Sequential Treatment of Mood and Anxiety Disorders

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Objective: Administration of treatments in a sequential order is a common practice in clinical medicine, but has received insufficient attention in psychiatry. The aim of this review was to survey the literature concerned with a sequential use of pharmacotherapy and psychotherapy in mood and anxiety disturbances.

Data Sources and Study Selection: A review of the clinical trials in which treatment components were used in a sequential order (i.e., pharmacotherapy followed by psychotherapy, psychotherapy followed by pharmacotherapy, one drug treatment following another, or one psychotherapeutic technique following another) was performed. Studies were identified by using MEDLINE (English language articles published from 1967 to March 2005; keywords: *sequential treatment*, *drugs and psychotherapy*, *combined treatment* related to *depressive disorder*, *bipolar disorder*, *depression*, *mania*, *anxiety disorders*, *panic disorder*, *social phobia*, *obsessive-compulsive disorder*, *generalized anxiety disorder*, and *posttraumatic stress disorder*) and a manual search of the literature and *Index Medicus* for the years 1960 to 2005.

Data Synthesis: In unipolar recurrent depression, the sequential use of pharmacotherapy was found to reduce relapse rate. In bipolar disorder, the use of psychotherapeutic strategies in patients who were already undergoing treatment with mood stabilizers was also found to yield clinical benefits. In anxiety disorders, the sequential use of pharmacotherapy and psychotherapy was not found to improve long-term outcome.

Conclusion: The sequential treatment of mood and anxiety disorders does not fall within the realm of maintenance strategies. It is an intensive, 2-stage approach, which is based on the fact that one course of treatment with a specific treatment (whether pharmacotherapy or psychotherapy) is unlikely to entail solution to the complex array of symptoms of patients with mood and anxiety disorders. The sequential model introduces a conceptual shift in current assessment methods.

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Administration of treatments in sequential order is a common practice in clinical medicine, particularly when treatment fails. If the physician prescribes antibiotic A to eradicate an infection and the ensuing response is judged to be unsatisfactory, he or she switches to antibiotic B, hoping to get a better outcome. The process is by approximation, applies only if treatment fails, and can be potentially avoided by appropriate pretreatment tests (e.g., in vitro determination of the susceptibility of bacteria to antimicrobial drugs). This sequential administration of treatments also occurs in clinical psychiatry. It may involve switches to different types of drugs, as is often the case in drug-refractory depression.[1] There are also examples of changes of type of treatment: use of antidepressants after unsuccessful cognitive-behavioral therapy (CBT) for depression[2] or panic disorder[3,4] and use of CBT in the management of drug-resistant major depressive illness[5] or obsessive-compulsive disorder.[6]

In clinical medicine, however, there is also another type of sequential treatment, which is not related to the partial remission or failure associated with a specific therapy. Instead of administering different therapies together, there is the planned sequential administration of different therapies, based on some specific effects induced by each therapy that provide additional benefits in the course of time. Examples are provided by the sequential administration of different cycles of pharmacotherapy in breast cancer,[7] human immunodeficiency virus (HIV)-1 infection,[8] chronic hepatitis,[9] psoriasis,[10] and essential hypertension.[11] In many illnesses, in fact, using

2 or more therapies is the rule rather than the exception, due to the failure of monotherapy to control moderate-to-severe disease or to yield remission. Reasons for administering 2 treatments in sequential order instead of simultaneously may include consideration of side effects, greater adherence of the patient with monotherapy, loss of efficacy over time of monotherapies, and antagonistic effects of 2 concurrent treatments. The differential goals of studies may be concerned with the effects of the addition of 2 modalities in sequence compared with single-mode treatment on acute response or long-term outcome (with particular reference to relapse or recurrence) or both. The characteristic of this type of treatment is that the sequence is performed regardless of the outcome of the first component (whether treatment failure occurred or not), as a preplanned strategy.

