How Often Do SSRIs and Other New-Generation Antidepressants Lose Their Effect During Continuation Treatment? Evidence Suggesting the Rate of True Tachyphylaxis During Continuation Treatment Is Low

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Objective: A substantial number of patients who respond to antidepressants experience a relapse despite ongoing pharmacotherapy. The return of symptoms has been interpreted as a loss of the effectiveness of antidepressant activity. However, patients who initially improve while taking antidepressants include an admixture of true drug responders and placebo responders. Consequently, symptom return despite ongoing treatment may not represent a loss of drug effect because the patient may not have experienced a true drug response in the first place. The goal of the present report is to estimate the proportion of relapse attributable to the loss of true drug response versus a loss of placebo response.

Data Sources: We reviewed continuation studies of new-generation antidepressants that began as placebo-controlled acute-phase studies. Studies were identified using MEDLINE (English-language articles published from 1980 to 2005 in 23 prespecified journals, using the search terms *depression*, *continuation*, and *tachyphylaxis*). Finally, we identified studies in reference lists of pertinent studies and review articles.

Study Selection: Five studies were reviewed and selected according to the following criteria: continuation studies of new-generation antidepressants that began as placebo-controlled acute-phase studies. One of the studies was excluded from our analyses because it did not report response rates in the acute phase, and we could not find acute-phase response rates in related reports.

Data Synthesis: Using the 2 formulas proposed by Quitkin and colleagues, we estimated the proportion of relapse attributable to the loss of true drug response versus the loss of response attributable to the nonspecific effects of treatment: The relapse rate in placebo responders was 24.1%, whereas the relapse rate in antidepressant responders was 7.4%. Two different methods of estimating relapse suggested that the majority of relapses in patients taking antidepressants during continuation treatment could be attributed to relapses occurring in patients who were not true drug responders.

Conclusion: Most of the relapse rate during new-generation antidepressant continuation treatment may be due to relapse in patients who were not true drug responders, which suggests that loss of true drug response may be less common than previously thought.

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The treatment of depression has been divided into 3 phases.[1] In the initial, *acute*, phase, the goal is to achieve a reduction in symptoms and psychosocial impairment. In the *continuation* phase, which is generally considered to occur during the first 6 months to 1 year after the initial treatment response, the goal is to maintain these gains and prevent a relapse of symptoms. And in the *maintenance* phase, which occurs after a sustained period of improvement, the goal is to further maintain the gains and prevent a recurrence of the disorder. A substantial number of patients who respond to treatment in the acute phase experience a relapse or recurrence despite ongoing pharmacotherapy during the continuation and maintenance phases.[2] The return of symptoms has been interpreted as a loss of the efficacy of antidepressant activity, and has been referred to as tachyphylaxis or "poop-out." It has been suggested that the loss of antidepressant efficacy is more common during treatment with selective serotonin reuptake inhibitors (SSRIs) than other antidepressant medications,[3] although empirical evidence supporting this assertion is minimal.

While it is certainly true that many patients experience a return of symptoms despite ongoing treatment with antidepressants, this relapse may or may not be due to a loss

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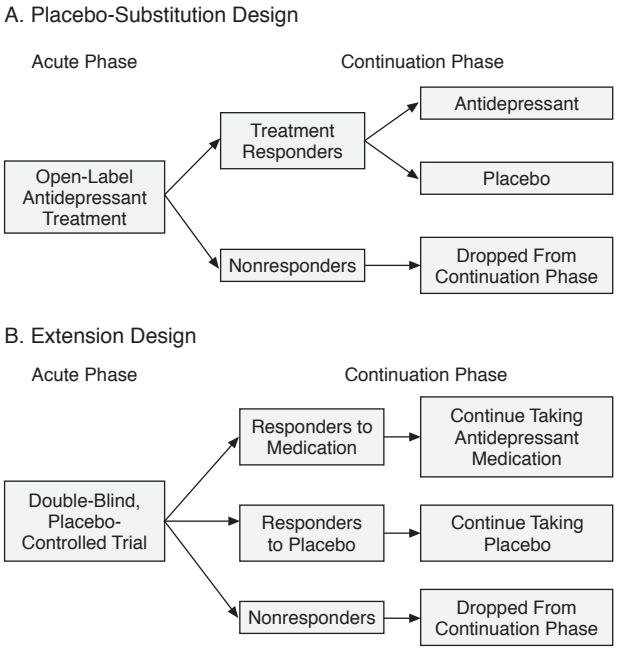
Figure 1. Two Designs of Continuation Trials of Antidepressant Medication



