Strategies and Tactics in the Treatment of Chronic Depression

A. John Rush, M.D., and Michael E. Thase, M.D.

Chronic depressions include major depressive disorder, recurrent, without full interepisode recovery; major depressive disorder, currently in a chronic (i.e., ≥ 2 years) episode; double depression; dysthymic disorder; and those depressive disorders—not otherwise specified (NOS)—that are persistent or predictably recurrent with substantial disability. Strategic treatment decisions include (1) whether to treat with medication, psychotherapy, ECT, or other methods; (2) selection among specific agents with long-term efficacy and tolerability (preferably established by randomized controlled trials); (3) selection of the next treatment should the initial treatment fail or be found intolerable; and (4) deciding whether to provide maintenance treatment. Tactical decisions are those needed to optimally implement the strategies selected; for example, (1) how to optimally dose, (2) how long to continue an acute phase treatment trial, (3) how to measure outcome, and (4) how to identify and manage subsequent symptomatic breakthroughs or side effects (which may also require revisions in the initial strategies). Some antidepressant medications evidence efficacy and safety in acute phase treatment of the chronically depressed, but continuation and maintenance phase treatments for these patients are less well investigated and deserve further study. The clinical implications of what is known to date for managing these patients are discussed. *(J Clin Psychiatry 1997;58[suppl 13]:14–22)*

The optimal management of depressed patients requires a consideration of a range of strategies and the careful implementation, often in a sequenced fashion, of those strategies selected.[1] Strategies refer to decisions regarding what to do (e.g., whether to select antidepressant medication, psychotherapy alone, or the combination of both). Tactics refer to the "hows" or the methods by which the strategy selected is to be implemented to obtain an optimal outcome (e.g., how to dose the medication chosen, how long to use the medication before deciding it is not adequate, etc.). The strategic and tactical decisions involved in the management of patients with chronic depressions may be particularly important since there is substantial evidence that such patients are neither treated early nor vigorously.[2–4]

There is also reason to believe that the more chronic the depression, the slower the response to medication treatment (see below) and the poorer the response to time-limited psychotherapy alone.[5,6] Thus, chronically depressed patients, even when correctly recognized and begun on medication, may have an inadequate drug exposure (e.g., too low a dose and/or too short a duration) such that only partial or poor responses are obtained. Then, the treatment may be inappropriately or unnecessarily changed or augmented, or even worse, the patient may become discouraged and exit treatment altogether, when the solution might have been a higher dose and/or a longer duration of exposure.

This paper discusses (1) the prevalence and disabilities associated with chronic depressions, (2) the evidence to date for the efficacy and safety of acute and maintenance phase medication treatments, and (3) some diagnostic and treatment strategies and tactics that we hope are of practical value in managing these patients. We conclude by suggesting several key clinical issues that call for further research.

From the Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas (Dr. Rush) and the University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pa. (Dr. Thase).

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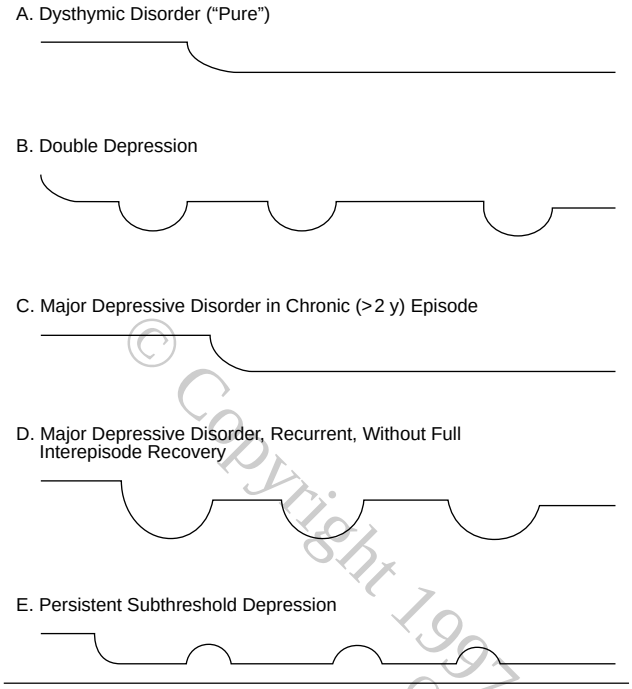
Reprint requests to: A. John Rush, M.D., Department of Psychiatry, University of Texas Southwestern Medical Center, St. Paul POB I, Suite 600, 5959 Harry Hines Boulevard, Dallas, TX 75235.

