REVIEW

Discontinuing Antidepressant Treatment in Major Depression

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Maintenance treatments in bipolar disorders and schizophrenia are securely established, and their discontinuation is associated with high but modifiable risk of early relapse. The benefits of long-term antidepressant treatment in major depression and the risks of discontinuing medication at various times after clinical recovery from acute depression are not as well defined. Computerized searching found 27 studies with data on depression risk over time including a total of 3037 depressive patients treated for 5.78 (0–48) months and then followed for 16.6 (5–66) months with antidepressants continued or discontinued. Compared with patients whose antidepressants were discontinued, those with continued treatment showed much lower relapse rates (1.85 vs. 6.24%/month), longer time to 50% relapse (48.0 vs. 14.2 months), and lower 12-month relapse risk (19.5 vs. 44.8%) (all $p < 0.001$). However, longer prior treatment did not yield lower postdiscontinuation relapse risk, and differences in relapses off versus on antidepressants fell markedly with longer follow-up. Contrary to prediction, gradual discontinuation (dose-tapering or use of long-acting agents) did not yield lower relapse rates. Relapse risk was not associated with diagnostic criteria. More previous illness (particularly three or more prior episodes or a chronic course) was strongly associated with higher relapse risk after discontinuation of antidepressants but had no effect on response to continued treatment; patients with infrequent prior illness showed only minor relapse differences between drug and placebo treatment. (Harvard Rev Psychiatry 1998; 5:293–306.)

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...if black blood issue forth, bleed on; if it be clear and good, let it be instantly suppressed, because the malice of melancholy is much corrected by the goodness of the blood. If the party's strength will not admit much evacuation in this kind at once, it must be assayed again and again.

—Robert Burton, *The Anatomy of Melancholy* (1652)[1]

Depression is one of the most common major psychiatric disorders and accounts for high rates of morbidity, substance abuse, family disruption, disability, medical comorbidity, and suicide.[2–6] In the United States short-term or lifetime prevalence of major depressive disorder has ranged from 5.2% to 17.1%,[2–4] with the highest rate found in the most recent survey.[4] Annual direct (treatment) plus indirect (disability and premature death) costs for depressive disorders in the United States alone total several tens of *billions* of dollars.[7,8] Timely diagnosis and adequate treatment of depression are therefore crucial challenges for contemporary medicine. Tendencies toward high rates of recurrence and sustained disability in major depression, particularly among persons with a past history of multiple episodes, are important factors in planning long-term treat-

TABLE 1. Characteristics of Studies of Discontinued versus Continued Antidepressant Treatment

Study[a]	n	Mean Age (y)	Gender (% F)	Diagnostic type	Diagnostic criteria	Previous episodes	Agents given	Dose (mg/d)
Mindham et al.[30]	92	48	62	Dep	MRC	—	AMI/NOR	75–150
Klerman et al.[31]	150	38	100	Dep	DSM-II	1	AMI	100–200
Coppen et al.[32]	29	51	81	Dep	MRC	—	AMI	—
Stein et al.[33]	55	42	65	MDD	DSM-III	≥1	AMI	100–150
Van Praag & De Haan[34]	20	44	65	Dep	Clinical	≥3	CMI	—
Bialos et al.[35]	17	57	18	MDD	RDC	Chronic	AMI	50–250
Kane et al.[36]	20	46	63	MDD[c]	RDC	≥2	IMI ± Li	150
Björk[37]	38	50	74	Dep	Clinical	≥3	ZIM	100–200
Davidson & Raft[38]	15	—	87	UPD	Feighner	—	PNZ	45–60
Glen et al.[39]	140	48	67	UPD	MRC	1	AMI or Li[d]	—
Prien et al.[40]	111	—	—	MDD	RDC	—	IMI ± Li[e]	75–150[f]
Cook et al.[41]	15	63	0	MDD	RDC	>4	TCAs	—
Harrison et al.[42]	12	83	35	MDD[g]	DSM-III	>3	PNZ	50
Montgomery et al.[43]	182	—	—	MDD	DSM-III	≥2	FLX	40
Georgotas et al.[44]	51	>55	54	MDD	RDC	≥3	NOR/PNZ	—
Frank et al.[45]	76	40	78	MDD	RDC	3	IMI	—
Eric[46]	135	—	—	MDD	DSM-III-R	>1	PRX	—
Robinson et al.[47]	47	43	81	MDD	RDC	≥3	PNZ	70
Rouillon et al.[48]	1141	46	70	MDD[g]	DSM-III[c]	≥1	MPR	75–150
Doogan & Caillard[49]	295	51	69	MDD	DSM-III	—	SRT	50–200
Kupfer et al.[50]	20	44	67	MDD	RDC	≥3	IMI	200
Maj et al.[51]	72	42	58	Mixed[h]	RDC	≥1	TCA ± Li	≥75
Depression Interest Group[52]	69	75	67	MDD	RDC	≥1	Any/DTP[i]	75[j]
Montgomery & Dunbar[53]	135	48	78	MDD	DSM-III-R	>2	PRX	40
Kishimoto et al.[54]	22	60	77	MDD	DSM-III	≥3	Any/MNS[i]	20–60[j]
Kocsis et al.[55]	50	37	57	MDD[g]	DSM-III-R	Chronic	DMI	200
Stewart et al.[56]	28	39	57	Mixed[c,g]	DSM-III	Chronic	PNZ[k]	90
Means	**112**	**50.0**	**63.8**	—	—	—	—	—

AMI, amitripyline; *B/P,* single-blind with placebo control; *CMI,* clomipramine; *DB,* double-blind; *DB/P,* double-blind with placebo control; *Dep,* depression; *DMI,* desipramine; *DSM,* Diagnostic and Statistical Manual of Mental Disorders; *DTP,* dothiepin; *FLX,* fluoxetine; *IMI,* imipramine; *Li,* lithium; *MDD,* major depressive disorder; *MNS,* mianserin; *MPR,* maprotiline; *MRC,* U.K. Medical Research Council; *NOR,* nortriptyline; *PNZ,* phenelzine; *PRX,* paroxetine; *RDC,* Research Diagnostic Criteria; *Readm,* readmission; *SRT,* sertraline; *TCA,* tricyclic antidepressant; *UPD,* unipolar disorder; *ZIM,* zimeldine.

[a]The 27 studies involved 3037 depressed subjects stabilized or maintained on antidepressants 5.78 ± 11.0 (0–48) months and followed 16.6 ± 12.8 (5–66) months. Nineteen studies (indicated by italic type) including 2615 subjects provided data for survival analysis.

