Loss of Antidepressant Efficacy During Maintenance Therapy: Possible Mechanisms and Treatments

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Background: Many patients with unipolar depression experience a return of depressive symptoms while taking a constant maintenance dose of an antidepressant.

Method: All cited studies were found using computerized literature searches of the MEDLINE database since 1966.

Results: The return of depressive symptoms during maintenance antidepressant treatment has occurred in 9% to 57% of patients in published trials. Possible explanations include loss of placebo effect, pharmacologic tolerance, increase in disease severity, change in disease pathogenesis, the accumulation of a detrimental metabolite, unrecognized rapid cycling, and prophylactic inefficacy.

Conclusion: Although several strategies have been proposed to overcome the loss of antidepressant efficacy, double-blind controlled studies are needed to ascertain the optimal strategy for this perplexing clinical problem.

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Although long-term antidepressant maintenance therapy in patients with recurrent unipolar depression protects them against future episodes, the protection is not complete. Some people experience a return of depressive symptoms while taking a constant maintenance dose of an antidepressant. In this paper, we review the literature pertaining to this phenomenon, attempt to estimate its frequency, and offer some possible explanations for it. These explanations include noncompliance, the loss of an initial placebo response, the loss of a true drug effect (due either to the drug therapy itself or to other causes), and a change in the pathogenesis of the depressive illness. The latter category is further divided into 2 possibilities: (1) in some people, an increasingly malignant form of depression develops despite treatment or (2) a depression that occurs in someone who is chronically treated with antidepressants is in some fundamental way different from prior episodes.

NATURAL HISTORY OF DEPRESSIVE ILLNESS

Unipolar depressive illness becomes chronic or recurrent in 50% to 80% of patients.[1–4] The risk of recurrence rises dramatically with successive episodes: there is at least a 10-fold greater risk of recurrence for a patient with 1 prior episode of depression than for a similar patient with no such history, and a 14- to 18-fold greater risk for a patient with more than 1 prior episode.[4] Psychotherapy and pharmacotherapy speed recovery from an acute episode and, when continued beyond the acute treatment phase, reduce the likelihood of relapses and recurrences.[2,3,5–11]

Relapse Versus Recurrence

The members of a task force convened by the MacArthur Foundation Research Network on the Psychobiology of Depression[12] suggest that the term *relapse* be used to refer to the return of symptoms during remission, while *recurrence* implies a new episode all together. The length of time defined as "remission" varies by author and study from 4 to 6 months. Because of this lack of consistent definition, and because many of the same considerations and possible explanations apply to both categories, we will consider both relapses and recurrences in this review.

The acute phase of antidepressant treatment lasts until a remission is achieved. Treatment given after that is called *continuation therapy* until the remission period has ended, and *maintenance therapy* thereafter.[3,6,9,11,13,14] Since the focus of this paper is the loss of antidepressant response *after* successful acute treatment, we will emphasize the results of continuation and maintenance studies because they include, by definition, only subjects who had responded in the acute phase of treatment.

The following antidepressants have been studied and proven effective for continuation or maintenance therapy for unipolar depression: fluoxetine,[15] maprotiline,[16] parox-

etine,[17,18] sertraline,[19] citalopram,[20] zimeldine,[21] phenelzine,[10,22] amitriptyline,[23] and imipramine (with and without lithium).[13,24–27] In contrast, monotherapy with lithium[13,27] or, in the elderly, with nortriptyline[22] may be ineffective for long-term maintenance.

It has been proposed that relapse or recurrence of depressive disorder occurring on a constant continuation or maintenance dose of an antidepressant represents the development of tolerance to the drug's antidepressant effect.[28] Observations of this phenomenon, interpreted as antidepressant tolerance, have been published, singly and as series of case reports, concerning tricyclic/heterocyclic antidepressants and monoamine oxidase inhibitors (MAOIs).[29–33] The paucity of side effects of the serotonin selective reuptake inhibitors (SSRIs) makes them particularly valuable agents for long-term maintenance therapy. However, they too seem prone in some patients to lose their efficacy after a period of good response, although only fluoxetine[34–37] and sertraline[36] have yet been cited in the literature in this regard.

