Review of Maintenance Trials for Major Depressive Disorder: A 25-Year Perspective From the US Food and Drug Administration

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ABSTRACT

Objective: The maintenance efficacy of antidepressants is usually assessed in postmarketing studies with a randomized withdrawal design. This report explores differences in relapse rates, trial characteristics, and success rates in maintenance efficacy studies submitted to the US Food and Drug Administration (FDA) over a 25-year period.

Data Sources: Clinical data from all maintenance trials with antidepressants submitted to FDA between 1987 and 2012.

Study Selection: Efficacy data were compiled from 15 maintenance clinical trials in adults diagnosed with major depressive disorder according to *DSM-III* or *DSM-IV* criteria.

Data Extraction: Trial characteristics, relapse rates, and time to relapse in each study were examined.

Results: Relapse rates were significantly lower ($P < .05$) in the drug arm than in the placebo arm in every study, with a mean relapse rate difference of 18% and an average percent reduction in relapse rate of 52% compared to placebo. Only 6% of the relapse events occurred in the first 2 weeks of the double-blind phase. The separation between treatment arms continued to increase throughout the double-blind phase only in the trial with longest response stabilization period.

Conclusions: Antidepressant maintenance trials have a high rate of success, indicating a benefit of continuing drug treatment after initial response to an antidepressant. This benefit appears to result mainly from a decreased rate of recurrent depression rather than from an effect of drug withdrawal in the placebo groups.

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Depression is a chronic disorder and an important cause of disability. In its assessment of overall worldwide disease burden,[1] the World Health Organization found unipolar depressive disorders to account for 4.3% of the global disease burden and to be the third leading cause of disease burden in the world. In the United States, major depressive disorder (MDD) has a lifetime prevalence of 16.6%, and it is estimated that almost 39 million Americans aged 18 years and over have met criteria for MDD at some point in their lives.[2]

Antidepressant drugs are the mainstay of treatment for an acute major depressive episode.[3] Because MDD is often characterized by recurrent episodes, and each major depressive episode is associated with an increased risk of future episodes,[4,5] maintenance treatment for patients who respond to initial antidepressant therapy is commonly recommended.[3]

The US Food and Drug Administration (FDA) approves antidepressants for marketing on the basis of results from short-term placebo-controlled trials in moderate to severe depression. There is a substantial improvement in the placebo group in those trials, perhaps because depressive episodes often resolve spontaneously. A recent FDA analysis of registration trials found an overall study success rate of approximately 50% for effective drugs, with a mean drug-placebo difference in improvement of 2.5 points, approximately −10.5 on drug versus −8.0 on placebo, on the Hamilton Depression Rating Scale (HDRS).[6] To date, no trial has been successful in the treatment of mild depression. The modest efficacy observed in the short-term trials and the apparent lack of meaningful effect in mildly ill patients has generated much debate on the effectiveness of these drugs.[7–11]

The longer term maintenance efficacy of antidepressants is usually assessed in postmarketing studies. The characteristics and results of maintenance trials with antidepressants submitted to the FDA have not been systematically evaluated, but several reviews and meta-analyses of controlled trials have reported the benefits of maintenance treatment with antidepressants in decreasing relapse rates after patients' recovery from an episode of major depression.[12–17]

A distinction between relapse and recurrence of depression can sometimes be found in the literature, with *relapse* often referring to the return of depressive symptoms promptly (ie, within 2–6 months) after remission is achieved in a major depressive episode and *recurrence* describing the appearance of a new major depressive episode at a later time.[18,19] In line with these definitions, clinical trials evaluating the effect of an antidepressant in decreasing the rate of relapse are often called *relapse prevention studies*, and longer-term studies aimed at reducing the rate of recurrence are often called *maintenance studies*. Whether or not *recurrence* might be the better term, FDA has used *relapse* and *recurrence* interchangeably and utilized the term *maintenance trial* to describe any study evaluating the efficacy of an antidepressant in reducing the rate of (or the time to) relapse/recurrence of depressive symptoms.

These maintenance trials utilized a randomized withdrawal design in which responders to an open-label course of the studied antidepressant are randomized to continue on the study drug or be switched to placebo

and are observed for relapse over a defined period of time. The data from these maintenance trials have raised several questions and concerns. One question is whether the length of antidepressant treatment before randomization has an impact on study outcome. Another question is whether some or all of the return of depressive symptoms seen in the placebo group represents an acute drug withdrawal phenomenon. It has also been suggested that the drug-placebo difference in relapse rates is largest in the first few months postrandomization and that there is no apparent added benefit of drug treatment after that initial period; that is, the difference in relapse rates between the 2 groups tends to stabilize after a few months.[4,20]

Another question regarding maintenance studies with a randomized withdrawal design is how the nature of the response achieved in the open-label phase influences the relapse rates in the randomized phase. Previous reports have suggested that patients with unstable remission or with residual symptoms after acute treatment of a depressive episode have a higher risk for relapse during the maintenance treatment.[21–24] FDA currently recommends that antidepressant maintenance trials randomize only patients who have achieved and maintained a stable response for at least 12 weeks following acute treatment. Also of interest, but not usually available, would be a well-described recurrence history for the years preceding the maintenance trial.

This report presents the results of exploratory analyses conducted with efficacy data from all of the completed antidepressant maintenance trials submitted to FDA since the approval of the first second-generation antidepressant in 1987.

Clinical Points

- Reappearance of depressive symptoms after recovery from a depressive episode and discontinuation of the antidepressant treatment reflects an actual depression relapse rather than an antidepressant withdrawal phenomenon.
- Maintenance treatment with antidepressants substantially reduces the number of relapse events after remission or symptomatic improvement in a major depressive episode has been achieved, and this effect seems to persist for about 6 months.
- How long to continue antidepressant treatment beyond 6 months after recovery from a depressive episode remains unclear.