[b]Weeks after clinical recovery or weeks of acute treatment in excess of 8.

[c]Includes some cases of bipolar II depression.

[d]AMI and Li subgroups gave indistinguishable results and are pooled.

[e]Li included before trial; data used are for IMI and IMI + Li.

[f]Dose is for IMI.

[g]Includes some cases of dysthymia or atypical depression.

[h]Includes major depressive episodes associated with other syndromes.

[i]Any antidepressant could be used before randomization to placebo or study drug.

[j]Dose is for study drug.

[k]Other patients, treated with IMI, were excluded due to a lack of IMI-placebo difference during follow-up.

ment and clinical management.[5–7] Despite compelling therapeutic indications and the availability of effective treatments, recognition and adequate treatment of depression remain limited.[8–13] Better-tolerated, more widely accepted antidepressants may improve these deficiencies.[13–15]

Clinical experience as well as controlled research studies, particularly over the past two decades, have demonstrated high risks of relapse or recurrence of major depression following discontinuation of antidepressant treatment after apparent recovery from an acute episode. In such investigations patients have typically received 1–3 months of active treatment with a drug of proven efficacy.[16–20] With

Stabilization[b] (wk)	Follow-up (mo)	Study design	Relapse criteria
≤2	8	DB/P	Clinical
0	8	DB/P	Clinical
0	12	DB/P	Readm
0	6	DB/P	Clinical
12–24	12	B/P	Clinical
192	6	DB/P	Clinical
24	6	DB/P	RDC
16	18	DB/P	Scale
4	5	DB	Clinical
0	36	DB/P	Scale
8	24	DB/P	Scale
≥52	8	DB/P	Clinical
18	6	DB/P	Clinical
16	12	DB/P	Scale
16	12	DB/P	Scale
10	42	DB/P	RDC
0	12	DB/P	Scale
16	24	DB/P	Clinical
≤8	12	DB/P	Scale
0	12	DB/P	Scale
144	24	DB/P	Scale
3	60	Open	Scale
8	24	DB/P	Scale
0	12	DB/P	Clinical
18–21	18	DB/P	Scale
20	24	B/P	Scale
30	6	DB/P	Clinical
23.1	**16.6**	—	—

a placebo or without active treatment, reported risk of a recurring episode of depressive illness has been approximately 50% within 6–12 months, rising more slowly thereafter to nearly 85% within 3 years.[16] With continued antidepressant treatment, the risk is appreciably lower for at least a year.[16–20] By current convention, continuation treatment for several months theoretically prevents *relapse* of an index episode during a period of presumably heightened vulnerability paralleling the course of untreated depression, whereas maintenance treatment for more than a year is intended to prevent *recurrences*, or new episodes.[19,20] The controlled research on this topic has generally been carried out over follow-up periods of a year or less and has involved a narrow range of antidepressants, most often imipramine,[16–20] but studies using newer agents are starting to appear (see Table 1).[14,18,20]

Several questions pertaining to therapeutic practices and their conceptual underpinnings in recurring unipolar depressive disorders, as well as to interpretation of research data in this field, remain unanswered. Research to define and guide optimal drug selection, dosing, and duration of antidepressant therapy for more than a few months is notably limited.[15–20] Also, further support of the theoretical distinction between continuation and maintenance therapy is needed.[15–20] This might include evidence of a falling relapse risk with longer stabilization over the months after recovery from an index episode of depression. High relapse risk has been found to follow discontinuation of lithium in bipolar disorder and neuroleptics in schizophrenia. This high risk may reflect, at least in part, a stressful effect of drug discontinuation itself and appears to be reduced, not merely delayed, by slow removal of lithium in bipolar disorders and antipsychotics in schizophrenia.[21–27] However, it is not clear whether such effects of drug discontinuation contribute to reported drug versus placebo contrasts in studies of long-term antidepressant treatment,[24,25,28,29] or whether slow discontinuation of antidepressants can reduce risk of early relapse/recurrence after stopping long-term treatment.

Given the several questions just raised, we undertook a systematic overview of experimental therapeutic studies in major depression to provide semiquantitative predictions of morbid risk after stopping or continuing treatment. A primary intention was to consider available data underlying the assumptions that guide contemporary clinical practices and research involving antidepressants and the syndrome of major depressive disorder. We also assessed the ability of the available data to permit testing the following specific predictions arising from our recent analyses of research on the treatment of bipolar and psychotic disorders:[21–29] (1) Shorter duration of preceding antidepressant treatment would yield a higher relapse risk after discontinuation of treatment, particularly within the first several months after clinical recovery from an index acute episode of depression. (2) Slow removal of an antidepressant, or stopping a long-acting agent (such as fluoxetine or a standard monoamine oxidase inhibitor [MAOI]), would be followed by less morbid risk in the ensuing months than would abrupt or rapid discontinuation of long-term treatment with a short-acting antidepressant.

METHODS

We sought studies involving discontinuation of antidepressant treatment in patients diagnosed with nonbipolar major depression, with blind, placebo-controlled, and randomized discontinuation or data suitable for survival analysis, involving at least 6 months of comparison of ten or more treated versus untreated patients. A *Medline* computerized literature search (search terms: depression, antidepressants, long-term) for articles published between January 1970 and January 1997 was supplemented with references cited in reports so identified. All studies accepted for further

consideration provided data on the time to a new depressive episode or permitted calculation of crude relapse rates (%/month) for cohorts whose antidepressant treatment was continued or discontinued. Some investigations[23–27] yielded data on time to relapse for individuals, or survival analyses of groups, suitable for testing for significance of differences in survival functions between subjects whose treatment was continued and those whose treatment was discontinued.

This process yielded 27 studies[30–56] involving a total of 3037 subjects; each included a cohort continuing and another discontinuing antidepressant treatment (to a placebo in 25 investigations). (See Table 1 for details of these studies.) Several reports did not provide certain relevant details, such as specific drugs, doses, history of past depressive episodes, or the precise time of stabilization prior to discontinuing antidepressant treatment. Diagnostic criteria varied, and some investigations included an unspecified minority of patients with bipolar II disorder, dysthymia, atypical depression, or major depressive episodes associated with another syndrome. Definitions of relapse usually involved clinical assessment or use of rating scale scores to indicate worsening of depressive symptoms severe enough to warrant hospitalization or reinstitution of antidepressant treatment. Twenty-six of the 27 studies were at least partially blinded comparisons of depressive disorder patients followed-up after continued vs. discontinued antidepressant treatment; 17 involved a tricyclic antidepressant (TCA) or similar agent, five an MAOI, and five a serotonin-reuptake inhibitor (SRI).

