Long-Term Nature of Depression

Michael E. Thase, M.D.

Many, if not most, people with depression are at high risk to develop a recurrent and potentially chronic disorder, characterized by deleterious effects on vocational, social, and family functioning. Recent evidence also suggests that recurrent episodes of severe depression are associated with changes in brain function that further heighten vulnerability and functional impairment. The best way to deal with these sobering problems is prevention via vigorous treatment of the index episode (to produce complete remission) and more routine use of longer term models of prophylactic therapy. After briefly reviewing the relevant data on epidemiology and natural history, this article focuses on the 4 "arms" of preventative treatment: psychoeducation, pharmacotherapy, adherence, and psychotherapy. Like the modern approach to treatment of hypertension, a conscientious and integrated approach to preventative therapy saves lives and has profoundly beneficial effects for our patients, their loved ones, and society.

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The depressive disorders are prevalent conditions that are commonly associated with high rates of disability, chronicity, and relapse/recurrence. Indeed, such examples of "illness burden" explain why depression is now considered to be the world's fourth greatest public health problem.[1] There are grounds for optimism, however, because a vast majority of people suffering from depression can be treated effectively and recurrence risk can be dramatically reduced by preventative or maintenance forms of treatment. This article will focus on the longer term aspects of the depressive disorders, including both the natural history and the treated course of these common conditions.

TERMINOLOGY

In 1991, a task force of clinical researchers working under the aegis of the MacArthur Foundation published a set of terms and definitions to describe the longitudinal course of major depressive disorder. Specifically, the task force outlined operational definitions for what our group refers to as the "5 *R*'s": *response*, *remission*, *relapse*, *recovery*, and *recurrence*.[2] To briefly summarize, a *response* is a significant reduction of symptoms to a level below the threshold for a major depressive disorder. The term *remission* is used to describe a qualitatively better outcome, i.e., a return to "wellness." A remission is thus defined by a lack of symptoms or signs of illness activity. The term *recovery* denotes a sustained period of remission. Generally, 4, 6, or even 9 months of sustained remission are necessary before one can be said to have recovered. The term *relapse* is used to describe an exacerbation of depression that occurs after the timepoint when the patient has achieved a response or remission, but before a complete recovery. By contrast, the term *recurrence* is reserved for a depressive episode that begins after a recovery. A relapse is thus framed conceptually as a reemergence of the index or most recent episode, whereas a recurrence is an entirely new episode of depression.

Although certainly arbitrary, these definitions have important practical applications. For example, an incomplete or partial remission is associated with a greater risk of relapse than a full remission.[3–5] The relapse/recurrence distinction also underlies the division of preventative therapies into continuation and maintenance phases. Specifically, 4 to 6 months of continuation therapy is recommended for almost all antidepressant responders to permit a remission to progress to recovery. A longer course of maintenance phase therapy is recommended for those who have already experienced multiple episodes of recurrent depression.

Two additional "R" terms also have important implications for the course of depressive episodes: *refractory* and *residual*. *Refractory* denotes that 15% to 20% of depressive episodes do not respond to multiple interventions and, hence, some patients will become chronically depressed despite vigorous treatment. However, it should be kept in

From the Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pa.

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Reprint requests to: Michael E. Thase, M.D., Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213-2593.

mind that the majority of chronic depressive episodes, i.e., episodes lasting at least 2 years, have not been treated adequately.[6] Thus, chronic depression is *not* synonymous with refractory depression and many chronically depressed patients will respond when finally treated with pharmacotherapy.[7] The term *residual* refers to the oft underrecognized core of "minor" or subsyndromal symptoms that continue to plague many depressed people despite treatment. One reason for persistent, residual minor symptoms after resolution of an acute depressive episode is antecedent dysthymia, a presentation commonly referred to as "double depression."[8] In this case, the more acute, major depressive exacerbation has remitted but the dysthymic disorder persists, unabated.