of medication effect. Patients who improve while taking antidepressants during the acute treatment phase include an admixture of true drug responders and responders to the nonspecific elements of treatment (i.e., placebo responders). Consequently, the return of symptoms despite ongoing treatment during the continuation and maintenance phases of treatment may not represent a loss of drug effect because the patient may not have experienced a true drug response in the first place.

In the early 1990s, Quitkin and colleagues[4] developed a method for estimating the proportion of relapse in patients taking medication attributable to the loss of true drug effect versus the loss of placebo response. In their analysis of patients treated for 6 weeks with phenelzine and imipramine, they estimated that the majority of relapses occurring in medication responders during the subsequent 6-week period were due to the loss of placebo response rather than the loss of true drug response. In their review of the literature of continuation and maintenance studies, Byrne and Rothschild[2] applied the formulas of Quitkin et al.[4] to the only continuation study of a new-generation antidepressant that had been published at the time. We are unaware of subsequent reports that have examined this issue.

The goal of the present report was to apply the formulas of Quitkin et al.[4] to continuation studies of the new generation of antidepressants in order to estimate the proportion of relapses attributable to the loss of true drug response versus those attributable to a loss of placebo response.

METHOD

To obtain a systematic and comprehensive collection of published continuation studies of new-generation antidepressants, we conducted a MEDLINE search of the terms *depression*, *continuation*, and *tachyphylaxis*. We also reviewed all articles published between January 1980 and December 2005 in 23 journals *(Acta Psychiatrica Scandinavica, The American Journal of Psychiatry, Annals of Clinical Psychiatry, Archives of General Psychiatry, The Australian and New Zealand Journal of Psychiatry, Biological Psychiatry, The British Journal of Psychiatry, The Canadian Journal of Psychiatry, Depression and Anxiety, European Neuropsychopharmacology, International Clinical Psychopharmacology, The Journal of the American Medical Association, The Journal of Affective Disorders, The Journal of Clinical Psychiatry, The Journal of Clinical Psychopharmacology, The Journal of Nervous and Mental Disease, Lancet, Neuropsychopharmacology, The New England Journal of Medicine, Pharmacopsychiatry, Progress in Neuropsychopharmacology and Biological Psychiatry, The Psychopharmacology Bulletin,* and *Psychotherapy and Psychosomatics*). Finally, we identified studies in reference lists of pertinent studies and review articles.[2,5]

Continuation studies of antidepressants have used 2 different designs (Figure 1). In the majority of continuation studies, all patients are initially treated with active medication in an open-label fashion, and then treatment responders are randomly assigned to continue with the active medication or switch to placebo in a double-blind manner. We refer to this as the *placebo-substitution* design. In contrast, some studies begin as a double-blind placebo-controlled acute study, and responders to active treatment and placebo are continued on the treatment to which they responded. We refer to this as the *extension* design. Only this latter group of studies provides information on the relapse rate in patients who initially responded to placebo, thereby providing the data necessary to apply the formulas of Quitkin et al.[4] (see below) and estimate the proportion of relapse attributable to loss of placebo response.

We reviewed continuation trials of the new-generation antidepressants and independently classified them as using a placebo-substitution or extension design, and extracted information regarding the number of patients who relapsed. Discrepancies were resolved by discussion. For studies with more than one definition of relapse, we used the definition based on the primary outcome measure.

