Is There a Delay in the Antidepressant Effect? A Meta-Analysis

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Objectives: It has long been thought that there is a delay of several weeks before a true antidepressant effect occurs, although this theory has increasingly come into question. The goals of this meta-analysis were to determine whether significant drug-placebo separation occurs during the first 2 weeks of treatment and to ascertain whether the timing of response to antidepressant medication and placebo is distinct.

Data Sources: Seventy-six double-blind, placebo-controlled trials conducted between 1981 and 2000, included in a recently published meta-analysis that evaluated placebo response rates in depressed outpatients, were reviewed. In addition, each issue of 6 psychiatric journals from January 1992 through December 2001 was reviewed.

Study Selection: Forty-seven studies that evaluated antidepressant medications with established efficacy, performed weekly or biweekly (every other week) evaluations, and presented the time course of improvement as measured by the Hamilton Rating Scale for Depression were included in our meta-analysis.

Data Synthesis: The time course of improvement on active medication and placebo was nearly identical, as 60.2% and 61.6% of the improvement that occurred on active medication and placebo, respectively, took place during the first 2 weeks of treatment. Drug-placebo differences were not only present but were most pronounced during the first 2 weeks of treatment and diminished in a stepwise fashion thereafter. A series of subanalyses confirmed that this early drug-placebo separation was clinically observable and represented a true drug effect.

Conclusion: These results challenge the notion that a delay exists before a true antidepressant effect occurs.

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In his seminal 1957 report[1] on imipramine, Roland Kuhn suggested that the response to antidepressant medications occurred quickly: "As a rule, the initial response [to imipramine] was evident within 2–3 days."[1,2(p464)] Other investigators at the time[3–5] also noted that the benefits of antidepressant medications could be observed early. Nevertheless, despite an absence of well-controlled studies suggesting otherwise, the notion that antidepressants take several weeks to work gradually became incorporated into clinical lore over the next 2 decades.[6–9] Although the delayed antidepressant response theory has been described by some leading affective disorders researchers as a "myth,"[10,11] it remains widely espoused to this day. In one authoritative psychiatric textbook, for example, it is suggested that "Antidepressants often require 2 to 4 weeks to produce substantial effects,"[12(p1164)] while another states that "It is difficult to assess the efficacy of an antidepressant in less than 4 weeks," since "no [antidepressant] has been able to reduce reliably the 3 weeks or longer it appears to take for the drugs to work."[13(pp41–45)] The delayed antidepressant response theory has also greatly influenced biological research,[14–16] as researchers have attempted to identify intraneuronal processes occurring "downstream" from the synapse that correspond to the delayed antidepressant effect: "A major problem with all versions of [the] early 'monoamine deficiency' hypotheses was the observation that the inhibitory actions of antidepressants on monoamine reuptake or on monoamine oxidase activity are immediate, whereas clinical efficacy requires weeks of treatment."[14(p127)]

Empirical support for the delayed antidepressant response theory comes almost entirely from a single group of researchers from Columbia University led by Frederic Quitkin. In their original landmark study published in 1984, Quitkin and colleagues[17] pooled the results of 3 separate antidepressant trials they had performed—all of which were 6 weeks in duration. They reported little or no benefit from active medication compared with placebo during the first 3 weeks of treatment, as the majority of drug-placebo separation occurred between weeks 3 and 6.[17] Historically, the study was instrumental not only in firmly establishing the delayed antidepressant response theory, but also in lengthening the recommended antidepressant trial duration from 4 to 6 weeks. The same group

subsequently published a series of studies[18–24] evaluating the time course of improvement on antidepressant medication and placebo. Using a technique called "pattern analysis,"[18] they suggested that the nature and timing of improvement for placebo responders and "true drug" responders were distinct. In brief, the placebo response was characterized as an abrupt and nonpersistent improvement that occurred during the first 2 weeks of treatment, whereas delayed, persistent improvement was more likely to represent a true drug effect. The Columbia group not only replicated their initial findings[19] but validated pattern analysis by distinguishing between spontaneous improvement and placebo response[20,21] and by demonstrating that patients who improve on active medication with a "placebo response pattern" are at significantly higher risk for relapse during the continuation[22,23] and maintenance[24] phases of treatment. The hypothesis was that these patients had initially responded to nonspecific factors and consequently derived significantly less benefit from continued antidepressant therapy.

