Strategies and Tactics in the Management of Maintenance Treatment for Depressed Patients

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This article focuses on the strategies and tactics in the clinical management of maintenance treatment for depressed patients. The phases of treatment, indications for maintenance treatment, steps necessary to prepare patients for maintenance treatment (e.g., attaining optimal symptomatic control, providing knowledge, and developing a constructive attitude toward chronic disease management), teaching patients to measure symptoms during treatment, and clinical tips for managing symptomatic "blips" and recurrences during maintenance treatment are discussed.

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Treatment of major depressive disorder has been divided into acute, continuation, and maintenance phases.[1] Acute phase treatment aims at maximum reduction of symptoms and preferably the attainment of complete symptomatic remission. During the acute phase, evidence also suggests that a substantial return of daily function occurs even when medication alone is the treatment.[2] Continuation phase treatment aims to prevent the symptoms of the most recent episode from returning (relapse) and aims at continuing to improve psychosocial functioning. Maintenance phase treatment is reserved for those with highly recurrent or more chronic depressions (i.e., those most likely to suffer another episode in the short term) and aims at preventing recurrences (new episodes).[3]

Acute phase treatment may consist of medication, psychotherapy, or the combination (or, for selected patients, electroconvulsive therapy or light therapy). The combination of medication and psychotherapy is recommended for those patients with chronic depression, those with more complex illnesses (i.e., concurrent psychiatric or general medical conditions such as substance abuse or Axis II disorders), or those who have failed to respond fully (remit) to either treatment alone.[1] Recent evidence[4,5] indicates that when residual depressive symptoms remain after optimal medication benefit—even in those with recurrent major depression—they can be successfully remediated with cognitive-behavioral therapy, a finding consistent with previous guideline recommendations.[1,6]

It must be emphasized that the aim of acute phase treatment is total symptom remission, which necessitates some measurement of symptom severity at critical decision points during and at the end of acute phase treatment to determine whether remission has been attained. Evidence indicates that functional restoration follows symptom reduction by several weeks and that complete remission, as opposed to response with residual symptomatology, is associated with better overall functional restoration.[2]

Continuation phase treatment with medication is typically conducted with the same drug at the same dose that was effective in the acute phase. Theoretically, the duration of the continuation phase is dictated by the presumed natural course of the episode for the individual patient; that is, continuation phase treatment ends when the episode itself would have naturally ended. This treatment phase aims at continuing the suppression of symptoms, as well as further improving psychosocial functioning where indicated (e.g., Fava et al.[5]). Further information about disease management should be provided during continuation phase treatment, especially for patients going on to maintenance treatment. Transient symptomatic worsening ("blips") are not uncommon in continuation phase treatment, but they do not constitute a basis for changing treatment strategies. In fact, Koran and colleagues (L. M. Koran, M.D.; A. J. Gelenberg, M.D.; S. G. Kornstein, M.D.; et al., unpublished data, August 1998) found that, for those patients with chronic depression who had responded but not remitted during acute phase treatment, 46% will ultimately remit following continuation treatment. Thus, more prolonged treatment, even with the same medication and without the addition of psychotherapy, enables a substan-

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tial number of patients who had initially only partially responded to attain full remission. Conversely, 19% of those who responded without remission in the acute phase relapsed, in which case either augmentation treatment or a switch to another treatment is recommended.

Maintenance phase treatment is nearly always recommended for those with chronic or highly recurrent depressions, preferably with the same drug at the same oral dose that was effective during the acute phase. Maintenance treatment has been shown in randomized, double-blind, placebo-controlled trials to be effective after 5 years.[7] Although many randomized, placebo-controlled trials attest to the efficacy of maintenance treatment,[8–19] all report a 10% to 25% recurrence rate over a span of 1 to 3 years, even for patients adhering to the maintenance treatment. Conversely, transient symptomatic worsening also occurs during maintenance, so treatment plan revisions must be targeted to those with true recurrences.

