Treatment Recommendations Versus Treatment Realities: Recognizing the Rift and Understanding the Consequences

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Depression is a treatable disorder, although it often requires long-term therapy. To aid physicians in the effective long-term management of depression, treatment guidelines have been established by a number of organizations with minimum treatment duration recommendations. Unfortunately, numerous studies document a significant disparity between these recommendations and clinical practice realities. In particular, studies have shown that fewer than half of treated patients receive the recommended duration of 6 months of continuation therapy. Other clinical practice studies have reported that early discontinuation from therapy is associated with a substantial increase in the risk of relapse or recurrence. Long-term treatment of depression in clinical practice settings may benefit from a closer approximation to the conditions found in clinical trial settings.

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Depression is a highly treatable disorder, although it often requires long-term therapy. Treatment options are numerous and include a variety of antidepressants with proven clinical efficacy in reducing the acute symptoms of the disorder and in preventing relapse and recurrence. A number of organizations have set forth guidelines for the treatment of depression, with minimum dosage and treatment duration recommendations to aid physicians in the effective management of depression.

Unfortunately, a significant disparity between these recommendations and clinical practice realities has been documented. This rift between treatment recommendations and treatment realities is likely related to the difference in context between trial and community settings. As physicians consider new dosing strategies in an effort to improve the long-term treatment of depression, we must also consider adapting other practice strategies to optimally manage long-term treatment of depression. This is an important treatment objective, as studies consistently document that not even half of patients in clinical practice complete the minimum recommended continuation therapy duration.

Below, we review data documenting the disparity between treatment recommendations and treatment realities, discuss the consequences of failing to treat depression adequately, and explore how techniques utilized in clinical trials can be applied to clinical practice to improve the long-term treatment of depression.

TREATMENT RECOMMENDATIONS

Depression treatment has 3 distinct phases: acute, continuation, and maintenance, as illustrated in Figure 1. Acute treatment aims to achieve remission and alleviate depressive symptoms experienced during a depressive episode. Continuation treatment follows the acute resolution of symptoms and intends to prevent relapse of the current episode. Finally, maintenance phase treatment is indicated to prevent recurrence of new episodes of depression.

A number of world and national bodies have developed guidelines for both continuation and maintenance phase treatment of depression. These guidelines were established because the adequate treatment of depression requires continuation of therapy beyond acute symptom resolution. The recommendation for an extended therapy period is directly related to the high rates of relapse and recurrence that are associated with the disorder. With each new episode of depression, the risk of future episodes increases,[2–4] disability and quality of life worsen,[5] and an estimated 20% of patients develop chronic depression.[6] Considering these factors, prevention of subsequent episodes through

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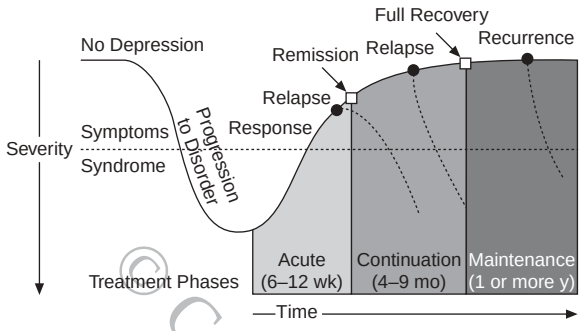
Figure 1. Development and Resolution of Depression[a]



[a]Adapted, with permission, from Kupfer.[1]

Table 1. Continuation Treatment Recommendations

Group	Duration
World Health Organization[7]	> 6 months
Royal College of Psychiatry/Royal College of General Practitioners[8]	4–6 months
American Psychiatric Association[9]	4–5 months

Table 2. Maintenance Treatment Recommendations

Group	Affective Morbidity	Duration
World Health Organization[7]	2 or more severe episodes	2 years
Royal College of Psychiatry[8]	2 or more severe episodes	Unspecified
American Psychiatric Association[9]	2 or more episodes	Unspecified
British Association for Psychopharmacology[12]	2 or more episodes	Indefinitely

the use of prophylactic treatment regimens is of paramount importance for patients who have suffered a second episode of depression.

The recommended duration of continuation treatment ranges from 4 to 6 months beyond the point of remission (Table 1). During the continuation period, patients with residual symptomatology, but who no longer meet diagnostic criteria for clinical depression, often experience further reduction in symptom severity and eventually reach an asymptomatic state (see Figure 1). Incomplete remission has been reported to increase the risks of both relapse[2,10] and recurrence.[10,11]

Treatment guidelines for maintenance phase therapy are summarized in Table 2. This treatment is not recommended for all patients suffering from depression. A number of organizations advocate maintenance therapy only for patients with a history of 2 or more episodes. Some organizations further limit the recommendation based on disease severity. In terms of the duration of maintenance phase therapy, the World Health Organization advocates a 2-year period,[7] whereas others do not specify a treatment duration, and the British Association for Psychopharmacology recommends that prophylactic treatment be continued indefinitely.[12]

Under ideal conditions, patients can reach full recovery and remain well indefinitely. Unfortunately, inadequate treatment is common, with frequent relapse and recurrence among patients seen in community practice.