In the past decade, several investigations in clinical psychiatry have suggested the usefulness of a sequential way of integrating pharmacotherapy and psychotherapy in mood and anxiety disorders. The aim of this article was to survey this literature and its implications for the current practice of psychiatry. Clinical trials in which treatment components were used in a sequential order (i.e., pharmacotherapy followed by psychotherapy, psychotherapy followed by pharmacotherapy, one drug treatment following the other, or one psychotherapeutic technique or component following another) in mood and anxiety disorders were included in this review. Studies involving treatment failures or in which the same treatment modality was used both for acute treatment and as a continuation or maintenance strategy were not considered. Trials were identified by using MEDLINE (English language articles published from 1967 to March 2005; keywords: *sequential treatment*, *drugs and psychotherapy*, *combined treatment* related to *depressive disorder*, *bipolar disorder*, *depression*, *mania*, *anxiety disorders*, *panic disorder*, *social phobia*, *obsessive-compulsive disorder*, *generalized anxiety disorder*, and *posttraumatic stress disorder*) and a manual search of the literature and *Index Medicus* for the years 1960 to 2005. The article consists of 3 parts: a discussion of the clinical rationale for integrating treatments in a sequential order; a review of the literature on clinical trials in unipolar depression, bipolar disorder, and anxiety disorders; and a consideration of the implications of the sequential model for current practice, with special reference to assessment.

RATIONALE

Residual symptoms, despite successful response to therapy, appear to be the rule after completion of drug or psychotherapeutic treatment in both mood and anxiety disorders.[12,13] The presence of residual symptoms has been correlated with poor long-term outcome.[12,13] These findings have led to the hypothesis that residual symptoms upon recovery may progress to become prodromal symptoms of relapse and that treatment directed toward residual symptoms may yield long-term benefits.[14]

Treatment that potentially aims to different effects (e.g., pharmacotherapy and psychotherapy) may thus be used in a sequential order. One type of treatment (e.g., psychotherapy) may be employed to improve symptoms that the other type of treatment (e.g., pharmacotherapy) was unable to affect. This use of sequential treatment may be particularly important when treatments provide different modulations of cortical-limbic pathways, such as CBT and antidepressant drugs in major depression.[15]

Even though psychotherapy-pharmacotherapy combinations have been shown to be more effective than monotherapy in a number of psychiatric disorders, the effect size observed favoring combined treatment has been generally rather modest in mood and anxiety disorders.[16–18] A synergistic interaction between treatments used in this combination has not emerged.[16] Indeed, a few studies in anxiety disorders[19–21] have also suggested the possibility of a detrimental effect, as may also occur in clinical medicine. An antagonistic effect of tamoxifen and simultaneous chemotherapy in breast cancer, for instance, has been recently reported and has introduced the possibility of sequential, instead of simultaneous, treatments.[22]

Another line of evidence potentially supporting the sequential model in affective disorders is the increasing awareness of the role of comorbidity.[23,24] In major depression, two thirds of patients meet the criteria for another Axis I disorder (particularly anxiety disorders) and one third have 2 or more additional disorders (i.e., in addition to major depression).[25] The presence of anxiety disorders appears to predict persistence and recurrence of depressive illness in major depression.[26,27] It is thus unlikely that monotherapy may entail solution to such complex disturbances, especially since some forms of comorbidity may be covered by the acute manifestations of the disorder and become evident only when the most severe symptoms have abated.[12]

Several modalities of clinical applications of the sequential model have been used in the treatment of mood and anxiety disorders.

USE OF PSYCHOTHERAPY AFTER PHARMACOLOGIC TREATMENT

Unipolar Depression

In a controlled therapeutic trial,[28] 40 patients with major depressive disorder who had been successfully treated with antidepressant drugs were randomly assigned to either CBT or clinical management of residual symptoms. In both groups, antidepressant drugs were tapered and discontinued. The group that received CBT treatment had a significantly lower level of residual symptoms after drug discontinuation in comparison with the clinical

management group. CBT also resulted in a lower rate of relapse, with achievement of statistical significance at a 4-year follow-up.[29] These differences faded at a 6-year follow-up.[30] However, when multiple relapses were considered, patients in the CBT group had a significantly lower number of depressive episodes than those in the standard clinical management group.[30] The aim of this approach was to spend CBT resources when they are most likely to make a unique and separate contribution to patient well-being and to achieve a more pervasive recovery. This sequential approach also was applied by the same group of investigators[31] to 40 patients with recurrent major depression. These patients met the criteria outlined by Frank et al.,[32] that is, 3 or more episodes of unipolar depression (with the immediately preceding episode being no more than 2.5 years before the onset of the present episode). Patients were randomly assigned to either CBT for residual symptoms—supplemented by lifestyle modification and well-being therapy[33,34]—or clinical management. In both groups, antidepressant drugs were tapered and discontinued. At a 2-year follow-up, CBT resulted in a significantly lower relapse rate (25%) than did clinical management (80%). The differential relapse rate was found to be significantly related to the abatement of residual symptoms.[35] At 6-year follow-up, CBT still resulted in a significantly lower relapse rate (40%) than did clinical management (90%).[36]