Data Analysis

Quitkin and colleagues[4] described 2 models for estimating the percentage of relapse during drug treatment that may be attributable to loss of initial placebo effect. In the *exclusive* model, it is assumed that placebo response

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and drug response are mutually exclusive. Patients who respond to the drug include those whose improvement is due only to the effect of drug, and patients who respond to the placebo include those whose improvement is due only to the placebo effect. According to Quitkin et al.,[4] in this model, it is assumed that patients who respond to placebo are incapable of a true drug response. In contrast, in the *independent* model, it is assumed that patients who respond when taking a drug include those whose improvement is due only to the placebo effect, those whose improvement is due only to the effect of drug, and those whose improvement is due to both effects. Quitkin and colleagues suggested that both models be used to estimate relapse during drug treatment that is attributable to loss of placebo effect, and that the correct answer probably lies between the 2 estimates. Based on these 2 models, different formulas are used to calculate the percentage of relapse in drug responders that can be attributed to relapse in presumptive placebo responders. To apply both formulas, 4 pieces of information are needed: (1) the response rate to medication during the acute phase; (2) the placebo response rate during the acute treatment phase; (3) the relapse rate in responders to active medication who are continued on active medication; and (4) and the relapse rate during the continuation phase in patients who responded to placebo during the acute phase and are continued on placebo.

In the exclusive model, the percentage of relapse in patients taking medication attributable to the loss of presumptive placebo response is calculated in the following 4 steps:

Step 1: Estimate of the percentage of drug responders during the acute phase attributable to placebo response = (acute-phase placebo response rate) divided by (acute-phase medication response rate).

Step 2: Number of patients treated with drug during the continuation phase after responding to it during the acute phase who are, in fact, presumptive placebo responders = (number of patients treated with drug during the continuation phase) multiplied by (percentage computed in Step 1).

Step 3: Number of patients treated with drug during continuation phase expected to relapse because they are presumptive placebo responders = (number computed in Step 2) multiplied by (relapse rate during continuation phase in acute-phase placebo responders who are continued on placebo).

Step 4: Percentage of relapse on medication attributable to loss of presumptive placebo response = (number computed in step 3) divided by (number of patients treated with drug during continuation phase who relapsed).

In the independent model, the calculations follow the same 4 steps but the calculations in Step 1 differ. The details of this complex calculation are presented in Quitkin et al.[4]

RESULTS

Five continuation studies of new-generation antidepressants have used the Extension design,[6–10] 3 of which included an SSRI treatment arm.[7,8,10] However, 1 of the studies was excluded from our analyses because it did not report response rates in the acute phase,[10] and we could not find acute-phase response rates in related reports.[11,12] We therefore computed the percentage of relapse attributable to loss of placebo response for 2 studies of SSRIs as well as all 4 studies of new-generation antidepressants.

Claghorn and Feighner[7] reported a 17% relapse rate during a 1-year continuation study of 46 placebo responders, significantly higher than the 10% relapse rate in responders to paroxetine. Detke and colleagues[8] conducted a 6-month follow-up of patients who responded to 8 weeks of treatment with one of 2 dosages of duloxetine, paroxetine, or placebo. The 29% relapse rate in the 58 placebo responders (estimated from Figure 2 in their paper) was significantly higher than the relapse rates in the 3 medication groups (80 mg duloxetine = 6% relapse rate; 120 mg duloxetine = 10%; paroxetine = 6% relapse rate). Anton et al.[6] found a 25% relapse rate during a 1-year continuation study of 71 placebo responders, significantly higher than the 9% rate in responders to nefazodone. Montgomery et al.[9] reported a 5-fold higher relapse rate in 57 placebo responders than in 74 mirtazapine responders. Table 1 summarizes these data. The results were nearly identical in the 2 SSRI studies and all 4 studies of new-generation antidepressants.

