

Antidepressants and Psychotherapy: A Clinical Research Review

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This review focuses on information concerning antidepressants and psychotherapy in the treatment of both acute and chronic forms of unipolar depression in the English language literature. We address the use of combination therapy both from the outset of treatment and in a variety of sequences, ie, we examine the advantages of adding a targeted psychotherapy to an incompletely effective pharmacotherapy and the advantages of adding pharmacotherapy to an incompletely effective psychotherapy. We do not address the use of these targeted psychotherapies alone, except inasmuch as to describe those targeted psychotherapies for which there is evidence of their efficacy in the treatment of various forms of unipolar depression, suggesting the potential utility of combining them with pharmacotherapy. Furthermore, although there is a burgeoning literature on the advantages of adding psychotherapy to pharmacotherapy in the treatment of bipolar disorder and, in particular, in the treatment of bipolar depression, the present review does not address the use of psychotherapy in the treatment of bipolar disorder.

FORMS OF TARGETED PSYCHOTHERAPY THAT HAVE BEEN COMBINED OR SEQUENCED WITH ANTIDEPRESSANT PHARMACOTHERAPY

To date, the English language literature provides evidence for the efficacy of several forms of time-limited psychotherapy in the treatment of unipolar disorder. These include the cognitive therapy (CT; or cognitive behavioral therapy [CBT]) of Beck and colleagues (1, 2), interpersonal psychotherapy (IPT) as developed by Klerman and Weissman (3, 4) the cognitive-behavioral analysis system of psychotherapy (CBASP) developed by McCullough (5, 6) problem-solving therapy (PST) developed by Gath, Catalan, Mynors-Wallis, and colleagues (7) in the UK, and psychodynamic-interpersonal (PI) psychotherapy (also known as Hobson's conversational model of psychotherapy) developed by Hob-

son (8) and extended by Guthrie and Shapiro in Manchester (9, 10).

For each of these treatments, there is a considerable body of knowledge regarding their efficacy as monotherapies in comparison with active or placebo-controlled conditions. Yet, intent-to-treat response rates for either antidepressant pharmacotherapy or psychotherapy alone rarely exceed 50% to 60% (11); full and sustained remission rates are even lower (12, 13). For the severely or recurrently depressed individual, monotherapy may be inadequate. The neurobiological substrate of an individual's depressive illness may be too severely disturbed to be responsive to psychotherapy alone. Likewise, psychosocial or interpersonal stressors may be so extensive that pharmacotherapy alone will not bring about full remission of an individual's depressive episode. Investigators consistently demonstrate an increased recurrence risk for individuals who experience a partial remission, delayed response to acute treatment, or residual symptoms posttreatment (14, 15). For these individuals, combined psychotherapy and pharmacotherapy may be the best treatment modality (16–18).

Considering the empirical support for the aforementioned psychotherapies, it is not surprising that various groups have generally chosen one of these nonsomatic treatments to combine or sequence with pharmacotherapy. For those not entirely familiar with CT, IPT, CBASP, PST, or PI, a brief description of each follows.

PSYCHOTHERAPY

COGNITIVE THERAPY

CT is a manualized, short-term, present-oriented psychotherapy that has demonstrated robust and replicable results, as both an acute and maintenance treatment for depression and residual symptoms (17, 19–21). Acute CT involves typically 12 to 26 weekly sessions.

CT, as developed by Beck (1), focuses on an individual's cognitive mediation and how one's thoughts and beliefs influence one's feelings and behavior. For depressed individuals, a clinician explores the relationship between negative thinking and the depressive state; specifically, how one's thoughts and beliefs exert influence on one's feelings and behavior. The primary goal of CT is to change the depressed person's negative view of the world, self, and future. Other goals include increasing the frequency of activities that bring about a sense of mastery or pleasure, highlighting how pessimistic, illogical, or maladaptive thinking contributes to psychological distress and functioning, and helping generate strategies for dealing with the current symptoms, problems, and triggers.