Rates of Return of Depression on Maintenance or Continuation Therapy

Although establishing the frequency of loss of antidepressant efficacy was not the original intention of major antidepressant maintenance and continuation treatment studies, we can use their published results to estimate the number of patients who experienced any relapse *or* recurrence of depression during each study period. We have included in Table 1 all of the studies found as a result of computerized (using the MEDLINE database 1966 to June 1997) and manual literature searches that met the following criteria: (1) double-blind and placebo-controlled; (2) randomization after acute treatment phase; (3) duration of treatment greater than 6 months; (4) at least 20 patients total; and (5) results published in English or French. We used *acquired drug tolerance*, *breakthrough depression*, *antidepressant tachyphylaxis*, and *antidepressant tolerance* as search terms as well as individual antidepressant drug names and variations of the terms *antidepressants* and *depression*. In the columns labeled "Relapses and Recurrences," we have reported the percentage of subjects who began the trial who had at least 1 depressive relapse or recurrence.

The range of relapses/recurrences on medication in Table 1 is 9% to 57%. If one looks at trials in which currently accepted maintenance regimens (i.e., full-dose antidepressant treatment and not lithium alone) were used, the range is 9% to 33%. A caveat is in order with respect to Table 1. McGrath et al.[38] noted that despite the return of depressed mood, apathy, and fatigue, the vegetative symptoms of depression generally did not return in patients who had become depressed while on maintenance SSRI treatment. Thus, the use of research tools that emphasize vegetative symptoms, such as the Hamilton Rating Scale for Depression,[39,40] when studying this phenomenon, may underestimate the frequency of relapses and recurrences. Without a better understanding of the pathophysiology of the symptoms of depression, we cannot know if the figures in Table 1 are accurate representations of breakthrough depression rates.

Survey of Massachusetts Psychiatrists

To augment the existing data, we decided to survey 300 members of the Massachusetts Psychiatric Society who identified their specialties as psychopharmacology or affective disorders regarding their response to a hypothetical case in which a patient became depressed while on long-term SSRI antidepressant therapy. The results of the survey indicate that most psychiatrists surveyed have observed breakthrough depressions in their patients on long-term SSRI therapy, but no clear picture of a typical patient emerged. Increasing the dose of the antidepressant is by far the most popular therapeutic strategy to such an occurrence.[41]

Is Return of Depression a Loss of a True Drug Effect?

Quitkin and Stewart[42] conducted a 12-week double-blind follow-up study of imipramine versus phenelzine versus placebo in depressed patients. Their results indicated a high likelihood that most of the relapses that occurred in the active drug groups within those 12 weeks were due to a loss of placebo response. They calculated the number of relapses to be expected from the loss of placebo effect in each group using 2 models: the exclusive model (no placebo responders can have a true drug response) and the independent model (placebo responders are as likely as other patients to have a true drug response). The number of expected relapses was between 12.6% (independent model; 90% confidence limits [CL] = 6.3%, 21.6%) and 16.6% (exclusive model; 90% CL = 8.9%, 26.3%) for the imipramine group, where the observed relapse rate was actually 11.8%, and between 6.4% (independent model; 90% CL = 3.2%, 10.9%) and 12.6% (exclusive model; 90% CL = 6.3%, 21.6%) for the phenelzine group, where the observed relapse rate was actually 8.8%. These calculations suggest that most of the relapses in the active drug groups were attributable to the loss of placebo effect, although this result is more certain for imipramine than for phenelzine. The probability that all of the relapses were due to the loss of placebo response was not calculated.

Other studies by the same authors[43,44] show, similarly, that subjects with "placebo pattern" responses (i.e., abrupt, fluctuating improvement) account for a high proportion of depressive relapses before week 12 of active drug therapy. No similar analyses have been done regarding relapses or recurrences that occur after 12 weeks, as follow-up studies including groups maintained only on