Figure 1. Course of Illness of Chronic Depressions



DEFINITIONS OF CHRONIC DEPRESSION

The now classic phases of treatment for depression (i.e., acute, continuation, and maintenance) reflect a growing awareness of chronicity.[7] Response (symptom reduction) and remission (i.e., no symptoms) are to be distinguished. Recovery from the episode is declared only after several months of sustained remission. A relapse (return of the index episode) occurs before recovery, whereas recurrences (new episodes) occur following recovery. Continuation phase treatment aims at relapse prevention, whereas maintenance phase treatment aims at recurrence prevention.

The often recurrent and chronic nature of mood disorders is now more widely recognized due to community studies,[8,9] as well as studies of psychiatric outpatient and inpatients.[10–14] In a cross-sectional follow-up study after 30 to 40 years, Tsuang and colleagues[15] were among the first to reveal the chronic nature of some mood disorders. They found a persistently poorer outcome in over 20% of formerly depressed inpatients. Angst[16] found that 13% of previously hospitalized inpatients had a chronic course of illness when followed for 21 years after discharge.

Because of the increasing recognition that a more chronic course of illness typifies at least a substantial subgroup of clinically depressed patients, DSM-IV[17] provided several methods by which to describe and designate these conditions. Major depressive disorder, currently in a chronic episode, describes those individuals whose current major depressive episode is ≥ 2 years in duration. Further, major depressive disorder itself can be coded as single or recurrent. Thirdly, dysthymic disorder (by definition) lasts at least 2 years without a major depressive episode in its initial expression, although major depressive episodes often develop and are superimposed on the dysthymic disorder over time.

DSM-IV also provided noncoded "course of illness specifiers" such that for major depressive disorder, one can specify with or without antecedent dysthymic disorder (i.e., before the first major depressive episode), as well as with or without full interepisode recovery. Finally, subthreshold depressions (e.g., depressive disorder, NOS) can be brief, or they may be persistent. Figure 1 provides a schematic representation for each of these various chronic courses of illness for nonbipolar mood disorders.

As with bipolar disorder,[18] nonbipolar mood disorders are characterized by an ongoing, if not ever increasing, risk of chronicity. That is, more prior depressive episodes increase the chances of more future episodes. Furthermore, incomplete interepisode recovery in the past predicts a similar pattern in the future. Finally, the longer the patient is in an episode, the lower the likelihood of spontaneous remission. For example, only 18% of those still in a major depressive episode after 1 year in the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression subsequently remitted over the next 4 years.[19–22] Of those patients with major depressive disorder who did remit, over 60% had a relapse or recurrence within the subsequent 5 years.[23]

In addition, when antecedent dysthymic disorder is combined with subsequent major depressive episodes (i.e., so-called "double depressions"), one finds that when the major depressive episode ends, most patients return not to an asymptomatic state, but rather to a dysthymic level of symptomatology; in other words, incomplete interepisode remissions from the major depressive episode are most likely.[24] Furthermore, double depressions appear to be associated with more relapse/recurrences in a major depressive episode over the following 2 years than is major depressive disorder alone.[25] Finally, when incomplete remissions follow the end of a major depressive episode, whether or not it is associated with antecedent dysthymic disorder, the greater the chance of another and earlier major depressive episode.[25–27] A variety of factors, including a longer duration and a greater severity of the index episode, a history of nonaffective psychiatric disorders, low family income, and marital status (married), appear to be associated with greater chronicity.[19,20,22,25]

CHRONIC DEPRESSIONS ARE DISABLING

Mood disorders in general,[28–32] and chronic depressions in particular,[33] are associated with significant impairment in work and interpersonal, family, and marital function.[34] These lower levels of functioning are associated with a poorer prognosis.[35–38]

Table 1. General Health in General Medical and [Mental Health] Sectors*

Condition	N	Baseline	2 Years
Subthreshold depression	243	54 [61]	57 [63]
Major depression	76	56 [57]	56 [64][a]
Dysthymia	47	50 [47]	47 [60][a]
Double depression	61	45 [48]	55[a] [50]
Hypertension	1074	64	64
Congestive heart failure	148	52	49
Myocardial infarction	84	63	64
Type II diabetes	355	59	58

*Adapted from Hays et al.[33] Values in brackets are general health status for patients in mental health sector. Note: Scale ranges are from 0 to 100, with higher values reflecting better general health status.
[a]Significant change from baseline to 2 years.

