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Knowing when — if ever — is the right time to discontinue antidepression medication is a subject of debate. This article will review the published data on maintenance treatment of depression and the long-term use of antidepressants. Specifically, it will address what currently is known regarding who is an appropriate candidate for long-term therapy; the long-term safety and efficacy data on antidepressants; whether antidepressants may be depressogenic or neuroprotective; and how and when to safely and effectively discontinue the medication. The article describes a patient-physician collaborative approach to medication discontinuation in which prescribing physicians educate their patients about the available data on risk and benefits with long-term antidepressant therapy and together make a decision on when, how, or if medications can be discontinued.

— The Editor

When Is It Safe to Stop Antidepressants? An Evidence-Based, Patient-Physician Collaborative Approach To Medication Discontinuation

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Introduction

Medication therapy has become a mainstay in the management of depression. Physicians across a variety of medical specialties increasingly are becoming familiar with the current medication options for treatment of depression. The dramatic rise in the use of antidepressants is fueled in part by the development of safe, effective, and easy to prescribe pharmacotherapies; growing recognition by patients and physicians of depression and treatment options; and pharmaceutical company promotion of medication to doctors and patients.[1]

Many physicians' primary source of education in the area of depression and antidepressant therapy comes from pharmaceutical representatives or sponsored programs.[2] The vast majority of this education centers on identifying disease states for which antidepressant therapy is appropriate and initiating therapy. We have good, well-controlled data on the efficacy of antidepressants in short-term depression trials typically lasting 6-8 weeks.[3] There are longer maintenance studies demonstrating that antidepressants work long term. However, these studies also show high rates of relapse when patients discontinue antidepressant therapy after extended treatment. There are expert consensus guidelines for how long to treat patients for depression, but they are limited in their evidence base and difficult to generalize for many different patient types.[4] The clinician often has a difficult time instructing patients on when they may be able to stop antidepressant therapy and how to do so.

Depression as a Chronic Illness

Major depressive disorder has a lifetime risk of 10-25% in women and 5-12% in men, based on community samples.[5] The point prevalence rates are reported to be 5-9% in women, and 2-3% in men.[5] The description of depression as a chronic disorder characterized by high relapse rates is well documented in the literature.[5] Estimates of the risk of a recurrence of depression in someone with a single episode of depression is 50-60%.[6] Individuals with two episodes of depression have a

70% of a third.[6] Those with three episodes of depression have a 90% chance of a fourth.[6] The course of recurrent major depressive disorder is variable and unpredictable. Some patients may go prolonged periods without a recurrence, while others have more frequent or clustered episodes. There does seem to be a trend to shorter episodes of remission as the person ages.[7] The National Institute of Mental Health/National Institute of Health (NIMH/NIH) Consensus Conference reports consistent findings that 50-85% of patients with a major depressive episode will have one subsequent episode in their lifetimes. Fifty percent will have a recurrence within two years of the initial episode.[8]

Keller et al have described the chronic nature of depression by following 431 patients treated in a community setting for five years.[9] Fifty percent of subjects recovered within six months, but after that, the rate of recovery declined dramatically. Twelve percent did not recover at all in the five years of observation. The more severely ill patients had lower rates of recovery. There was an 18-fold greater likelihood of recovery in subjects with moderately severe symptoms, dysthymia, or minor depression than those with full criteria for a major depressive episode and more severe symptomatology. The subjects who did not recover as well had symptoms more consistent with co-morbid dysthymia with low grade, persistent, interepisode symptoms than major depression with more complete interepisode recoveries. The rate of recovery decreased from 15% in the first three months to 1-2% per month in the third, fourth, and fifth years.[9]

Diagnostic and Statistical Manual (4th ed.), Text Revision (DSM-IV-TR) gives longitudinal specifiers of "full" or "without full" interepisode recovery.[6] One-third of patients with major depression have partial or no remission, which will reduce the chance of achieving a full interepisode recovery.[10] These patients may have chronic depression defined as episodes of depression lasting two or more years, major depression with dysthymia, or dysthymia alone.[11] Additionally, some patients may have a dysthymic disorder prior to the episode, which also may affect the chance for interepisode recovery and require a longer course of treatment. Dysthymia has a lifetime prevalence of 6% and a point prevalence of 3%. There is only a 10% chance of dysthymia spontaneously remitting. Other depression qualifiers in DSM-IV-TR include atypical, melancholic, seasonal, psychotic, and catatonic.[6]

Establishing Some Working Definitions

Any discussion of long-term treatment of depression must include a review and agreement of the definitions of the following terms: response, remission, relapse, and recurrence. There is inconsistency in the use of these terms in multiple studies and review articles on the management of depression. This can make interpretation and relevancy of the results of such studies confusing.[12] Most experts agree with Frank et al's description of these concepts.[13] Response generally implies at least 50% improvement of symptoms. Examples of rating scales that measure these symptoms are the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS). *(See Tables 1 and 2.)* Frank et al defines full remission as complete resolution of symptoms and return to premorbid level of functioning. Relapse is a return of those symptoms from the most recent episode of depression. Relapse may occur when there has been partial or full remission from that episode. Recurrence is a new episode of depression that has occurred after a prolonged period of remission.