Table 1. Major Antidepressant Maintenance and Continuation Trials*

Trial	Drug and Mean Daily Dosage	Duration of Preinclusion Therapy	Duration of Trial	Number of Patients: Active/ Placebo	Relapses and Recurrences on Medication[a]	Relapses and Recurrences on Placebo[a]	Significant Difference for Depressive Recurrences?	Notes
Coppen et al, 1978[23]	Amitriptyline (150 mg)	6 wk	1 y	16/16	19%[b]	31%	Yes ($p < .01$), when noncompliers excluded	Plasma levels monitored. Remission = 16-item HAM-D ≤ 6; relapse = hospitalization
Prien et al, 1973[26]	Imipramine (dose not reported)	4 mo	2 y	21/13	29%	85%	Yes	Inclusion criteria: 2 episodes requiring hospitalization in past 5 y
Prien et al, 1984[27]	Imipramine (137 mg)	2 mo	2 y	39/34	33%	65%	Yes ($p < .008$)	Inclusion criteria: 1 prior episode in past 36 mo; Remission = RSDM > 7 and GAS < 60
Kupfer et al, 1992[25]	Imipramine (200 mg)	3 y	2 y	11/9	9%	67%	Yes ($p < .005$)	Patients recruited from those in a prior long-term trial (Frank et al, 1990,[24] see below) who had no recurrences during the trial
Frank et al, 1990[24]	Imipramine (208 mg)	20 wk	3 y	28/23	21% at 3 y; 21% at 2 y; 18% at 1 y	78%	Yes ($p < .0001$)	Inclusion criteria: 3 or more episodes; remission = HAM-D ≤ 7 for 3 wk; recurrence = HAM-D ≥ 15 for 1 wk
Prien et al, 1984[27]	Imipramine + lithium (137 mg) (0.66 mEq/L)	2 mo	2 y	38/34	26%	65%	Yes ($p < .008$)	Inclusion criteria: 1 prior episode in past 36 mo; remission = RSDM > 7 and GAS < 60
Montgomery et al, 1988[15]	Fluoxetine (40 mg)	6 mo	1 y	108/112	23%	54%	Yes ($p < .001$)	Inclusion criteria: 2 episodes in past 5 y; remission = HAM-D < 8; recurrence = HAM-D > 18
Prien et al, 1973[26]	Lithium (dose not reported)	4 mo	2 y	22/13	41%	85%	Yes	Inclusion criteria: 2 episodes requiring hospitalization in past 5 y
Prien et al, 1984[27]	Lithium (0.66 mEq/L)	2 mo	2 y	37/34	57%	65%	No	Inclusion criteria: 1 prior episode in past 36 mo; remission = RSDM > 7 and GAS < 60
Rouillon et al, 1989[16]	Maprotiline (75 mg)	2 mo	1 y	385/188	14%	27%	Yes ($p < .0001$)	Inclusion criteria: 1 prior episode in 18 mo (MDD or dysthymia); remission = MADRS < 10; recurrence = MADRS > 27 or > 25 for 8 days
Rouillon et al, 1989[16]	Maprotiline (37.5 mg)	2 mo	1 y	382/186	20%	32%	Yes ($p < .0004$)	Inclusion criteria: 1 prior episode in 18 mo (MDD or dysthymia); remission = MADRS < 10; recurrence = MADRS > 27 or > 25 for 8 days
Montgomery and Dunbar, 1993[18]	Paroxetine (20–30 mg)	2 mo	1 y	68/67	16%	43%	Yes ($p < .01$)	Inclusion criteria: 3 episodes in past 4 y; remission = HAM-D ≤ 8; recurrence = variety of clinical impressions
Doogan and Caillard, 1992[19]	Sertraline (69.3–82.1 mg)	2 mo	8 mo	185/110	13%	46%	Yes ($p < .001$)	Remission = CGI ≥ "much improved"; relapse = CGI ≥ 4

*Abbreviations: HAM-D = Hamilton Rating Scale for Depression; RSDM = Raskin Severity of Depression and Mania Scale; GAS = Global Assessment Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; CGI = Clinical Global Impressions scale.
[a]Reported as percentage of subjects who began the trial who had at least 1 depressive relapse or recurrence.
[b]All with undetectable serum levels.

placebo for longer than 3 months are, for ethical and logistical reasons, rare.

One such study found in our MEDLINE search was a 1-year extension[45] of a 6-week, placebo-controlled study involving 717 subjects, designed to evaluate the short- and long-term efficacy of paroxetine and imipramine.[46,47] The extension included 219 of the original subjects; 25% of the subjects taking placebo who chose to continue into the extension phase relapsed (HAM-D of 8 or less increased to 18 or more) within 1 year. Using the same general methodology as Quitkin and colleagues described above,[42] we estimate that the number of relapses due to the loss of placebo effect would be expected to be between 10.2% (independent model; confidence limits not available) and 12.1% (exclusive model; confidence limits not available) for the imipramine group, where the observed relapse rate was actually 3.8%, and between 11.3% (independent model; confidence limits not available) and 13.1% (exclusive model; confidence limits not available) for the paroxetine group, where the observed relapse rate was actually 15.0%. These figures suggest that for the paroxetine group, though not for the imipramine group, at least a few of the observed relapses were due to a loss of true drug effect.