METHOD

Data Collection

Sixteen maintenance trials with antidepressants were identified in New Drug Applications submitted to the FDA between January 1987 and June 2012. Data were not included for 1 trial with too few relapse events to justify analysis. The database was populated with data from the remaining 15 trials for 13 approved antidepressant products.

All of these trials utilized a randomized withdrawal design in which responders to study drug during an open-label treatment phase were randomized in a double-blind fashion to either continue the same drug to which they had responded or switch to placebo. They were then observed for relapse of depression over defined periods ranging from 6 to 12 months.

Patients enrolled in the open-label phase of these trials were adults (age ≥ 18 years) diagnosed with MDD according to *DSM-III* or *DSM-IV* criteria. All enrolled patients received open-label treatment with study drug at standard doses for defined periods ranging from 6 to 26 weeks and must have responded to treatment of an acute episode of depression. The criteria used to identify patients for randomization into the double-blind phase were based on improvement on a standard depression scale such as the 17-item or 21-item HDRS and the Montgomery-Asberg Depression Rating Scale (MADRS), or the Clinical Global Impression–Improvement scale (CGI-I).

Patients classified as responders in the open-label phase were randomized into the double-blind phase to receive the study drug or placebo for a period of time ranging from 24 to 52 weeks. During this treatment period, patients were observed for relapse of depression, defined by some combination of the following: the investigator's clinical judgment, *DSM* criteria for MDD, or reaching some defined threshold score on the HDRS-17, the MADRS, or the Clinical Global Impression–Severity scale (CGI-S) or CGI-I. None of the 15 trials was stratified for patients' number of prior depressive episodes.

The primary efficacy measure in 8 of the 15 studies was time to relapse. The remaining 7 studies designated relapse rate as the primary efficacy measure, with time to relapse designated as a secondary efficacy measure.

Study data were available both as trial-level data included in the sponsors' clinical study reports and as patient-level datasets submitted with the reports. For trial-level data, the variables of interest included the criteria for enrollment, dose and regimen of study drug in the open-label and double-blind phases, response and relapse criteria, subject disposition, number of relapse events in each study arm, and year of study initiation. Patient-level data were used to identify the randomized treatment and relapse/censoring time.

Data Analysis

Patients' baseline demographic characteristics, including age, gender, and race, and baseline mean HDRS total scores, as well as the dropout rates for all 15 studies, were summarized as part of the descriptive analyses.

Given the variability of trial characteristics, pooling of data from all studies was not considered informative. Rather, results are reported for each study based on the patient-level data and study reports provided by the sponsors. The overall results and conclusions of the studies are then considered.

Several features of the open-label phase were examined to determine whether they influenced relapse rate, specifically, response rate during the open-label phase, the duration of the open-label phase, and whether there was a response

stabilization period, that is, a specified period of time for which patients were required by protocol to meet the response criteria before randomization. Relapse rates were calculated as the number of patients meeting relapse criteria at the end of the double-blind phase divided by the number of patients randomized into the double-blind treatment phase.

The efficacy population for each of the 15 maintenance studies was defined as all patients randomly assigned to the double-blind treatment phase. The primary efficacy analysis for studies focusing on time to relapse was the log-rank test comparing time to relapse in the active treatment arm with that in the placebo treatment arm. We were able to use patient-level data from 14 trials to produce Kaplan-Meier curves and compare patients' time to relapse in the treatment and placebo control arms. We also conducted 3 analyses to assess whether symptoms related to antidepressant discontinuation played a role in the observed difference in relapse rates and time to relapse between drug and placebo groups. In one analysis, we censored patients who had relapse events before the first 2 weeks of the double-blind phase for each of the 14 studies. A second analysis censored patients who relapsed in the first 4 weeks of the double-blind phase. The third analysis compared the placebo-drug relapse rate differences at each 2-month interval of the double-blind phase for each of the 14 trials.

To explore the influence of the open-label phase characteristics on study outcomes, we compared relapse rates in the placebo and drug arms, as well as the drug-placebo relapse rate differences, by the length of the open-label phase. We also compared relapse rates and relapse rate differences by response rates in the open-label phase and separately in studies with or without a response stabilization period. The current recommendation of FDA's Division of Psychiatry Products to include a 12-week response stabilization period is fairly recent, so that only 1 of the 15 trials analyzed included this condition (study O). For the purpose of this analysis, we defined the response stabilization period as any period of time for which patients were required by protocol to meet the response criteria before randomization.

In exploring the effects of the double-blind phase features on study results, we compared the relapse rates and relapse rate differences between drug and placebo groups by the length of the double-blind phase. We also looked at trials grouped by similarity in the prespecified relapse criteria for the efficacy analysis, grouping those trials that used the CGI-S or the investigator's judgment as the main relapse criteria (group 1: studies A, B, G, H, J, M) and those trials that defined relapse based on a threshold on the MADRS or the HDRS score (group 2: studies C, D, E, F, I, K, L, N, O). We then compared relapse rates and relapse rate differences between groups 1 and 2.

We also compared studies with randomization criteria that allowed patients with residual depressive symptoms at the end of the open-label phase to enter the double-blind phase with studies that did not allow this. In some trials, for example, patients with HDRS-17 scores up to 11 were eligible to enter the randomized phase. In other studies, patients had to be in a clinical status close to remission (ie, no longer meeting *DSM-III-R* or *-IV* criteria for MDD and HDRS-17 scores ≤ 9) before randomization.

Finally, we assessed possible changes in effects over time by comparing trials started before and after 1995. The year 1995 was chosen as the cutoff point for this comparison because it split the number of studies approximately in half.