Despite the elegance and internal consistency of the Columbia group's results, the validity of the delayed antidepressant response theory is undermined by 2 findings. First, recent studies have consistently shown that of the patients who ultimately respond to an antidepressant trial, the overwhelming majority demonstrate significant improvement within the first 1 to 2 weeks of treatment.[25–36] In fact, improvement during the first 2 weeks of treatment has repeatedly been found to be the best predictor of response to an antidepressant medication at endpoint.[31,34–36] Second, independent investigators who have compared the patterns of improvement in responders to either active medication or placebo have found that the time course of improvement is almost identical between the 2 cohorts, and none have found evidence of a delayed antidepressant effect.[26,29,37–39]

Because of the enormous clinical and research implications inherent in these issues, we sought to determine whether or not the delayed antidepressant response theory could be confirmed by systematically analyzing the results of a diverse collection of antidepressant trials published over the last 2 decades. If the delayed antidepressant response theory is correct, we would predict that minimal drug-placebo differences will be elicited during the first 2 weeks of treatment and the timing of response to antidepressant medication and placebo will be distinct, i.e., subjects who respond to placebo will improve earlier than subjects who respond to antidepressant medication.

METHOD

Sources of Data and Criteria for Review

To obtain a systematic and thorough collection of antidepressant trials, we reviewed the studies collected in a recent meta-analysis by Walsh et al.[40] that evaluated placebo response rates in antidepressant trials published over the last 2 decades. In addition to using the results of another meta-analysis,[41] Walsh et al.[40] generated their database via a computer search of MEDLINE and PsychLit by specifying the generic names of all putative antidepressants and the word *placebo*. Trials were included in the Walsh et al. meta-analysis[40] if they were reported in English, published between January 1981 and December 2000, composed of outpatients with major depressive disorder according to research diagnostic criteria, had at least 20 subjects in the placebo group, were at least 4 weeks in duration, randomly assigned subjects to receive an antidepressant medication or placebo, assessed subjects under double-blind conditions, reported the total number of subjects assigned to placebo and medication group(s), and reported the number of treatment responders in each group. Response was defined in each of these studies as either a 50% or greater reduction in baseline Hamilton Rating Scale for Depression[42] (HAM-D) scores or a Clinical Global Impressions[43] (CGI) rating of "very much improved" or "much improved" (CGI score of 1 or 2).

Seventy-six studies[39,44–118] were included in the Walsh et al. meta-analysis.[40] Twenty-two of these studies* presented only endpoint results and did not present weekly or biweekly (once every other week) changes in HAM-D scores (a criterion for inclusion in our meta-analysis) and therefore were excluded from our analysis. The study by Stark and Hardison[107] was excluded because it reported only weekly HAM-D reductions in subjects who completed at least 3 weeks of treatment. In addition, we excluded those studies that did not report a mean baseline HAM-D score[114] or evaluated agents whose antidepressant properties are unproven or debated, such as minaprine,[45] ipsapirone,[77] zalospirone,[95] buspirone,[96] sulpiride,[99] hypericum,[101] gepirone,[117] and moclobemide.[86] In studies that included multiple cohorts on active medication—some of whom received a proven antidepressant and others, an unproven one—we included data only from the cohort randomized to the established antidepressant. Similarly, we excluded cohorts that received active medication at what are generally considered to be subtherapeutic doses. One cohort that received 50 to 75 mg/day of venlafaxine[82] and another that received 50 to 300 mg/day of nefazodone[119] were therefore excluded. In addition, one study by Rickels et al.[92] had to be excluded because 3 weeks transpired between the first and second assessment ratings. Finally, because the time course of response to antidepressants may be slower in geriatric patients,[120–122] we excluded 4 studies that focused on this population.[70,85,103,112]

*References 39, 46, 49, 56, 57, 60, 62, 69, 73, 74, 79, 80, 84, 87, 88, 90, 94, 102, 108, 109, 111, 115.