Other groups of investigators lent support to the sequential use of pharmacotherapy and psychotherapy for relapse prevention in unipolar depression. Paykel et al.[37] randomly assigned 158 patients with recent major depression, partially remitted with antidepressant treatment but with residual symptoms, to clinical management or clinical management plus cognitive therapy. Patients received continuation and maintenance antidepressants during a 1-year follow-up. The relapse rate was 47% in the clinical management group and 29% with clinical management plus CBT. There was a small but statistically significant effect on residual symptom levels.[38] Cost-effectiveness analyses showed substantial benefits with the CBT approach.[39] At a 6-year follow-up,[40] effects in prevention of relapse and recurrence were found to persist up to $3^1/_2$ years after the end of CBT.

Similar results were obtained with mindfulness-based cognitive therapy (MBCT). Teasdale et al.[41] randomly assigned 145 patients in remission or recovery from major depression to treatment as usual (TAU) or TAU supplemented by MBCT. For patients with 3 or more previous episodes of depression, who constituted 77% of the sample, relapse rates were 66% for the TAU controls and 37% for the patients also receiving MBCT.[41] Since MBCT was administered in groups, this study provided the first demonstration that the sequential model may yield beneficial results in the group format as well. There were no significant differences in outcome, however, for patients with only 2 previous episodes of depression. The favorable results with MBCT were replicated in a subsequent study[42] involving 75 patients in remission or recovery from major depression.

Bockting et al.[43] have recently reported the outcome of a randomized controlled trial of cognitive group therapy to prevent relapse in a group of high-risk patients diagnosed with recurrent depression. One hundred eighty-seven patients were randomly assigned to TAU, including continuation of pharmacotherapy, or to TAU plus group cognitive therapy. During a 2-year follow-up, cognitive therapy resulted in a significant protective effect, which increased with the previous number of depressive episodes experienced.

One study, however, has failed to substantiate the clinical advantages of the sequential model.[44] One hundred thirty-two patients with major depression who achieved remission with fluoxetine were randomly assigned to receive CBT and medication or medication management alone and were followed for up to 28 weeks. Relapse rates did not differ between the 2 groups, even though the addition of CBT was associated with attributional style gains.[45] A major limitation of this study was, however, the duration of follow-up (in previous studies, maximal gains tended to occur at a later point).

The results of the randomized controlled trials lend support, therefore, to the use of a sequential treatment model (pharmacotherapy followed by psychotherapy) for preventing relapse in unipolar depression. This approach appears to be particularly important in recurrent depression. However, since incomplete recovery from the first lifetime major depressive episode was found to predict a chronic course of illness during a 12-year prospective naturalistic follow-up,[46] this sequential approach may be indicated whenever substantial residual symptomatology is present.

The advantages of keeping medication during psychotherapy versus tapering and discontinuation have not been directly compared with sequential studies. Some inferential indications may come from a study by Blackburn and Moore.[47] In their study, 75 outpatients with recurrent major depression were allocated to 1 of 3 groups: short-term and maintenance (2 years) treatment with antidepressant drugs, CBT in the short-term and maintenance phases, or antidepressant use in the short-term phase and CBT for maintenance. CBT displayed a similar prophylactic effect to maintenance medication. There were no significant differences among treatments. Those results have been confirmed in a recent trial by Hollon et al.[48] involving 104 patients who responded to treatment (either CBT or medication). Patients who responded to CBT were withdrawn from treatment and compared to medication responders who had been randomly assigned to either continuation medication or placebo withdrawal during a 12-month period. Patients who survived the continuation phase with-

out relapse were withdrawn from all treatment and monitored during a 12-month naturalistic follow-up. Patients who had completed CBT were significantly less likely to relapse (31%) than patients on placebo (76%) and no more likely to relapse than those who kept on taking continuation medication (47%). Survival analysis of the naturalistic follow-up indicated that CBT, unlike antidepressant drugs, had an enduring effect extending beyond the end of treatment.[48] The results of these 2 studies[47,48] therefore suggest that discontinuation of antidepressant drugs may be feasible in subgroups of patients when CBT is provided.