Crude relapse rates (% of subjects becoming depressed per month) for the 27 studies were evaluated in several ways. First, within-study paired *t*-tests were used to provide an overall comparison of monthly relapse rates with and without continued antidepressant treatment. Relations of treatment duration and subsequent relapse risk after stopping treatment were tested by linear regression (r) or Spearman nonparametric rank correlation (r_s) and by analysis of variance (ANOVA) to compare risks after discontinuing treatment at different times.

The prediction that relapse risk would be reduced by slow discontinuation of medication[23–27] after long-term treatment of depression was tested by using ANOVA to compare relapse rates following abrupt (same day) or rapid (≤2 wk) discontinuation of medication with those after gradually tapering doses of standard antidepressants (>2 wk) or stopping agents of long elimination half-life (fluoxetine) or functional recovery time (irreversible MAOIs such as phenelzine).[14,15]

Unless stated otherwise, data are presented as mean ± standard deviation. Survival times computed by Kaplan-Meier analysis are shown as time to 50% relapse ± standard error (SE) and plotted with actuarially computed monthly risks and their 95% confidence intervals (CI). Differences in survival functions are evaluated with the Mantel-Cox or Wilcoxon χ^2 statistics. All statistical tests are two-tailed, with probability considered not significant (NS) at $p > 0.05$, at defined degrees of freedom (df). Computations used StatView 4.5 programs for the Macintosh microcomputer (Abacus Concepts, Berkeley, California).[23–27]

RESULTS

Characteristics of Studies and Subjects

The 27 studies considered involved 3037 depressed patients; 1186 of them were discontinued and 1851 continued on antidepressant maintenance treatment (see Table 1). In the studies providing such data, age averaged 50.0 ± 11.4 years, and 63.8 ± 21.3% of the patients were female. Patients discontinuing treatment had been treated and then were stabilized for an average of 5.78 ± 11.0 (0–48) months after recovery from an index depressive episode; subsequent follow-up on or off active medication averaged 16.6 ± 12.8 (5–66) months.

Relapse Rates versus Treatment Status

Relapse rates (%/month) derived from all studies averaged 6.24 ± 5.34 with discontinued antidepressant treatment versus 1.85 ± 1.51 with continued treatment (a 3.37-fold difference), and within-study risk ratios (off/on antidepressant, reported as quotients) averaged 3.60 ± 2.58 (paired-t [26 df] = 5.01, $p < 0.0001$; see Table 2). Across studies, relapse rates after discontinuing and continuing treatment were strongly correlated (r [26 df] = 0.663, $p = 0.0002$). In support of the comparability of results across studies, the relapse rates did not differ significantly, with or without medication, in studies involving SRIs or older antidepressants (relapse averaged 1.35 ± 0.68 on SRIs and 1.96 ± 1.63 on TCAs or MAOIs (F [1,25 df] < 0.01; NS), or between TCAs and other types of agents (F [1,25 df] < 2.13; NS), although most studies involved TCAs. Moreover, crude relapse rates with antidepressant continued or discontinued did not differ significantly by diagnostic criteria for depression (both F [5,21 df] ≤ 1.84; NS), and they were affected very little by the choice of criteria for a relapse. For example, risk after stopping antidepressants was nearly identical, although more variable, with Research Diagnostic Criteria than with clinical criteria (9.27 ± 10.5% vs. 9.41 ± 6.01%/month, respectively), but these rates pooled were somewhat higher than those found when a rating scale or rehospitalization was used to define relapse (3.23 ± 1.33%/month, F [3,23 df] = 3.98, $p = 0.02$). With continued treatment, there was no difference in relapse rate based on any of these definitions (all F [3,23 df] ≤ 1.78; NS).

TABLE 2. Recurrences with Discontinued versus Continued Antidepressant Treatment

Study	Months at risk	Antidepressants discontinued: Relapsed/ total n	Antidepressants discontinued: Relapse risk	Antidepressants continued: Relapsed/ total n	Antidepressants continued: Relapse risk	Risk ratio
Mindham et al.[30]	8	21/42	6.25	11/50	2.75	2.27
Klerman et al.[31]	8	27/100	3.38	6/50	1.50	2.25
Coppen et al.[32]	12	5/16	2.60	0/13	0.00	>2.60
Stein et al.[33]	6	19/27	11.70	9/28	5.36	2.19
Van Praag & De Haan[34]	12	8/10	6.67	3/10	2.50	2.67
Bialos et al.[35]	6	8/10	13.30	0/7	0.00	>13.30
Kane et al.[36]	6	6/6	16.67	5/14	5.95	2.80
Björk[37]	18	16/19	4.68	6/19	1.75	2.67
Davidson & Raft[a,38]	5	8/8	20.00	1/7	2.86	7.00
Glen et al.[39]	36	8/9	2.22	88/131	1.86	1.32
Prien et al.[40]	24	25/34	2.27	28/77	1.52	2.02
Cook et al.[41]	8	3/9	4.17	0/6	0.00	>4.17
Harrison et al.[42]	6	7/7	16.67	1/5	3.33	5.00
Montgomery et al.[43]	12	54/94	4.79	23/88	2.18	2.20
Georgotas et al.[44]	12	15/23	5.43	9/28	2.68	2.03
Frank et al.[45]	42	18/23	1.86	12/53	0.54	3.44
Eric[46]	12	21/67	2.61	3/68	0.37	7.05
Robinson et al.[47]	24	13/16	3.39	9/31	1.21	2.80
Rouillon et al.[48]	12	120/374	2.67	140/767	1.52	1.76
Doogan & Caillard[49]	12	48/110	3.64	24/185	1.08	3.37
Kupfer et al.[50]	24	6/9	2.56	1/11	0.38	7.33
Maj et al.[51]	60	17/19	1.49	39/53	1.23	1.22
Depression Interest Group[52]	24	20/36	2.31	10/33	1.26	1.83
Montgomery & Dunbar[53]	12	29/67	3.61	11/68	1.35	2.68
Kishimoto et al.[54]	18	13/13	5.56	4/9	2.47	2.25
Kocsis et al.[55]	24	13/23	2.36	3/27	0.46	5.13
Stewart et al.[56]	6	13/15	14.40	3/13	3.85	3.74
Means	**16.6 ± 12.8**	—	**6.24 ± 5.34**	—	**1.85 ± 1.51**	**3.60[b]**

[a]Includes some patients on doses of phenelzine slowly removed over 4 months, with high relapse rates.
[b]Paired t-test [26 df] = 5.01, $p < 0.0001$).