Table 1. Number of Cohorts and Number of Subjects Randomly Assigned to Placebo or Active Medication in 47 Studies

Medication	Cohorts	Subjects
Placebo	47	3418
Antidepressant	74	5158
Venlafaxine	13	1120
Imipramine	16	998
Amitriptyline	10	618
Fluoxetine	7	511
Sertraline	5	444
Paroxetine	9	414
Doxepin	2	306
Zimelidine	3	169
Mirtazapine	4	166
Nefazodone	2	122
Bupropion	1	110
Citalopram	1	103
Fluvoxamine	2	77

In total, 39 of the 76 studies from the Walsh et al. meta-analysis[40] were included in the present study.* To augment this database, we next systematically reviewed each article published from January 1992 through December 2001 in 6 prominent psychiatric journals (*American Journal of Psychiatry, Archives of General Psychiatry, British Journal of Psychiatry, The Journal of Clinical Psychiatry, Journal of Clinical Psychopharmacology,* and *Psychopharmacology Bulletin*). From this search, we identified 8 additional studies[119,123–129] not included in the Walsh et al. meta-analysis[40] that met our inclusion criteria. In total, 47 double-blind, placebo-controlled trials were included in our primary analysis with 74 cohorts randomized to active medication, each of which had superior outcomes compared with their placebo control group counterpart. Of the 74 cohorts on active medication, 67 were at least 5 weeks in duration and 66 were at least 6 weeks. This sample comprises more than 5100 subjects randomly assigned to active medication and more than 3400 randomly assigned to placebo (Table 1).

Method of Establishing Time Course of Improvement on Active Medication and Placebo

All 47 studies used either the 17- or 21-item version of the HAM-D, both of which are highly correlated with each other when measuring response to antidepressant therapy ($\kappa = 0.97$).[130] To establish a mean HAM-D baseline score that would account for sample size differences, we multiplied the baseline HAM-D score from each cohort by the sample size. For example, if a cohort comprised 50 subjects with a reported mean baseline HAM-D score of 20.0, the total baseline HAM-D would be $50 \times 20.0 = 1000$ HAM-D "points." We next added the HAM-D points of all studies together and divided this number by the total number of subjects randomly assigned to either active medication or placebo.

To determine the weekly decrease in HAM-D scores, we performed similar analyses. For example, if one study enrolled 100 subjects on active medication, and their mean changes in HAM-D points were reported to be –2.1, –1.4, –0.4, and +0.1 during weeks 1, 2, 3, and 4, respectively, their weekly changes in HAM-D scores as a group would be calculated as –210, –140, –40, and +10 in weeks 1, 2, 3, and 4. In cases in which data were missing for 1 week, the change in HAM-D points for the subsequent week was assumed to occur equally over the 2-week period. Thus, in the above example, if evaluations were performed at weeks 1, 2, 3, 4, and 6 (i.e., no evaluation was performed at week 5), and a change in HAM-D of –0.5 was reported from week 4 to week 6, then for our analyses we posited that the mean change in HAM-D scores for week 5 was –0.25 and for week 6 was –0.25 as well. Almost all of the rating assessments during the first 4 weeks of treatment were collected on a weekly basis (462 of 484; 95.5%), while 68.8% (150 of 218) of the outcome ratings for weeks 5 and 6 were collected on a weekly as opposed to a biweekly (every other week) basis.

In studies in which the changes in HAM-D scores were depicted graphically rather than numerically, we extracted the weekly change in HAM-D scores by measuring each data point, rounding to the nearest 0.5. A research assistant who was unaware of the purposes of our study replicated each data point. Of the 476 data points extracted from graphs, 456 (95.8%) were replicated by the research assistant within 0.5 points, suggesting that the data extraction was performed reliably and without bias. Effect sizes were not elicited because none of the studies reported standard deviations along with the weekly mean HAM-D scores.

