups may not actually change.

From the clinical perspective, there are several reassuring findings that include: (1) drug response rates with or without a placebo run-in are the same, (2) whether or not there is a placebo treatment arm, seems not to affect drug response (except a better response may be present for SSRIs) when there is no such arm, and (3) the drug class involved does not change the above findings. To estimate effects in the "real world" of clinical practice (effectiveness) from RCTs with/without placebo run-ins or placebo cells, these data suggest that these design features do not profoundly affect overall efficacy. That is, if practitioners follow the other procedures (e.g., weekly visits, measuring outcome, dose adjustments), an equal or better outcome for similar kinds of patients treated with the medication in question can be anticipated.

From a research perspective, however, these findings raise serious questions as to the value of a single-blind pill placebo run-in to exclude patients in efficacy trials. As with any retrospective analysis, especially when combining many studies, one cannot be completely convinced of these results. The only sure test would be an RCT in which half the patients received a single-blind placebo run-in, whereas the other half did not. This type of study would determine if these two different procedures, each designed to exclude patients under different conditions, would perform

equally, excluding the same types and numbers of subjects.

In summary, these findings lend no support to the need for a pill placebo run-in, as compared to a multi-visit run-in without a pill placebo. Further, empirical studies of the utility of the percent drop rule often used during the run-in period are needed.

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