Survival Analyses for Treatment Continued versus Discontinued

Survival analysis based on data provided by 19 studies[30,32,35,37,39,40,43–45,47–56] with follow-up averaging 19.4 ± 14.1 (6–60) months yielded a computed time to 50% risk of relapse (± SE) of 48.0 ± 4.7 months in 1663 subjects with antidepressant treatment maintained. The interval was much shorter (14.2 ± 0.5 months) in 952 patients whose treatment was terminated after 6.92 ± 13.1 (0–48) months. This 3.37-fold difference in the time to 50% risk of relapse is highly significant (χ^2 [1 df] = 216, $p < 0.00001$; see Figure 1). In support of the comparability of results across investigations, there was no significant difference in survival, with medication continued or not, between studies involving modern and older antidepressants. (Computed 12-month survival [CI] was 83.0% [79.2–86.9%] [n = 649] on SRIs and 79.7% [77.4–82.0%] [n = 1966] on TCAs or MAOIs.) Moreover, results obtained with the unusually large single study by Rouillon and colleagues[48] (n = 1141) included or excluded were very similar: the computed chance of remaining stable (surviving) for 36 months with these data included versus excluded was 16.7% (95% CI = 5.70–27.7%) versus 13.4% (4.50–22.4%) after discontinuing treatment, and 56.9% (51.8–61.9%) versus 55.4% (50.2–60.5%) with antidepressant treatment continued (neither difference is significant). Similarly, inclusion versus exclusion of the one open study, by Maj and colleagues,[51] yielded virtually identical survival analyses with antidepressant

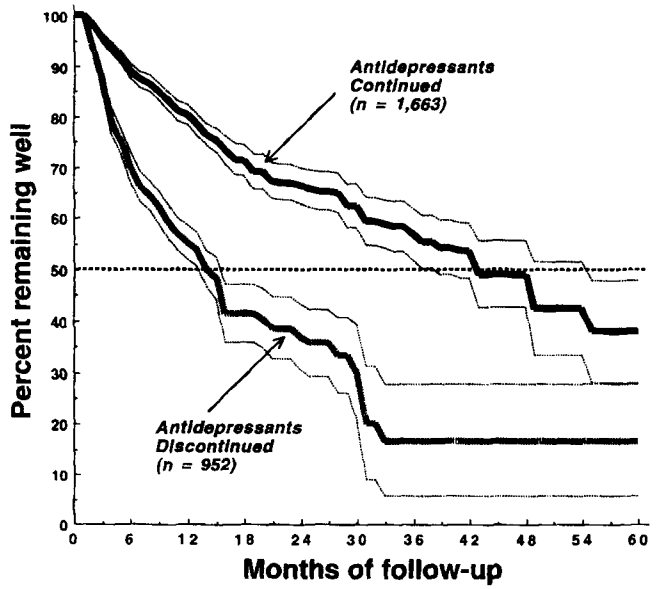

FIGURE 1. Survival analysis, shown as percent of subjects with major depression remaining well versus months of follow-up with antidepressants continued or discontinued, in 19 studies (see Table 1) in which cohorts of both kinds were included. The 95% confidence intervals are shown for each function (dotted lines); the 50% survival level is indicated as a horizontal dashed line. The time to 50% risk ± SE was 14.25 ± 0.49 months after discontinuing antidepressants and 48.00 ± 4.69 months on antidepressants (a 3.37-fold difference). The overall difference in survival functions is highly significant (χ^2 = 216, p < 0.00001).

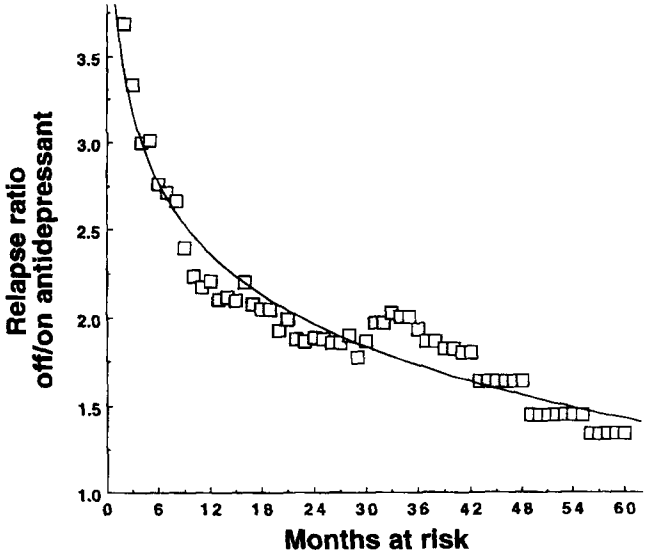

FIGURE 2. Ratio of relapse rate (%) without antidepressant/with antidepressant continued versus months of follow-up, based on the survival analyses for Figure 1, computed for monthly intervals. The data are well fit (r = 0.962) by a logarithmic function (line): relapse ratio = 3.82 − 1.34 $\log_{10}$ (time in months).

continued or with treatment discontinued (Wilcoxon χ^2 for shared subjects both ≤ 0.003; NS).

Stability over Time with Treatment Continued versus Discontinued

Even after discontinuing antidepressant treatment, substantial proportions of patients remained stable for 1 or 2 years (55.2% [CI = 52.0–58.5%] and 36.8% [30.5–43.1%], respectively; see Figure 1). The effect of apparent reduction of depressive relapse was estimated as the ratio of relapse rates on placebo versus on drug during follow-up. Interestingly, this ratio fell continuously, in apparently logarithmic fashion, from a high of 3.69 at 2 months, to 2.21 at 12 months, to only 1.34 by 5 years of follow-up, and averaged 1.92 ± 0.55 across follow-up times; a ratio of 1.0 indicates no difference in risk with versus without drug (see Figure 2). In addition, survival analysis indicates that the difference in the proportion of patients surviving with versus without continued medications averaged 27.9 ± 8.62% over 5 years of follow-up.

Effect of Length of Treatment

No study systematically varied duration of antidepressant treatment before its controlled interruption, but across the 27 investigations analyzed, duration of follow-up differed greatly, and independently of the length of prior treatment (r = −0.017 [25 df]; NS; see Table 1). Contrary to expectation, even within the first year of recovery, relapse risk did not fall with longer stabilization prior to discontinuation of an antidepressant (0–48 months; r = 0.190 [25 df]; NS; see Table 3). Relapse rates (%/month) off medication averaged 5.78 ± 5.80 after stabilization for 0–3 weeks following clinical recovery in ten studies, 6.47 ± 5.34 after stabilization for 2–7.5 months in 14 studies, and 6.76 ± 5.74 after stabilization for 13–48 months in three studies (overall F [2,24 df] = 0.06; NS). Moreover, survival analyses for 19 individual studies also indicated no significant reduction of risk with longer stabilization, even within the first year after clinical recovery: the 6-month relapse rates were 37.2 ± 11.6% after only 0–3 weeks of stabilization in six studies, 48.0 ± 24.2% after 2–7.5 months in 11 studies, and 56.6 ± 33.0% after more than 12 months in two studies (overall F [2,16 df] = 0.88; NS).