The results of this trial differed from many antidepressant trials in that the initial placebo response rate was very low—12.9% (31 of the 240 subjects randomly assigned to placebo); the average placebo response rate for antidepressant trials is 35%.[48] The 1-year relapse rate for paroxetine was comparable to that in the 1993 maintenance trial by Montgomery and Dunbar[18] (see Table 1) (15% vs. 16%; $\chi^2 = 0.03$, df = l, NS). The 1-year relapse rate for imipramine, however, was lower than would be expected when compared with the relapse rate at 1 year in, for example, Frank and colleagues' 1990 trial[24] (3.8% vs. 18%; $\chi^2 = 4.60$, df = l, $p < .05$). This discrepancy indicates a difference in the study populations, so the conclusions above are not generalizable to all groups of patients with recurrent depressions.

PUBLISHED REPORTS OF ANTIDEPRESSANT TOLERANCE

A total of 75 cases described as demonstrating tolerance to antidepressants or "breakthrough depression" (relapse or recurrence of depression while on antidepressant maintenance therapy) have appeared in the medical literature (identified by MEDLINE and manual literature searches). The criteria used to diagnose major depressive episodes are not always stated in these reports, and may differ. The cases are summarized below.

Monoamine Oxidase Inhibitors

Mann[31] described 4 patients taking MAOIs (phenelzine and tranylcypromine) whose depressive symptoms returned despite maintenance of full platelet MAO inhibition. Although the time from initiation of therapy to antidepressant response was not given, from the graphical data presented, the time lapse appears to have been approximately 2 weeks. The loss of response occurred between 6 and 11 weeks of treatment (4 to 9 weeks of remission). Donaldson[29] reported apparent tolerance to phenelzine in 3 cases. Two patients had had responses in less than 1 week (the response time of the third was not reported), and they experienced a loss of response in 2 months, 3 months, and 1 year, respectively. Two cases had transient improvements with dose increments. Lieb and Balter[30] described 3 patients who were taking MAOIs and had depressive recurrences after "a few" to 6 months (2 cases) and 1 year (another case). Four other patients were taking MAOIs and had relapses (several relapses each) within 8 to 12 weeks (initial response time not given). Cohen and Baldessarini[28] published 2 cases of apparent antidepressant tolerance to MAOIs (tranylcypromine and phenelzine) after 6 months and 2 years of treatment, respectively. The patient taking tranylcypromine achieved a long-lasting remission after a dose increase.

Tricyclic and Heterocyclic Antidepressants

Zetin et al.[33] described 8 patients taking amoxapine who experienced relief of depressive symptoms after 5 to 9 days of therapy and relapsed after 24 to 83 days (days 45 to 90 of therapy) (except 1 patient who experienced only transient responses). The unusually rapid response of these patients is inconsistent with a true antidepressant effect and may represent either a placebo response or a reduction in anxiety and agitation due to amoxapine's neuroleptic effects.[49] In Cohen and Baldessarini's case series,[28,50] 5 of the 6 patients described were taking tricyclic antidepressants (1 of these patients later relapsed while taking tranylcypromine). Depressive relapses occurred after several weeks to 14 months of effective treatment. The phenomenon arose at least twice in each patient, and the drugs involved were amitriptyline, imipramine, maprotiline, and trazodone. In the case series of Lieb and Balter,[30] 1 patient taking amitriptyline and 1 taking imipramine relapsed after 1 year of euthymia.

Serotonin Selective Reuptake Inhibitors

Fava and colleagues[35] found 26 cases of loss of response to fluoxetine among the 77 patients being maintained on 20 mg of fluoxetine in a double-blind maintenance study. All of these patients had experienced a full remission of symptoms during a 12-week open phase of the trial, and experienced a return of depressive symptoms from 2 to 42 weeks after the end of that phase (14 to 54 weeks of treatment). McGrath et al.[38] described 11 patients (including 1 with a diagnosis of bipolar I, 4 with bipolar II, and 6 with unipolar depression), each of whom had relapsed after being stabilized on an SSRI for at least

1 month, in their trial of bromocriptine potentiation therapy (see below). Rapport and Calabrese[37] reported 1 case of a patient who experienced a response after 4 weeks on 20 mg of fluoxetine and relapsed after 22 weeks of response. Diamond and colleagues[34] reported 2 cases of apparent tolerance to the antidepressant effects of fluoxetine, but no details about these cases have been published. Metz and Shader[51] reported 2 cases of depression that returned after 11 months and 6 months despite continued fluoxetine therapy. Finally, a single case reported by Goldberg et al.[36] was of a patient who responded to fluoxetine, 20 mg/day, for 3 months before experiencing a return of symptoms. The patient entered another remission after beginning sertraline, 100 mg/day, and methylphenidate, 5 mg/day, which again lasted only 3 months. The duration of treatment before the initial response is not noted in the report.