Only the report by Detke et al.[8] presented response rates for the acute phase. The acute-phase results of the mirtazapine trial were reported by Stahl et al.[13] The acute-phase results of the nefazodone trial were reported in a review article by Rickels et al.[14] The acute-phase results of the paroxetine trial were reported in multiple articles by Feighner and colleagues.[15,16] Different definitions of response were used in these reports (HAM-D < 10 vs. 50% improvement in HAM-D). In the report of the continuation study by Claghorn and Feighner,[7] *acute-phase response* was not defined. We used the acute-phase response rates based on a 50% change in symptoms, because the HAM-D scores at the beginning of the continuation phase were approximately 10, thereby indicating that the definition of response could not have required a score below 10. Summing across all 4 studies, the acute-phase response rates were 61.9% in the medication group and 35.7% in the placebo group. In the 2 SSRI studies, the acute-phase response rates were 67.2% in the medication group and 35.4% in the placebo group.

Using the formulas of Quitkin et al.,[4] we calculated the relapse rate attributable to relapse in presumptive placebo

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Table 1. Relapse Rates in Patients Taking Antidepressant Medication in 4 Double-Blind, Placebo-Controlled Studies of Continuation Treatment

Study	Medication	Length of Acute Phase, wk	Length of Continuation Phase, wk	Active Medication		Placebo	
				N	Relapse, N (%)	N	Relapse, N (%)
Claghorn and Feighner[7]	Paroxetine	6	52	94	9 (9.6)	46	8 (17.4)
Detke et al[8]	Paroxetine	8	26	70	4 (5.7)	58	17 (29.3)
	Duloxetine, 80 mg	8	26	70	4 (5.7)		
	Duloxetine, 120 mg	8	26	75	7 (9.3)		
Anton et al[6]	Nefazodone	6–8	52	139	12 (8.6)	71	18 (25.4)
Montgomery et al[9]	Mirtazapine	6	20	74	3 (4.1)	57	13 (22.8)
All studies				522	39 (7.5)	232	56 (24.1)
SSRI studies				164	13 (7.9)	104	25 (24.0)

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 2. Estimates of Relapse Rates Attributable to Placebo in Patients Taking an SSRI or Any New-Generation Antidepressant According to the Exclusive and Independent Models

Model and Treatment Group	Observed Relapses, %	Relapses Attributable to Placebo				
		Calculated Relapses, %	95% CL		Lower CL Divided By Observed Relapse Rate	Upper CL Divided By Observed Relapse Rate
			Lower Limit	Upper Limit		
Exclusive model						
SSRIs[a]	7.9	12.6	7.6	17.8	0.96	2.25
Any new-generation antidepressant[b]	7.4	13.9	10.9	16.9	1.47	2.28
Independent model						
SSRIs[a]	7.9	6.4	2.7	10.1	0.34	1.28
Any new-generation antidepressant[b]	7.4	8.2	5.8	10.6	0.78	1.43

[a]Claghorn and Feighner[7] and Detke et al.[8]
[b]Claghorn and Feighner,[7] Detke et al.,[8] Anton et al.,[6] and Montgomery et al.[9]
Abbreviations: CL = confidence limit, SSRIs = selective serotonin reuptake inhibitors.

responders with 95% confidence limits using the exclusive and independent models (Table 2). For the SSRIs, the estimated relapse rate due to loss of placebo effect was 12.6% (exclusive model) and 6.4% (independent model). The observed relapse rate in patients taking active medication was 7.9%. For all of the studies of any new-generation antidepressant medication, the estimated relapse rates due to loss of placebo effect were 13.9% (exclusive model) and 8.2% (independent model), both of which were higher than the observed rate of 7.4%. For the SSRIs, the 95% CI of the percentage of relapse on medication attributable to loss of presumptive placebo response was 96% to 225% based on the exclusive model and 34% to 128% based on the independent model. The point estimates were 159% and 81%, respectively. For all medications, the 95% CI was 147% to 228% based on the exclusive model and 78% to 143% based on the independent model. The corresponding point estimates were 186% (exclusive model) and 110% (independent model).

DISCUSSION

Continuation and maintenance studies of antidepressants have clearly established the benefit of ongoing treatment beyond the acute phase.[2,5] This literature, along with the improved tolerability of the new generation of antidepressant medications, such as the SSRIs, and a greater appreciation of the chronic course of depression, have resulted in increasing numbers of depressed patients taking medication for more prolonged periods of time. Simultaneously, it has been observed that many patients who take the SSRIs seem to lose the beneficial effect over time. It is uncertain how much of this loss of response should be attributed to the loss of a true drug effect and how much might be represented by the reemergence of symptoms in patients who were presumptive placebo responders. Our results suggest that most of the "poop-out" effect during the continuation phase of treatment can be attributed to the loss of an initial placebo response.