TABLE 3. Relapse Rate, Length of Stabilization, and Rapidity of Discontinuing Antidepressants

Study	Stabilization (mo)[a]	Withdrawal		Relapse rate[b] (%/mo)
		Length (wk)	Type	
Mindham et al.[30]	0.50	<1	Abrupt	6.25
Klerman et al.[31]	0.00	<1	Abrupt	3.37
Coppen et al.[32]	0.00	<1	Abrupt	2.60
Stein et al.[33]	0.00	<1	Abrupt	11.70
Van Praag & De Haan[34]	4.50	<1	Abrupt	6.67
Bialos et al.[35]	48.00	3	Gradual	13.30
Kane et al.[36]	6.00	<1	Abrupt	16.70
Björk[37]	4.00	<1	Abrupt	4.68
Davidson & Raft[38]	1.00	12 (MAOI)[c]	Gradual	20.00
Glen et al.[39]	0.00	2	Gradual	2.46
Prien et al.[40]	2.00	<1	Abrupt	3.06
Cook et al.[41]	13.00	6	Gradual	4.17
Harrison et al.[42]	4.50	2 (MAOI)	Gradual	16.70
Montgomery et al.[43]	4.00	<1 (FLX)	Gradual	4.79
Georgotas et al.[44]	4.00	<1 (incl. MAOI)	Abrupt	5.43
Frank et al.[45]	2.50	3	Gradual	1.86
Eric[46]	0.00	<1	Abrupt	2.61
Robinson et al.[47]	4.00	3 (MAOI)	Gradual	3.39
Rouillon et al.[48]	2.00	<1	Abrupt	2.67
Doogan & Caillard[49]	0.00	<1	Abrupt	3.64
Kupfer et al.[50]	36.00	3	Gradual	2.78
Maj et al.[51]	0.75	<1	Abrupt	1.35
Depression Interest Group[52]	2.00	<1	Abrupt	2.31
Montgomery & Dunbar[53]	0.00	<1	Abrupt	3.61
Kishimoto et al.[54]	4.88	<1	Abrupt	5.56
Kocsis et al.[55]	5.00	4	Gradual	2.36
Stewart et al.[56]	7.50	2 (MAOI)	Gradual	14.40

FLX, fluoxetine; *MAOI*, monoamine oxidase inhibitor.

[a]Defined as for Table 1; some studies with stabilization for 0.00 months discontinued treatment as soon as patients met criteria for recovery from an acute depressive episode.

[b]Relapse rates averaged 5.14 ± 3.95 after abrupt (16 studies) and 7.84 ± 6.80 after gradual (11 studies) discontinuation (F [1,25 df] = 1.71; NS).

[c]Includes some patients with phenelzine slowly removed over 4 months.

Effect of Drug Discontinuation Rate

Although no study included both rapid and gradual discontinuation conditions, 16 (n = 753 subjects) involved abrupt or rapid discontinuation of antidepressant therapy and 11 (n = 199) involved gradual dose-tapering over at least 2 weeks, or stopping long-acting antidepressants. This distinction was used in our previous work with lithium discontinuation in bipolar disorders and yields approximately equal subgroups of rapidly and gradually discontinued patients; 2 weeks is also congruent with the recovery time from MAOIs and the washout of norfluoxetine.[15,25] Moreover, a preliminary analysis indicated no significant relationship between relapse rates and continuously varied drug discontinuation times (r_s = 0.176 [NS]; if one aberrant study[38] with a 20.0%/month relapse rate after 3 months of tapering off an MAOI is eliminated, r_s = 0.077 [NS]).

Contrary to expectation, relapse rates off medication did not differ significantly between studies involving rapid discontinuation and those in which tapering was more gradual (5.14 ± 3.95 vs. 7.84 ± 6.80%/month, respectively; F [1,25 df] = 1.70; NS) (see Figure 3). These results did not change appreciably whether the one ambiguous study involving both a TCA and an MAOI[44] was considered to represent either rapid or gradual discontinuation or was excluded. Moreover, there was no effect of discontinuation rate when past history was also considered (with severe history, considered as chronic or at least three prior episodes, contrasted with less-severe histories: 2-way F [1,23 df] ≤ 1.20; NS). Overall survival analysis indicated that 12-month survival was actually 16.3% *higher* after more-rapid discontinuation, at 58.7% (CI = 55.1–63.2%) versus 42.4% (CI = 35.2–49.2%), respectively. A similar but non-

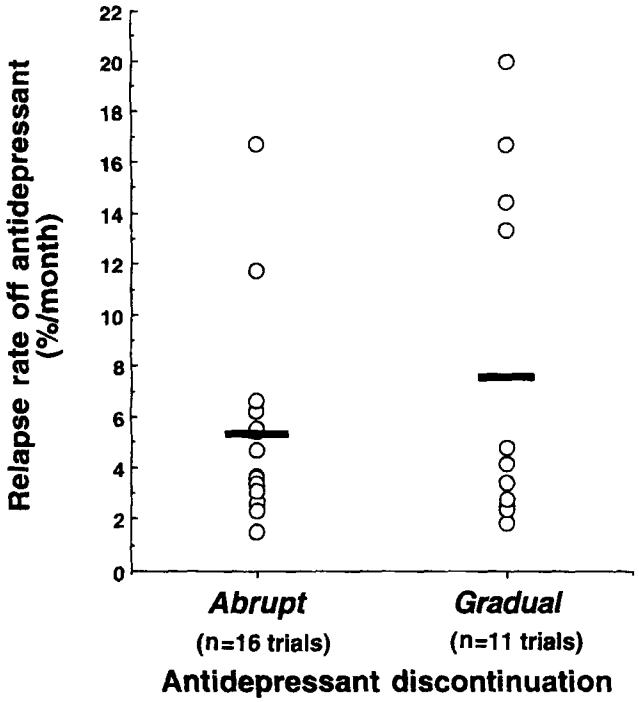

FIGURE 3. Relapse rate (% of patients relapsing per month) after discontinuing antidepressant treatment abruptly vs. gradually, based on data and definitions shown in Table 3. The mean rates (bold bars) did not differ significantly: after abrupt discontinuation, 5.14 ± 3.95 %/month; after gradual discontinuation, 7.84 ± 6.80 %/month (F [1,25 *df*] = 1.71; NS). (Some plotted points overlap.)