Definition of Terms

Most of our analyses focus on the time course of improvement. Improvement refers to the overall reduction from baseline in symptom severity scores as measured by a validated outcome ratings scale—in this case, the HAM-D. No clear consensus exists on how to best define antidepressant response.[131,132] In clinical trials, response is most commonly defined as a 50% or greater reduction from baseline in symptom severity scores or an endpoint CGI rating of "much improved" or "very much improved." *Onset of response* is a term that has recently been introduced by several investigators[34,122,133–135] and has variably been defined as the point at which a sustained reduction in symptom severity scores of 20% to 33% from baseline is first observed. Remission occurs when no or minimal symptoms of major depression are

*References 44, 47, 48, 50–55, 58, 59, 61, 63–68, 71, 72, 75, 76, 78, 81–83, 89, 91, 93, 97, 98, 100, 104–106, 110, 113, 116, 118.

Table 2. Weekly Reduction in HAM-D Scores From Baseline for Subjects Receiving Antidepressant Medication (N = 5158) and Placebo (N = 3418)[a]

Medication	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Antidepressant, points (% improvement)	4.54 (34.8)	3.31 (25.4)	2.08 (15.9)	1.49 (11.4)	0.91 (7.0)	0.72 (5.5)
Placebo, points (% improvement)	3.55 (39.6)	1.97 (22.0)	1.58 (17.6)	0.85 (9.5)	0.67 (7.5)	0.34 (3.8)

[a]Values in parentheses represent the percentage of improvement that occurred for each respective week in proportion to the overall improvement that occurred for the entire 6 weeks. For example, for subjects receiving antidepressant medications, 34.8% (4.54 of 13.05 points) of the improvement that was observed in HAM-D scores over the course of 6 weeks took place during week 1.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

present; in antidepressant trials, an endpoint HAM-D score of 7 or less is the most common method for assessing remission.[131,132] Treatment is inherent in the notion of response, but it is not possible to know whether an observed response is a specific effect of treatment or whether it stems from nonspecific factors such as spontaneous improvement or placebo.[131] Thus, *onset of response*, *response*, and *remission* are terms used to denote various degrees of improvement but reflect no judgment about the etiology of that improvement. In the present article, we define antidepressant effect as the amount of improvement that occurs in cohorts receiving active medication minus the amount of improvement that occurs in cohorts receiving placebo. The antidepressant effect is considered the best gauge for assessing the true benefits of active medication.[19]

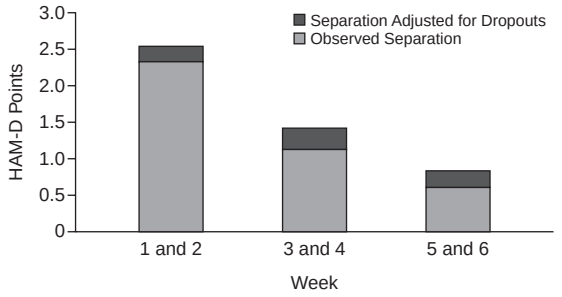
RESULTS

Time Course of Improvement on Antidepressant Medication and Placebo

The mean (SD) baseline HAM-D scores for subjects randomly assigned to antidepressant medication and placebo were 25.56 (2.32) (range, 19.7–37.0) and 25.32 (2.57) (range, 19.2–36.5), respectively. The mean (SD) overall reductions in HAM-D scores over the course of 6 weeks were 13.05 (3.14) for subjects on active medication and 8.96 (2.93) for subjects receiving placebo, which represents a 51.1% and a 35.4% decrease, respectively. For both active medication and placebo, the largest decrease in HAM-D scores occurred during the first week of treatment, and reductions in HAM-D scores diminished in each subsequent week thereafter (Table 2).

According to the delayed response theory, a disproportionately greater percentage of improvement in HAM-D scores should occur between weeks 3 and 6 in subjects receiving active medication compared with those receiving placebo. However, for subjects receiving active medication, only 39.8% (5.20 of 13.05 points) of the overall reduction in HAM-D scores occurred between week 3 and week 6, which was nearly identical to the proportion of improvement (38.4%; 3.44 of 8.96 points) observed in cohorts receiving placebo during this time frame (Table 2). Stated another way, 60.2% and 61.6% of the improvement that occurred on active medication and placebo, respectively, took place during the first 2 weeks of treatment.