Friedman and Thase (22) explain that CT stresses collaborative empiricism. That is, the clinician guides the patient into developing a scientific attitude toward testing the validity or effectiveness of certain thoughts or behaviors. Together, the clinician and patient develop hypotheses about cognitions and behaviors, determine ineffective or erroneous patterns by examining data, explore alternatives, and, finally, change cognitions or behaviors to be more effective and positive. Socratic questioning, a primary strategy of CT, teaches the use of rationality and inductive reasoning. Initial CT techniques include psychoeducation, behavioral activation, identifying and modifying automatic thoughts via Socratic questioning or thought recording, and the reduction in symptoms via behavioral techniques (eg, desensitization, relaxation training, social skills training, exposure and flooding, and distraction) (1). Intermediate strategies may include examining data, generating alternatives, rehearsing and practicing new behaviors and cognitions, and modifying core beliefs or "schemas." Beck (1) conceptualizes schemas as cognitive templates that are learned early in life and guide perception, organize experience, and shape the probability of certain kinds of responses in specific situations. Schemas often include dysfunctional attitudes that may increase one's vulnerability to a first episode or recurrence of depression (19).

INTERPERSONAL PSYCHOTHERAPY

Like CT, IPT is a manualized, short-term, present-oriented psychotherapy that has demonstrated robust and replicable results, as both an acute and maintenance treatment for depression (3, 22–24). Acute IPT typically involves 16 to 24 weekly sessions. Recently, however, investigators have begun testing the relative efficacy of a briefer, 8-session, course of IPT (25). Often, in cases of

recurrent depression, monthly or biweekly continuation or maintenance sessions are recommended for at least 6 months following remission (23).

IPT was originally developed in a research context by Klerman and colleagues as part of a so-called maintenance treatment trial beginning in 1968 (26, 27). This first efficacy study of IPT would probably be considered a continuation treatment trial today. IPT was subsequently codified as an acute treatment by Klerman et al (4, 28) and as a maintenance treatment by our research group (23, 29).

The theoretical rationale for IPT derives from the relationship between interpersonal distress or problems in social role functioning and depressive illness. IPT makes no etiological assumptions, ie, no assumptions about whether interpersonal distress causes depression or depression causes interpersonal distress, but rather assumes that when depression is present there are almost always problems in interpersonal relationships or social role functioning, and that the amelioration of those problems is likely to result in an amelioration of depressive symptoms as well as an improvement in functioning. The techniques of IPT were developed to manage four basic interpersonal problem areas: (i) unresolved grief; (ii) role transitions; (iii) interpersonal role disputes; and (iv) interpersonal deficits (see Klerman et al (4) and Weissman et al (3) for an explanation of the theoretical background and development of IPT). The major goals of IPT are achieved by ascertaining with the patient which of these four problems was associated with the onset of the current episode of depression and, subsequently, by working with the patient to renegotiate interpersonal difficulties associated with the primary problem area. IPT strategies include role-play, communication analysis, and direct suggestion.

Although maintenance interpersonal psychotherapy (IPT-M) preserves the four distinctive problem areas and employs the strategies and techniques of IPT, it differs in that its primary goal is prevention of recurrence and it is conceptualized as a long-term rather than an acute intervention. Because of the length of maintenance treatment, a number of problem areas are typically addressed and the therapist often focuses on long-standing patterns of interpersonal behavior that appear non-adaptive for the patient (23).

COGNITIVE BEHAVIORAL ANALYSIS SYSTEM OF PSYCHOTHERAPY

CBASP is a manualized psychotherapy specifically designed to help severely and chronically depressed individuals build new problem-solving and

relationship skills (6). Hirschfeld et al (30) explain that CBASP is similar to IPT, inasmuch as treatment focuses on interpersonal interactions, but is substantially more directive and structured than IPT, and frequently focuses on the therapist–patient interactions. CBASP is an acute treatment that is scheduled twice weekly for the first 4 weeks, and weekly thereafter until week 12, with a maximum session allowance of 20 sessions (6).

CBASP evolved from McCullough's view of the specific cognitive correlates of dysthymia or chronic depression (6). He argued that individuals with dysthymia tend to have a series of dysfunctional attitudes, particularly with respect to dependence, competence, and trust. They also tend to have an attributional style that views these problems as internal, global, and irreversible. Their sense of self-efficacy relative to that of the general population is low and they tend to have a highly reactive response to problems and stressors consistent with Eysenck's concept of neuroticism. The primary goal of CBASP is to teach patients to understand the consequences of their situational behavior and address the interpersonal difficulties and cognitive correlates of dysthymia through situational analysis, interpersonal discrimination exercises, and behavioral skill training and rehearsal.