Candidates for maintenance treatment are those patients who have had 3 previous major depressive episodes or those with 2 prior episodes and an associated risk factor (e.g., family history of bipolar or recurrent major depressive disorder, psychotic or severe prior episodes, closely spaced prior major depressive disorder episodes, incomplete recovery between episodes). Patient preference also plays a role in determining whether or not maintenance treatment should be implemented.[1]

PREPARING PATIENTS FOR MAINTENANCE PHASE TREATMENT

No one medication or psychotherapy is a panacea. By the end of 8 weeks of any single acute phase treatment, only about 50% to 60% of patients respond; remission occurs in only about 30%. Therefore, it is wise to consider various treatment options and plan specific treatment sequences to attain symptomatic remission during acute phase treatment. Response is associated with improved functioning, but remission (compared with response without remission) is associated with even better functioning. Furthermore, the disadvantages of response without remission include (1) reduced work, family, and other functional roles; (2) poorer prognosis (i.e., increased chances of recurrences); (3) higher health care utilization; (4) increased family burden; (5) a worsened prognosis—morbidity and mortality—for associated general medical conditions, based on more recent evidence[20–22]; and (6) theoretically, the potential for developing either treatment resistance or complications such as substance abuse.

In sum, when preparing patients for maintenance treatment, it is useful to have a multistep acute phase treatment plan in mind with which to attain full symptom remission and full psychosocial recovery. Such plans are sometimes called disease management protocols, guidelines, or algorithms. Treatment can be divided into strategies (what treatments to choose and in what order) and tactics (how to implement these strategies once chosen? what dose and duration of the medication are to be used?).[23,24] Table 1 outlines the principles upon which these guidelines (algorithms) are based.[25]

Table 1. Principles of Medication Guidelines

Individually tailor guidelines
Use proven treatments first
Select best drug that is
Safe and tolerable
Easiest to use (for patient)
Easiest to manage (for doctor)
Aim for symptom remission, not just response
Measure symptomatic outcome
No drug is a panacea
Do not give up
Psychosocial restoration follows symptom relief
Depression-targeted psychotherapies can help
More chronic depressions may respond more slowly

PATIENT/FAMILY EDUCATION

A multistep treatment plan should inform the patient and family of the potential need of attempting several steps to attain full symptom remission. Since depressed patients often have very negative outlooks, this information may further the therapeutic alliance and reduce premature treatment attrition. In fact, evidence indicates that patients who receive this education compared with those who do not are more likely to continue, rather than prematurely leave, acute phase treatment, and they are more likely to attain better outcomes.[26]

To achieve optimal control of the disorder and thereby facilitate successful maintenance treatment, it is important to develop a partnership with patients and families (or important others). This partnership aims at anticipating and overcoming obstacles to adherence, detecting and managing symptomatic or functional worsening, and implementing and utilizing psychosocial treatments should symptomatic or functional response be suboptimal. This partnership also anticipates and overcomes intermittent life events, such as general medical conditions, pregnancy, job, school, or family transitions, that could decrease function, impair adherence, or worsen depressive symptomatology.

There are 2 time points at which nonadherence is most likely: (1) when patients begin medication and encounter side effects (to which there is often substantial adaptation) and need to psychologically adapt to the notion of having a medical disorder that entails prolonged treatment, and (2) after substantial improvement and a return to normal functioning (i.e., once the disorder is under control). At each time point, patients weigh the apparent immediate costs and benefits of treatment. In the first case, the costs (side effects) seem too high; in the second, the benefits are not immediately apparent to patients.

Table 2. Obstacles and Solutions to Adherence Problems

Obstacle	Solution
Attitudes/misconceptions	Patient/family education
Side effects	Side effect monitoring, dose adjustment, adjunctive agents, medication switch
Euthymia leading to treatment discontinuation	Patient/family education
Symptom worsening	Symptom monitoring, psychotherapy, medication changes
Suboptimal functioning or psychosocial problems	Support, formal therapy, rehabilitative efforts
Discouragement	Patient/family groups (eg, Depressive and Manic Depressive Association, National Alliance for the Mentally Ill, Mental Health Association)

Table 3. Elements in Patient/Family Education

What is the disorder?
How to monitor symptoms and side effects?
What are treatment options?
What to do if first treatment fails? Or succeeds?
What if the depression returns?
When does treatment end?
What obstacles to adherence can be foreseen?
How to manage longer term life issues (work, marriage, pregnancy, intercurrent illnesses)?