Figure 1. Drug-Placebo Separation on the HAM-D Over the Course of a 6-Week Trial



Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Time Course of Drug-Placebo Differences

We next examined the time course of drug-placebo differences (i.e., the antidepressant effect) in the 47 trials by subtracting the mean weekly HAM-D decrease on placebo from the mean weekly HAM-D decrease on active medication. Drug-placebo differences, after adjusting for the fewer number of subjects in weeks 5 and 6, were week 1: 0.99; week 2: 1.34; week 3: 0.50; week 4: 0.64; week 5: 0.24; and week 6: 0.38. Thus, 57.0% (2.33 of 4.09 HAM-D points) of the drug-placebo differences that occurred during a 6-week trial occurred during the first 2 weeks of treatment (Figure 1). Rather than a delayed response pattern, antidepressant medications separated from placebo early, and their benefits diminished in a stepwise fashion thereafter.

The HAM-D has 3 items devoted to sleep disturbances, which could account for as many as 6 points on this rating scale. Theoretically at least, early drug-placebo differences could be attributable to the amelioration of sleep disturbances. To account for this possibility, we reanalyzed our dataset after excluding subjects who received an antidepressant with prominent sleep-enhancing properties such as imipramine, amitriptyline, doxepin, mirtazapine, and nefazodone. Of the subjects randomly assigned to a nonsedating antidepressant (N =2210), reduction in HAM-D scores over the course of 6 weeks was 3.45 points greater than for those ran-

Table 3. Percentage of Subjects Remaining in Treatment on Antidepressant Medication (N = 2905) and Placebo (N = 1852)[a]

Medication	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Antidepressant	96.4	89.7	81.0	73.4	67.3	62.7
Placebo	96.2	90.4	79.9	70.9	63.4	56.6

[a]Values based on weighted averages from 25 studies.[44,45,47,48,50,51,53–55,64,65,68,71,72,78,91–93,102,105,107,113,114,116,128]

domly assigned to placebo (N = 2123). Drug-placebo differences during week 1 and week 2 were 0.44 and 1.13 HAM-D points, respectively, which, combined, accounted for 45.5% (1.57 of 3.45 HAM-D points) of the overall drug-placebo differences. Thus, drug-placebo differences during the first 2 weeks of treatment cannot be attributed to the soporific side effects of antidepressant medications but appear to represent a true antidepressant effect.

Adjusting for Dropouts

In antidepressant efficacy trials, analyses of dropouts are almost always handled using the last-observation-carried-forward (LOCF) method of analysis. By this method, subjects who drop out at week 2 have their week 2 ratings carried forward to endpoint; consequently, no further improvement can occur in these subjects. The LOCF method therefore tends to underestimate the amount of improvement that occurs in subjects who remain in treatment. Furthermore, if a differential rate of attrition occurs on drug and placebo, this would distort any interpretation of the true effects of medication and placebo over time.[136]

Nineteen* of the 47 studies reported weekly attrition rates. To most accurately estimate attrition rates of subjects in antidepressant trials, we rereviewed the 37 antidepressant studies not included in our primary analyses from which 6 additional studies[45,47,92,102,107,114] were located. As can be seen in Table 3, the time course of attrition is remarkably similar between active medication and placebo. Nevertheless, we reanalyzed our primary results after accounting for attrition rates in each respective cohort. Overall, drug-placebo differences were somewhat higher than what was elicited by the LOCF method: 4.79 versus 4.09 on the HAM-D. The time course of improvement remained largely unaffected, however, with the majority (52.8%) of drug-placebo differences occurring during the first 2 weeks of treatment (Figure 1).

Is a Delayed Response Pattern Evident in Some Studies?

To evaluate the degree of variation among the studies in our meta-analysis and to determine whether some studies displayed a delayed antidepressant effect, we reviewed the results of each antidepressant trial that was at least 6 weeks in duration. In 91% (60 of 66) of the cohorts randomized to active medication, 50% or more of the overall reduction in HAM-D scores occurred during the first 2 weeks of treatment. The range of reduction in HAM-D scores during the first 2 weeks was 42% to 84%, with 25%, 50%, and 75% quartiles equaling a 53%, 59%, and 67% reduction, respectively.