Summary of Case Reports

The cases discussed above appear to have little in common beyond, in most cases, a history of recurrent depression and female gender (21 female, 9 male). Their ages ranged from under 20 to 75 years (mean ± SD = 42 ± 14). Seventeen cases had 1 episode of breakthrough depression, 8 had 2 episodes, 6 had more than 2, and the others were not reported. The duration of successful antidepressant treatment before depression returned averaged 24 weeks, but varied widely (SD = 22 weeks); the median length of remission was 12 weeks. Eight patients were eventually stabilized on a medication regimen, while 13 became resistant to any treatments they could tolerate; the outcome of the other cases was not reported. The relative paucity of reports of relapses occurring during tricyclic antidepressant (TCA) treatment is consistent with the general impression of many clinicians that this problem is greater with MAOIs and SSRIs.

POSSIBLE CAUSES OF REAL OR APPARENT TOLERANCE

The recognized causes of acquired tolerance to medications are outlined in Table 2. Not included is the most obvious and probably most common cause of apparent loss of efficacy: noncompliance.

Pharmacologic Tolerance

The term *acquired drug tolerance* refers to hyporeactivity to some or all of the effects of a drug acquired as a result of exposure to the drug. For instance, tolerance to the side effects of antidepressant medications frequently occurs without loss of their beneficial effects. Tolerance to drugs with CNS effects occurs at many levels, from behavioral to cellular. Cohen and Baldessarini[28] point out that the phenomenon of antidepressant tolerance would only be recognized in patients with chronic or recurrent depression who had at some time been responsive to medication. It is conceivable that the processes that lead to tolerance occur to some extent in everyone who receives antidepressants, but only manifest themselves in this subgroup. *Pharmacokinetic tolerance* is defined as "a change in the concentration of a drug acting at its target site [resulting] from alterations in absorption, distribution, biotransformation, or elimination of the drug as a result of previous exposure to it."[52] *Pharmacodynamic tolerance* involves adaptations at a cellular or subcellular level, which comprise changes in sensitivity and/or number of cellular receptors, second-messenger systems, and ion channels. In the discussion of his case series, Mann[31] suggests that either depressed levels of brain amines or postsynaptic receptor adaptations such as down-regulation of the 5-HT_1 receptor might be responsible for the loss of antidepressant effect he observed with MAOIs. Lieb[53] also favors receptor and postreceptor adaptations as explanations for the cases of "antidepressant tachyphylaxis" he reported.

Pharmacokinetic Changes

A loss of antidepressant response may be caused by a change in serum drug levels, which can occur at a constant dose.[54] Antidepressant pharmacokinetics are altered by various exogenous factors. Absorption from the gastrointestinal tract can be impaired by local disease. Drug-drug interactions, including those with recreational drugs and alcohol, are possible at many levels from absorption to receptor binding[55]; these can result in increased serum levels (e.g., from plasma protein binding site displacement) or decreased serum levels (e.g., from faster metabolism due to the induction of hepatic cytochromal enzymes) of antidepressant medication.

A "therapeutic window" is thought by some authors to exist for nortriptyline,[56–59] but may exist for other antidepressants, including the SSRIs.[56–59] Altamura and colleagues[60] found 60 mg/day of fluoxetine to be no better than placebo in treating depression, while 20 mg/day was efficacious. This finding runs counter to most clinical experience, but the idea is intriguing when applied to fluoxetine in particular, as the half-life of fluoxetine is 1 to 3 days (4 to 6 days after chronic administration[61]) and that of norfluoxetine is 7 to 15 days.[62] Depressive symptoms might return after several months of therapy with fluoxetine if the maintenance plasma level range had just been exceeded. Fichtner et al.[57] and Cain[56] point out that although a generally applicable therapeutic window for fluoxetine or norfluoxetine is unlikely, there may be individuals in whom such a window exists. This phenomenon would be less likely to occur with sertraline, desmethylsertraline (sertraline's main metabolite, which has some weak serotonin uptake inhibition activity), and paroxetine, which have elimination half-lives of 25, 66, and 20 hours, respectively.[62,63]