The other important concept is that of acute, continuation, and maintenance phases of treatment. Kupfer developed a schematic representation of the course of depression and these different phases of treatment.[14] *(See Figure.)* There are fairly

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Table 1. Hamilton Rating Scale for Depression

Patient's Name _____ Date of Assessment _____

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression. **For each item, write the correct number on the line next to the item. (Only one response per item.)**

___ **1. Depressed mood** (Sadness, hopeless, helpless, worthless)
- 0 = Absent
- 1 = These feeling states indicated only on questioning.
- 2 = These feeling states spontaneously reported verbally.
- 3 = Communicates feeling states non-verbally — i.e., through facial expression, posture, voice, and tendency to weep.
- 4 = Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication.

___ **2. Feelings of guilt**
- 0 = Absent
- 1 = Self-reproach, feels he has let people down
- 2 = Ideas of guilt or rumination over past errors or sinful deeds
- 3 = Present illness is a punishment. Delusions of guilt.
- 4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

___ **3. Suicide**
- 0 = Absent
- 1 = Feels life is not worth living
- 2 = Wishes he were dead or any thoughts of possible death to self
- 3 = Suicidal ideas or gestures
- 4 = Attempts at suicide (any serious attempt rates 4)

___ **4. Insomnia—early**
- 0 = No difficulty falling asleep
- 1 = Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
- 2 = Complains of nightly difficulty falling asleep

___ **5. Insomnia—middle**
- 0 = No difficulty
- 1 = Patient complains of being restless and disturbed during the night
- 2 = Waking during the night—any getting out of bed rates 2 (except for purposes of voiding).

___ **6. Insomnia—late**
- 0 = No difficulty
- 1 = Waking in early hours of the morning, but goes back to sleep
- 2 = Unable to fall asleep again if he gets out of bed

___ **7. Work and activities**
- 0 = No difficulty
- 1 = Thoughts and feelings of incapacity, fatigue, or weakness related to activities (work or hobbies)
- 2 = Loss of interest in activity (hobbies or work) — either directly reported by patient, or indirect in listlessness, indecision, and vacillation (feels he has to push self to work or activities)
- 3 = Decrease in actual time spent in activities, or decrease in productivity
- 4 = Stopped working because of present illness

___ **8. Retardation: Psychomotor** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
- 0 = Normal speech and thought
- 1 = Slight retardation at interview
- 2 = Obvious retardation at interview
- 3 = Interview diffcult
- 4 = Complete stupor

___ **9. Agitation**
- 0 = Absent
- 1 = Fidgetiness
- 2 = Playing with hands, hair, etc.
- 3 = Moving about, can't sit still
- 4 = Hand-wringing, nail-biting, hair-pulling, biting of lips

___ **10. Anxiety** (psychological)
- 0 = No difficulty
- 1 = Subjective tension and irritability
- 2 = Worry about minor matters
- 3 = Apprehensive attitude apparent in face or speech
- 4 = Fears expressed without questioning

___ **11. Anxiety (somatic)**: Concomitants of anxiety (butterflies, tremor, etc.)
- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Incapacitating

___ **12. Somatic symptoms** (gastrointestinal)
- 0 = None
- 1 = Loss of appetite but eating without encouragement from others.
- 2 = Difficulty eating without urging from others. Reduction of appetite.

___ **13. Somatic symptoms** (general)
- 0 = None
- 1 = Heaviness in limbs, back, or head. Backaches, headache, muscle ache.
- 2 = Any clear-cut symptom rates 2.

___ **14. Genital symptoms** (Loss of libido; menstrual disturbances)
- 0 = Absent
- 1 = Mild
- 2 = Severe

___ **15. Hypochondriasis**
- 0 = Not present
- 1 = Self-absorption (bodily)
- 2 = Preoccupation with health
- 3. Frequent complaints, requests for help
- 4. Hypochondriacal delusions

___ **16. Loss of weight**
- 0 = None
- 1 = Weight loss associated with present illness
- 2 = Definite (according to patient) weight loss
- 3 = Not assessed

___ **17. Insight**
- 0 = Acknowledges being depressed and ill
- 1 = Acknowledges illness but attributes to bad food, climate, work, etc.
- 2 = Denies being ill

___ **18. Diurnal variation**
- A. If present, note if worse in A.M., worse in P.M., or no variation
- B. If present, mark severity of variation: 0 = none; 1 = mild; 2 = severe

___ **19. Depersonalization and derealization** (feelings of unreality, etc.)
- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3. Severe
- 4. Incapacitation

___ **20. Paranoid symptoms**
- 0 = None
- 1 = Suspicious
- 2. Ideas of reference
- 3. Delusions of reference

___ **21. Obsessional and compulsive symptoms**
- 0 = Absent
- 1 = Mild
- 2 = Severe

____ **Total Score**

Adapted from Hedlung S, Vieweg V. The Hamilton rating scale for depression. *J Operat Psychiatry* 1979;10:149-165.