TREATMENT REALITIES

Although the current treatment guidelines for major depression are largely consistent, are put forth by respected organizations, and are based on widely available clinical trial findings, implementation of these recommendations in clinical practice has not been established. A number of naturalistic studies have examined length of therapy and adherence to current depression treatment regimens in clinical practice settings. These studies consistently document that treatment in the community fails to reach recommended levels in a significant number of patients.

One recent retrospective study of a primary care health maintenance organization database examined treatment completion, defined as 180 days of therapy, among a small number of patients (N = 187) beginning treatment with fluoxetine, paroxetine, or sertraline.[13] The 6-month treatment completion rate was 30.5% overall, ranging from 22.3% to 45.1% across the 3 treatment groups (p = .009).

Another study examined a medical claims database of 1242 primary care patients.[14] Medical and pharmacy claims dated from 1990 through 1992 were reviewed for a 6-month period following a diagnosis of depression and the filling of a prescription for one of the qualifying antidepressant medications. Overall, only 35.8% of patients received 6 months of stable antidepressant therapy. A small number of patients switched or augmented (8.6%) their antidepressant treatment during the 6-month period, while the majority (55.7%) of patients discontinued treatment earlier than 6 months.

Somewhat disparate findings were reported in a prospective study of primary care patients (N = 536) randomly assigned to open-label treatment with one of 3 antidepressants.[15] On the one hand, the proportion of patients overall who remained on antidepressant therapy after 180 days remained high, at 70%. This finding was explained by the fact that many patients, particularly in the tricyclic antidepressant (TCA) cohorts, switched from their original antidepressant during the 180-day period. Alternatively, analysis of pharmacy refill data found that only 48% to 60% of patients received guideline-consistent treatment in terms of dosage for at least 90 days' duration. Treatment outcome did not differ across treatment groups. The study authors speculated as to whether feedback received during monthly efficacy assessments acted to improve treatment adherence.

In another retrospective database review,[16] 935 patients were followed for a 12-month period after initiating treatment on 1 of 3 selective serotonin reuptake inhibitors (SSRIs). Mean duration of continuous antidepressant treatment over the 1-year period ranged from 157 to 193 days across treatment groups. Although these therapy lengths are in the range of the 180-day benchmark used in other studies, treatment was assessed over a 1-year period that encompassed both the acute and continuation treatment phases for all patients and may have included maintenance phase treatment for a number of patients.

Taken together, this evidence demonstrates that despite broadly available treatment guidelines, the majority of patients in clinical practice are not receiving adequate antidepressant treatment for their depression. The data consistently indicate that duration of treatment and prescription refill rates are poor, and early discontinuation from treatment is unacceptably high. Although the data from these studies offer some insight into practice conditions, retrospective database review studies are limited in that they do not provide disease severity or clinical outcome measures.

CONSEQUENCES OF UNDERTREATMENT

Depression treatment guidelines are based on studies from clinical trial patients that demonstrate antidepressant efficacy in the prevention of relapse and recurrence with long-term treatment. Application of these guidelines in practice presumes that patients in clinical practice will also benefit from long-term therapy. However, treatment of patients in practice is often complicated by the presence of comorbidities and other life events that can impact a patient's ability to remain on treatment. Two recent naturalistic studies have examined the relationship between pattern of antidepressant usage during continuation therapy and subsequent risk for relapse and/or recurrence among clinical practice patients.

In a retrospective database study of a United States Medicaid population,[17] approximately 4000 patients who were treated during the years of 1989 through 1994 with TCAs or SSRIs were followed for up to 24 months. This included a 6-month treatment period following an index date of depression diagnosis coincident with an antidepressant prescription and up to an 18-month follow-up period to assess relapse or recurrence. A proxy definition of relapse or recurrence was determined by a gap of 6 months or more between antidepressant prescriptions, admission to the hospital or emergency room for mental health treatment, electroconvulsive therapy (ECT), or attempted suicide.

The patient population (N = 4052) studied included a large proportion of African Americans (47%), females (93%), and persons who were eligible for Aid to Families With Dependent Children (63%). TCAs and SSRIs were prescribed approximately equally (48% vs. 52%, respectively), psychotherapy was given to 18% of the patients, mental health specialist providers were seen by 40% of the sample, and a mean of 6 comorbid conditions were reported by patients.