Nonadherence can present in many forms, such as too low or too high a dose, incorrect timing of doses, substance abuse, and so on. Factors contributing to nonadherence include forces within the patient's social system (e.g., negative attitude toward treatment by a spouse), return of symptoms (which may lead patients to believe that no treatment will work), intercurrent illnesses, and use of medications that worsen antidepressant side effects, among others. While it is not possible to anticipate solutions to all potential obstacles to adherence, Table 2 suggests that certain solutions can be recommended to commonly encountered obstacles including attitudes and misconceptions, side effects, attainment of the well state, symptomatic worsening, suboptimal functioning, and ongoing discouragement or demoralization.

Table 3 outlines recommended elements for patient education. It is particularly important to educate patients and families that depression is like any other medical illness, is defined by signs and symptoms, has a specifiable course, and has a range of available treatments. As with the treatment of other general medical conditions, patients need to know that selection among treatment options often takes a trial-and-error approach; several different treatments may need to be tried before the best treatment is identified. As patients improve, it is important that they learn how to measure symptoms and side effects. Figure 1 shows such a tool now used in the Texas Medication Algorithm Project.[23–25,27] This approach is highly acceptable to patients and is feasible, not only in acute treatment to obtain maximal medication benefit, but also in maintenance treatment to detect symptomatic fluctuations.

Figure 1. Symptom and Side Effects Sheet for Depression[a]

In the last week the symptoms of my illness were:

No Symptoms (0)	Borderline (1)	Mild (2)	Moderate (3)	Marked (4)	Severe (5)	Extreme (6)

List the 3 most bothersome symptoms in the last week:

1.

2.

3.

Things I did for me:

The side effects of my medication were:

No Symptoms (0)	Borderline (1)	Mild (2)	Moderate (3)	Marked (4)	Severe (5)	Extreme (6)

List the 3 most bothersome side effects in the last week:

1.

2.

3.

Things I did for me:

List the medications you are currently taking:

1. 3.

2. 4.

About how long have you been taking each medication?

Weeks Months Years

[a]Adapted from reference 23. This material is in the public domain and can be reproduced without permission.

We believe that a self-report inventory to gauge symptom severity is more accurate than global reports or even clinician-rated global reports. Such self-report inventories include the Inventory for Depressive Symptomatology,[28,29] the Zung Depression Rating Scale,[30] the Beck Depression Inventory,[31,32] and the Carroll Rating Scale for Depression.[33] As patients become more stable, having gained symptomatic benefit from acute treatment, it is useful to provide additional education on a longer term perspective of the illness, including discussions of continuation and maintenance treatments. We have found particularly useful written pamphlets such as "Conquering Depression"[34] or "Treating Major Depression: A Patient's Guide."[35]

Table 4. Differential Diagnosis of Symptomatic Worsening

Nonpathologic spontaneous fluctuations (blips)
Precursors to the return of illness
Substance abuse
General medical conditions
Other medications
Drug interactions
Nonadherence
Change in psychiatric diagnosis
Life events

MANAGING PATIENTS DURING MAINTENANCE TREATMENT

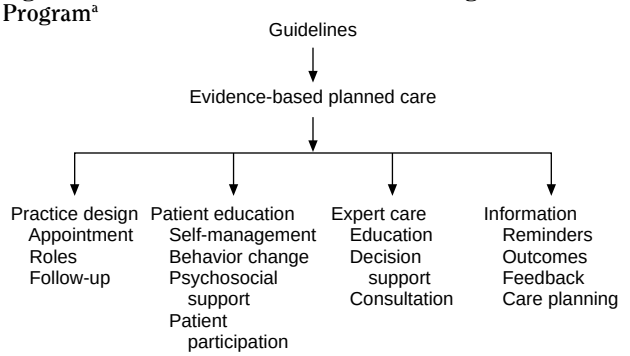
Once patients attain symptomatic remission (or at least maximum symptom reduction and functional improvement during acute and continuation treatments), clinicians should formally discuss maintenance treatment with those for whom it is the next logical step. The preferred length of maintenance treatment is unknown. My own preference is to provide the opportunity to discontinue on a once-every-other-year basis.

The main issue in managing patients during maintenance treatment is the differential diagnosis of symptomatic worsening. It is important to distinguish blips (spontaneous symptomatic fluctuations), which are not pathologic and do not herald the return of a major depressive episode, from true recurrences. Three tips may help in this differentiation. Does the pattern or progression of symptom worsening follow the same "symptomatic signature" associated with the onset of prior major depressive episodes? Does the symptom worsening extend over time based on repeated symptom severity measures? Is symptomatic worsening associated with significant reduction in functional capacity?