We next examined whether drug-placebo separation displayed a delayed response pattern in some studies. To do so, we calculated a "delayed ratio" of drug-placebo differences for each antidepressant cohort. This ratio was calculated by dividing drug-placebo differences from weeks 3 through 6 by the drug-placebo differences that were observed from baseline through week 2. Because the time course of the numerator is twice as long as that of the denominator (4 weeks vs. 2 weeks), a delayed response pattern would have to be at least > 2. (If the response pattern were linear, i.e., drug-placebo differences were equivalent at each week of follow-up, then the calculated delayed ratio would equal exactly 2. In this scenario, 50% of the studies would be expected by chance to demonstrate a "delayed" ratio.) Thirteen (19.7%) of 66 antidepressant cohorts from 8 studies† met this criterion.

Time Course to Response Among Individuals: A Subanalysis

In the data heretofore presented, all analyses have been based on the results of grouped means. In theory, it is possible that the occurrence of individual responses, particularly a "true drug" response pattern, could get obscured when merged with the overall cohort. To account for this possibility, we rereviewed all 84 studies to see if any presented data demonstrating the time course of response on an individual basis. Seven studies[51,52,58,64,82,83,116] reported weekly cumulative response rates over the course of a 6-week trial: six[52,58,64,82,83,116] used a 50% or more decrease in HAM-D scores from baseline as the definition of response, and 1 study[51] defined response as a HAM-D score of 9 or less.

As can be seen from Table 4, there is no evidence that the pattern of response to antidepressant medication is delayed compared with the pattern of response to placebo. In fact, in comparing the timing of individuals' responses to a 6-week trial of either antidepressant medication or placebo, the pattern of response to placebo was even slightly delayed compared with the pattern of response to active medication for each of the first 5 weeks of treatment (Figure 2).

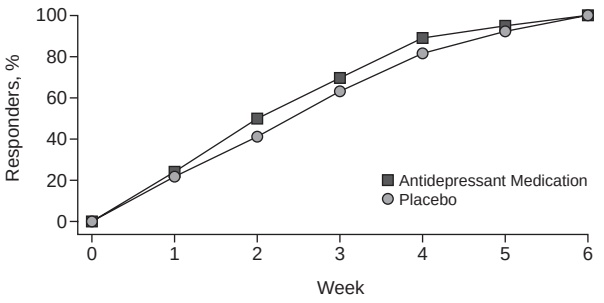
*References 44, 48, 50, 51, 53–55, 64, 65, 68, 71, 72, 78, 91, 93, 105, 113, 116, 128.
†References 48, 53, 106, 119, 124, 125, 128, 129.

Table 4. Cumulative Weekly Response Rates for Individuals Who Were Responders to Antidepressant Medication or Placebo at Week 6[a]

Medication	N[b]	Week 1, %	Week 2, %	Week 3, %	Week 4, %	Week 5, %	Week 6, %
Antidepressant	487	23	50	69	90	95	100
Placebo	308	22	41	63	82	92	100

[a]A meta-analysis of 7 studies.[51,52,58,64,82,83,116]
[b]N = number of subjects rated as positive responders at endpoint. All values are estimates.

Figure 2. Timing of Response for Individual Treatment Responders Receiving Antidepressant Medication and Placebo



Is This Early Drug-Placebo Separation Clinically Apparent?

Statistically significant differences are not necessarily clinically meaningful. One way to determine whether early drug-placebo separation is clinically apparent is to evaluate whether subjects randomly assigned to active medication are more likely to be rated as "much improved" or "very much improved" on the CGI scale during the first 2 weeks of treatment. Because the CGI scale is a global measure of overall improvement that lacks any sleep-specific items, it has clear face validity in establishing a clinically meaningful effect. Furthermore, the CGI scale was the instrument used by the Columbia group to establish the delayed antidepressant response theory. In both of the group's original[17] and replication[19] studies, active medication did not separate from placebo during the first 3 weeks of treatment using the CGI instrument.