During the 6-month treatment period, more than twice as many patients (70% vs. 30%) discontinued treatment early (had fewer than 4 antidepressant prescriptions) as received continuous therapy (having 4 or more antidepressant prescriptions). This finding is consistent with previous reports of the low numbers of patients receiving appropriate continuation therapy.

During the follow-up period, 24% of all patients experienced a relapse/recurrence. Survival analysis indicated that patients who discontinued treatment early were the most likely to experience a relapse/recurrence, whereas patients who had continuous use of a single antidepressant (no switching or augmentation) were least likely. In fact, patients who discontinued treatment early had a 77% increase in risk of relapse/recurrence.

A similarly designed study examined a population of patients in the United Kingdom who were treated with SSRIs.[18] This retrospective review of a primary care patient database included 7493 depressed adults who were treated with 1 of 3 selected antidepressants from January 1993 through November 1995. Again, patients were followed for 24 months, including a 6-month treatment period and an 18-month follow-up period. The treatment period provided data on the antidepressant use pattern, which was categorized as Early Discontinuation (< 120 days of antidepressant therapy), Switching/Augmentation (a change or addition to the original antidepressant), Titration (change in dose of original antidepressant), or Stable Use (≥ 120 days of therapy of original antidepressant). The 18-month follow-up period provided data on relapse/recurrence, which was again defined by proxy indicators. This included a gap of 6 months or more between antidepressant prescriptions, hospitalization, suicide attempt, ECT, or specialist referral.

Again, the duration of treatment received by patients during the 6-month treatment period was not consistent with guideline recommendations. The majority of patients were found to discontinue treatment early. In fact, more than twice as many patients were in the Early Discontinuation group (73%) than were in the Switching/Augmentation (4%), Titration (2%), or Stable Use (21%) groups combined.

During the 18-month follow-up period, approximately one quarter (23%) of all patients were found to have a relapse/recurrence. Patients in the Stable Use treatment group had the lowest rate of relapse/recurrence (20%), while patients in the Switching/Augmentation group had the highest rate (29%). Relative to patients in the Stable Use group, patients in both the Early Discontinuation and Switching/Augmentation groups had a significantly increased risk of relapse/recurrence ($p = .04$, $p < .001$, respectively). Additional factors, such as patient age, an-

xiolytic use, and number of nonpsychiatric diagnoses, were also found to significantly impact risk of relapse/recurrence.

The design of these studies was heavily skewed to identifying recurrence, rather than relapse. The endpoint is described as "relapse/recurrence," reflecting the lack of distinction provided by use of the proxy measures. Although the results of both studies highlight the importance of stable antidepressant therapy, consistent with treatment recommendations, in the prevention of relapse or recurrence, many fewer patients actually received stable therapy than discontinued early. However, as the authors of one of the studies point out,[17] the use of resource-based measures to proxy for relapse/recurrence may in fact seriously underestimate the risks because many depressed patients do not seek treatment for a subsequent episode.

An unresolved issue surrounding long-term treatment is whether classes of antidepressants differ in their ability to prevent new episodes. Limited evidence has been reported that may suggest improved prevention with older medications, such as TCAs, than with newer medications, such as the SSRIs. In one small study (N = 20) that examined the effect of dosage on recurrence prevention during maintenance treatment,[19] a 2-year survival rate of 60% was reported among patients given full-dose TCA treatment compared with patients given half of their acute treatment dose. It is noteworthy that this was a highly vulnerable group of patients who had a median of 5 prior episodes and who had already experienced one prospectively observed recurrence in the context of a larger trial[20] in which they had participated previously. In comparison, in a slightly larger study (N = 51) of full-dose SSRI maintenance treatment,[21] the 2-year survival rate was 45%. Both studies were conducted in patients with recurrent depression, which may have contributed to the low survival rates reported and highlight the need for continued research on prophylactic treatment strategies.

Regardless of the specific antidepressant medication chosen, long-term treatment has been shown to be effective in reducing the risk of relapse and/or recurrence in clinical practice patients. Therapy consistent with treatment guidelines has been associated with lower rates of relapse/recurrence among patients treated in clinical practice settings.[17,18] Unfortunately, these studies also document that a significant number of patients do not continue with therapy for the minimum recommended treatment duration.

IMPROVING LONG-TERM MANAGEMENT OF DEPRESSION

Although there is ample evidence that patients are not achieving long-term therapy goals in actual practice, the reasons behind the disparity between treatment recommendations and treatment realities are less clear. A number of potential contributing factors are presented in Table 3. For example, as was discussed earlier, clinical practice patients are often distinct from those seen in clinical trials in that their treatment is complicated by the existence of comorbidities.