NATURAL HISTORY

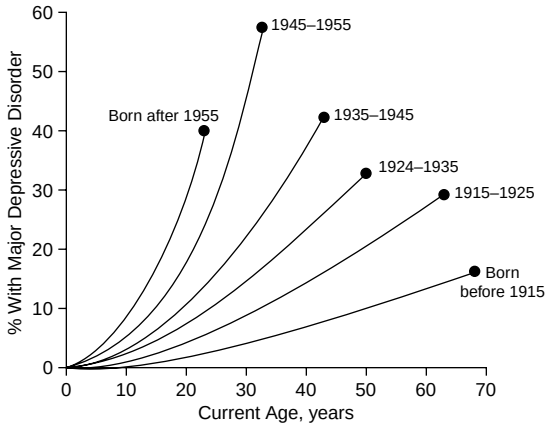
Many episodes of depression are short-lived and remit, even without specific treatment, within 6 to 9 months.[8–10] For a fortunate minority, a single episode will resolve without sequelae; perhaps 30% will never suffer another episode. For the majority, however, major depressive disorder is a recurrent and potentially lifelong illness.[8–10]

There is some evidence that the risk of future depressive episodes increases progressively with each recurrence.[8] Thus, people who have already suffered through 3 or more lifetime episodes may face a 3-year recurrence risk as high as 85% unless they receive preventative treatment.[11–13] Post[14] has proposed that such a progressive increase in risk represents a form of illness transduction or kindling. The kindling hypothesis states that the pathophysiologic changes associated with the depressive episodes alter brain stress response mechanisms such that progressively less stress or provocation is necessary to provoke subsequent, recurrent episodes. Although the illness transduction model remains hypothetical, there is evidence that people with recurrent depression have more pronounced abnormalities of adrenocortical regulation[15] and sleep neurophysiology[16] when compared with those suffering a single or initial episode.

Current age and age at first onset of major depression also influence recurrence risk. An early age at onset (e.g., prior to age 21) is associated with a high risk of recurrent depression.[17] Elderly patients suffering an initial depressive episode after age 60 also appear to be at greater risk especially for development of chronicity and/or relapsing episodes.[18] In the former case, an early age at onset is clearly associated with a greater familial or genetic "loading,"[17,19] and there is also an increased likelihood of subsequent onset of mania or hypomania.[20] Such early onset depressions are also associated with higher rates of dysthymia, psychosis, substance abuse, anxiety disorders, and personality pathology.[17,19–21]

The relationship between an early age at onset and subsequent risk of both recurrent and chronic forms of depression is made more ominous by evidence of a cohort effect across the past several generations.[22] As illustrated in Figure 1, it appears that there has been a shift toward earlier age at onset and greater lifetime risk of depression in each age cohort born since 1900. If this trend continues, it would appear that children born in the year 2000 will have an *average* age at onset of depression of only 20 years.

Figure 1. The Cumulative Probability of Developing a Diagnosable Major Affective Disorder for Relatives and Controls by Birth Cohort (life-table method)[a]



[a]From reference 22, with permission.

Personality pathology may have an interactive relationship to both genetic and acquired risk factors associated with an early age at onset.[23] On the one hand, a depressive temperament or the early-onset form of dysthymia undoubtedly colors personality development. On the other hand, the children of people with severe mood disorders are more likely to be exposed to a wide range of maltreatments. Thus, an inherited vulnerability may be amplified during development by the effects of parental loss, neglect, or abuse. In any event, once the constellation of cognitive, behavioral, and interpersonal characteristics that define personality pathology have been established, the affected individual will both (1) experience a greater number of stressful life events and (2) tend to handle those events less capably.[23]

The greater risks associated with older age may reflect a different pathophysiology (i.e., the vascular depression hypothesis),[24] the impact of increasing medical burden, or the effects of declining economic status and social support. In actuality, all 3 factors may be operative to greater or lesser degrees for each person. Older age should not, however, deter vigorous efforts to treat depressive episodes to complete remission.

A seasonal pattern of fall-winter depressions may represent yet another unique risk factor, perhaps triggered by sensitivity to a decrease in the length of the daily photoperiod or a reduction in the amount/intensity of light expo-

sure.[25] Between 10% and 20% of patients with recurrent depression meet criteria for a seasonal pattern.[26] Despite substantial evidence from short-term clinical trials, however, it has not yet been established that phototherapy with bright white light can be used prophylactically to suppress a seasonal pattern of recurrent depression.