A novel indication for the sequential model has been provided by a very small pilot study, which concerned 10 patients with recurrent depression who relapsed while taking maintenance antidepressant drugs.[49] Patients were randomly assigned to dose increase and clinical management or to CBT and maintenance of the antidepressant drug at the same dose. Four of 5 patients responded to a larger dose, but all had relapsed again at that dose during a 1-year follow-up. Four of 5 patients responded to CBT, but only 1 relapsed during follow-up. The data from this pilot study[49] and from a case report[50] should, of course, be interpreted with caution and need to be confirmed with large-scale controlled studies, but they may suggest that the application of a sequential model is feasible when there is a loss of clinical effects during long-term antidepressant treatment.[51]

Bipolar Disorder

The hypothesis that reduction of residual symptoms by CBT could yield long-term beneficial effects in patients with bipolar disorder, as was found to be the case in recurrent unipolar depression, was specifically tested in a pilot study.[52] Fifteen patients with bipolar I disorder, who relapsed while on lithium prophylaxis despite initial response and adequate compliance, were treated by CBT in an open trial. A 2- to 9-year follow-up was performed while the patients were on lithium treatment. Five of the 15 patients had a new affective episode during follow-up. CBT was associated with a significant reduction of residual symptomatology. These clinically impressive results suggested that a trial of CBT may enhance lithium prophylaxis and improve long-term outcome of bipolar disorder.[52]

Four randomized controlled studies concerning the addition of psychotherapy in patients already undergoing treatment with mood stabilizers support these indications. In a study by Scott et al.,[53] 42 patients with bipolar I or II disorder who were on medication were randomly assigned to CBT or 6-month waiting-list control, which was then followed by CBT. There were significantly greater reduction in symptoms and improvements in functioning with CBT. Lam et al.[54] randomly assigned 103 patients with bipolar I disorder, who experienced frequent relapses despite the prescription of commonly used mood stabilizers, to a group who received individual CBT or a control group with regular psychiatric follow-up. The CBT group displayed significantly fewer bipolar episodes, fewer residual symptoms, and higher social functioning. Colom et al.[55] evaluated the effects of group psychoeducation to prevent recurrences in bipolar I and II disorders. One hundred twenty patients in remission for at least 6 months prior to inclusion in the study, who were receiving standard pharmacologic treatment, were randomly assigned to group psychoeducation or nonstructured group meeting. Psychoeducation involved 20 sessions of 90 minutes each aimed at improving illness awareness, treatment compliance, early detection of prodromal symptoms, and lifestyle modification. It significantly reduced relapses during a 2-year follow-up. The results were replicated in a smaller study[56] involving 50 patients with optimal treatment adherence, suggesting that the effects of psychoeducation go beyond compliance enhancement, and in a study involving caregivers of stabilized bipolar patients.[57]

These studies suggest the clinical advantages of adding psychotherapy to the treatment regimen of patients who are already taking mood stabilizers.

Anxiety Disorders

There are only 2 anxiety disorders (panic disorder and obsessive-compulsive disorder) in which sequential treatment involving the use of psychotherapy after pharmacotherapy was performed. In an open pilot study by Mavissakalian,[58] 35 patients who had panic disorder with agoraphobia and had successfully completed 8 weeks of treatment with imipramine were offered further 8 weeks of treatment with imipramine and the addition of exposure. Significant improvements occurred on all measures in the first 8 weeks. However, further significant improvements took place between weeks 8 and 16 of treatment.

De Beurs et al.[59] investigated whether the effects of exposure treatment for panic disorder with agoraphobia could be enhanced by adding specific interventions before the start of exposure treatment. Ninety-six patients were randomly assigned to double-blind, placebo-controlled fluvoxamine followed by exposure, psychological panic management followed by exposure, or exposure alone. The combination of fluvoxamine and exposure demonstrated efficacy superior to that of other treatments at the end of the trial.[59] However, these advantages faded at a 2-year naturalistic follow-up.[60]

Marks et al.[61] randomly assigned 40 chronic obsessive-compulsive ritualizers to treatment with clomipramine or placebo for 8 months. During weeks 4 to 7, these 2 groups were each randomly split into treatment by relaxation or exposure in vivo, and during weeks 7 to 10 all patients had exposure in vivo. Clomipramine produced significant improvements in both rituals and mood, relaxation produced little change, and exposure produced improvement

in rituals. Clomipramine enhanced compliance both with exposure and with relaxation. Drug effects on obsessive-compulsive symptoms, unlike effects of exposure, faded at a 2-year follow-up.[62]

Van Balkom et al.[63] randomly assigned 117 patients with obsessive-compulsive disorder to 5 treatment conditions: cognitive therapy, exposure in vivo with response prevention, fluvoxamine with addition of cognitive therapy at mid-treatment, fluvoxamine with addition of exposure with response prevention at mid-treatment, and a waiting-list control condition. All treatments were significantly more effective than the waiting list condition, but did not differ among each other.