Most depressed patients have a rather repeatable pattern of symptomatic progression from the euthymic to the depressed state. For example, one individual may note insomnia first, followed by a lack of interest, then a sad mood, and finally impaired concentration and decision-making. Another might notice concentration problems first and only encounter insomnia as a later symptom. This symptom progression signature may help distinguish blips from recurrences, as the former often do not follow the typical symptom progression for that individual as defined by the history of prior recurrences.

Table 4 outlines the differential diagnosis of symptomatic worsening. It also includes occult substance abuse, the development of general medical conditions (e.g., thyroid disease), the presence of drug interactions (e.g., medications for intercurrent general medical conditions that lower the blood level of antidepressants), nonadherence, and the presence of severe life events. Having a record of symptom severity over time (e.g., patient self-report ratings) allows one to distinguish whether or not a return of symptoms is profound or modest and whether it is transient or prolonged.

Figure 2. Elements of a Chronic Disease Management Program[a]



[a]Adapted from reference 36. This material is in the public domain and can be reproduced without permission.

IMPLICATIONS FOR SYSTEMS OF CARE

Figure 2 outlines the elements of the chronic disease management program as recommended by Katon and colleagues.[36] This program is suitable for patients with major depressive disorder in maintenance treatment as well as for those with other chronic medical conditions (e.g., diabetes, arthritis, heart disease). Critical elements include a practice structure (e.g., aggressive follow-up of missed appointments; roles assigned to nonphysicians to contact, monitor, and support these patients frequently; the routine and repeated provision of information, education, and support). This structure follows similar models used to manage diabetes; in other words, missed appointments are not viewed as relief from a busy schedule, but rather a flag to call or otherwise contact the patient to ensure proper disease control.

Patient/family education should begin with the basics—what are the symptoms, signs, and treatment options? Including patients and families in long-term management of these conditions is recommended. Long-term planning of anticipated life events such as pregnancy, job change, or retirement, as well as education on how to manage intercurrent medical events, surgical or dental procedures, and so on, should be part of the information provided to families and patients. Because knowledge evolves rapidly and patients deserve expert care, provider education with easily accessible consultation and decision support is recommended. State-of-the-art information systems can provide reminders to both providers and patients and facilitate the use of outcome measures with timely feedback to both provider and patient.

Finally, changes are likely needed in the current incentive system to support providers in managing chronic diseases, especially maintenance treatment of major depression. This includes preferential access to and use of safer and better tolerated medications earlier rather than later; paying clinicians to provide patient/family education on a recurrent basis; payment for the measurement of symp-

toms and for visits to obtain adherence and educate patients, even if dose adjustment is not required and even if the patient is not symptomatic; and the development, training, and use of nonphysician staff to assist in long-term management. It may even prove cost-effective to pay for the screening of high-risk groups (e.g., the offspring of those with recurrent major depressive or bipolar disorder) before they seek treatment. Such individuals may go for years before coming to treatment, thereby suffering 5 to 10 years of disability and potentially developing a more difficult-to-treat disorder than might otherwise be the case if early detection and intervention were attained.

CONCLUSIONS

While much can be said about the practical art of managing patients in long-term maintenance treatment, many questions remain unanswered. For example, does earlier as opposed to later intervention actually increase the likelihood of success for more patients (i.e., Do patients respond faster if treatment begins earlier in the course of illness? Do they respond more thoroughly?)?

Secondly, can we find practical, clinical, biological, or other disease correlates by which to titrate and manage treatment instead of relying only on symptom measures? Most general medical diseases are associated with some intermediate biological or physiologic variable by which to manage treatment (e.g., blood sugar in diabetes). Other remaining questions include (1) Do multistep medication guidelines actually improve outcomes? (2) Which guidelines are best for which individuals? (3) Do antidepressant agents with dual, as opposed to single, mechanisms of action produce better remission rates? and (4) Does an aggressive disease management program that includes the above elements produce better outcomes?

On the other hand, we can conclude that many patients will require maintenance treatment. This treatment includes medication, education, symptom monitoring, and providing a supportive social system. The attainment and maintenance of complete remission—not just a response—by long-term partnerships with patients, families, and providers will optimize disease control and minimize both the burden of treatment and the disability due to the illness. Chronic disease management may likely require changes in our daily practices and changes in current delivery system incentives.

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