TREATMENT

A successful course of treatment includes acute, continuation, and, if appropriate, maintenance phases. This is true for both pharmacotherapy and the newer depression-specific psychotherapies. The duration of the acute phase is variable, based on the time to response. If an acute phase therapy is going to be effective, some significant reduction in symptoms is usually apparent within 4 to 6 weeks. Titration of antidepressant dosage and consolidation of early clinical gains may take an additional 4 to 6 weeks, such that time to remission averages 8 to 12 weeks for an effective course of treatment. The acute phase of therapy is completed when the patient has achieved a stable response and no further adjustments in antidepressant dosage are anticipated.

Continuation Phase Therapies

There is a 40% to 60% risk of relapse if an antidepressant medication is discontinued within the first few months of a response.[27] Continued antidepressant treatment, by contrast, reduces this risk to 5% to 10% during the same time frame.[27] These findings have held true for all classes of antidepressants studied—tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), venlafaxine, nefazodone, and, most recently, mirtazapine.[28–30] Continuation pharmacotherapy is thus the standard of practice following an antidepressant response.[28,29] Relapse is similarly common after a course of electroconvulsive therapy (ECT), particularly when responders are not provided appropriate continuation pharmacotherapy.[31] Although cost, inconvenience, and memory side effects limit the widespread use of continuation phase ECT, this option can be lifesaving for patients with marked histories of antidepressant resistance and frequent relapse.

Psychotherapies such as cognitive behavior therapy (CBT) and interpersonal psychotherapy (IPT) have typically been discontinued after acute phase treatment of depression. Although typically more costly than pharmacotherapy in the short run, psychotherapies offer some promise of reducing relapse/recurrence risk by helping patients to develop and master more effective ways to cope with adversity or manage "minor" fluctuating symptoms after treatment termination. There is some evidence that acute phase CBT, once discontinued, has a sustained preventative effect over the next 12 to 18 months when compared with outcome in patients withdrawn from antidepressants.[3,5,32] In one small study, this relapse prevention effect was comparable to that of continuation pharmacotherapy.[32] However, a number of psychotherapy responders do relapse after therapy is terminated, and such patients may benefit from either longer term models of continuation psychotherapy or a switch to preventative antidepressant therapy.[5] Research by our group at the University of Pittsburgh School of Medicine indicates that CBT responders who did not achieve a full remission by the 10th week of acute phase therapy represented a particularly high-risk group.[5]

Maintenance Phase Treatment

The goal of maintenance phase therapy is prevention of recurrent depression. Key elements of this treatment phase include patient psychoeducation, pharmacotherapy, adherence monitoring, and psychotherapy.

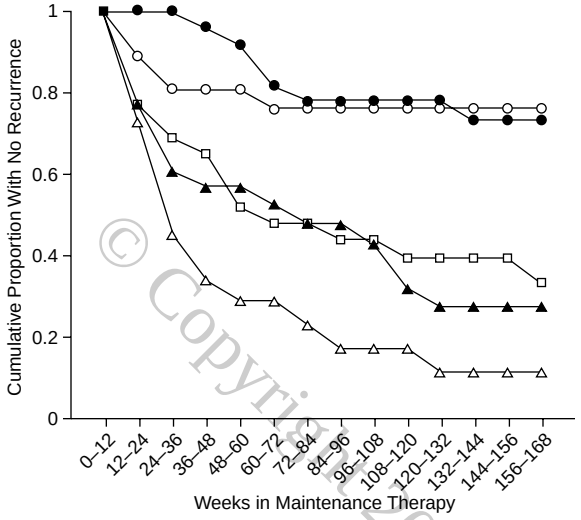
Psychoeducation. Psychoeducation is a clinically sophisticated form of teaching patients about the disorder and its treatment. This normally includes discussion about recurrence risks, stigma, vulnerability, and the benefits and risks of preventative treatment. It is essential that patients learn that recurrent depression is an illness (or biopsychosocial disorder), not a moral weakness, and that antidepressants are not habit forming. Although the "crutch" metaphor may be denigrating if used synonymously with "cop-out," it is not wholly inaccurate: a crutch is a legitimate way to cope with a broken ankle. Should the issue arise, it may be preferable to make the analogy to an athlete's use of a knee brace. In both cases, an external, stabilizing intervention is prescribed by a physician to minimize the vulnerability and maximize function.