The available studies on anxiety disorders do not substantiate long-term benefits from the sequential combination of pharmacotherapy and psychotherapy. However, more research is needed, also in view of the fact that many patients with phobic disorders who are referred to tertiary care centers for psychotherapy are already undergoing treatment with psychotropic drugs[64,65] and that the sequential approach has not been applied to generalized anxiety disorder, social phobia, and posttraumatic stress disorder (PTSD).

USE OF PHARMACOTHERAPY AFTER PSYCHOLOGICAL TREATMENT

There is little research on the sequential use of psychotherapy and pharmacotherapy in patients with mood and anxiety disorders, despite the fact that successful psychotherapy is also associated with substantial residual symptomatology.[12,13,64,65] The literature is limited to partial or unsatisfactory response to psychotherapy.[2–4] Frank et al.[66] used a successive cohort approach to compare 2 similar groups of patients with recurrent unipolar depression: one in which the combination of interpersonal psychotherapy (IPT) and pharmacotherapy was initiated at the beginning (N = 180), and a second in which IPT alone was provided first and only those who did not remit were given the combination treatment (N = 159). The remission rate was significantly higher in the latter group. The results thus suggested that the strategy of offering IPT to women with recurrent depression, adding pharmacotherapy only in case of incomplete remission, might be advantageous.

SEQUENTIAL USE OF TWO PSYCHOTHERAPEUTIC TECHNIQUES

Within psychotherapeutic approaches, Emmelkamp et al.[67] deserve credit for suggesting the feasibility of applying different therapies consecutively instead of in combination and the need to compare the 2 approaches in controlled studies. The sequential approach may involve the use of 2 different psychotherapeutic ingredients (e.g., behavioral therapy consisting of exposure homework followed by cognitive restructuring), which can also be provided in the same package (CBT). An attempt to demonstrate the effectiveness of this sequential approach (involving exposure in vivo followed by cognitive therapy) compared to a strategy in which the 2 approaches were integrated from the start did not yield significant differences in social phobia.[68] Similarly, exposure preceded by self-instructional training was not found to be more effective in obsessive-compulsive patients than exposure alone.[69]

Fava et al.,[70] however, recently evaluated the sequential combination of different psychotherapeutic strategies and not simply of treatment components in generalized anxiety disorder. Twenty patients were randomly assigned to 8 sessions of CBT or the sequential combination of 4 sessions of CBT followed by 4 sessions of well-being therapy (WBT). WBT is a short-term psychotherapeutic strategy that is aimed at improving psychological well-being and has several points of differentiation from CBT, including the fact that the focus in WBT is on instances of emotional well-being, whereas the focus of CBT is on distress.[33] Significant advantages of the CBT-WBT sequential combination over CBT only were detected, and such gains were maintained at 1-year follow-up. These preliminary results lend support to a sequential use of treatment components for achieving a more sustained recovery in generalized anxiety disorder.

Cloitre et al.[71] treated 31 adult female victims of child abuse with chronic PTSD with a sequential combination of skills training in affective and interpersonal regulation and prolonged imaginal exposure and compared these results with those obtained in a minimal attention waitlist condition consisting of 27 women. The goal of the first phase of treatment was to address problems in affective and interpersonal functioning in order to strengthen the therapeutic alliance and improve emotion regulation skills and thus facilitate subsequent use of exposure. There was a significantly greater reduction of symptoms in patients who had been treated, and a lower rate of symptom worsening. The lack of a control group with exposure only hinders demonstration of a clear support to this sequential approach.[72]

Current psychotherapeutic strategies, particularly in the CBT realm, use several ingredients from the beginning (e.g., cognitive restructuring, exposure, relaxation). It would be of interest to verify whether sequential use of single treatment components may yield significant advantages in both mood and anxiety disorders. For instance, in a modified CBT approach to drug-resistant major depression,[5] therapeutic ingredients were introduced at different times (behavioral activation first and cognitive restructuring later). Psychotherapy research comparing different times of administration of ingredients may yield important modifications in current protocols.