PROBLEM-SOLVING TREATMENT

Problem-solving treatment (PST) was developed at Oxford University by Gath, Mynors-Wallis, and colleagues as a very brief form of psychotherapy to be used in the treatment of major depressive disorders in primary care settings (7, 31). They developed PST with an eye toward reducing emotional symptoms by addressing “problems with living” (7). The primary goal of PST is to increase patients' sense of mastery and self-control. PST is a three-phased treatment intended to be carried out in six sessions over 12 weeks (31). Mynors-Wallis (31) explains that the goal of phase 1 is linking symptoms to problems; phase 2 is clarifying and defining problems; and phase 3 is attempting to solve problems in a structured way. Phase 3 includes sessions focused on finding ways to address the problem and reviewing “homework assignments” related to the resolution of the problem, and sessions focused on reviewing how the problem was solved and generalizing the strategy to other problems the patient might wish to confront.

PSYCHODYNAMIC INTERPERSONAL THERAPY

PI therapy, originally termed Hobson's conversational model of psychotherapy, was developed by

Hobson (8) and has been more recently studied by other investigators, most notably Guthrie and Shapiro. Guthrie (9, 10) describes PI as an integrative model of therapy that combines psychodynamic, humanistic, and interpersonal theory and techniques. A typical course of PI is three to eight sessions.

Unlike IPT, the primary tools of PI include transference and metaphors (32). Much like CBASP, the therapist–patient relationship is core to PI and important to the exploration of the connection between depressed mood and problematic interpersonal relationships. The therapist makes no assumptions concerning the patient's problems or feelings, adopting a stance of individuality. Together, the therapist and client develop negotiation and communication skills. The goal of a PI therapist is to understand the patient's personal, individual feelings concerning problems and the consequence or influence of these problems, and to offer interventions only in a tentative and nondogmatic way.

GOALS OF TREATMENT OF UNIPOLAR DISORDERS

In trying to understand the efficacy of psychotherapy, pharmacotherapy, combinations, and sequences, it is important to be clear about what the goals of treatment are in the management of unipolar disorders. Although nearly 50% to 60% of depressed outpatients will respond and experience a meaningful improvement in response to a first trial of antidepressant pharmacotherapy (33), only 1 in 3 patients will experience a *full and complete remission* of their symptoms and depressive episode (12). The goals of treatment should extend beyond response to a full and sustained remission of symptoms and an improvement in psychosocial functioning (34). Ample evidence points to the negative consequences of treatments that fail to target such complete remission. Thase (15) has demonstrated an increased recurrence risk for individuals who experience a partial remission, delayed response to acute treatment, return of symptoms during continuation treatment or within 1 year post-treatment, or residual symptoms post-treatment.

Researchers have demonstrated that baseline severity and chronicity of the affective disorder substantially undermines treatment response and increases the risk of recurrence. Greater depression severity at baseline generally predicts a poorer response to pharmacotherapy (35) and/or psychotherapy (36). Duration of the index episode and the number of prior episodes are the strongest baseline predictors of the subsequent well interval (35, 37–41).

The presence of Axis I comorbidity, both at the syndromal and the subsyndromal level, impedes the achievement of full remission. Panic or anxiety symptoms or disorder are particularly pernicious in this respect (42–45). Axis II comorbidity has also been found by numerous investigators to be associated with incomplete remission of depression (35, 46–48). To some extent, the association of both of these forms of comorbidity (Axis I and Axis II) with incomplete remission may represent an artifactual inflation of depression rating scale scores via the presence of symptoms associated with the Axis I or Axis II condition. However, there also are well-articulated descriptions of how, for example, anxiety disorders or subsyndromal anxiety conditions and Axis II conditions might interfere with obtaining the full benefit from a treatment such as CT or IPT (49).

More recently, Katon and colleagues (50, 51) have focused on the extent to which medical comorbidities, such as diabetes (Axis III conditions), may interfere with remission of depression. Again, some of this may be artifact caused by inflation of depression scores or by somatic symptoms associated with a comorbid medical condition. On the other hand, there are specific hypothesized routes through which medical comorbidity might interfere with either pharmacotherapy or psychotherapy. Somatic preoccupation may preclude the individual's ability to focus on the specific work involved in the psychotherapy, whereas the medical condition or the pharmacological treatment of the medical condition may interfere with the metabolism of antidepressant pharmacotherapy. Finally, failure to adhere to the requirements of either a pharmacotherapeutic or a psychotherapeutic regimen can certainly interfere with the achievement of full remission of symptoms.