Table 1. Baseline Demographic and Disease Characteristics of MDD Patients and Dropout Rate in Each Trial Phase

	Open-Label Phase: Drug	Double-Blind Phase	
		Placebo	Drug
Total no. of patients per study, mean (range), ITT population	554 (172–866)	120 (42–276)	138 (48–272)
Age, mean (SD), y	43.2 (3.4)	43.9 (3.2)	43.6 (3.5)
Gender, mean (SD), % female	67.8 (5.2)	68.3 (7.8)	67.3 (6.3)
Race, mean (SD), % Caucasian[a]	87.1 (8.6)	87.6 (8.2)	90 (7.4)
Baseline HDRS total score, mean (range)[b]	23.3 (14–27)	9.4 (3–24)	9.4 (3–24)
Dropout rate, mean (range) %	36.5 (18–62)	64.6 (35–83)	47.9 (22–79)

[a]Data from 12 trials for the double-blind phase.
[b]Data from 14 trials for the double-blind phase.
Abbreviations: HDRS = Hamilton Depression Rating Scale, ITT = intent to treat, MDD = major depressive disorder.

RESULTS

All 15 studies demonstrated superiority of drug treatment maintenance to placebo. Table 1 summarizes the total numbers of patients included in each phase, as well as their demographic characteristics, baseline disease status, and the average dropout percentage of the trials. A mean total of 554 patients (range: 172–866) were enrolled in each study to receive open-label treatment with study drug. In the double-blind phase, which randomized patients who responded in the open-label phase, the number of patients ranged from 42 to 276 in the placebo groups and from 48 to 272 in the drug groups with a mean of 120 and 138 patients, respectively. The mean age of patients was 44 years in both the placebo and the drug arms. The mean percentages of female (~ 68%) and Caucasian patients (~ 89%) were similar in both study treatment arms. There was no difference on average between study treatment arms in the mean HDRS total score at randomization (mean = 9.4). As would be expected, given that depression relapse led to dropout, the mean dropout rate was higher in the placebo arm (~ 65%) than in the drug arm (~ 48%).

As shown in Table 2, response and relapse criteria varied greatly among studies, as did the response stabilization period. For example, in study E, patients had to have a HDRS-17 score ≤ 7 and not meet *DSM-III-R* criteria for MDD for 3 consecutive weeks before randomization. In contrast, in study A, patients entered the double-blind phase if they had a single CGI-I score ≤ 2 at the end of the open-label phase. With respect to defining relapse, in study J, worsening of depressive symptoms based on the investigator's judgment

Table 2. Trial Characteristics of Longer Term Antidepressant Maintenance Studies

	Open-Label Phase		Double-Blind Randomized Phase	
Study	Duration (wk)	Response Criteria	Duration (wk)	Relapse Criteria
A	8	CGI-I ≤ 2 at week 8	44	CGI-S ≥ 4 or discontinuation due to lack of efficacy
B	8	HDRS-21 ≤ 8 and not meeting *DSM-III-R* criteria for MDD	52	Need for drug treatment, CGI-S ≥ 2-point increase, CGI-S ≥ 4, deterioration in depressive symptoms at least 7 d, and meeting *DSM-III* criteria for MDD
C	6–8	MADRS ≤ 12	24	MADRS ≥ 25 and investigator's judgment
D	6–8	MADRS ≤ 12 at week 6	24	MADRS ≥ 22 and investigator's judgment
E	12	HDRS-17 ≤ 7, and not meeting *DSM-III-R* criteria for MDD for 3 consecutive wk	38	Meeting *DSM-IV* criteria for MDD for 2 wk, or HDRS-17 ≥ 14 for 3 wk
F	16	HDRS-17 ≤ 10 at 2 consecutive visits from weeks 6 to 10; and HDRS-17 ≤ 10 at week 16 and at 1 previous visit	36	HDRS-17 ≥ 18 at 2 consecutive visits, or investigator's judgment
G	26	HDRS-21 ≤ 12 at day 56; no HDRS-21 ≥ 20, no more than 2 HDRS-21 > 10; and no single CGI-S ≥ 4 between days 56–180	52	CGI-S ≥ 4
H	8	HDRS-21 ≤ 10, and CGI-S ≤ 3 at day 56	26	Meeting *DSM-IV* criteria for MDD and CGI-S ≥ 4, CGI-S ≥ 4 at 2 consecutive visits, or final CGI-S ≥ 4 if withdrawn from study
I	8–12	HDRS-17 ≤ 8, and CGI-I ≤ 2 at 2 consecutive visits after week 6	40	Investigator's judgment, HDRS-17 ≥ 18 at a single visit, HDRS-17 of 15–17 at 2 consecutive visits, suicide or suicide attempt
J	8	CGI-I ≤ 2 on weeks 6, 7, and 8	44	Investigator's judgment
K	10	Two consecutive HDRS-17 ≤ 10 at week 8 or 9 and at week 10	52	HDRS-17 ≥ 14, CGI-S ≥ 3 (with ≥ 2-point increase), and meeting *DSM-IV* criteria for MDD at 2 consecutive visits
L	8	MADRS ≤ 12	36	MADRS ≥ 22 or discontinuation due to insufficient response
M	12	Not meeting *DSM-IV* criteria for MDD, HDRS-17 ≤ 9, and CGI-S ≤ 2 at weeks 10 and 12	26	CGI-S of ≥ 2-point increase and meeting *DSM-IV* criteria for MDD at 2 consecutive visits
N	12	HDRS-17 ≤ 11 at week 12	24	HDRS-17 ≥ 16, CGI-I ≥ 6, or discontinuation for insufficient response
O	20 (8 wk response, 12 wk stability)	Response: HDRS-17 ≤ 11 and CGI-I ≤ 2 at week 8 Stable response: HDRS-17 ≤ 11, CGI-I ≤ 2, and no HDRS-17 ≥ 16 nor CGI-I ≥ 4 at any visit in stability phase	26	HDRS-17 ≥ 16, discontinuation for insufficient response, hospitalization for depression, suicide attempt, or suicide

Abbreviations: CGI-I = Clinical Global Impression–Improvement scale, CGI-S = Clinical Global Impression–Severity scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.