Table 2. Montgomery-Asberg Depression Rating Scale

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. The items should be rated with regard to how the patient has done over the past week.

1. Apparent sadness — Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

___ **0** = No sadness
1
2 = Looks dispirited but does brighten up without difficulty
3
4 = Appears sad and unhappy most of the time
5
6 = Looks miserable all the time. Extremely despondent.

2. Reported sadness — Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

___ **0** = Occasional sadness in keeping with the circumstances.
1
2 = Sad or low but brightens up without difficulty.
3
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 = Continuous or unvarying sadness, misery or despondency.

3. Inner tension — Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

___ **0** = Placid. Only fleeting inner tension.
1
2 = Occasional feelings of edginess and ill-defined discomfort.
3
4 = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 = Unrelenting dread or anguish. Overwhelming panic.

4. Reduced sleep — Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

___ **0** = Sleeps as usual.
1
2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
3
4 = Sleep reduced or broken by at least two hours.
5
6 = Fewer than two or three hours sleep.

5. Reduced appetite — Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

___ **0** = Normal or increased appetite.
1
2 = Slightly reduced appetite.
3
4 = No appetite. Food is tasteless.
5
6 = Needs persuasion to eat at all.

6. Concentration difficulties — Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

___ **0** = No difficulties in concentrating.
1
2 = Occasional difficulties in collecting one's thoughts.
3
4 = Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 = Unable to read or converse without great difficulty.

7. Lassitude —Representing a difficulty getting started or slowness initiating and performing everyday activities.

___ **0** = Hardly any difficulties in getting started. No sluggishness.
1
2 = Difficulties in starting activities.
3
4 = Difficulties in starting simple routine activities, which are carried out with effort.
5
6 = Complete lassitude. Unable to do anything without help.

8. Inability to feel — Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

___ **0** = Normal interest in the surroundings and in other people.
1
2 = Reduced ability to enjoy usual interests.
3
4 = Loss of interest in surroundings. Loss of feelings for friends, acquaintances.
5
6 = The experience of being emotionally paralyzed, inability to feel emotions, and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts — Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin.

___ **0** = No pessimistic thoughts.
1
2 = Fluctuating ideas of failure, self-reproach or self-depreciation.
3
4 = Persistent self-accusations. Increasingly pessimistic about the future.
5
6 = Delusions of ruin, remorse, and unredeemable sin.

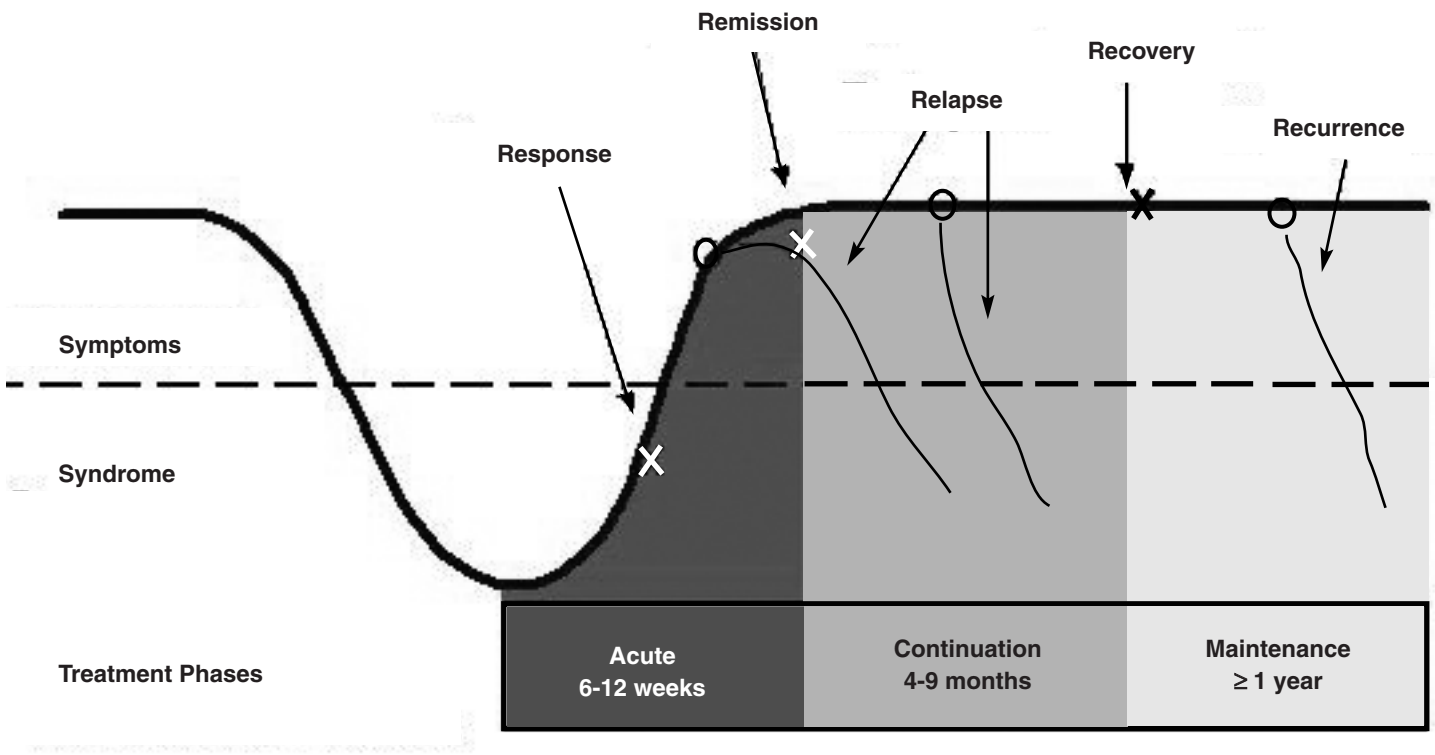
10. Suicidal thoughts — Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