The Medical Outcomes Study found that physical, social, and general health functioning were worse in depression than in most other chronic general medical conditions (e.g., hypertension, diabetes mellitus, arthritis, and gastrointestinal and pulmonary disorders).[39–41]

Not only are the mood disorders very disabling, but the more chronic forms are particularly disabling and unlikely to be improved over a 2-year period. Table 1 shows the functional disability at baseline and at 2 years hence for various mood and general medical disorders (adapted from Hays et al.[33]). For example, over a 2-year follow-up, both chronic and nonchronic forms of depression were largely unimproved in general health and emotional status.[33] Conversely, use of health care services by these patients is high.[28,42] Further evidence of the toll of depression on function is the estimated $17 billion per annum loss due to time lost from work.[43] On the other hand, symptomatic improvement is associated with improved functioning,[30,44–46] although chronic depressions have not been well studied in this regard.

The poorer prognosis for chronic depressions may be due in part to the relatively high level of Axis I and Axis II concurrent comorbidities.[12,47,48] The Markowitz et al.[12] study of lifetime comorbid diagnoses in dysthymic disorder showed that 68% had comorbid major depressive disorder, 26% had panic disorder, 68% had some type of anxiety disorder, and 24% had substance abuse.

Other studies also reveal the high rate of Axis I concurrent comorbidities in the chronically depressed—particularly panic disorder, social phobia, generalized anxiety disorder, and alcohol abuse. Keller and Sessa[47] estimated that 75% of patients with double depression had anxiety symptoms. Studies of dysthymic disorder have reported rates of 22% to 56% for comorbid anxiety disorders. Rates of comorbidity for anxiety disorder and double depression seem to be higher than for recurrent major depressive disorder (i.e., without antecedent dysthymia).[48]

As for Axis II comorbidity, Markowitz and colleagues[12] found that 85% of patients with dysthymia had some type of concurrent Axis II disorder. In a larger sample, one half of patients in a chronic major depressive episode for ≥ 2 years and those with "double" depression were found to meet strict criteria for one or more personality disorders, with the majority having Cluster C (anxious or fearful) conditions.[49] Both Axis I and Axis II concurrent comorbidities are likely to be reflected by even greater psychosocial impairment.[50]

Finally, Axis III (general medical) conditions are known to be common among depressed patients,[32] and may be particularly common among those with more chronic courses of illness.[51,52] This coassociation of mood and Axis III conditions not infrequently leads to a worse prognosis for the concomitant general medical condition.[32] For example, Frasure-Smith and colleagues[53] found that the presence of depression—even modest levels of depressive symptoms—in patients following myocardial infarction (MI) was associated with a significantly higher death rate within 18 months following the MI. This is one of several studies[54–56] to reveal that when depressions accompany general medical conditions, it is a very serious clinical situation that requires substantial attention, and presumably, an intervention specifically aimed at relieving the depression.

TREATMENT OF CHRONIC DEPRESSION

Presently, adequate treatment for the chronically depressed is far from ubiquitous. In fact, it may well be the exception rather than the rule. A significant proportion of patients either receive no treatment or are given inadequate medication doses.[4,12,44,57,58] Further evidence of undertreatment comes from a variety of additional studies.[48,59–63] In a recent report, over one half of the chronically depressed patients—either with double depression or having been in a current major depressive episode for ≥ 2 years—had received no previous treatment at all.[62] These findings are of special concern, not only because of the evidence to date that an excellent treatment response may be expected for this group (see below), but also because the more longstanding the illness, the greater the fear that multiple treatment trials may be needed to obtain a response.

These disheartening clinical reports are in contradistinction to evidence from randomized controlled efficacy trials that standard medications are effective, safe, and tolerable for the acute phase treatment of double depression (Table 2) and dysthymic disorder (Table 3), as well as in continuation, maintenance, or discontinuation phase trials of recurrent depressions (Table 4).