SEQUENTIAL USE OF TWO PHARMACOLOGIC STRATEGIES

The sequential use of pharmacologic strategies in affective disorders has been traditionally limited to instances of treatment resistance.[1] A notable exception has been the use of lithium to reduce relapse in unipolar depression.[73]

It has also been suggested[74] that the most effective drugs in treating acute depression may not be the most suitable for postacute or continuation treatment. During the 6-year follow-up of a randomized controlled trial comparing the sequential use of CBT versus clinical management in 40 patients with recurrent depression,[36] when the first relapse ensued, patients were treated with the same antidepressant drug that had been used in the previous episode. Clonazepam was added to the treatment regimen and was continued when the antidepressant drug was stopped. The mean survival time after introduction of clonazepam was significantly longer than the one before the first relapse. Even though the uncontrolled nature of the intervention hinders any conclusion, the issue is worthy of further research in view of the beneficial effects of treatment of phobic disturbances on the incidence of depression during long-term follow-up of anxiety disorders[64,65] and of coadministration of clonazepam and antidepressants in major depression.[75]

Menza et al.[76] have reviewed the literature on residual symptoms in unipolar depression and have postulated the sequential use of antidepressants and drugs that may specifically reduce fatigue, sexual dysfunction, anxiety, and sleep disturbances. Such treatment may potentially affect quality of life and improve long-term outcome by decreasing or eliminating the residual symptomatology.

IMPLICATIONS FOR ASSESSMENT AND TREATMENT PLANNING

The literature that has been reviewed has several potential implications for clinical practice, but should be interpreted with caution in view of several issues. First of all, there are insufficient studies exploring the various types of sequential approaches in mood and anxiety disorders, with the exception of pharmacotherapy followed by psychotherapy in unipolar depression and bipolar disorder. Second, the sequential design is exposed to the risk of providing one treatment in a more expert manner than another (e.g., use of psychotropic drugs compared with psychotherapy). Third, certain types of treatment that have been used, such as mindfulness therapy and WBT, may not be widely available and entail difficulties in translation to practice from the "expert" site. Fourth, when a sequential treatment is compared with a minimal intervention control group (such as clinical management or TAU), the effect might have been achievable by any active treatment and may not be specific to the treatment at hand. Finally, several of these studies were based on patients who had responded to initial treatment; thus, these studies may have excluded patients at high risk who may have dropped out early. As a result, the indications arising from the literature we reviewed should be seen as tentative.

Nonetheless, there are considerable implications for assessment and treatment planning that are worthy of clinical attention. The sequential model calls in fact for a substantial modification of the flat, cross-sectional approach based on DSM-IV criteria only. This modification is based on a longitudinal view of the development of disorders.[14] A satisfactory assessment requires multiple points of observation during the course of affective illnesses. Such observations may disclose psychopathologic features that are overshadowed by the acute manifestations of the affective disorder. As a result, 3 assessment phases are required, with modalities that depart from those commonly used in psychiatric practice. The key issue is in fact to match treatment ingredients with psychopathologic findings.

Initial Assessment

The majority of patients with mood and anxiety disorders do not qualify for one, but for several Axis I and Axis II disorders.[23–25] Very seldom, these different diagnoses undergo hierarchical organization (e.g., generalized anxiety disorder and major depression), or attention is paid to the longitudinal development of disorders. There is comorbidity that wanes upon successful treatment of one disorder, e.g., recovery from panic disorder with agoraphobia may result in remission from co-occurring hypochondriasis, without any specific treatment for the latter.[13] Other times, treatment of one disorder does not result in disappearance of comorbidity. For instance, successful treatment of depression may not affect preexisting anxiety disturbances.[28]

Emmelkamp et al.[67,77] have introduced the concept of macroanalysis (a relationship between co-occurring syndromes is established on the basis of which condition should be treated first). For instance, a patient may present with major depressive disorder, obsessive-compulsive disorder, and hypochondriasis. In terms of macroanalysis, the clinician may give priority to the pharmacologic treatment of depression, leaving to posttherapy assessment the determination of the relationship of depression to obsessive-compulsive disorder and hypochondriasis. Will they wane as depressive epiphenomena, or will they persist, despite some degree of improvement? Should, in the latter case, further treatment be necessary? What type of relationship do obsessive-compulsive symptoms and hypochondriasis have? If the clinical decision of tackling one syndrome may be made during the initial assessment, the subsequent steps of macroanalysis require a

reassessment after the first line of treatment has terminated. Macroanalysis also requires reference to the staging method, whereby a disorder is characterized according to seriousness, extension, and longitudinal development.[78] For instance, certain psychotherapeutic strategies can be deferred to a residual stage of depression, when state-dependent learning has been improved by use of antidepressant drugs.[79]

The planning of sequential treatment thus requires determination of the symptomatic target of the first-line approach (e.g., pharmacotherapy) and tentative identification of other areas of concern to be addressed by subsequent treatment (e.g., psychotherapy). Organization of different DSM syndromes by macroanalysis is thus the key to successful implementation of the sequential model.