significant trend was found with separate survival analyses of individual studies, which yielded 6-month relapse rates of 39.6 ± 16.3% versus 53.6 ± 26.2% for rapid versus gradual discontinuation (F [1,17 *df*] = 2.05; NS). Finally, one would expect maximum relapse risk with abrupt discontinuation of treatment soon after recovery from acute depression. Therefore, the apparent lack of greater risk after abrupt than after gradual discontinuation of antidepressant treatment is particularly surprising since it was associated with substantially *shorter* average preceding stabilization on medication (1.91 ± 2.10 vs. 11.4 ± 15.7 months, respectively; F [1,25 *df*] = 5.78, $p < 0.025$).

Effect of past history of depression

Finally, in view of the evident clinical heterogeneity regarding past history, studies were compared after segregating them into five (overlapping) subgroups according to patients' history of previous episodes, as specified in Table 1: (a) chronically depressed, (b) at least three previous episodes, (c) at least two prior episodes, (d) at least one previous episode, or (e) not specified and presumably including a variety of histories. Survival analyses comparing these subgroups revealed striking and highly significant differences in relapse rates over time after treatment was stopped. Following the end of treatment, relapse in the subgroups ranked a > b > c = e > d, but past history showed no apparent effect on response to continued antidepressant treatment (see Figure 4, Table 4). Even though contrasts of relapse rates with treatment continued versus discontinued were significant at all levels of past history (differing by 3.6-fold), the off/on treatment risk ratio was highly sensitive to the level of previous illness, as indicated by survival rates at 1 year of follow-up.

Further support for this conclusion is indicated by markedly different 2-year survival rates between treatment conditions in patients with a more severe past history but not in those with a less severe history. In those with at least three past episodes or a chronic course, the 2-year survival rate computed by survival analysis was 71.7% (CI = 64.6–78.9%, n = 198) with antidepressant versus 14.7% (CI = 7.10–22.2%, n = 151) without—a highly significant 4.88-fold difference. In contrast, among patients with only one or more past episodes, the corresponding 2-year survival rates differed little: 64.1% with treatment (CI = 58.7–69.4%, n = 984) versus 52.7% without (CI = 42.9–62.6%, n = 438)—a nonsignificant 1.22-fold difference. Since the ≥1 episode condition subsumes all others, presumably even larger contrasts would be found if past history were more discretely segregated. These findings indicate a strong impact of greater previous depression, with a higher risk of earlier relapse after stopping antidepressant maintenance treatment and a much more robust difference in relapse risk between discontinued and sustained antidepressant treatment with a more severe past history.

DISCUSSION

This review of 27 studies[30–56] involving 3037 patients diagnosed mainly with recurring major depression compared morbidity over time during prolonged antidepressant treatment and after its discontinuation. These investigations represent most of the research available on maintenance antidepressant therapy in unipolar depression that reports on morbid risks over time. Table 1 indicates that the studies involve substantial heterogeneity; for example, different diagnostic criteria were employed, and several studies probably involved depressive illnesses other than recurrent unipolar major depression, whereas others included chronically depressed patients. None systematically varied clinical features such as past history, the period of stabilization after recovery from an index depressive episode, or the rate of antidepressant discontinuation. These limitations con-