Both Howland[64] and Harrison and Stewart,[65] in their recent literature reviews, conclude that the efficacy of medication for the more chronically depressed is equal to or slightly lower (40%–55%) than that for nonchronic populations. Also of note is the lower placebo response rate in these patient groups. In addition, it is important to note that even in the chronically depressed, when symptomatic improvement occurs, it is associated with functional restora-

Table 2. Acute Phase Treatment in Randomized Controlled Efficacy Trials of Patients With Double Depression*

Study	N	Diagnosis (Symptom Severity)	Duration (wk)	Results
Reyntjens et al[93]	57	DSM-III dysthymic disorder (moderate symptoms)	6	Ritanserin > placebo
Vallejo et al[94]	39	DSM-III dysthymic disorder (HAM-D > 16)	6	Phenelzine > imipramine
Kocsis et al[44]	76	DSM-III dysthymic disorder, in major depressive episode (HAM-D > 14)	6	Imipramine (59%) > placebo (12.5%)
Guelfi et al[95]	265	DSM-III dysthymic disorder (MADRS > 20; anxiety)	6	Tianeptine (78%) = amitriptyline (83%)
Stewart et al[81]	57	DSM-III dysthymic disorder (HAM-D ≥ 20)	6	Imipramine (78%) > phenelzine (58%) > placebo (33%)
Bersani et al[96]	30	DSM-III dysthymic disorder (possible major depressive episode) (HAM-D > 20)	5	Ritanserin (67%) > placebo (29%)
Versiani[97]	315	DSM-III-R primary dysthymia (≥ moderate symptoms)	8	Moclobemide = imipramine > placebo

*Percent responders shown in parentheses when reported (rates based on all randomized sample). Abbreviations: HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale.[107]

Table 3. Acute Phase Treatment in Randomized Controlled Efficacy Trials of Patients With Dysthymic Disorder*

Study	N	Diagnosis (Symptom Severity)	Duration (wk)	Results
Bakish et al[98]	50	DSM-III dysthymic disorder, not in major depressive episode (HAM-D ≥ 13)	7	Ritanserin (28%) = imipramine (22%) > placebo (2%)
Hellerstein et al[99]	32	DSM-III-R primary dysthymia, not in major depressive episode	8	Fluoxetine (62.5%) > placebo (18.8%)
Thase et al[66]	410	DSM-III-R primary dysthymia ≥ 5 y duration, not in major depressive episode (HAM-D >12)	12	Imipramine (64%) = sertraline (59%) > placebo (44%)

*Percent responders shown in parentheses when reported (rates based on all randomized sample).

tion. A large, multicenter study of outpatients with dysthymic disorder found marked improvement in social adjustment in both the sertraline- and imipramine-treated groups, but only a modest improvement in the placebo group over the course of the 12-week acute phase treatment trial (see Figure 2).

Furthermore, Thase and colleagues[66] reported significantly more patients treated with sertraline (84%) than imipramine (67%) completed the acute phase trial, and significantly more both responded (59% for sertraline; 64% for imipramine) and remitted (50% for sertraline; 44% for imipramine) with either active treatment than with placebo (44% responders and 28% remitters, respectively) (see Figure 3). These response rates are comparable to those found in episodic forms of major depressive disorder.[2]

What about longer term benefits of continuing treatment in the chronically depressed once an acute phase treatment response or remission has been obtained? Most continuation or maintenance phase studies to date have included those with recurrent forms of major depression to ensure that there would be a reasonable chance of detecting relapses or recurrences (Table 4). Nearly all of these studies are positive, meaning that continuation/maintenance phase treatments appear to offer protection not afforded by placebo (an exception is Georgotas et al.,[67] wherein phenelzine, but not nortriptyline, was an effective maintenance treatment in the elderly). The most definitive study to date revealed maintenance phase benefit of imipramine after 3 years[7] and even after 5 years[68] in highly recurrent major depressive disorder with full interepisode recovery. However, maintenance trials specifically aimed at the chronically depressed are not yet available, although a large multicenter comparison of imipramine and sertraline is ongoing.

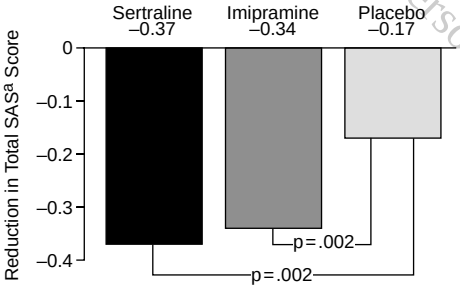
What is an Adequate Acute Phase Trial in the Chronically Depressed?