Table 3. Response and Relapse Rates in Antidepressant Maintenance Studies

	Open-Label Phase Response Rate (%)	Double-Blind Randomized Phase Relapse Rate (%)			
Study	Drug	Placebo	Drug	Difference[a]	Percent Reduction
A	63	39	8	31	79
B	78	32	12	20	63
C	58	24	14	10	42
D (2 doses)	66	31	8	23	74
			12	19	61
E	47	59	39	20	34
F	27	14	2	12	86
G	49	48	25	23	48
H	65	46	27	19	41
I	38	44	20	24	55
J	51	48	34	14	29
K	48	31	16	15	48
L	54	33	23	10	30
M	52	29	17	12	41
N	64	42	24	18	43
O	63	28	14	14	50
Mean (SD)	52 (15)	37 (11)	18 (10)	18 (6)	52 (17)

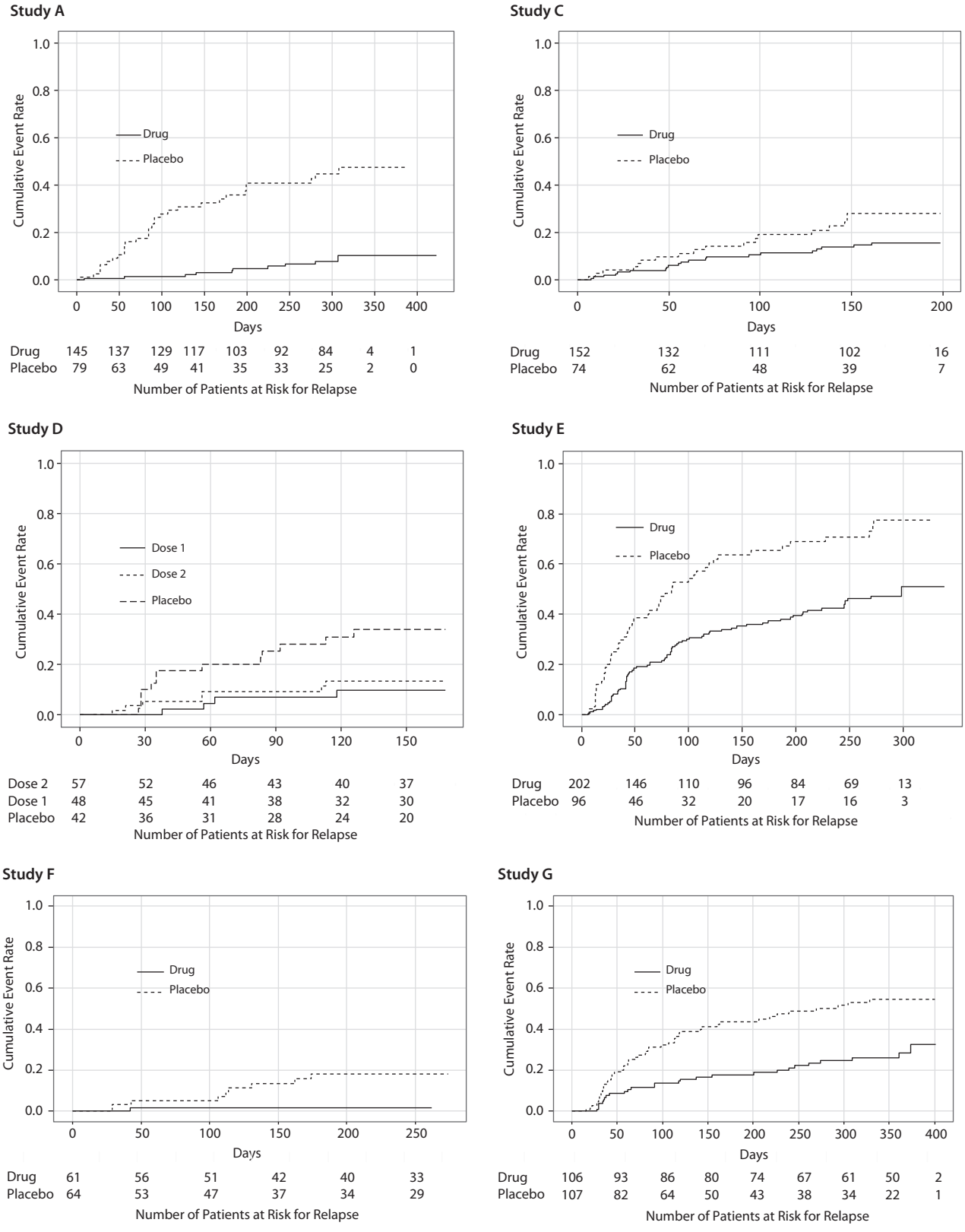
[a] $P < .05$ for the relapse rate difference between drug and placebo groups in each study.

was sufficient to consider a patient to have relapsed, whereas in study B, a relapse event was defined by the need for drug treatment, an increase of ≥ 2 points in the CGI-S score, a CGI-S score ≥ 4, a deterioration in depressive symptoms for at least 7 days, and meeting *DSM-III* criteria for MDD. These differences in both entry criteria for the double-blind phase and definition of relapse would be expected to result in substantial differences in relapse rates across the different trials; eg, less stringent relapse criteria would be likely to lead to a greater number of relapse events in the double-blind phase. Whether they would lead to differences in relative effectiveness of drug and placebo is less clear.

The response rate in the open-label phase ranged from 27% to 78%, with a mean of 52% (Table 3), although the rate was between 38% and 66% in 13 of 15 studies. In the double-blind phase, patients on active drug had significantly lower relapse rates than those on placebo in every study. The mean absolute difference in relapse rates between drug and placebo arms was 18%, ranging from 10% to 31%. In terms of relative risk, patients in the drug groups had a reduction in relapse rate compared to placebo between 29% and 86%, with an average reduction of 52%.