Table 3. Reasons for Failing to Achieve Long-Term Therapy Goals

Factors	Examples
Incentives	$
Structural	Staff density/coordination
Patient	Comorbidity, chronicity, complexity
Procedural	Diagnosis, outcomes, visits
Contextual	Reason for treatment, "expert" vs local medical doctor
Informational	Patient education, consent

Another potential contributing factor is the clear difference between clinical practice and clinical trial settings. The long-term management of depression in clinical practice may benefit from adaptation of practice conditions that more closely mimic trial conditions. Of particular importance may well be the areas of diagnosis, patient education, outcome monitoring, and visit schedule and structure.

Diagnosis

A structured diagnosis is central to most clinical trial designs to ensure that the appropriate patient population is being studied. Performance of a structured diagnostic interview allows for more accurate identification of depressed patients, as well as determination of disease severity, symptom profile, and comorbidities. The benefits to clinical practice patients of receiving a structured diagnosis are readily apparent, as patients then have an increased likelihood of being offered an appropriate treatment given their symptoms, disease severity, and consideration of complicating comorbidities. However, making a structured diagnosis requires an adequate amount of time to administer the necessary diagnostic tools. Visit times, particularly in primary care, are frequently insufficient to allow for this kind of structured diagnosis.[22]

Patient Education

Patient education received during a treatment trial begins with the consent process, in which patients are provided information about both the disorder and the specific treatment being offered. Furthermore, the consent process provides patients with a more accurate appraisal of the changes that can be anticipated with treatment and the rate at which they are likely to occur. Patient education is thought to reduce attrition and improve management over the long term of the disease[23] and may also improve compliance with the drug treatment regimen.[3,24] Treatment knowledge has been associated with treatment preference,[25] thus, patient education may have the effect of promoting informed decision making and active involvement in treatment selection by the patient. Medication counsel-

ing was shown in one recent trial of depressed primary care patients to result in improved compliance and increased duration of treatment.[26]

Outcome Assessment

The rationale for measuring outcomes during clinical trials is equally applicable to community practice. Having a measure of symptoms and depression status at key decision points in therapy aids physicians in guiding an effective course of treatment.[23] In particular, appropriate adjustments to medication and treatment strategy and determination of remission can be made when physicians measure outcomes in a systematic way. Furthermore, it is important that proven methods be used for regular monitoring of treatment outcomes. Patient and physician global ratings may lack the precision needed to optimally implement treatments, whereas valid and reliable self-report inventories can provide this precision.[23]

Visit Schedule and Structure

During clinical trials, patients are seen on a regular visit schedule, the visit is structured to ensure adequate assessment, sufficient time is allowed for performance of the necessary visit objectives, and significant efforts are made to follow up with patients who fail to return. Unfortunately, this is not the case in routine community practice. As noted earlier, an inadequate visit duration may initially impact proper diagnosis of depression, but will also negatively affect efforts at patient education, adverse event assessment, and outcome measurement.[22] Furthermore, in practice settings there are often no defined targets for outcome, time limits for treatment, or incentives for continuing in treatment.

The long-term management of depression in practice settings may benefit from some lessons learned in clinical trials, but unique challenges remain. In particular, the prevalence of co-occurring conditions is often higher in naturalistic settings than in randomized trials. Additionally, trials are of a limited duration, whereas treatment in practice can continue indefinitely. The impact of these variables on treatment received by clinical practice patients has not been fully explored. Continued efforts to improve our understanding of clinical practice dynamics will ultimately benefit patients facing long-term treatment for depression.

CONCLUSIONS

In the effective management of depression, long-term therapy beyond acute symptom resolution has been shown to reduce the risks of relapse and/or recurrence. Treatment guidelines have been set forth by a number of world and national bodies. In general, these guidelines recommend a continuation treatment phase of 4 to 6 months' duration for all patients and a 2-year or longer maintenance phase for patients at risk for recurrence.

A number of studies have documented the short duration of actual antidepressant treatment received by many patients who suffer from depression. In these studies, less than half the patients continue on therapy for even 6 months. Two naturalistic database review studies reported that patients who discontinued treatment early were at increased risk of relapse or recurrence. However, patients who were maintained on stable therapy for 6 months, with no switching, augmentation, or titration, were found to have the lowest risk of relapse or recurrence.

Nearly ideal prophylaxis can be achieved when nearly ideal treatment conditions prevail. These conditions include treatment with an appropriate medication, use of regular assessments at regularly scheduled visits, and complete remission of symptoms being required prior to entry into continuation or maintenance phase therapy. In order to meet these conditions and achieve ideal prophylaxis, optimization of medication, clinician, patient, and setting factors must all be considered.

Drug names: fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft).

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