There is a belief (not yet fully evaluated by clinical research studies) that the longer a patient has been depressed, the longer the acute phase trial should be before the treatment may be expected to work. Schweizer and colleagues[69] found that there were faster and slower acute phase treatment responders to fluoxetine in a mixed (i.e., chronic and nonchronic) group of outpatients. That finding is corroborated by a number of other trials of medication alone,[70,71] and in combination with psychotherapy.[72,73] A recent investigation found both faster and slower responders (defined as 2 consecutive weeks of 17-item Hamilton Rating Scale for Depression [HAM-D][74,75] score ≤ 10) to either amitriptyline or desipramine in an outpatient population with major depressive disorder.[76] The latter group tended to have more chronic, longer standing

Table 4. Relapse/Recurrence Rates in Continuation/ Maintenance Phase of Randomized Controlled Efficacy Trials

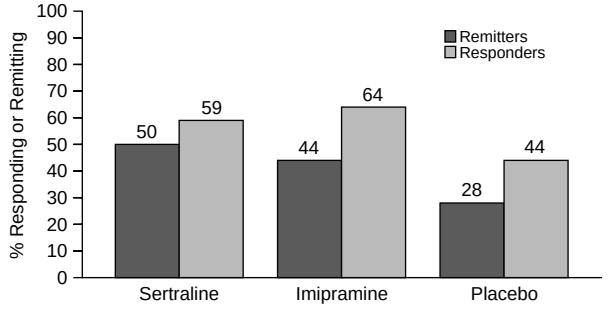
Study	Duration (wk)	Drug	Placebo
Mindham et al[85]	24	22% (amitriptyline or imipramine)	50%
Prien et al[100]	104	29% (imipramine)	85%
Stein et al[101]	24	28% (amitriptyline)	69%
Glen et al[102]	24, 52, 104, and 156	30%, 53%, 63%, and 69% (amitriptyline)	66%, 67%, 78%, and 89%
Prien et al[38]	52	45% (imipramine)	60%
	104	45% (imipramine)	75%
Montgomery et al[103]	52	26% (fluoxetine)	57%
Georgotas et al[67]	52	13% (phenelzine) 54% (nortriptyline)	65%
Frank et al[7]	156	21% (imipramine)	78%
Robinson et al[104]	52	30% (phenelzine)	80%
Montgomery and Dunbar[105]	52	15% (paroxetine)	39%
Doogan and Caillard[106]	44	13% (sertraline)	46%
Kupfer et al[68]	260	18% (imipramine)	67%
Kocsis et al[46]	104	11% (desipramine)	52%

Figure 2. Improvement in Occupational Functioning, Family Role, and Personal Relationships as Reflected in Total SAS Score*†



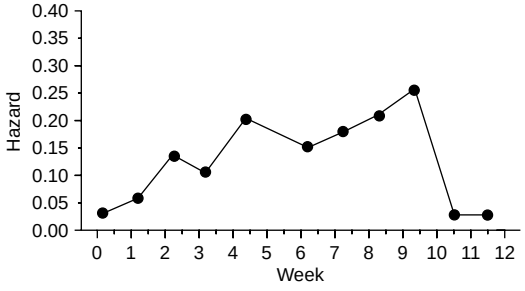
*Data on file. Pfizer Inc, New York, NY.
†Multicenter, double-blind, randomized, placebo-controlled study in 410 outpatients with DSM-III-R early-onset primary dysthymia of at least 5 years' duration and no concurrent major depression. Daily dosage range: sertraline—50–200 mg; imipramine—50–300 mg.
[a]Social Adjustment Scale (self-reported) (Weissman and Bothwell, 1976[108]).

Figure 3. Response and Remission Rates in Patients With Dysthymic Disorder in Acute Phase (12 Weeks) Treatment*



*Data from Thase et al.[66]

Figure 4. Overall Hazard Function (Response Declared If 2 Consecutive Weeks of HAM-D ≤ 10)*



*Data from Rush et al.[76]

major depressive disorder—as evidenced by either an earlier age at onset, longer overall length of illness (time from first onset to the present), and/or incomplete interepisode recoveries (Figure 4).

Thus, independent of the medication used, it may be true that the longer standing the depression, the longer the acute phase trial should be. That is, the more chronically depressed patients, even though they may have equivalent current symptom severity, take longer to respond to acute phase treatment than the less chronically depressed. Further, some evidence suggests that the more chronically and severely depressed may have a lower overall chance of responding to any one acute phase treatment.[5,77,78] These findings, which are similar to the treatment of congestive heart failure or other general medical conditions, deserve further study.