Psychoeducation also frequently needs to extend to family members and other significant others. Not uncommonly, an informed spouse, adult child, or parent may have a profound positive influence on the decisions made by the identified patient. Although such discussions generally require patient consent, they can have manifold beneficial effects on medication adherence and patient self-esteem.

Pharmacotherapy. Most experts recommend maintenance phase pharmacotherapy for patients who have suffered 3 or more lifetime episodes of depression. An even more vigilant approach may be recommended for first- or second-episode patients who have made serious suicide attempts, required multiple medication trials, or have other marked vulnerability characteristics.

Despite the ubiquity of recurrent depression, there are less than a dozen well-controlled studies of maintenance phase pharmacotherapy. The study led by my colleagues Drs. Ellen Frank and David Kupfer is perhaps the most widely cited.[12,13] This was a 3-year, randomized clinical trial of preventative treatment with imipramine and IPT, singly and combined, in a group of outpatients with highly recurrent (unipolar) depression. All of the 126 patients en-

Figure 2. Outcome of the Maintenance Therapies in Recurrent Depression Protocol[a]



[a]From reference 12, with permission. ○ represents group that underwent medication clinic and active imipramine; ●, interpersonal psychotherapy and active imipramine; □, interpersonal psychotherapy alone; ▲, interpersonal psychotherapy and placebo; and △, medication and placebo.

rolled in the long-term study had remitted on the combination of imipramine and IPT, and all had remained well for 4 months of continuation therapy prior to randomization. Thus, the entire study group was fully recovered at the start of the long-term treatment trial.

The results of the 36-month double-blind study were striking (Figure 2); there was almost a 4-fold advantage favoring active imipramine maintenance over placebo.[12] This effect was almost twice the magnitude seen in prior studies (e.g., Prien et al.[33]), perhaps because patients in the active imipramine groups of the Frank-Kupfer study received full dose (mean = 210 mg/day) maintenance pharmacotherapy. Monthly maintenance IPT sessions had an intermediate preventative effect—better than placebo but inferior to active imipramine. The combination maintenance therapy condition was not more effective than imipramine alone. There was, however, little room for further improvement, and it should be recalled that all patients entering the maintenance phase trial were fully recovered and that they already had received at least 6 months of IPT.

Equally compelling evidence exists for maintenance therapy of chronic depressions. To date, studies have been completed for the TCA desipramine,[34] the MAOI phenelzine,[35] and the SSRI sertraline.[36] Interestingly, Stewart et al.[35] found that phenelzine had a significantly better preventative efficacy than imipramine among a group of outpatients with atypical (reversed neurovegetative) depressive symptoms.

Several studies have addressed prevention of recurrent depression among older people. In a study of people aged 55 and older, Georgotas et al.[37] found phenelzine was an effective maintenance therapy of recurrent depression, although, curiously, nortriptyline was no more effective than placebo in this study.

Subsequently, the TCA dothiepin was shown to be an effective preventative therapy in a multicenter study conducted in the United Kingdom.[38] Interestingly, the elderly women in this study were at greater risk of recurrent depression than the men, a sex-specific vulnerability that was not fully offset by active maintenance therapy. It has been proposed that illness transduction (i.e., recurrence risk) occurs more rapidly for women after menopause because of the loss of the neuroprotective effects of estrogen.[39]

Most recently, Reynolds et al.[40] found that both maintenance IPT and nortriptyline were effective preventative therapies in a study of older patients with recurrent depression initially treated with the combination of IPT and pharmacotherapy. Unlike the earlier study of mid-life recurrent depression, the study by Reynolds et al.[40] found an additive effect for the combination of psychotherapy and medication.