___ **0** = Enjoys life or takes it as it comes.
1
2 = Weary of life. Only fleeting suicidal thoughts.
3
4 = Patient believes he/she is probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

____ **Total Score**

Adapted from Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-389.

Figure. Outcome of Depression Treatment — The Five Rs



Used with permission from: Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry* 1991;52:28-34.

consistent data on how to manage an acute episode of depression and achieve symptom relief with at least a response to therapy, if not full remission. Furthermore, short-term studies with abrupt medication discontinuation after 6-8 weeks of treatment clearly have demonstrated the need for the continuation phase to prevent relapse. We will focus primarily on the maintenance phase, in which treatment is used to prevent a recurrence of depression. This is a more difficult area to research and obtain consistent findings that will generate guidelines useful in clinical care.

Conventional Treatment Guidelines

Current conventional treatment standards for depression are based on evidence that depression is a chronic illness for many patients. The goal of treatment is eliminating all symptoms of depression, restoring social and occupational functioning, and reducing the risk of relapse and recurrence.[15] Acute treatments may range from 6-12 weeks, until symptom relief is achieved. Interventions in this phase may include a change in initial therapy, more aggressive dosing, or augmentation with additional medications. The acute phase should continue until there is a full response to therapy. The continuation phase is generally 16-20 weeks following remission in the acute phase. The same dose of medication used in the acute phase is recommended for the continuation phase. Specific forms of psychotherapy may be useful in this phase to prevent relapse. American Psychiatric Association treatment recommendations identifies patients who are at high risk for recurrence and offers guidelines for continuing pharmacotherapy in a patient. *(See Tables 3 and 4.)* This consensus of experts does not specifically provide time frames for continuing patients in the maintenance phase. They do recommend using the same medication doses in the maintenance phase that were successful in the acute and continuation phases.[16]

Methodological Problems in Maintenance Studies

There clearly is a significant dearth of well-controlled studies in maintenance therapy of depression.[7] Most current research is funded through pharmaceutical sponsorship and typically focuses on short-term efficacy of available or investigational treatments. Pharmaceutical companies may be more likely to fund short-term research due to the high cost of long-term studies or a fiduciary need to get new therapies to market as quickly as possible. There are considerable logistical challenges, in addition to cost, that may complicate researchers' efforts to conduct such studies. These may include difficulties

Table 3. Considerations in the Decision to Use Maintenance Treatment

Factor	Component
Risk of recurrence	Number of prior episodes; presence of comorbid conditions; residual symptoms between episodes
Severity of episodes	Suicidality; psychotic features; severe functional impairments
Side effects experienced with continuous treatment	
Patient preferences	

Adapted from American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision, Washington D.C: American Psychiatric Association; 2000.

in controlling for such factors as spontaneous remission and relapse, psychiatric co-morbidity, medication compliance, and psychosocial stresses.[17]

Researchers also must consider how subtypes of depression (e.g., concomitant dysthymia, chronic relapsing depression, atypical, melancholic, or single-episode depression) may respond differently to certain therapies.[17] Antidepressants are effective in short-term treatment of all these subtypes of depression. There may be some preferential response of certain antidepressant to certain types of depression, such as monoamine oxidase inhibitors for atypical depression.[18] The majority of patients with mood and anxiety disorders, however, are treated in a primary care setting and these physicians generally do not distinguish between these different types of depression.[19,20] Physicians often choose an antidepressant based on side effects or specific target symptoms. However, long-term treatments may differ in dosing requirements, length of therapy, or overall outcome for these different forms of depression. Long-term maintenance studies that differentiate between these different subtypes of depression to support this position remain an unmet need in psychiatric research.