Of the 47 studies in our meta-analysis, four[51,64,82,83] presented weekly response rates using the CGI scale. The antidepressants used and sample sizes randomly assigned to active medication were paroxetine (N = 168),[51] imipramine (N = 240),[64] venlafaxine (N = 79),[82] imipramine (N = 38),[83] and zimelidine (N = 39).[83] Combining the results from these 4 studies, 100 (17.7%) of 564 subjects receiving active medication were considered positive responders at the end of week 1, compared with 60 (11.5%) of 521 subjects receiving placebo ($\chi^2 = 8.32$, df = 1, p = .004). After 2 weeks, 172 (30.5%) of 564 and 104 (20.0%) of 521 subjects were considered positive responders on active medication and placebo, respectively ($\chi^2 = 15.85$, df = 1, p < .001). Thus, clinically apparent drug-placebo differences were elicited as early as week 1 and were even more pronounced by week 2. At endpoint, 62.2% (351 of 564) of the subjects receiving antidepressant medications were considered positive responders compared with 46.4% (242 of 521) of those receiving placebo—a difference in response rates of 15.8%. Because subjects receiving active medication displayed a 10.5% advantage over placebo by the end of week 2, approximately two thirds of the benefits of active medication over placebo occurred during the first 2 weeks of treatment by this method of analysis.

DISCUSSION

It has long been recognized that many individuals initiated on antidepressant medications respond quickly, but this early improvement has generally been attributed to nonspecific (placebo) factors. Over the years, the notion that there exists a delay in the antidepressant response has greatly influenced the expectations of clinicians and patients alike and has influenced the focus of biological research.

Our analysis of 47 independent antidepressant trials comprising more than 5100 subjects on active medication and 3400 on placebo, however, challenges the notion that there is a delay in the antidepressant effect. Contrary to what the delayed antidepressant response theory would predict, we found that (1) most (60%) of the improvement that occurred on antidepressant medication occurred during the first 2 weeks of a 6-week trial, (2) 57% of drug-placebo differences that were elicited during a 6-week trial also occurred during the first 2 weeks of treatment, (3) these results can be attributed neither to the soporific side effects of antidepressant medications nor to a differential attrition rate, (4) only 1 in 5 studies elicited a greater proportion of drug-placebo differences during weeks 3 through 6 compared with the first 2 weeks of treatment, and (5) similar to other investigators,[26,38,39] we found that the time course of improvement for subjects who responded to either antidepressant medication or placebo was nearly identical. This finding was true both when we examined improvements in group means of HAM-D scores (Table 2) and when we performed a subanalysis of when individuals responded to active medication or placebo (Table 4 and Figure 2). Interestingly, a recently published meta-analysis that evaluated the delayed antipsychotic effect hypothesis using very similar

methodology arrived at almost identical conclusions: "We found that antipsychotic action starts early after drug administration and is cumulative during the ensuing weeks. The empirical data are not consistent with the widely cited delayed-onset hypothesis."[137(p1232)]

How many individuals initiated on an antidepressant medication respond during the first 2 weeks of treatment? Based on the studies that report weekly CGI response rates, approximately 1 in 3 patients (30.5%) initiated on an antidepressant medication respond within 2 weeks, and about 1 in 9 (10.5%) demonstrate a "true" antidepressant response, i.e., one that cannot be accounted for by nonspecific factors. Our results suggest that approximately one half of all patients who respond to a 6-week antidepressant trial will respond during the first 2 weeks of treatment. It remains unknown why some patients might respond earlier than others to antidepressant therapy.

It would be important to understand why our results differ from those of the Columbia group. In comparing the methodologies used in the Columbia group's studies with those of the present meta-analysis, we elicited 5 methodological differences: subjects in the present study were less likely to be diagnosed with atypical depression and were more severely depressed; outcome ratings in the Columbia group's studies were carried out by psychiatrists rather than research assistants; the Columbia group utilized only the CGI instrument rather than the HAM-D; and, as described in the introduction, the group incorporated the notion of "persistence" into their definition of response. The critical question in considering these methodological differences, however, is not whether differences exist but whether they would be expected to account for the disparate results. Although subjects in the Columbia group's studies tended to have a milder illness and more atypical features than the subjects in our review, these attributes have been associated with *earlier* rather than *later* antidepressant effects[19,138]; this fact argues in the opposite direction of what might explain the disparate results. The use of research assistants and the use of a theoretically less rigorous definition of response should, if anything, make it *more* difficult to elicit drug-placebo separation in the first 2 weeks of treatment. Finally, our results were confirmed in a subanalysis of studies that employed the CGI scale, the same instrument used by the Columbia group. Thus, after carefully considering the potential impact of each of these differences, we are unable to offer a satisfactory explanation to explain the differing results.