Figures 1 and 2 depict the cumulative event rate curves, Kaplan-Meier estimation of proportion of patients with

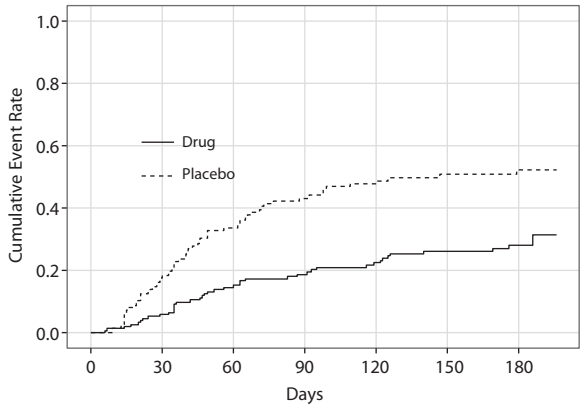
Figure 1. Kaplan-Meier Estimation of Proportion of Patients With Relapse in Antidepressant Maintenance Studies Started Before 1995[a]



[a]The Kaplan-Meier curve for study B could not be reproduced due to incompleteness of the dataset for this older study.

Figure 2. Kaplan-Meier Estimation of Proportion of Patients With Relapse in Antidepressant Maintenance Studies Started After 1995

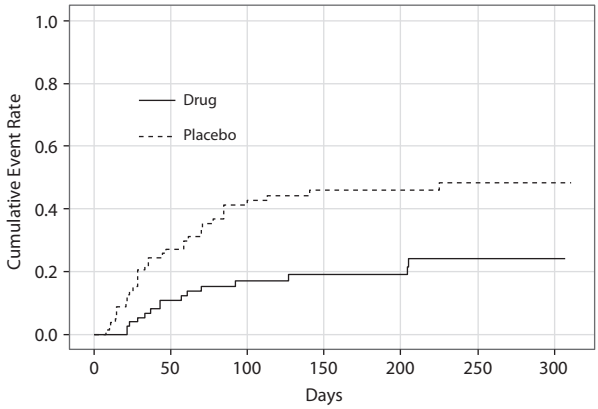
Study H



Drug	154	142	124	114	104	89	56
Placebo	138	110	79	63	54	48	27

Number of Patients at Risk for Relapse

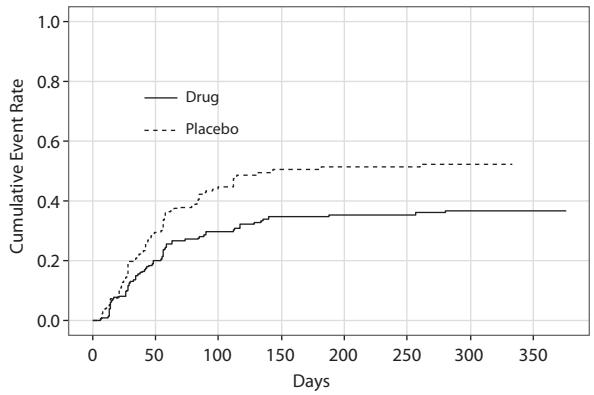
Study I



Drug	76	64	49	37	32	26	3
Placebo	80	54	39	30	24	19	2

Number of Patients at Risk for Relapse

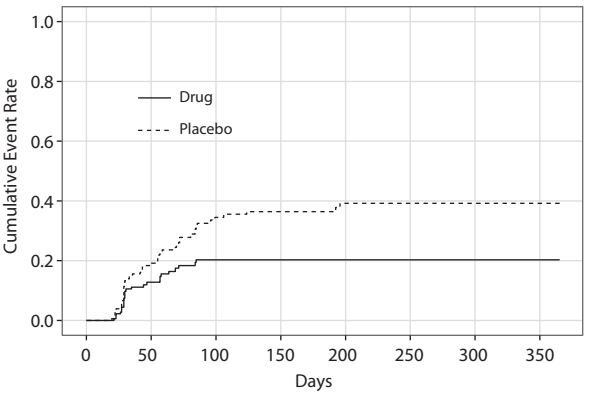
Study J



Drug	207	160	125	104	94	87	81	1
Placebo	210	135	98	76	65	62	59	0

Number of Patients at Risk for Relapse

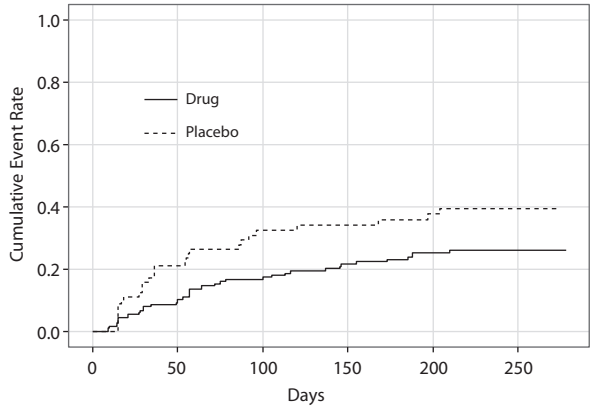
Study K



Drug	149	100	75	64	51	44	38	32
Placebo	163	111	67	57	43	37	31	29

Number of Patients at Risk for Relapse

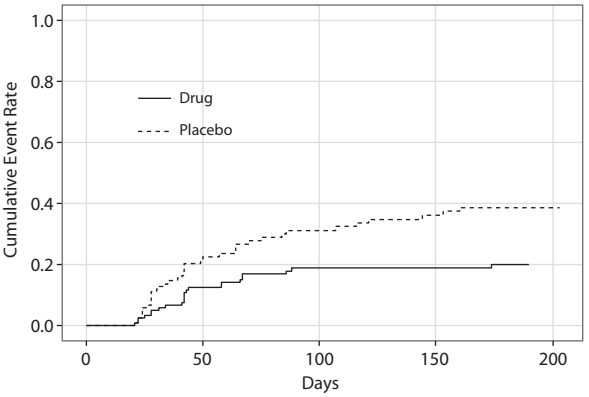
Study L



Drug	181	148	122	107	96	80
Placebo	92	60	44	38	34	26

Number of Patients at Risk for Relapse

Study M



Drug	132	102	83	77	0
Placebo	137	76	59	50	1

Number of Patients at Risk for Relapse

(continued)