There is, of course, a clear need to confirm the utility of maintenance phase therapy of recurrent depression with the newer antidepressants, including the SSRIs, bupropion, venlafaxine, nefazodone, and mirtazapine, among both younger and older age groups. Aside from Keller and colleagues' multicenter study[36] of chronic depression, only a handful of studies of newer antidepressants have been completed that meet the following criteria: (1) enrollment limited to patients with recurrent depression, (2) sustained remission across at least 4 months of continuation therapy, and (3) at least 12 months of follow-up after randomization to double-blind therapy.[41–43]

Despite emerging evidence of long-term efficacy, there continues to be some concern that therapeutic tolerance may develop during longer term SSRI therapy. Montgomery et al.[41] studied fluoxetine (40 mg/day) in a placebo-controlled randomized clinical trial. All 220 patients had responded to fluoxetine acutely and had completed 6 months of continuation pharmacotherapy prior to randomization to active or placebo maintenance therapy conditions. The active drug was significantly more effective than placebo during the 1-year study, although 26% of patients ultimately failed on active drug. More recently, Stewart et al.[42] found a similarly modest, but statistically significant preventative effect for maintenance fluoxetine therapy. A reexamination of maintenance phase outcome in relation to the pattern of response to acute phase therapy was more revealing. Specifically, there was no benefit for active fluoxetine among the subgroup of patients who had a fluctuating or extremely rapid response to acute phase therapy. Previous research[44] by this group had suggested that this pattern of improvement was indicative of a placebo response. By contrast, patients whose responses devel-

oped after several weeks of therapy and persisted thereafter (i.e., a "true drug response") had a clear-cut advantage when maintained on active fluoxetine as compared to placebo. It thus is possible that the so-called "Prozac poop-out" effect actually is an artifact created by the favorable tolerability of the SSRIs. In other words, treatment with the better tolerated newer medications may inadvertently permit a larger number of patients who respond to placebo-expectancy factors to remain on pharmacotherapy.

For patients who develop a multi-relapsing course despite preventative antidepressant therapy, alternatives include lithium (either alone or in combination with antidepressants) or anticonvulsant mood stabilizers. Although lithium prophylaxis was only moderately effective in one U.S. trial,[33] its value as an augmenter is well established. There is also increasing interest in the therapeutic effects of divalproex, lamotrigine, and gabapentin for patients with highly recurrent (kindled?) depressive disorders.

Adherence. Although loss of effect during maintenance therapy may herald some sort of therapeutic tolerance, the pharmacologic and neurophysiologic mechanisms underlying such an effect remain obscure. Rather, it is much more likely that nonadherence is the cause of an apparent loss of therapeutic effect. There are informative data from a wide range of sources to document just how common nonadherence is during longer term treatment of chronic medical disorders,[45] and, in the Pittsburgh study, variability in tricyclic blood levels was the only predictor of recurrence in the active imipramine conditions.[46] It therefore is useful to continue to inquire about adherence with maintenance pharmacotherapy and to take note when the frequency of medication refills begins to lag behind the expected rate. Although people certainly have the right not to adhere to therapeutic regimens, it is better to test the need for continued treatment more directly and collaboratively. Further, nonadherence during longer term therapy is usually not a willful, strategic act, but rather an intermittent, slowly progressive process—more passive than volitional. Ongoing attention to treatment adherence, further psychoeducation, and, when necessary, use of various compliance aids can offset this process. Common compliance aids include the use of a calendar or "prompt sheet" to keep track of daily dosages; locating medication in a central, predictable place (e.g., adjacent to the toothpaste, multivitamin container, coffee maker, or night stand); and use of daily pill boxes. Physicians can similarly enhance compliance by prescribing the simplest and most straightforward medication regimen possible.

Psychotherapy. Despite the grand tradition of longer term models of insight-oriented psychotherapy, we know very little about the effectiveness of these types of treatment for prevention of recurrent depression. As noted earlier, provision of monthly maintenance sessions of IPT in the Pittsburgh study yielded a modest preventative effect—superior to placebo but clearly inferior to ongoing pharmacotherapy.[12] Maintenance IPT was more effective among patients with normal slow wave sleep (i.e., a possible "marker" of a lower level of neurobiological vulnerability),[47] and it was a significantly better preventative treatment when the patient-therapist dyad was able to maintain focus on key interpersonal areas (i.e., role disputes, role transitions, unresolved grief, or social deficits).[48] In fact, patients who had normal sleep and participated in "above average" therapy had outcomes every bit as favorable as those who remained on active imipramine.[49] Dr. Frank and colleagues are currently studying the value of 3 doses of maintenance IPT in a series of women who responded to acute phase therapy with IPT alone. It will be interesting to see if more frequent sessions of therapy will broaden the efficacy of maintenance IPT.