Psychotherapy and pharmacotherapy combinations and sequences also have a clear role in the prevention of recurrence, another key goal of treatment of unipolar disorders. Since we now recognize that the majority of unipolar depressions are recurrent, perhaps the most challenging part of depression treatment is that which focuses on the prevention of relapse and recurrence. As we describe below, it is here that pharmacotherapy–psychotherapy combinations and sequences have shown themselves to be particularly valuable approaches to treatment.

COMBINATION ACUTE TREATMENT: ACHIEVING REMISSION AND RETURN OF FUNCTION

As noted above, efforts to achieve full remission and return of function have encompassed the eval-

uation of combination therapy in comparison with either pharmacotherapy or psychotherapy monotherapy as well as treatment sequences. The literature on the benefit of combining pharmacotherapy with psychotherapy from the outset of the treatment is relatively small in terms of randomized controlled trials. We know much less than we should about this approach to treatment on an empirical basis.

Hollon et al (52) suggest that combined treatments may confer additive benefits because the strengths of each modality are promoted while the weaknesses of each modality are minimized. Thus, response and remission rates for combined treatment should be superior to those of either treatment modality as a monotherapy. They argue that combined treatment increases the magnitude, probability, and breadth of clinical response. Adding drug therapy to psychotherapy may bring about a more rapid relief of symptoms than psychotherapy alone, permitting the patient to participate more productively in psychotherapy (Thase ME, personal communication). Conversely, adding psychotherapy to drug therapy may increase medication adherence, decrease the presence and risk of residual symptoms following drug discontinuation, and facilitate the patient's development of healthy coping skills (53).

Thase has argued that combination treatment as a general approach for the treatment of unipolar depression has yet to receive adequate empirical support. While the Agency for Health Care Policy and Research guideline supports the use of combined treatments for depressive disorders (54). Thase and Howland believe it is best indicated for patients with severe, refractory, or incapacitating mood and anxiety disorders (55). Below, we review the relatively small number of randomized controlled trials in the English language literature that test the relative efficacy of monotherapies and polytherapies for depression.

COMPARING MONOTHERAPY AND POLYTHErapy

The study by Klerman et al in 1974 examined the effects of 8 months of psychotherapy in comparison with continued pharmacotherapy in 150 depressed women who had been receiving amitriptyline therapy for 4 to 6 weeks (26). Patients then received weekly IPT, medication, combination IPT and medication, or placebo and no therapy. Relapse rates were highest for patients receiving placebo alone (36%). Relapse rates in the other three active treatment groups were 12% on medication alone, 16.7% on IPT alone, and 12.5% on combined IPT and medication. This was one of the first controlled

trials reported in the literature examining the protective capacity of psychotherapy.

The first combined treatment trial of cognitive therapy was conducted by Blackburn and colleagues in Scotland in 1981 (56). They compared CT, tricyclic antidepressant (TCA) therapy, and CT combined with TCA (CT+TCA) among 64 hospital outpatients or general practice patients diagnosed with recurrent depression (≥ 1 previous episode). After 12 to 20 weeks of acute treatment, among the hospital outpatients, response rates (50% reduction in the Hamilton Rating Scale for Depression [HRSD]) suggested that CT was minimally more effective than TCA, and CT+TCA was more effective than monotherapy. For general practice patients, response rates were equivalent for the CT and CT+TCA groups, but significantly less for the TCA group. In a follow-up report, Blackburn et al (57) reported that TCA was less effective than CT or CT+TCA for sustaining remission in both the hospital outpatient and general practice groups. They note that TCA alone may have been less effective than the two other conditions because of poor medication adherence; plasma levels were not monitored during the trial. Two years of naturalistic follow-up revealed that no patients receiving CT+TCA relapsed during the first 6 months of follow-up, compared with 30% in the TCA group and 6% in the CT group. Despite a small sample size, Blackburn et al's results suggested to many that combination treatment may bring about the greatest change and improvement among depressed individuals (58).