STRATEGIES, TACTICS, AND MANAGEMENT PRINCIPLES FOR THE CHRONICALLY DEPRESSED

Diagnostic Issues

As noted above, depressions—especially chronic depressions—are likely associated with other concurrent Axis I, II, and III disorders. Such comorbidities can make diagnosis more difficult. Clinically, chronic depressions are too often mistaken for Axis II disorders (i.e., the Axis II disorder may be recognized, but the concomitant mood disorder is not). However, careful diagnostic evaluation will often reveal that these patients have both an Axis II and a chronic mood disorder. Thus, the chronic course of the depressive illness should not be taken as evidence of an Axis II condition. Recall that while slightly over one half of chronically depressed patients have an Axis II condition, nearly one half do not.[49]

In order to obtain an accurate history of the patient's depressive episodes and interepisode depressive symptomatology, other informants who know the patient well

are especially helpful, in part because chronically depressed patients typically cannot recall times when they were not depressed. The effort to establish an accurate course of illness is critical because, if the depression is indeed chronic, both clinician and patient will more strongly consider multi-year maintenance medication treatment from the outset. Conversely, if the patient has substantial symptom-free intervals, the strategy for maintenance treatment may change.

To elicit this history rapidly, it is often helpful to show patients and families pictures of the different courses of depressive illness (as in Figure 1). Such pictorial representations help depressed patients select the course of illness that best describes themselves, and it helps to set the stage for a focused diagnostic interview.

It is also important to keep in mind that chronic mood symptoms or formal syndromes often coexist with other psychiatric disorders (obsessive-compulsive disorder, bulimia, or substance abuse) that may require additional specific treatments. So, the presence of chronic depressive symptoms should very quickly alert us to look for other nonmood psychiatric disorders, as well as for undiagnosed general medical conditions.[1,32,79]

Strategic Issues

To date, acute phase efficacy trials suggest that the chronically depressed deserve one (or more than one) medication trial(s) (see Thase and Rush[109] in this issue). Their chances of responding are good—maybe the same or, at worst, only somewhat less than the less chronic forms of depression.[80,81] This recommendation applies to dysthymic, double, and chronic major disorders. There is little evidence by which to decide what particular medication is likely to be effective, since tricyclics, serotonin selective reuptake inhibitors, and other agents (e.g., nefazodone and venlafaxine) appear to be effective. Thus, an empirical trial, and, if warranted, serial trials of several different medications may be needed. Of special importance are medications with longer term tolerability.

What is an acceptable acute phase response? Most data support the recommendation that a full remission, not simply a response (or improvement), should be the objective of acute phase treatment[2] (for a review, see Rush and Trivedi[82]). It has been reported that 20% to 30% of depressed patients may show only a partial response to treatment.[83,84] These partial responses are associated with higher rates of relapse.[26,27,85–87] Residual symptoms (e.g., as evidenced by HAM-D scores between 10 and 16) are also associated with continuing poor psychosocial, family, and work function. Montgomery et al.[87] have recommended a threshold value of < 8 on the HAM-D as evidence of a full remission. However, ongoing depressive symptoms of an even lower magnitude may herald an increased risk of relapse if the depressed individual is not receiving continuation phase pharmacotherapy.[26,27]

Does the combination of psychotherapy and medication offer a particular advantage in patients with chronic forms of depression? Data to address this question are sparse, although many clinicians view the combination as particularly useful in the chronically depressed.[2,6] Conversely, it is not true that all chronically depressed patients *require* concomitant psychotherapy. Evidence to date (e.g., Thase et al.[66]) reveals not only that a substantial proportion of patients attain a symptomatically remitted state, but that those who remit (as well as those who respond, albeit to a lesser degree) gain substantial improvements in function with medication and clinical management alone. A number of clinicians believe that those who respond but fail to remit with an adequate medication trial will benefit from the addition of psychotherapy (i.e., recommend a sequenced treatment approach, using psychotherapy for those with residual symptoms or impairment once medication has produced maximal benefits).[2]

Another key strategic decision is what to do should the initial drug fail or be found intolerable in the chronically depressed patient. Studies focusing on this issue are few indeed. Thase and Rush[109] (this issue) review the data for depressed patients that are particularly applicable to the more chronic forms.