Additionally, most patients for long-term studies are recruited from psychiatric settings, which are not representative of the population at large, or of those treated by non-psychiatric physicians. This makes it difficult to generalize the findings of these long-term studies. Van Weel-Baumgarten et al reviewed outcome studies in community and primary care settings.[21] They found a 30-40% recurrence rate of depression. However, the authors did not control for the different types of treatment patients may have received during this observation period. They found that young adults and elderly patients were at higher risk for recurring illness. They did not include recurrence rates for those suffering from residual or minor depression. They concluded that recurrence rates might not be as high in community and family practice as in psychiatric settings, where rates have been reported as high as 90%.[21]

Table 4. Risk Factors for Recurrence of Major Depressive Disorder

- Prior history of multiple episodes of major depressive disorder
- Persistence of dysthymic symptoms after recovery from an episode of major depressive disorder
- Presence of an additional, nonaffective psychiatric diagnosis
- Presence of a chronic, general medical disorder

Adapted from American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision, Washington D.C: American Psychiatric Association; 2000.

Defining Maintenance vs. Prophylaxis; Reviewing Study Design

There are two types of studies for assessing antidepressant use in prevention of relapse and recurrence—continuation and crossover design. Crossover design involves treatment to remission, brief maintenance therapy, and then randomization to medication continuation or placebo.[22] These studies often last for up to one year. Continuation studies begin with random assignment to either active medication or placebo in the acute phase. Responders to either placebo or active medication stay on the therapy they responded to and are followed up to one year. Janicak, in a review of study design, suggests that continuation phase studies are a useful design to rule out drug withdrawal affecting relapse and for maintaining the blind during this phase of treatment. He further points out that there are no medications where both types of studies have been performed. Prophylaxis studies are described as those geared to prevention of a new episode as opposed to maintenance therapy to prevent a relapse. These are even further limited in number and scientific rigorousness.[22]

Predictors and Rates of Relapse and Recurrence

There are a few studies looking prospectively at the risk factors for relapse and patterns of recurrence following a major depressive episode. In one single-site study following 72 non-psychotic, unipolar depressed patients for 20-108 months (mean = 66 months), three out of four of those who had recovered from an episode relapsed within five years. A history of three or more episodes was the only predicator of relapse within the first three years. Recurrence by five years was predicted by number of prior episodes, underlying minor depressive episodes, and family history. The risk of relapse was highest during the first few months after the episode and progressively diminished over time. In other words, the longer you stay well, the less likely you are to relapse. Patients who prophylactically were treated with antidepressants had fewer recurrences over a five-year period. The severity of subsequent episodes, though, was the same in treated and untreated groups (each had worsening depression with subsequent episodes).[23]

Hirschfeld reviewed a number of available studies on long-term treatment of depression and identified multiple risk factors for recurrence.[7] *(See Table 5.)* He also concluded that

recurrence rates are lower on active medication therapy (10-30%) vs. placebo (60-90%). He also supported the belief that the doses used to achieve remission are the doses needed to maintain remission in the long term. He felt that the relapse rates reported may be an underepresentation, since most studies exclude chronically depressed patients.

Fava reports that residual symptoms are one of the strongest risk factors for relapse.[24]

Melfi et al conducted a study to assess the effect of treatment adherence on relapse and recurrence of depression.[25] He tracked 4052 adult patients in a Medicaid database and followed them up to two years. One-quarter of patients had relapse/recurrence, but the authors felt that number may have been even higher because many patients probably did not seek care for their subsequent episodes. There were several predictors of relapse, including early discontinuation of antidepressant therapy, co-morbid substance abuse, benzodiazepine use, prior hospitalization, and Caucasian vs. African American population.

Also of note is that fewer than 30% received antidepressants at doses minimally consistent with treatment guidelines. Premature discontinuation of antidepressants was associated with a 77% increase in risk of relapse/recurrence.[25] The assumption is that continuous use of a single antidepressant reduces risk of recurrence. However, those that use one medication reliably may be more compliant patients or may have a biological substrate that allows them good response to such therapy. This possible selection bias may negate the conclusion from this study—that reduced risk of recurrence is a direct result of medication compliance.