Figure 2 (continued). Kaplan-Meier Estimation of Proportion of Patients With Relapse in Antidepressant Maintenance Studies Started After 1995

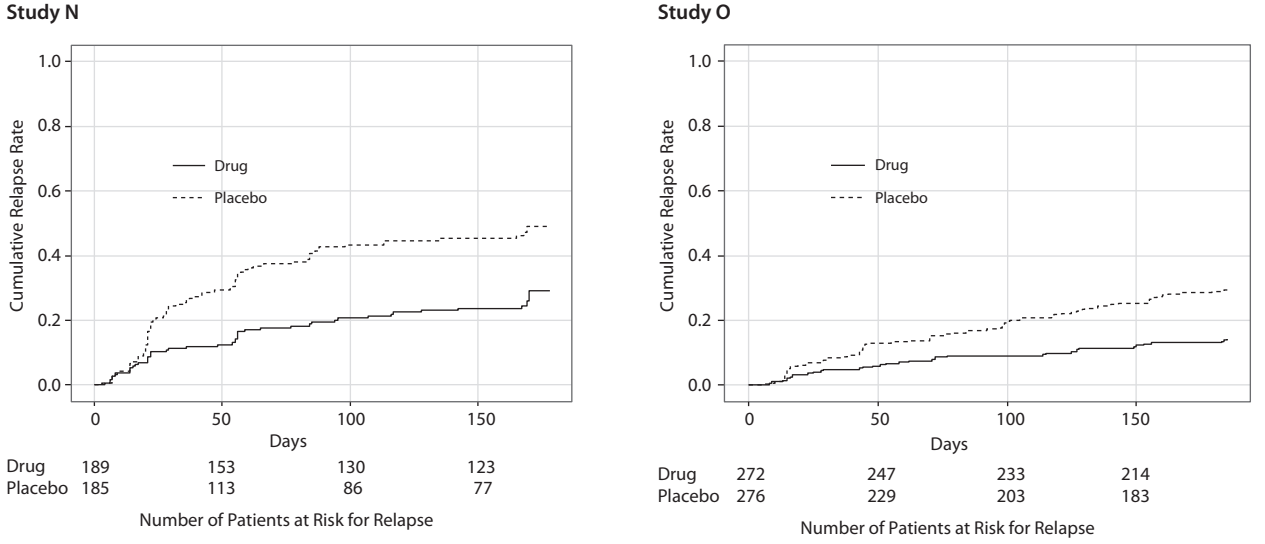
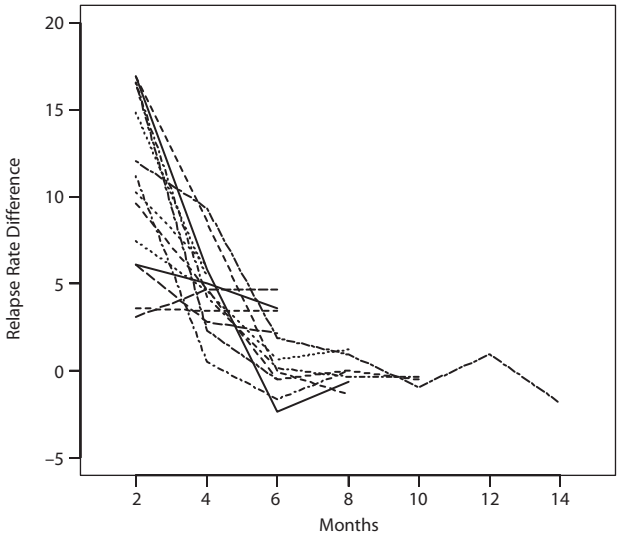


Figure 3. Relapse Rate Differences Between Drug and Placebo Arms at Each Double-Blind Phase Time Point in Antidepressant Maintenance Studies[a,b]



[a]Each curve represents a study.
[b]Only 14 studies are presented. The Kaplan-Meier curve for study B could not be reproduced due to incompleteness of the dataset for this older study.

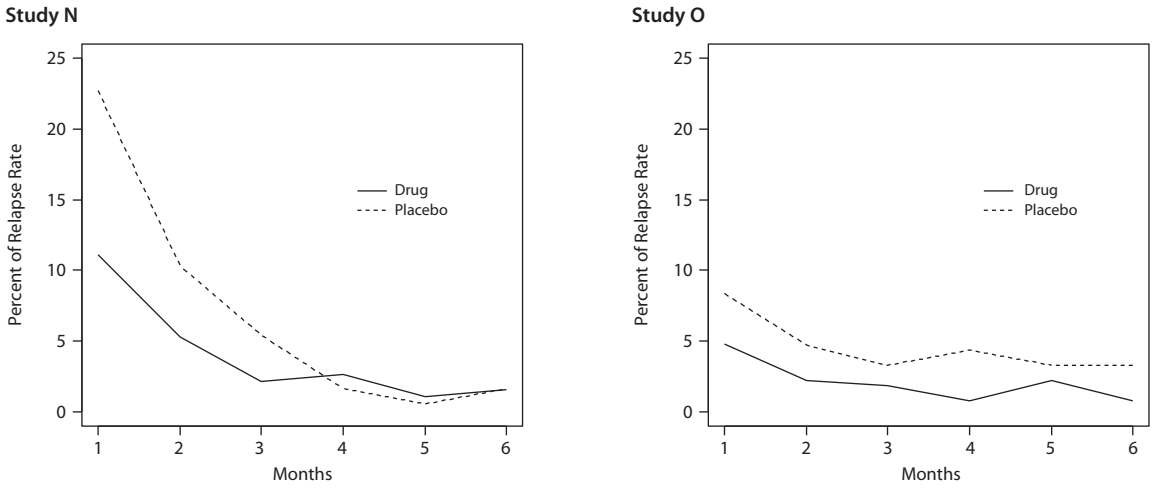
relapse, for trials started before and after 1995, respectively. As can be seen from each of these curves, every clinical trial in our database demonstrated superiority of drug over placebo. That is, patients with MDD who responded to active drug in the open-label phase and continued the active drug treatment experienced, on average, longer times to relapse (and fewer relapse events during the study) than those who switched to placebo in the double-blind phase. The mean relapse rates were 18% and 37% in the drug and placebo groups, respectively. As noted, it has been suggested that in these randomized withdrawal studies, the increased rate of depression on placebo is a pharmacologic consequence of antidepressant withdrawal. If that were true, an early high rate after withdrawal would be expected. To evaluate this, we examined data after 2 and 4 weeks postrandomization. When patients who had a relapse during the first 2 weeks of the double-blind phase were censored from the efficacy analysis, the mean relapse rates were 17% for the drug arm and 34% for the placebo arm. Similarly, when censoring was performed for the first 4 weeks after randomization, results were little changed (15% vs 27%). This suggests that relapse rates are unrelated to withdrawal of drug effects.