Table 2: Some Recognized Mechanisms and Treatments of Pharmacologic Tolerance

"Pure" Syndrome	Example	Typical Time Course	Response to Increase in Dose	Response to "Similar" Drug	Response to "Different" Drug	Response to Augmentation	Response to Same Drug After Drug Holiday
Pharmacodynamic tolerance	Euphoriant/analgesic effects of opioids	Days to weeks	Temporary return of response	Works if no cross-tolerance	Works as well as in naive subjects	May work	Restoration of original response
Pharmacokinetic tolerance	Blood levels of ethanol	Weeks	Temporary return of response	Works as well as in naive subjects	Works as well as in naive subjects	May work	Restoration of original response
Increase in disease severity	Systemic lupus erythematosus requiring increasing doses of corticosteroids	Months to years	Return of response	Inadequate response	Inadequate response	May work	Inadequate response
Change in disease pathogenesis	Hypertension due to kidney dysfunction (renal artery stenosis) developing in setting of essential hypertension	Depends on disease	Inadequate response	Inadequate response	May work	May work	Inadequate response
Depleted effector substance	Hypotensive effect of nitric oxide (glutathione depletion)	Days to years	Inadequate response	Inadequate response	May work	May work	Temporary return of response
Serum level too high	Nortriptyline level exceeding antidepressant therapeutic window	Days to weeks	Inadequate response	Works as well as in naive subjects	Works as well as in naive subjects	Inadequate response	Temporary return of response
Detrimental metabolite	?	Depends on drug	Temporary return of response	Works as well as in naive subjects	Works as well as in naive subjects	Inadequate response	Temporary return of response

There are reports of loss of antidepressant efficacy despite constant platelet MAO inhibition by phenelzine and tranylcypromine[31] and with adequate serum imipramine levels,[28] so peripheral pharmacokinetic changes do not explain all documented cases of breakthrough depression.

A real or apparent depressive relapse or recurrence could occur because of the accumulation of some detrimental metabolite. High plasma levels of norfluoxetine and of norzimeldine[64] are significantly negatively correlated with antidepressant response to the parent drugs. Although a correlation does not necessarily imply causality, there is some evidence that 10-hydroxynortriptyline may block the antidepressant effects of nortriptyline, at least in the elderly.[65] In the case of fluoxetine, as described above, norfluoxetine can build up over months, and Cain has suggested that the serotonergic overstimulation it can produce may mimic the return of depressive symptoms.[56] High levels of a detrimental metabolite could occur because of an increase in the half-life of the metabolite. Alternatively, an increase in the rate of parent drug metabolism could decrease the ratio of parent drug to metabolite. Release of an antidepressant-derived product from body depots could perhaps explain the 2 cases of recurrent depression associated with weight loss noted by Kraft.[66]

Unrecognized Rapid Cycling

Antidepressant-induced rapid mood cycling in unrecognized bipolar disorder can mimic recurrent depression if the mood elevations are mild and masquerade as euthymic remissions.[32,50] Hurowitz and Liebowitz[67] described 6 such patients, all of whom required the cessation of antidepressant therapy for recovery. Zetin and colleagues[33] suggest rapid cycling as one explanation for the breakthrough depressions in their case series.

Prophylactic Inefficacy

Although many antidepressants have been shown to be effective for maintenance therapy (see above), there are exceptions. Nortriptyline, for example, is effective acutely but may not be sufficient for prophylaxis of recurrent depression.[9,22] Even if a drug has proven effective for maintenance in a clinical trial, those patients for whom it is effective acutely may not be the same patients for whom it is effective for prophylaxis against relapse or recurrence. Similarly, if the different phases of treatment have different pharmacodynamic mechanisms, then it is possible that maintenance therapy in some individuals may require higher or lower doses than acute therapy.

Change in Disease Due to Drug Therapy

Another possibility is that treatment with antidepressant drugs produces a fundamental change in the pathophysiology of depression in individual patients. It has been suggested that tricyclic antidepressants may shorten the time between recurrences in unipolar depressive illness as well as in bipolar disorder.[6] By analogy with

rapid-cycling bipolar disorder, frequently recurrent unipolar depression (possibly drug-induced) may respond differently to pharmacologic intervention than the earlier stages of the disease.[32,68] Donaldson[29] suggests that apparent antidepressant tolerance to MAOIs is due to "long-term changes in neurotransmitter systems," analogous to the changes by which antipsychotic drugs produce tardive dyskinesia. McGrath and colleagues[38] postulate that, after a period of treatment with an antidepressant, decreased dopaminergic tone due to direct or indirect antidopaminergic effects of the drug can cause a return of depressive symptoms.