Reassessment After the First Line of Treatment Has Been Completed

It is of the greatest importance to reassess the patient after the first line of treatment has been completed. In 2 studies concerned with the sequential treatment of depression,[28,31] reassessment was performed after 3 months of drug treatment, when maximal benefits were likely to be present.[80] There are several major obstacles to a satisfactory assessment of the patient in this stage. The first lies in exploration of only a few target symptoms instead of the full spectrum of psychopathology (as if he or she were a new patient). The second pitfall derives from the fact that the hidden conceptual model in clinical assessment is psychometric: severity is determined by the number of symptoms, not by their intensity or quality, to the same extent that a score on a self-rating scale depends on the number of symptoms that are scored as positive.[81–83] The preferential target of therapy is then based on syndromes resulting from a certain number of symptoms (which may be of mild intensity and of doubtful impact on quality of life) instead of individual symptoms that may be incapacitating for the patient. Third, the assessment of subclinical symptomatology, as frequently occurs in the setting of remitted or partially remitted disorders,[12–14] cannot be exempt from consideration of the longitudinal development of symptoms (the prodromal phase, the fully developed disorder, and residual states). Detre and Jarecki[84] provided a model for relating prodromal and residual symptomatology in psychiatric illness, referred to as the "rollback phenomenon": as the illness remits, it progressively recapitulates (though in reverse order) many of the stages and symptoms that were seen during the time it developed. Finally, in clinical as well as in research practice, collection of symptoms is performed during a clinical interview. However, self-observation (the patient is instructed to report in a diary the most important episodes of distress that may have ensued in a specific time period, such as a couple of weeks) is an important source of information concerned with allostatic load (i.e., chronic and often subtle life stresses that exert harmful consequences on the individual over a certain amount of time, such as excessive workload and inability to protect oneself from requests that exceed one's ability to meet them).[34]

The assessment performed in this phase is thus crucial in determining the patient's level of remission after the first line of treatment—whether residual symptoms occur and further treatment is necessary.[85] This treatment may take the form of psychotherapeutic or pharmacologic approaches that substitute for or supplement the first line of treatment.

Final Assessment After the Second Line of Treatment Has Been Completed

There is extensive evidence that the amount of residual symptomatology that patients experience when their mood and anxiety disorders are in remission is an important predictor of outcome.[12–14] Yet, little attention is generally paid to symptoms once the patient has responded to treatment. Assessment at some point after termination of treatment is crucial. According to the sequential model, such assessment should take place after the second line of therapy has been completed, for instance, in a depressed patient when psychotherapy following pharmacotherapy has been performed and medications have been discontinued.[85] If substantial residual symptomatology persists despite clinical response, then new treatment strategies, such as long-term, indefinite drug therapy, should be discussed with the patient.

CONCLUSIONS

The sequential treatment of mood and anxiety disorders does not fall within the realm of maintenance strategies, which have the aim of prolonging clinical responses that treatments have obtained.[86] It is an intensive, 2-stage approach that derives from the awareness that one course of treatment with a specific tool (whether pharmacotherapy or psychotherapy) is unlikely to provide resolution of the affective disturbances of patients, in both research and clinical practice settings.[12–14,87] The aim of the sequential approach is to add therapeutic ingredients as long as they are needed. In this sense, the sequential treatment model introduces a conceptual shift in clinical practice. Therapeutic targets are not predetermined, but depend on the response of patients to the first course of treatment. The approach calls for a critical examination and modification of the design, assessments, and methods of comparative clinical trials.[88–92] The sequential model is thus pragmatic—realistic instead of idealistic—in keeping with the complexity of the balance of positive and negative affect in health and disease[93] and the clinical needs of patients with affective disorders.[94]

Drug names: clomipramine (Anafranil and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), tamoxifen (Nolvadex and others).

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