The placebo-drug relapse rate differences consistently favored the drug groups throughout the double-blind phase for each trial. However, the differences within each successive time period became less obvious after 6 months; that is, the curves do not continue to separate as much and in some cases do not separate at all after that time. This is evident in Figure 3, which shows relapse rate differences for each period. The population, of course, changes over time. Presumably, by 6 months, most patients likely to relapse on placebo will have done so, and new relapses become less frequent. The overall drug-placebo difference in relapse rate, however, is maintained.

Overall, there seemed to be no relationship between the length of the open-label phase and relapse rates in the placebo and drug arms or relapse rate differences between drug and placebo arms, but most (10 of 15) studies had open-label phases of 8–12 weeks, so that there were few opportunities to see differences. As noted, the between-treatment differences in relapse rates were largely established by 6 months, so study duration did not have an important effect.

No significant difference was found in the study outcomes between trials with (8 studies) and without (7

Figure 4. Time Course of Relapse Rate in Studies N and O



studies) a stabilization period (ranging from 2 to 12 weeks) after achievement of response during the open-label phase. The average relapse rates in the drug arms were 21% and 16%, respectively. In the placebo arms, these percentages were 38% and 35%, respectively. The average placebo-drug relapse rate difference was 17% in studies with a response stabilization period in the open-label phase and 19% in those studies without one.

Studies N and O in Figure 2 represent 2 trials with the same antidepressant product using doses in the high end and low end of the effective dose range, respectively. Study N had no stabilization period, while study O had the longest response stabilization period of any of the studies, requiring patients to remain stable in their response for 12 weeks before randomization. Figure 4 shows the relapse rates for drug and placebo groups at each month of the double-blind phase in these 2 studies. The relapse rate difference between drug and placebo appears to be larger for study N than for study O in the first few months of the double-blind phase, with a high early placebo relapse rate. In study N, the difference does not continue to increase beyond 4 months. Study O, in contrast, does not show a marked early effect but shows a growing advantage for drug compared to placebo out to 180 days. Whether these differences relate to stabilization or dose differences is not clear.

The efficacy analysis also showed similar results in studies defining relapse on the basis of the CGI-S or the investigator's judgment (group 1: studies A, B, G, H, J, M) and in studies in which definition of relapse included meeting some threshold score on the MADRS or HDRS and/or meeting MDD criteria (group 2: studies C, D, E, F, I, K, L, N, O). The average relapse rates in group 1 (6 studies) were 21% and 40% in the drug and placebo arms, respectively. As would be expected, given the stricter relapse criteria, the average relapse rates in the drug and placebo arms were slightly smaller in group 2 (9 studies), 17% versus 34%. Despite these different rates, the average relapse rate differences between drug and placebo arms (19% for group 1 and 17% for group 2) and the average percent reductions in relapse rate with drug relative to placebo (48% and 50%) were similar for both groups of studies.

Eleven of 15 trials had randomization criteria that allowed patients with a low level of residual depressive symptoms at the end of the open-label phase to enter the double-blind phase. Average relapse rates for the drug and placebo groups in these studies were 17% and 35%, respectively, with a relapse rate difference between treatment arms of 18%. In the remaining 4 studies, in which patients were required to achieve full remission before randomization, these values were slightly higher, with an average relapse rate of 22% in the drug arms and 41% in the placebo groups, and a relapse rate difference between treatment arms of 19%. There was, thus, no clear difference related to whether open-label remission was more or less demanding.

The year in which the study started appeared to have a small impact on study outcomes, with somewhat larger differences in relapse rates between drug and placebo arms in the trials started before 1995 compared to those initiated after 1995. Average relapse rate differences between drug and placebo arms in studies started before and after 1995 were about 20% and 16%, respectively. Percent reductions also were somewhat higher in the early period, about 58% versus 42%.

DISCUSSION

This report focused on the maintenance trials for MDD submitted to FDA and, as such, has some limitations. It is possible that combining the results of all 15 studies in a meta-analysis could have yielded more generalizable conclusions. However, as noted above, the heterogeneity in the length of the open-label and double-blind phases and in the response and relapse criteria precluded the pooling of the data from different studies for this purpose. The studies in this report collected no data on the patients' number of past depressive episodes, a known predictor of relapse,[4,5] prior to study enrollment. In this scenario, the risk of relapse among study participants cannot be ascertained and could

constitute another limitation when contrasting the results of the studies in this report. We recognize that many other maintenance trials with antidepressants have been published in the literature but not submitted to FDA. These studies were intentionally excluded from our analysis for several reasons. First, several reviews and meta-analyses of those studies, some of which we referenced, have been previously published. Second, the goal of this review was not to be an exhaustive analysis of all MDD maintenance trials to date, but to present the 25-year-long experience with these trials in the regulatory arena. Third, many of the analyses described here were based on patient-level data, which are scarce in studies found in the literature. The ability to replicate study results and to perform additional evaluations with the raw data was unique, in our view, to the studies included in this report.