There are a few studies looking at other subtypes of depression such as dysthymia or subsyndromal depressions. There is growing evidence that these may not be distinct diseases states, each with unique clinical qualities and biological etiologies, but more likely they are part of a continuum with different clinical presentations at different times. Judd et al completed a 12-year prospective study of 431 patients with depression.[26] Patients presented over the course of time with different severity levels and prolonged periods of dysthymia or subsyndromal depressive symptoms. Interepisode dysthymia was the most common symptomatic expression of major depressive illness. Patients were in a dysthymic state 27% of the time vs. 15% in a major depressive episode.[26] Haykal followed 42 patients with a diagnosis of dysthymia for a mean of five years. He found that 75% were responsive to long-term pharmacotherapy, with a return to a high level of functioning for much of that time.[27]

We were able to locate a number of studies showing effectiveness of antidepressants in preventing relapse and recurrence. These studies clearly document the need for continuation therapy, but give little information on specifically how long to continue medication therapy.[10] An analysis of maintenance studies with tricyclic antidepressants showed that in 18 studies with a combined 2225 patients, the risk of relapse was 26% on active medication vs. 50% on placebo.[22] Table 6 summarizes relapse prevention studies on selective serotonin reuptake inhibitors (SSRIs).[22]

Table 5. Risk Factors for Recurrence

- History of frequent or multiple episodes
- Double depression (major depression plus dysthymia)
- Onset after 60 years of age
- Long duration of illness
- Severe index episode
- Seasonal pattern
- Family history of depression
- Poor symptom control during continuation phase
- Co-morbid anxiety or substance abuse

Adapted from Hirschfield RMA. Antidepressants in long-term therapy: A review of tricyclic antidepressants and selective serotonin reuptake inhibitors. *Acta Psychiatr Scand* 2000:101:35-38.

A long-term study comparing relapse prevention of venlafaxine, imipramine, trazodone, and placebo showed relapse rates respectively of 18%, 31%, 29%, and 32%.[28] This study, unlike the SSRI studies shown in Table 6, was not a crossover design. Janicak points out that the findings were less robust in this study than in those comparing relapse rates of the SSRIs with placebo. This may be a result of the study design. In the SSRI studies, many patients had responded to active medication in the acute phase and then were randomized to placebo after a period of stabilization. In the venlafaxine study, some patients were placed on placebo in the acute phase, responded to placebo, and then were left on placebo in the maintenance phase. Therefore, patients switched to placebo in the maintenance phase in the SSRI studies may have required active drug to respond, but their placebo counterparts in the venlafaxine studies did not.

This difference in study design brings up the question of whether relapse is due to withdrawal from active drug or to progression of the illness. A similar finding was noticed in a one-year maintenance study comparing nefazadone, imipramine, and placebo. Relapse rates were 10%, 7%, and 22%, respectively.[29] Again, fewer patients on placebo relapsed vs. those in the SSRI studies, a finding that was attributed to the lack of crossover design.

In one of the largest studies looking at prophylaxis for depression recurrence, imipramine with interpersonal psychotherapy was shown to be more effective than either placebo or interpersonal psychotherapy alone.[30] Fifty patients were on imipramine alone or in combination with interpersonal psychotherapy, while 75 were on placebo with or without interpersonal psychotherapy. However, the generalizability of this study is questionable because the study population was at high risk of recurrence. Another study that evaluated prophylactic treatment for relapse of depression followed patients who were responsive to amitriptyline or imipramine acutely, and then randomly assigned them to stay on the antidepressant or receive placebo. Approximately 50% of those patients

Table 6. Prevention of Relapse — Design to Continue on SSRI or Change to Placebo

MEDICATION	DURATION (WEEKS)	DRUG RELAPSE (%)	PLACEBO RELAPSE (%)	P VALUE
Fluoxetine	52	26	57	< 0.01
Paroxetine	52	16	43	< 0.01
Sertraline	44	13	46	< 0.001

Adapted from Janicak PG, Davis JM, Preskorn SH, et al. *Principals and Practice of Psychopharmacology*. Baltimore: Williams and Wilkins:1997.

on placebo relapsed vs. 22% on tricyclics after 15 months.[31] In fact, most studies examining medication therapies in the maintenance phase typically have focused on patients at high risk for relapse.[32,33]

A Contrary View of the Protective Effect of Long-Term Use of Antidepressants

Many review articles on the management of depression encourage long-term maintenance therapy to prevent relapses. However, there have been some recent challenges to that conventional wisdom that merit some consideration. There is a small body of literature suggesting that antidepressant therapy may negatively affect the course of depression. A review of 27 studies with variable duration of therapy demonstrated that length of treatment did not positively affect long-term outcome.[34] There was an inidcation that longer treatment was associated with higher rates of relapse once the drug was discontinued. This finding, however, did not reach statistical significance.[34] In a comprehensive review of long-term maintenance studies, Fava found very little evidence that duration of drug therapy affects long-term prognosis once the medication is discontinued, writing, "In clinical terms, this means that whether you treat a depressed patient for three months or three years, it does not matter when you stop therapy with the drug."[35]