A third strategic issue involves how long to continue an effective medication in the chronically depressed. The evidence to date supports multi-year maintenance phase treatment. This recommendation may be particularly strong for those with a previously chronic course since such histories typically predict substantial future chronicity and disability.

Tactical Issues

What can be said with regard to the treatment tactics for the chronically depressed? (1) The same antidepressant medication doses used in nonchronic forms have demonstrated efficacy; lower doses have not been diligently evaluated and, therefore, are not recommended. (2) Because of the suggestive evidence that at least some chronically depressed patients may take longer to respond to acute phase medication treatment (regardless of medication type), longer acute phase trials (e.g., 6–8 weeks) are reasonable.[88] As a rule of thumb, one should expect at least a 25% reduction in symptoms by Week 6 of an adequate dose if the chronically depressed patient is to have an ultimate satisfactory response. (3) With regard to doses in continuation and maintenance phases, recent studies showing efficacy have generally relied on the acute phase dose to which the patient responded.[7] Thus, dose reductions are not recommended during the longer term prophylactic treatment phases.[89]

Management Issues

We have found that it is often useful to specify and discuss with the patient several planned treatment steps at the

beginning of treatment, because if patients do not adequately respond to the first medication or are unable to tolerate it, their negative thinking biases may lead them to exit treatment prematurely. Furthermore, a chronic course of illness often destroys psychosocial supports, as well as occupational stability, with consequent economic stresses that compound the problem of adherence.[6]

To preemptively combat (and reduce) poor adherence, which is a common problem contributing to both nonresponse or partial response, as well as to relapses, once an effective medication is found, clinicians may find it most useful to engage their patients as collaborators, providing education and information to both the patient and family.[2,90,91] This approach is especially useful for the chronically depressed patient who may have had other treatment attempts (see Thase and Rush,[109] this issue). By mapping out an incremental, sequenced treatment program, by laying out specific treatment steps, by defining what patients and families might reasonably expect, and by identifying obstacles to adherence before they occur, clinicians can engage their patients as full partners in their own treatment.

Failure to obtain the desired results after the initial acute phase medication trial should lead clinicians and patients to reappraise, rediagnose (e.g., search for occult substance use; use of prescription medications or general medical conditions that could cause depression, etc.), and to recommit to the second "next" step—often another medication trial. The chances of responding to the second trial appear to be nearly as good as the chances of responding to the initial trial (e.g., 50%–60%) in previously untreated patients.[92]

CONCLUSIONS

Still unresolved (or largely uninvestigated) are a host of clinical issues critical to improving care for the chronically depressed patient. What is the next best step if the first medication fails? When is combined psychotherapy and medication indicated? Is a sequenced treatment plan (i.e., adding psychotherapy to those responsive to but not remitting with medication alone) strongly advised? Are persistent subthreshold depressions (i.e., depression, NOS) likely to go on to major depressive or dysthymic disorder? What treatments are called for in these patients? Does intervening early, thoroughly, and consistently lead, over the ensuing decades, to a lower likelihood of needing lifetime medication? Is longer term psychotherapy called for in some chronically depressed patients? Finally, are there ways to standardize and prospectively evaluate a range of adherence-enhancing procedures that truly help patients' families and practitioners? These are only a few of the most interesting, clinically important, and vexing clinical issues that need resolution in order to provide optimal patient management.

Conversely, substantial knowledge is now available to help those with chronic depression. We know that there are different kinds of chronic depression with differing courses of illness. They all have disastrous consequences on functioning and quality of life. They are not uncommon, and they are costly both in terms of patient suffering and the economic burden to society.

The aim of treatment is full symptomatic remission, which can be obtained with medication alone in some, but not all, patients. Both response and symptom remission are associated with significant functional improvement. Even though we are just beginning to learn how to treat these conditions, current evidence reveals that responses to a single medication are probably somewhat lower and may take a bit longer than for the nonchronic forms. While chronic depressions appear to respond to a range of medications, more definitive prospective trials, especially maintenance trials, are needed.

Since only about 40% to 50% of patients with chronic depression get well with the first acute phase treatment, it is important to consider subsequent steps should the first attempt be intolerable or fail. Whether improved remission rates could be further increased by combining medication and psychotherapy remains to be studied. Because of the high cost, substantial disability, and the likely efficacy of appropriate treatment, these patients not only deserve our patience, but also the more intensive and extensive clinical management required to obtain optimal results.

Drug names: amitriptyline (Elavil and others), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

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