Antidepressant maintenance trials for MDD patients submitted to FDA have had a high rate of success. It is true, of course, that these are enriched studies in which only responders to drug therapy are randomized. Moreover, the cyclical nature of acute episodes, leading to large improvements in placebo groups, is not a relevant factor in maintenance studies. Nevertheless, given the finding that only half of short-term trials with antidepressants succeed,[6] the positive outcome of every maintenance study in our database is an impressive finding. It should also be appreciated that most use of antidepressants is as maintenance treatment.[25]

Other reviews and meta-analyses of antidepressant maintenance trials have shown that continuing antidepressant treatment reduces the risk of relapse and that this benefit seems to be consistently found for all classes of antidepressants.[12,14,15] The average relapse rate has been reported to be approximately 40% in the placebo arm and 20% in the active drug arm.[12,14] Our analysis revealed similar results, with mean relapse rates at 37% and 18% for placebo and drug, respectively. Overall, these findings consistently show a halving of the relapse rate in patients who stay on antidepressant therapy compared to those who discontinue treatment after recovery from a major depressive episode. Decreasing the relapse rate by half in patients with recurrent MDD is a substantial public health benefit.

It has been observed that, when antidepressant response or remission has been achieved and sustained for a sufficient period of time, the risk of relapse falls (with or without continuing treatment).[3,26] It might therefore be expected that, in studies with a randomized withdrawal design, the duration of the open-label treatment and the time patients remain in responder status before randomization could influence the rate of relapse. Likewise, the length of the postrandomization observation period could potentially affect the rate of relapse and thus the effect of the drug. Within the limits of what was available in these studies (all but 2 studies had open-label treatment of ≤ 12 weeks), no major differences were seen. The length of the double-blind phase also has not been found to affect the drug-placebo relapse rate difference or the reduction in risk of relapse,[12,14,15] but the drug-placebo difference does not continue to increase after 6 months (perhaps because relapse-prone patients will have relapsed by then).

FDA's Division of Psychiatry Products has asked that sponsors include an adequate period of stabilization (12 weeks) after patients achieve treatment response to the study drug. On face, our data did not show a significant difference in the study outcomes between trials with and without a stabilization period after achieving response during the open-label phase. However, this comparison may not be fully informative, since the period of symptomatic stability in these studies (except in study O) did not exceed 3 weeks.

In this regard, an interesting comparison can be made between studies N and O (Figures 2 and 4). Both trials studied the same antidepressant, using different doses but within the effective dose range, and had similar durations for the double-blind phases and similar response and relapse criteria. They differed in that study N had no stabilization period, while study O had a 12-week stabilization period prior to randomization. Although the response rate in the open-label phase was similar in both studies (64% and 63%, respectively), relapse rates were much lower in study O for both treatment arms (42% vs 28% for placebo; 24% vs 14% for drug in studies N and O, respectively). As shown in Table 3, however, the percent reduction in relapse rates with active treatment was similar in study O and study N (50% vs 43%). It is also noteworthy that a low rate of relapse (similar to study O) was seen in studies C and F, with open-label duration of 6–8 and 16 weeks, respectively.

The time course of the observed benefit of drug treatment continuation after response to an antidepressant has also been scrutinized by other investigators. El-Mallakh and Briscoe[4] have reported that the slope of the survival curves is similar between drug and placebo after the first 6 months postrandomization. In the analysis by Viguera et al,[16] the ratio of relapse rates for placebo versus drug fell continuously during the follow-up period from a high of 3.7 at 2 months to 1.3 at 5 years. However, this ratio was still approximately 2 after 36 months of observation. In our analysis, the relapse rate differences between drug and placebo consistently favored the drug arms at different time points in the first few months of the double-blind phase for each trial. These differences lessen after 6 months postrandomization (Figure 3). It is of note, however, that the study population changes over time in the double-blind phase, with fewer patients left in the study because most patients have either dropped out or relapsed. Nonetheless, it is clear that with continued therapy the relapse-free proportion of patients remains significantly greater in the treated group, and this effect seems to persist for 6 months. The question of how long to continue antidepressant treatment beyond 6 months after recovery from a depressive episode, however, remains unanswered. The studies presented in this report are not able to address this relevant clinical issue. This is mainly due to the length of the double-blind phases (no longer than 1 year) and the fact that the difference between drug and placebo groups is difficult to assess after 6 months postrandomization given the decreasing number of patients left in the studies.

Our analysis does not support the suggestion that the higher relapse rate in placebo arms reflects antidepressant withdrawal symptoms rather than the actual recurrence or relapse of a depressive episode. If this were the case, an excess of relapse events in the first 1 or 2 weeks of treatment discontinuation would be expected. Our data show, however, that 94% of all relapse events occurred after the first 2 weeks postrandomization in both the placebo and drug arms. In addition, our efficacy analyses that censored patients who had a relapse event in the first 2 and in the first 4 weeks of the double-blind phase, respectively, yielded results similar to the analysis including all postrandomization relapse events. Other investigators have also found no excess of relapse events early in the randomized phase and have observed that relapse rates did not differ significantly between studies involving rapid discontinuation of the antidepressant and those in which the tapering of the drug was employed as a discontinuation strategy.[14–16]

In short-term trials with antidepressants, an increase in the placebo response leading to smaller effect sizes has been noted.[6] In maintenance antidepressant studies, even though we found a modest trend toward larger differences in relapse rates between drug and placebo arms in earlier studies, this apparent decrease of the effect size over time does not seem to be related to changes in the relapse rates in the placebo arms.

In conclusion, our analysis showed a high rate of success in antidepressant maintenance trials, demonstrating a substantial reduction in relapse rates from continuing drug treatment after remission or symptomatic improvement in a major depressive episode has been achieved.

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