Long-Term Safety of Antidepressants

Any decision in medicine regarding a medical intervention involves a balance between risk and benefit. Certainly, the risk of untreated depression or recurrent depression is commonly known. There are risks of significant social impairment, occupational disability, and mortality from associated medical conditions and suicide.[36] However, keeping patients on antidepressants for maintenance or prophylaxis of depression is not a benign intervention. Fortunately, there have been no known serious long-term safety or late emergent tolerability issues with the SSRIs and other newer agents such as venlafaxine, bupropion and mirtazipine. Recently, there has been a label change for nefazodone suggesting that some patients may be at risk for rare but life-threatening liver toxicity.[20,37]

There are uncomfortable side effects associated with long-term antidepressant treatment that may effect long-term compliance, patient satisfaction, and outcome. These include insomnia, somnolence, weight gain, asthenia, and sexual side effects. These may abate over time, or if not, there are a variety of treatment strategies to eliminate or reduce the severity of these problems.[38] Antidepressant discontinuation syndromes also are very uncomfortable for patients. Common symptoms include dizziness and light-headedness; nausea and vomiting; fatigue, lethargy, myalgia, chills, and other flu-like symptoms; sensory and sleep disturbances; irritability; and depression. These symptoms can be mild to severe in intensity and usually are transient, but may affect the patient's ability to discontinue medication.[39] There are other considerations to consider and discuss with the patient in addition to safety and side effects. Patients often relate concerns regarding costs of medication, time and expense of physician visits, stigma of ongoing need for pharmacotherapy, and a general wish to be well and free of illness.

Are Antidepressants Depressogenic or Neuroprotective?

One current debate that could affect the pervasive use of long-term pharmacotherapy is whether antidepressants provide some sort of protection to the depressed individual or actually exacerbate the condition over the long run. The phenomenon of tolerance to antidepressants is well established.[40] Rates of tolerance are difficult to assess, since other factors may contribute to high rates of recurring depressive symptoms, i.e., loss of placebo effect, worsening diseases state, accumulation of a detrimental metabolite, prophylactic inefficacy, or a change in disease pathogenesis.[41] Some patients have responded to increased doses of their medication when symptoms reoccurred, while others have not responded to such interventions.[42,43]

Some have questioned whether antidepressants may be depressogenic.[44] Fava proposes that there may be a sensitizing effect from antidepressants.[45] This may lead to a worse outcome when patients discontinue their therapy, and may actually worsen the long-term course. There are several possible explanations, including sensitization and tolerance to effects on the neurotransmitter balance. Fava discusses implications of the sensitization hypothesis on use of antidepressants in maintenance therapy, and liberal use of medication therapy in dysphoria or other sub-clinical depressive states. This possible senitization may affect the patient's ability to discontinue antidepressant treatment even in the less severe types of mood impairment.[45]

On the other side of the coin is a body of evidence that antidepressants may be neuroprotective. Imaging studies have shown impairments in neuroplasticity and cellular resilience in patients with mood disorders including depression. This includes reduced volume/cortical thickness, reduced neuronal size and/or density, and reduced glia. Stress and its effect on

the hypothalamic-pituitary-adrenal axis regarding glucocorticoids have been attributed to atrophy of hippocampal neurons as well as impaired hippocampal neurogenesis.[46]

Manji reviews a number of studies showing that antidepressants have neurotrophic effects that may increase neurogenesis.[46] Chronic, but not acute, use of a variety of classes of antidepressants have shown increased proliferation and survival of new neurons. Fava concludes that effects of medications on neurotransmitters may not be as important in treating depression as their neurotropic and neuroprotective properties.[42] This certainly would change how clinicians regard the benefit of long-term treatment vs. any potential risks of such therapy.

Maintenance Drug Doses and Medication Discontinuation

American Psychiatric Association treatment guidelines suggest that patients continue the same dose of medication that was required to achieve response during acute and continuation phase of treatment during the maintenance phase. However, Keller reports that standard maintenance doses were one-half to one-third of acute dosing from the 1970s to the early 1990s.[36] Kupfer et al demonstrated that the recurrence rates for those treated with half the imipramine dose vs. the full dose was 70% vs. 30%.[30] Brugha et al conducted a naturalistic, prospective study that showed low-dose antidepressant therapy was less effective than higher doses or non-medication management of depression.[47] All the studies we reviewed in which medication was discontinued made no reference to how the medicines were stopped. We could find no literature on gradual discontinuation of therapy to determine whether this would have made a difference in outcomes.

Non-Medication Therapies in Prevention of Recurrence

While many forms of psychotherapy have been shown to be beneficial in the acute treatment of depression, there is limited data demonstrating effectiveness of psychotherapies in the prevention of depression relapse and recurrence. Adjunctive interpersonal psychotherapy was not shown to lengthen time to relapse in a group randomly assigned to imipramine or placebo.[23] Prien et al reported psychotherapy did not prevent depression recurrence but did improve social adjustment.[48] There are some randomized, controlled trials demonstrating that cognitive-behavioral therapy reduces residual depressive symptoms, improves long-term outcome of depression, and may facilitate medication discontinuation.[16,49]

Conclusion

Our conclusion is that patients should be educated using the available data we have on relapse prevention and recurrence with long-term antidepressant therapy. They should be educated that the consensus recommendations are: acute treatment generally lasts 6-12 weeks; the continuation phase lasts 6-9 months; and maintenance is considered for those at high risk of recurrence. Clinicians should discuss the escalating recurrence rates. They also need to reinforce the importance of complete symptom resolution in the acute and continuation phases to reduce the risk of relapse or recurrence.