Other clinical issues. Experts differ on their views of the proper duration of maintenance phase therapy. Some prefer to view it as a lifelong intervention, whereas others (including me) describe it as an "indefinite" course of treatment. I favor the latter model because of the lack of knowledge about ultra–long-term pharmacotherapy and because of the very real possibility that more definitive or truly curative treatments could be developed in the future.

What is known is that, across the first 3 to 5 years of successful preventative pharmacotherapy, the risk of "failure" of active drug is about 10% per year and the risk of recurrence off active medication is at least 30% to 50% during the first 6 months following discontinuation. Thus, it appears that there is a relatively constant risk of relapse/recurrence whether medication is discontinued after weeks, months, or years of pharmacotherapy.

It remains to be seen if the risk of relapse/recurrence can be lessened by a slow, tapered discontinuation of medication. The studies of longer term fluoxetine treatment (which by virtue of the long elimination half-life of norfluoxetine naturally "auto-tapers" the patient over 6 to 8 weeks) are suggestive but, ultimately, not conclusive.[41,42] It does little good, ultimately, to delay the time to recurrence by only a few months if the overall risk is not reduced.

Most experts now recommend use of full antidepressant doses for maintenance phase therapy. There are 2 lines of evidence to support this practice. First, studies employing lower "maintenance doses" of TCAs or MAOIs typically report lower rates of successful prophylaxis than studies utilizing full acute phase antidepressant doses (see Thase[50]). Second, a small study conducted by the Pittsburgh group[51] found that a lower dose maintenance phase therapy (i.e., 50% reduction of the acute phase dosage of imipramine) was significantly less effective than a full-dose preventative treatment.

An indefinite course of higher dose antidepressant therapy does raise some concerns about pregnancy and teratogenicity, particularly because premenopausal women are the largest sociodemographic group now

treated with antidepressants. Must younger women who need to take maintenance pharmacotherapy choose to do so at the expense of childbearing? Fortunately, it appears that neither the TCA nortriptyline nor the SSRI fluoxetine is associated with a definite risk of specific birth defects or complications. Breast-feeding is not recommended, however, because a small amount of medication is concentrated in breast milk. Smaller or rarer risks, of course, cannot be ruled out, however, and each woman's potential risks of recurrence and benefits of ongoing treatment must be considered. Much greater experience is also needed with the other newer antidepressants before safety during pregnancy can be properly assessed. For some, the unknown (but probably small) risk of maintenance pharmacotherapy will be deemed acceptable when compared with an almost certain 50% risk of recurrence off pharmacotherapy. For others, the prospect of adding any risk to the developing fetus is unacceptable. In either case, the effects of depression on the mother-infant relationship should not be minimized.

If, for whatever reason, the patient elects to come off medication, the following steps are recommended. First, the psychiatrist should provide psychoeducation about the risk of recurrence and review potential "early warning signs." Second, a plan of action to deal with an impending recurrence should be discussed. Third, medication should be tapered, if possible, at a cautious pace. A 6-, 12-, or even 16-week taper is not unheard of after months of maintenance therapy. Fourth, the psychiatrist should help to decatastrophize the prospects of recurrence—"*If* it happens, it simply proves the need for ongoing maintenance pharmacotherapy, nothing more, nothing less." Pharmacotherapy can be resumed and vigorously titrated in the case of emerging depressive symptoms. And fifth, if clinically indicated, psychotherapy may be considered as an alternative or transitional intervention. For example, Fava et al.[52,53] have shown that a time-limited course of CBT focusing on management of residual symptoms significantly reduced subsequent recurrence risk.

CONCLUSION

Major depressive disorder is most commonly a recurrent illness, and, for the majority, longer term preventative models of treatment can greatly reduce the risk of recurrences and prevent the development of chronic or refractory depressive states. Whether viewed as an indefinite or lifelong enterprise, maintenance antidepressant therapy is facilitated by psychoeducation and a collaborative approach to adherence. Full-dose pharmacotherapy is usually recommended, and, although not a substitute for all patients, longer term models of CBT and IPT provide nonpharmacologic alternatives for a subgroup of patients.

Drug names: bupropion (Wellbutrin), desipramine (Norpramin and others), divalproex sodium (Depakote), fluoxetine (Prozac), gabapentin (Neurontin), lamotrigine (Lamictal), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

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