The long-term use of antidepressants could cause the depletion of 1 or more effector or precursor substances. As a hypothetical example, serotonin reuptake inhibition, by increasing extrasynaptic serotonin levels, could cause a depletion of tryptophan in the brain by down-regulating the mechanism by which tryptophan is transported across the blood-brain barrier.

Change in Disease Independent of Drug Therapy

"Breakthrough" depression might be analogous to any other disease (ischemic heart disease, for example) where the primary pathophysiology continues to worsen. In this case, the manifestations of the disease should respond to increasing doses of medication until adverse effects prevent further increases. This probably fits a subgroup of those who become depressed while taking medication. But what about those for whom dosage increments do not produce another remission? In these cases, the maintenance antidepressant medication could have ceased working because the disease had undergone a maturation process,[37] resulting in increased severity and/or decreased stability.[68,69] Recurrent unipolar depressions could evolve in such a way that pharmacologic therapy that was beneficial in early episodes is less effective in later ones.

In a similar vein, different episodes of major depression in the same individual may respond to different therapies, as Remillard and colleagues' 1994 retrospective study suggests[70] (although Kupfer and colleagues' 1989 prospective trial[71] showed no such difference). If this were a major factor in antidepressant "tolerance," one would expect a later return of symptoms than is often observed (i.e., recurrences rather than relapses), but a change in the pathophysiology of the disease may account for some cases.

STRATEGIES FOR ADDRESSING A LOSS OF ANTIDEPRESSANT EFFICACY

Several strategies have been proposed to overcome tolerance to antidepressants. Adjusting the drug dosage (obtaining serum levels where appropriate), augmentation with various medications, the use of drug holidays, and switching to a different antidepressant have all been reported to work in some patients, but no double-blind, controlled studies have been done, although 2 open-label trials have recently appeared.[35,38]

Increase Dose

Raising the dose of a drug that has stopped working is a natural response to the development of tolerance. In the case reports and series summarized above, dosage increments of MAOIs and TCAs typically produced incomplete or transient improvements, if any. This may be different in the case of fluoxetine, at least: Fava and colleagues[35] observed that raising the dose of fluoxetine from 20 mg to 40 mg produced full remissions in 12 (67%) of 18 patients who had had depressive relapses while on fluoxetine maintenance. (Two of the 12 later relapsed again, after 4 months and 1 year, but responded again to dose increments, while 1 of the 12 relapsed and subsequently did not respond fully to any pharmacologic treatment.)

Decrease Dose

If we accept the hypothesis that antidepressant response can be lost by exceeding the therapeutic dose range (either by leaving the therapeutic window or by serotonergic overstimulation), then decreasing the dose is an alternative approach, though poorly supported in the literature. This strategy may be efficacious in therapy with fluoxetine when there has never been a sustained satisfactory response to the drug.[56] There are a total of 7 published case reports of restoration of initial efficacy when the dosage of an SSRI was lowered.[56,57,59]

Dopaminergic Agonists

Dopamine is important in the pathophysiology of mood disorders.[72] Preclinical experimental evidence indicates that decreased dopaminergic transmission, especially in the mesocorticolimbic pathway, causes decreased motivation and anhedonia. The dopaminergic agonist bromocriptine has been shown to have antidepressant activity.[73] Dopaminergic transmission could be decreased either secondary to antidepressant drug therapy or as part of the natural course of the disease, and thus cause breakthrough depressive symptoms. McGrath and colleagues[38] theorized that depletion of dopamine stores caused the return of depressive symptoms in some of their patients taking SSRIs and reasoned that postsynaptic dopamine receptor stimulation by direct dopamine agonists would overcome such a depletion. They found augmentation of SSRIs with low doses of bromocriptine to be of sustained (> 2 months) benefit in 6 of 12 patients who had had a remission of depression lasting at least 1 month in response to SSRI treatment, but who had then relapsed. Pemoline, a psychostimulant with dopaminergic properties, was also reported to be effective in treating depres-

sive relapses in 2 patients who had been euthymic while taking fluoxetine for 6 months and 11 months.[51]

Other Strategies

There are a number of strategies that have not been reported in the literature, or have appeared in case reports only, but either are in use clinically or have some theoretical plausibility; we will discuss a few of these in the next paragraphs.