Clinicians might consider informing patients that there are some data indicating potential sensitizing effects with antidepressant use, and of the implications for possible medication resistance. This could lead to a need for medication changes throughout treatment or a requirement for longer-term therapy. This may be balanced by awareness of possible neuroprotective effects of antidepressants. They should be made aware of the current research on cognitive-behavioral therapy that shows a potential role in facilitating symptom relief and possible antidepressant discontinuation in the future.

If the patient is at high risk for relapse or recurrence, the clinician strongly should encourage ongoing medication therapy. When clinicians choose to continue their patients on medication, they should consider the following: 1) Should the question of possible sensitization to depression be cause to limit patient exposure to antidepressants? 2) What specific concomittant therapies would be helpful in facilitating medication discontinuation? 3) Should we continue medication for even more prolonged periods of time if antidepressants are neuroprotective? 4) If appropriate maintenance stabilization is achieved, would gradual tapers of medication be helpful in successful medication discontinuation? Physicians also must educate their patients on positive lifestyle changes that may facilitate a medication taper. This may include such interventions as healthy diet, exercise, and a number of different psychotherapies.

We believe many patients welcome physician education on the potential risks and benefits of long-term antidepressant therapy. We suggest a collaborative approach in which physicians partner with them to help them discontinue medication when possible. If patients do choose to discontinue medication, they should be educated about the warning signs of relapse or recurrence so intervention can begin early to prevent further decline. However, they may wish to continue on the medication because of their past experience with relapses and recurrence of illness and fear of their depression returning. Patients often will comply better with medication therapy and be more invested in treatment if they feel they have options and can partner with their doctors.[50]

Our knowledge base on the long-term management of depression and the "when and how" to discontinue medications is limited. Physicians have a responsibility to inform their patients on the available information we do have in this area to ensure their patients get well and stay well.

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The CME objectives for *Psychiatric Medicine Reports* are to help psychiatrists:

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After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided; a certificate of completion will be mailed to you.

Physician CME Questions

31. The risk of recurrence of depression is:
    A. 50-60% after a single episode of depression.
    B. 80% after two episodes of depression.
    C. 90% after three episodes of depression.
    D. A and C only
    E. A, B, and C

32. Fifty percent of patients suffering from depression will have a recurrence within two years of the initial episode.
    A. True
    B. False

33. Which of the following statements is/are true of dysthymia?
    A. Dysthymia has a lifetime prevalence of 10%.
    B. It spontaneously remits 25% of the time.
    C. It may affect interepisode recovery and require a longer course of treatment.
    D. All of the above are true.

34. Regarding phases of antidepressant treatment:
    A. The acute phase generally lasts 6-12 weeks.
    B. Continuation phase usually only is indicated for management of chronic depression.
    C. There are no consistent guidelines for length of maintenance phase.
    D. Both A and C are true.
    E. A, B, and C are true.

35. Medication doses used in maintanance phases of treatment often may be lower than those used in acute treatment.
    A. True
    B. False

36. Which of the following is/are risk factors for recurrence of depression?
    A. Prior history of depression
    B. Chronic medical problems
    C. Persistent interepisode dysthymic symptoms
    D. Both A and C
    E. A, B, and C all are risk factors.

37. Imaging studies in patients with depressive mood disorders show:
    A. increased volume/cortical thickness.
    B. reduced neuronal size and/or density.
    C. increased glia.
    D. All of the above

38. Regarding studies evaluating effectiveness of psychotherapies in prevention of depression recurrence:
    A. Adjunctive interpersonal psychotherapy did not lengthen time to relapse.
    B. Prien's study did not show psychotherapy prevented depression recurrence.
    C. Cognitive therapy has been shown to improve long-term outcome of depression.
    D. All of the above are true.

39. There is abundant, clear evidence that antidepressants are sensitizing and prolong the need for ongoing medication therapy.
    A. True
    B. False

40. Studies have shown which of the following medications prevent relapse vs. placebo in long-term therapy?
    A. Tricyclic antidepressants
    B. SSRIs
    C. Venlafaxine
    D. Nefazadone
    E. All of the above

Answer Key:

31. D	**36. E**
32. A	**37. B**
33. C	**38. D**
34. D	**39. B**
35. B	**40. E**

In Future Issues:

Non-medication Intervention for Psychiatric Diseases