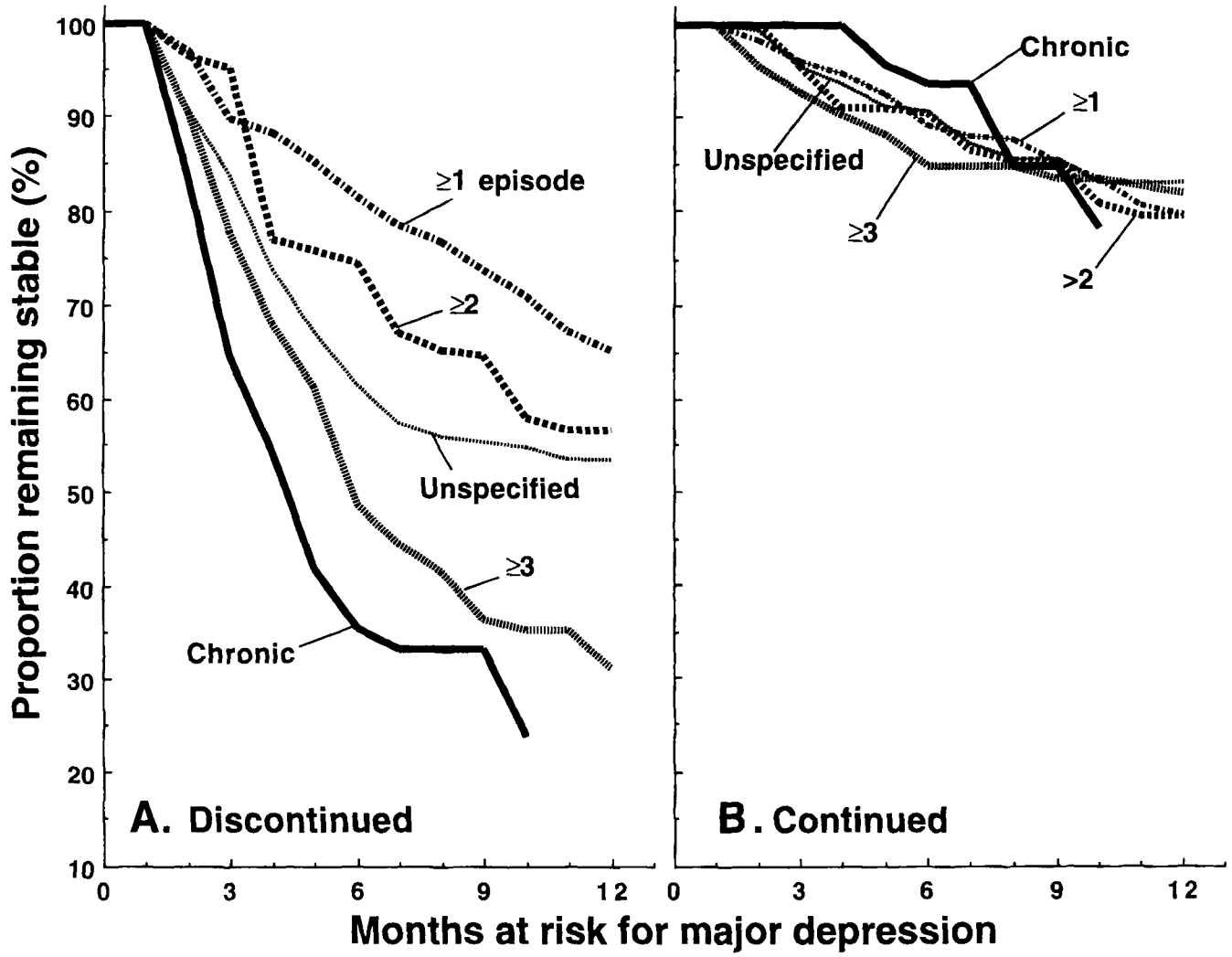

FIGURE 4. Survival analyses of patients with major depression after antidepressant treatment was **(A)** discontinued (usually to a placebo) or **(B)** continued, as a function of the reported past history of depressive illness: chronic (n = 48 discontinued, 95 continued), with ≥ 3 prior episodes (n = 103, 151), ≥ 2 (n = 161, 156), ≥ 1 (n = 438, 983), or unspecified (n = 202, 326). The survival functions differed highly significantly (χ^2 [4 *df*] = 97.5, $p < 0.0001$) after discontinuation but not with antidepressant continued ($\chi^2 = 0.86$; NS).

strain conclusions that can be derived from the present analyses. Moreover, major depression, as currently broadly defined by widely accepted diagnostic systems, may not represent a clinically homogeneous syndrome, even though we did not find significant differences in relapse rates on or off antidepressant versus diagnostic criteria reported.

Limitations notwithstanding, the studies reviewed represent much of the knowledge base underlying contemporary clinical recommendations with respect to long-term antidepressant treatment and the risks following its discontinuation at various times. Accordingly, the present results can be viewed as a summary of the state of current knowledge of the effects of discontinuing antidepressants. They lead to several impressions that are of research interest and clear clinical relevance, including some unexpected findings, and their consideration highlights specific questions that require further research.

As expected, there was a striking overall difference in depressive morbidity between subjects continuing and discontinuing antidepressant treatment, usually to a placebo

TABLE 4. Relationship of Past History of Major Depression to 1-Year Survival Rate with and without Continued Antidepressant Treatment[a]

Past history	Antidepressant continued	Antidepressant discontinued	Off/on risk ratio
Chronic depression	78.1 (61.5–94.6) [95]	23.7 (9.10–38.4) [48]	3.30
At least 3 previous episodes	82.0 (75.8–88.1) [151]	31.1 (22.0–40.2) [103]	2.64
Unspecified episode history	83.0 (78.9–87.1) [326]	53.3 (46.3–60.3) [202]	1.56
At least 2 previous episodes	79.5 (73.2–85.8) [156]	56.5 (48.9–64.2) [151]	1.41
At least 1 previous episode	79.7 (77.1–82.3) [983]	65.2 (60.6–69.7) [438]	1.22

[a]Data are computed as cumulative percent recurrence risk within 1 year (95% CI in parentheses; n in brackets), based on survival analyses and statistics shown for Figure 4, and are in rank order by treatment-based risk ratios. Computed times to 25% relapse risk ± SE: after discontinuation, 1.25 ± 0.28 months (chronic), 2.50 ± 0.44 months (≥3 episodes), 3.00 ± 0.27 months (unspecified), 5.00 ± 1.32 months (≥2 episodes), and 7.50 ± 0.83 months (≥1 previous episode); with treatment continued, 14.6 ± 0.68 months.

after approximately 6 months of stabilization following an index episode of depression. Average rates of relapse (%/month) and times to defined levels of relapse risk derived by survival analysis indicated a highly significantly lower risk with treatment sustained than with treatment discontinued, with follow-up over an average of 1.4 (0.5–5.0) years. Crude relapse risk averaged 1.85%/month with treatment continued versus 6.24%/month after discontinuation, and the corresponding computed time to 50% risk of a first recurrence was 4.00 versus 1.19 years. These marked risk differences (about 3.4-fold) seem to support the generalization that long-term antidepressant treatment has important prophylactic benefits in recurring major depression, and that is how such data have conventionally been interpreted.[15–20]

Although this may be a valid and sufficient interpretation, the apparent benefits of prolonged treatment may be marginal in some patients or at some times. Moreover, recent findings pertaining to the effects of discontinuing lithium in bipolar disorder and antipsychotics in schizophrenia[21–29] indicate that drug discontinuation itself may represent a clinically significant stressor that may temporarily increase relapse risk. This possibility is consistent with the finding that the differences in relapse risk off versus on antidepressant medication decreased over time, from over 3.5-fold within 3 months after discontinuing treatment to less than 1.5-fold by 4 or 5 years of follow-up. However, several factors in addition to an early impact of drug discontinuation might contribute to such a diminution of difference over time. These include a growing risk of noncompliance with longer treatment, as well as possible changes in risk over the natural course of recurring depressive illnesses. Related factors include clinical heterogeneity within and between samples of depressed patients: patients who are more vulnerable or more severely ill probably relapse earlier, while others can sustain prolonged periods without treatment. It may be instructive to compare the course of illness over time before versus during long-term treatment as a way of estimating the impact of discontinuing treatment. Whether narrower definitions of major depression syndrome, as well as past history or other specific morbidity criteria, might limit variance in responses to antidepressant discontinuation also remains to be tested.

A past history of severe and frequently recurring depressive episodes is a plausible clinical predictor of increased recurrence risk after discontinuation of treatment.[17–20] Such an association is strikingly supported by the present findings, in which a chronic course or a history of three or more past episodes, compared with fewer past episodes, was associated with much greater risk of early relapse after stopping antidepressants, even though the reported definitions of past history overlapped. In striking contrast, past history apparently had little bearing on relapse risk during active maintenance treatment. The difference in relapse risk with antidepressant continued versus discontinued also varied with past history. By 2 years of follow-up, the difference was nearly negligible (35.9% vs. 47.3%) in patients with one or more past episodes but threefold (28.3% vs. 85.3%) in those with three or more past episodes or a chronic course. Past history should thus be taken into account in the clinical management of patients who are discontinuing antidepressant treatment, as well as in the ethical design of research protocols and in the informed consent process. Future studies should evaluate relapse risk as a function of specific past history measures and other clinical features and should attempt to determine whether a more severe past history implies a need for indefinitely continued maintenance treatment or merely increases vulnerability to the discontinuation of treatment.