Augmentation. Strategies that have proven useful in treatment-resistant depression are a natural place to turn. Our survey of Massachusetts psychiatrists[41] indicates that some of these strategies are already in clinical use for treating breakthrough depressions. These include augmentation with lithium carbonate, thyroid hormones, other antidepressants, and anticonvulsants. Amphetamine,[74–76] methylphenidate,[76–78] and pemoline[51] are used as stimulants to potentiate antidepressant treatment; this rationale overlaps with their use as dopaminergic agonists (see above). Blockade of 5-HT_{1A} receptors (e.g., with pindolol) to prevent the negative feedback of increased somatodendritic serotonin is a strategy that has good theoretical and, recently, clinical support,[79–81] but has not yet been used for acquired antidepressant tolerance.

Anticonvulsants. Adjunctive anticonvulsant treatment of unipolar depression is a strategy to be explored on the basis of published reports regarding sodium valproate[82,83] and by analogy with "advanced" bipolar disorder.[68]

Lithium and thyroid hormones. Augmentation of any antidepressant with lithium is a common strategy for converting antidepressant nonresponders or partial responders to full responders.[84–86] Thyroid hormone supplements are also used to potentiate antidepressants; triiodothyronine may be as effective as lithium in augmenting tricyclics in tricyclic-resistant depression.[85]

Tricyclic and other antidepressants. Whether through complementary actions at CNS sites or simply by mutually increasing serum levels, combinations of antidepressants of different classes are often used to combat treatment-resistant depression.[82,86–90]

Drug holiday. Classical drug tolerance (e.g., to opioids) can be overcome by temporarily ceasing use of the drug to allow a return to preexposure homeostasis. Regular drug holidays have been explored as a way to maximize the benefits of dopaminergic agents in Parkinson's disease. This strategy is sometimes used, with a hiatus of a few weeks, in cases of apparent tolerance to TCAs. The appropriate length of an antidepressant drug holiday is unknown, as we do not know what kind of adaptive phenomenon must be reversed.

Change to a different drug. If the loss of response is due to pharmacodynamic tolerance or to a change in pathogenesis, switching to an antidepressant with a different mechanism of action would be the best strategy. The selection of a sufficiently "different" drug must by necessity be based on pharmacodynamic data (i.e., receptor affinities determined in vitro), which may or may not be clinically relevant.[91]

Change to another, similar drug. If the loss of response is due to a pharmacokinetic change, using a drug that approximates the end-organ effects of the originally effective one, but is eliminated or partitioned differently, would replicate the initial antidepressant effect of the first drug.

CONCLUSION

The return of depressive symptoms during maintenance antidepressant treatment is a perplexing clinical problem typically occurring in 9% to 33% of patients in published trials. When assessing loss of antidepressant efficacy in a particular patient, the physician is faced with the difficult question as to whether this is loss of a true medication response or loss of a placebo effect.

Although little is known regarding the mechanism of loss of antidepressant efficacy, possible mechanisms include pharmacologic tolerance (either pharmacodynamic or pharmacokinetic), increase in disease severity, a change in disease pathogenesis (either due to or independent of antidepressant therapy), the accumulation of a detrimental metabolite, unrecognized rapid cycling, or simply prophylactic inefficacy. Although there are no double-blind, controlled studies that point to a particular strategy to employ when loss of antidepressant efficacy occurs, possible strategies include changing the dose of the antidepressant, adding an adjunctive agent, stopping and then restarting the antidepressant, or changing to a different medication. We recommend tailoring therapy based on individual circumstances, but in general, raising the antidepressant dose, adding an adjunctive agent such as bromocriptine or pindolol, and changing the medication would seem to be the most sensible initial steps in addressing breakthrough depression.

Further studies are needed to ascertain the rate of loss of antidepressant efficacy during maintenance treatment, whether it occurs more often with a particular type of antidepressant, and whether there are particular patients who are more at risk for the occurrence of loss of efficacy. Finally, further study of a large group of patients experiencing loss of antidepressant efficacy with systematically investigated strategies is needed. These studies would enroll patients with well-documented breakthrough depressions and randomly assign them in a double-blind fashion to the various interventions discussed above, with a control group remaining on the same dose of medication. Ideally, measurements of initial and subsequent serum levels of the relevant drug would be done.

Drug names: amitriptyline (Elavil and others), amoxapine (Asendin), bromocriptine (Parlodel), fluoxetine (Prozac), imipramine (Tofranil and others), maprotiline (Ludiomil), methylphenidate (Ritalin), nortriptyline (Pamelor and others), paroxetine (Paxil), pemoline (Cylert),

phenelzine (Nardil), pindolol (Visken), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), triiodothyronine (Cytomel, Triostat).

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