Our group has examined the efficacy of maintenance medication and IPT in preventing recurrences (29). The Pittsburgh Study of Maintenance Therapies in Recurrent Depression contrasted IPT-M with maintenance pharmacotherapy (imipramine [IMP]), combination pharmacotherapy–psychotherapy, and a control condition (placebo and no therapy) over a period of 3 years in depressed patients who had clear histories of recurrent depression (at least three episodes; sample mean was seven episodes) and had been treated acutely with a combination of IPT and IMP. Active medication provided the best prophylaxis, with or without IPT-M. No advantage was observed for the combination; however, survival time without a new episode of major depression following discontinuation of medication was significantly and positively related to monthly IPT-M alone or with a placebo tablet.

We conducted a similar placebo-controlled study of maintenance pharmacotherapy and psychotherapy (IPT) in 180 geriatric patients with nonpsychotic unipolar major depression (59). Patients

were treated acutely with nortriptyline (NTP) and IPT. After 16 weeks of stabilized depression scores, patients were randomly assigned to one of four maintenance therapy conditions: (i) medication clinic plus NTP; (ii) medication clinic plus placebo; (iii) IPT-M plus NTP; or (iv) IPT-M plus placebo. Survival analyses suggest that maintenance NTP and IPT, together and singly, is superior to medication clinic visits and no pharmacotherapy in preventing or delaying a depressive recurrence. Patients assigned to the combined treatment condition had the best outcome, with 80% remaining depression-free during the 3-year maintenance period.

A 1997 analysis involving patients from several studies conducted at Western Psychiatric Institute and Clinic (60) revealed that, among 595 patients experiencing a unipolar major depressive episode, for the more severely depressed patients, remission rates (HRSD < 7 for 4 weeks) were higher for those receiving concurrent IPT and antidepressant pharmacotherapy with IMP than were remission rates for CT or IPT alone (43% versus 25%, $P = 0.001$). For the less severely ill, combination treatment had no additive effect.

Keller et al (5) demonstrated the superiority of combination treatment among 681 patients with chronic depression (episode exceeds 2 years). In this trial, 85% of patients treated with combined CBASP and nefazadone (CBASP+NFZ) experienced a response during acute phase treatment compared with 55% of patients treated only with NFZ and 52% of patients treated only with CBASP ($P = 0.001$). Despite impressive response rates after 12 weeks, many patients experienced residual symptoms (5).

Results from one study are less than definitive concerning the efficacy of combination treatment. Hollon et al (52) compared CT and IMP as monotherapies with combined CT and IMP among 107 patients (only 64 completed the study) with major depression. They found no significant differences in acute-phase response rates and no significant differences in full remission rates, although there was a trend among individuals (who completed the study) receiving combined treatment (75%) to reach and sustain remission more frequently than individuals receiving monotherapy (50% CT, 56% IMP). For the 64 patients who completed the study, Evans et al (61) report no significant differences at 2-year follow-up.

SEQUENTIAL TREATMENT STRATEGIES

Fava (62) contends that the goal of sequential treatment strategies is to increase or boost the therapeutic effect of a first-treatment by augmenting with a second treatment. Hence, the sequencing of

treatment is dependent upon the degree of acute treatment response. Fava (62) details four clinical applications of sequential treatments: (i) changing the orientation of psychotherapy when a first orientation of psychotherapy has not achieved treatment goals; (ii) introducing a second medication when the first medication has not achieved adequate symptom relief; (iii) introducing psychotherapy when medication alone has not been fully effective; and (iv) introducing medication when psychotherapy alone has not been fully effective. Only in the past decade have investigators really begun to investigate the benefits of sequential treatment strategies.

Fava and colleagues investigated a sequential approach for the treatment of residual symptoms and recurrence risk (63, 64). After initial treatment with antidepressant medication, 40 patients (who demonstrated an initial, but not full response to medication) were randomly assigned to receive 20 weeks of CBT and pharmacotherapy or clinical management and pharmacotherapy. All patients eventually discontinued pharmacotherapy. Patients were instructed to call immediately if any new symptoms appeared and were guaranteed a renewed course of drug therapy in the event of a relapse. Fava et al (17) found that the CBT group had significantly fewer residual symptoms following drug discontinuation than the clinical management group. More interestingly, the benefits of short-term CBT after successful antidepressant treatment had a substantial effect on recurrence risk. Treatment gains persisted at year 2, 4, and 6 of post-treatment follow-up (see section below on relapse and recurrence prevention) (63, 64). In another trial, Fava et al (65) added CBT to patients who experienced a response but not a remission to sertraline and found similar results.