Some of the present findings were unexpected[25,27] and so are particularly interesting. First, the computed time to 50% relapse was 14.2 months after stopping antidepressant treatment that had been continued for nearly 6 months following apparent clinical recovery. This is a much more

extended (up to 2.0- to 2.4-fold) median period of wellness (latency to relapse) than was found in comparable analyses of studies of lithium in bipolar disorders (6.0 months after rapid discontinuation of treatment averaging 4.2 years)[25] or an antipsychotic in schizophrenia (7.2 months after abrupt discontinuation of treatment averaging 7.8 months).[27] Such differences probably reflect dissimilarities in the natural histories of the disorders, with relatively slow average cycling in unipolar depression, such that prolonged follow-up for several years may be required to document more than one period of risk of a recurrence in some slowly cycling patients. The long average latency to a recurrence of major depression without medication also suggests that some depressed patients, particularly those with relatively few past episodes, can remain stable for prolonged periods without maintenance treatment.

Second, longer stabilization on medication was not found to be followed by a lower relapse rate after discontinuing antidepressant treatment, whether treatment was stopped soon after clinical recovery or after stabilization on medication for several months or (in a few studies) several years. This unexpected finding may simply reflect random variation among heterogeneous investigations; if so, it strongly encourages studies in which the duration of continuation treatment is controlled by systematic variation and random assignment. Alternatively, it may reflect an impact of treatment discontinuation that, itself, is powerful enough to overcome any protection afforded by longer periods of euthymia. A similar lack of protection from drug-discontinuation recurrence risk by prolonged stabilization periods was found previously with lithium in bipolar disorders.[25,28] Regardless of their interpretation, the available findings do not support the clinical expectation that risk of relapse is increased soon after recovery from an episode of acute depression. That expectation encourages the currently recommended practice of continuing antidepressant treatment for at least several months after apparent clinical recovery.[15–20] Until the risks involved in stopping antidepressant continuation therapy soon after recovery from an acute episode of depression are better clarified, we recommend that this widely accepted clinical practice continue, particularly for patients with a past history of several episodes of depression or evidence of chronic illness.

Third, slower discontinuation (gradual dose reduction or stopping long-acting agents as opposed to abruptly stopping short-acting agents) did not yield a lower subsequent relapse risk, in contrast to our previous findings in bipolar disorders and in schizophrenia.[23–27] A very optimistic view of this finding would be that any early negative impact of discontinuing an antidepressant, even abruptly and without prolonged stabilization, may be less than was found with lithium and antipsychotic agents. However, such a conclusion is premature in view of a lack of protocols designed to compare stabilization times and discontinuation rates *within* studies, directly and under matched conditions. The apparent lack of an association of relapse risk with the rate of antidepressant removal might reflect differences in the natural history of major depression and other disorders. In addition, the reported differences in drug discontinuation rates by days or a few weeks may have been insufficient to produce an effect on time to recurrence that averaged over a year. Another likely factor noted previously with antipsychotic drugs[27] is a difference of conditions across studies, which would increase variance and limit the power of comparisons made here.

The possibility of limiting postdiscontinuation relapse risk by slowing the rate of discontinuing antidepressants has obvious clinical significance and is also an important matter to resolve for the ethical design of placebo-controlled studies in experimental therapeutics. Furthermore, scientific interpretability of such studies would be improved if the proposed effect of treatment discontinuation itself could be limited. An additional ethical challenge is the withdrawal of antidepressant treatment from persons with chronic depression or a past history of multiple recurrences. Whether the higher relapse risk with more previous episodes reflects the pressure of a more severe natural history, greater vulnerability to drug discontinuation, or their interaction is unclear. Given the ambiguity of the available research on the subject, clarification requires studies with appropriate scientific and ethical design that include systematically varied rates of discontinuing antidepressants and specification of past history.

The observed average interval to a new episode of depression after stopping maintenance treatment was 1.2 years, and the risk-over-time functions with and without medication were nearly parallel after the first year. Moreover, 55% of depressed subjects remained stable for a year after stopping treatment, and 37% remained stable for 2 years. Outcome was clearly associated with severity of past history: only one-quarter to one-third of those with three or more past episodes or a chronic course, but nearly two-thirds of patients with one or more episodes, remained euthymic without medication for a year. The net gain in avoiding relapse (survival off medication minus survival on medication) averaged only 28% across all months at risk, and the risk ratio (relapse risk off/on medication) fell rapidly during the first few months of follow-up, approached unity within 5 years, and also decreased with a diminishing number of past episodes. These surprising findings may indicate that only a minority of patients, particularly those with multiple past episodes, required many months of treatment, with associated clinical and financial costs, to avoid a future episode of depressive illness. These considerations lead us to question whether the hypothesis has been proved that prolonged antidepres-

sant treatment is more effective, more efficient, or safer than treatment to full clinical remission and clinical follow-up and remedication as indicated by clinical progress, particularly following a first or second lifetime episode of major depression. Actual contemporary clinical practice evidently only infrequently includes prolonged maintenance treatment with substantial doses of antidepressants.[9–13] Whether such practice is entirely explained by insufficient awareness of major depression and its appropriate medical treatment is unclear. Many experienced clinicians and patients are reluctant to continue antidepressant treatment indefinitely, particularly when episodes are infrequent, not life-threatening, and either mild or brief.

It would thus be informative to subject long-term antidepressant therapy to cost-benefit analyses. Future studies involving planned discontinuation of antidepressant treatment should randomly vary the duration of stabilization before discontinuation and discontinue medication at defined rates over weeks or months, or compare short- versus long-acting agents within the same study—all with stratification by number of previous episodes. Specific assessments are also needed to determine the efficacy of retreatment[57] and to compare newer agents with the TCAs most often represented in reported trials. Finally, the clinical effectiveness, safety, and costs of sustained versus intermittent treatment of major depressive episodes remain to be determined.

Although further studies are necessary to address questions raised in this review, continuation treatment for several months after recovery from an acute depressive episode—at least until apparently secure remission of acute illness is achieved—is recommended as a prudent practice and a hedge against subtle continued morbidity. More-prolonged antidepressant maintenance treatment might best be decided by considering compelling clinical indications, including the lack of full clinical recovery from a current depressive episode, a past history of multiple and severe or life-threatening episodes, or the rapid return of symptoms after cautiously lowering the dose or gradually stopping antidepressant maintenance treatment.[13,15,19,20] This conclusion seems particularly appropriate, given the evident heterogeneity of conditions diagnosed as "major depression" by contemporary criteria and represented in studies found for the present review.

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