A limitation that must be considered in any meta-analysis is the potential impact of publication bias, i.e., that negative results are less likely to be published than positive ones.[139] Publication bias leads to an overestimation of effect size in meta-analyses that rely only on published data. Our goal, however, was not to determine how effective antidepressants are, nor did we even attempt to establish that they are effective. Instead, we sought only to delineate the *timing* of response in those instances where antidepressants were found to be effective. Even if we had collected and included dozens of negative, unpublished studies, the results depicted in Figure 1 would essentially be unchanged, except that the *magnitude* of drug-placebo separation (y-axis) would be less.

Another potential limitation is that all of our primary analyses relied on the HAM-D, which has been criticized for overemphasizing somatic symptoms. The HAM-D, however, is considered the gold standard for evaluating antidepressant efficacy, as evidenced by the fact that all 47 studies in our meta-analysis utilized it as the primary outcome measure. The delayed antidepressant response theory predicts that drug-placebo differences would be most prominent between weeks 3 and 6—the opposite of what we found. If our results are considered suspect because they relied on the HAM-D, then the efficacy of antidepressants themselves would also be suspect since the HAM-D is the edifice on which antidepressant efficacy has been established. Furthermore, an analysis of studies using the CGI scale—the same instrument used by the Columbia group—confirmed our principal findings.

The majority of the studies (43 of 47) included in the present meta-analysis employed a placebo lead-in phase. Previous research suggests that a placebo lead-in has minimal impact on outcomes during the active phase of treatment, but we cannot know for certain how this design feature might have affected our results. A placebo lead-in was also used in each of the pattern analysis studies conducted by the Columbia group.

It should also be pointed out that the present meta-analysis focuses on only 1 interpretation of what constitutes a delayed antidepressant effect, i.e., an absence of drug-placebo separation during the first 2 weeks of treatment. From a clinical perspective, another interpretation exists as well—that the full benefits of an antidepressant medication may not be observed for several weeks or longer.[140,141]

Recent biological studies lend support to the notion that antidepressants work within the first 1 to 2 weeks of treatment. A positron emission tomography study evaluated changes in brain glucose metabolism in subjects who responded to a 6-week trial of fluoxetine or placebo.[142] Similar regionally specific metabolic changes were evident in both cohorts, but responders to fluoxetine showed distinct metabolic changes in the hippocampus and brainstem that were not present in placebo responders. Importantly, these changes were evident within the first week of treatment and did not occur in fluoxetine nonresponders. A second study using quantitative electroencephalography compared differences in brain functioning between responders to active medication and placebo.[143] The investigators found that responders to active medication were markedly distinguishable by week 2

from both medication *non*responders and placebo *responders* (outcomes were not assessed at week 1). Although these findings are suggestive of distinct biological processes occurring early in an antidepressant trial, there is no way to confirm a direct correlation between these processes and a clinically observable antidepressant effect. A recent study by Harmer et al.,[144] however, suggests that an antidepressant effect may be observable even within 24 hours. In that study, 24 healthy volunteers were randomly assigned to an antidepressant agent or placebo. Emotional processing was assessed using techniques to measure facial expression recognition, emotional categorization, and emotional memory. Subjects receiving active medication were found to display significantly greater positively valenced emotional processing in comparison with subjects receiving placebo after only a single dose of an antidepressant. The authors concluded that the benefits of antidepressant medications may be observable almost immediately, which corresponds to the time frame of monoamine reuptake inhibition in the brain, as well as to Kuhn's original observations.[2]

In conclusion, the present study sought to determine whether or not the existence of a delayed antidepressant effect could be confirmed by systematically reviewing the results of 47 double-blind, placebo-controlled studies published over the last 2 decades. After examining this question from multiple perspectives, we found no evidence to support the delayed antidepressant response theory. Although some patients may take several weeks or longer to respond to an antidepressant trial, our results clearly suggest that many patients demonstrate a true antidepressant effect within the first 1 to 2 weeks of treatment.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), doxepin (Sinequan, Zonalon, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

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