Our conclusion is limited to the continuation phase of treatment, because studies of placebo responders have only examined relapse during the continuation phase and have not examined recurrence during maintenance treatment. However, we recently reviewed the likelihood and risk of symptom return in continuation and maintenance studies of responders to new-generation antidepressants and found that the 2 sets of studies produced similar findings (M.Z., Camilo J. Ruggero, Ph.D., Michael A. Posternak, M.D., unpublished data). That is, patients who responded to open-label treatment with an antidepressant and who were switched to placebo had approximately a 40% likelihood of symptom return in both continuation and maintenance studies, whereas approximately 20% of patients who continued treatment with antidepressants

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experienced a relapse or recurrence. If the similarity of results between continuation and maintenance studies in antidepressant responders is also true of placebo responders, then our conclusions regarding the "poop-out" effect being predominantly attributable to the loss of placebo response would apply equally well to continuation and maintenance treatment. Nonetheless, caution is warranted in extrapolating these findings to the maintenance phase.

We expect our findings to be somewhat controversial because they seemingly belie clinical observation. Certainly, in our own practice we have seen patients who, after doing well for a sustained period of time, experience a return of symptoms. This is typically accompanied by patients' comments such as "the medication has lost its effect." Likewise, when eliciting information about prior history of treatment, many patients who describe a return of symptoms after an initially positive response ascribe this phenomenon to a loss of therapeutic efficacy.[3,17,18]

However, for the individual patient, it is not possible to determine whether response during the acute phase represents true drug response or response to the nonspecific elements of treatment. Consequently, when symptoms return in someone who was previously responding to treatment, it is not possible to determine if this phenomenon represents a loss of effectiveness of the medication or symptom reoccurrence in a placebo responder. The results of the present analysis suggest that most relapses occur in presumptive placebo responders.

The "poop-out" effect has been most frequently linked to continuation treatment with SSRIs. We suspect that this association is made because the SSRIs have been so widely prescribed during the past decade and, consistent with treatment guidelines,[19] continued for extended periods of time beyond symptom resolution attained during the initial phase of treatment. Loss of response to SSRI treatment has been salient to treating clinicians who maintain large numbers of depressed patients on these medications. Yet, a review of the literature on continuation studies of antidepressants failed to find higher relapse rates associated with any particular class of antidepressants.[2,5] This failure is consistent with the results in the present article, which found that the majority of relapses following apparent response to SSRI and non-SSRI new-generation antidepressants might be due to the loss of placebo effects.

The results in the present analysis were similar to the findings reported by Quitkin and colleagues,[4] who found that the majority of relapses to imipramine and phenelzine during weeks 7 to 12 of a 12-week trial could be attributed to loss of placebo effect that had been achieved by week 6 of the trial. In fact, our results tended to attribute an even higher percentage of relapse to loss of placebo response, because the differences between active drug and placebo acute-phase response rates were lower than they were in the study by Quitkin et al.[4]

A limitation of our analysis is the uncertain generalizability of these findings to clinical practice because of the limited generalizability of antidepressant efficacy trials.[20,21] However, because antidepressant efficacy trials are designed to minimize placebo effects and maximize the likelihood of detecting a true drug effect and because expectancy effects are likely to be higher in clinical practice in which patients knowingly receive active medication, we would expect our conclusions to apply at least as strongly in clinical practice.

A second limitation is the small number of continuation studies that have used an extension design and thus that could be included in the analysis. However, confidence in the results is supported by the similarity of our findings to those of Quitkin et al.[4] Also, despite the small number of studies, the analysis of all 4 trials included more than 750 patients who were treated during the continuation phase.

Drug names: duloxetine (Cymbalta), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), phenelzine (Nardil).

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