Paykel et al (66) randomly assigned 158 patients with major depression who had experienced only partial remission with at least 8 weeks of antidepressant treatment (either fluoxetine or a TCA) to continue monotherapy with the antidepressant or receive 20 sessions of CT in addition to continuing antidepressant treatment for 1 year. While 47% of patients receiving only antidepressant treatment relapsed, only 29% of patients receiving combination treatment relapsed ($P = 0.02$).

Our own group observed a substantial advantage for sequencing IPT and the combination as opposed to combination therapy from the outset in an effort to achieve sustained remission (67). We noted that when combination therapy was provided from the outset of treatment to a group of patients with moderately severe episodes of recurrent depression, 66% achieved sustained remission of symptoms, while when we took the approach of

adding pharmacotherapy to the IPT of patients who appeared unable to achieve full remission with IPT alone, 78.6% achieved remission ($\chi^2 = 6.55$, $P = 0.02$). Our interpretation of this finding is that the failure to achieve remission with IPT monotherapy stands as a kind of marker for those most likely to benefit from the addition of pharmacotherapy.

On the basis of our results and those of other groups, we see the sequencing of monotherapy followed by combination when monotherapy alone fails to bring about remission as a particularly efficient strategy and one that is likely to lead to considerable cost savings as compared with a strategy that involves treating all patients with a pharmacotherapy–psychotherapy combination from the outset of acute treatment.

MAINTENANCE TREATMENT: SEQUENTIAL STRATEGIES TO PREVENTING RELAPSE AND RECURRENCE

As noted above, Fava and colleagues have been interested in the protective effect of the addition of cognitive therapy for patients with unipolar depression. For instance, in a series of reports investigating the long-term protective effects of CBT, Fava and colleagues (63, 64) demonstrated that providing a short course of CT to patients with highly recurrent depression and who had already responded to antidepressant treatment was additive: 25% of patients in the CT group relapsed compared with 80% of patients in the clinical management group by year 2. In another report, Fava and colleagues (17) demonstrated that, following successful antidepressant treatment and discontinuation, only 35% of patients who received CT during drug discontinuation relapsed compared with 70% of patients who received only clinical management. Our own group has examined the benefit of maintenance IPT in combination with pharmacotherapy in both midlife and elderly patients. Interestingly, we found no advantage whatever for sustained combination treatment in comparison to maximally dosed pharmacotherapy alone in the prevention of recurrence among midlife patients (29). In a subsequent trial of elderly patients aged 60 to 80 years with recurrent depression, Reynolds et al (59) reported a modest advantage for the combination over maintenance pharmacotherapy alone in this more brittle population.

FUTURE DIRECTIONS

As we proceed into the 21st century, there is a clear need for more information about the relative

efficacy of pharmacotherapy–psychotherapy combinations or sequences versus either pharmacotherapy or psychotherapy provided as monotherapies. This is a particularly striking lack inasmuch as we know that the majority of private practitioners, at least in the USA, still see combination as the ideal treatment, and combination therapy is recommended in the treatment guidelines promulgated by the American Psychiatric Association. Not only do we need to know whether combinations are superior to monotherapies, but we also need to know how combination treatment is best practiced, ie, what are the advantages and disadvantages to both treatments being provided by a single practitioner versus pharmacotherapist–psychotherapist treatment teams working in coordination versus completely independent practitioners providing pharmacotherapy and psychotherapy to the same individual. While the fully integrated approach in which a single clinician provides both pharmacotherapy and psychotherapy may represent the most efficient method, it may not be the most economical method of providing combination treatment. Fully integrated teams of practitioners who are in continuous communication would appear to have multiple advantages over independent practitioners providing pharmacotherapy and psychotherapy separately to the same patient.

In addition to more information about the benefits of combining classic forms of the empirically validated psychotherapies with pharmacotherapy, there is increasing interest in adaptations of these treatments designed to address specific patient needs. Our own research group, for example, has taken on the challenge of adapting IPT to the needs of patients with syndromal and subsyndromal anxiety comorbidity. Results of an initial open study suggest that this adaptation, which focuses particularly on the ways in which anxiety may interfere with the ability to make use of and benefit from traditional IPT, clear advantages of this treatment over traditional IPT both when used as a monotherapy and when offered in a sequential design that permits the addition of pharmacotherapy (49).

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