The promise of cognitive behavior therapy for treatment of severe mental disorders: a review of recent developments

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Cognitive behavior therapy (CBT), as exemplified by the model of psychotherapy developed and refined over the past 40 years by A.T. Beck and colleagues, is one of the treatments of first choice for ambulatory depressive and anxiety disorders. Over the past several decades, there have been vigorous efforts to adapt CBT for treatment of more severe mental disorders, including schizophrenia and the more chronic and/or treatment refractory mood disorders. These efforts have primarily studied CBT as an adjunctive therapy, i.e., in combination with pharmacotherapy. Given the several limitations of state-of-the-art pharmacotherapies for these severe mental disorders, demonstration of clinically meaningful additive effects for CBT would have important implications for improving public health. This paper reviews the key developments in this important area of therapeutics, providing a summary of the current state of the art and suggesting directions for future research.

Key words: Cognitive behavior therapy, adjunctive therapy, severe mental disorders, schizophrenia, major depressive disorders, treatment refractory depression, bipolar disorder

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Despite both steady advances in neuroscience and the introduction of newer generations of medications for treatment of schizophrenia and severe mood disorders, there remain many unmet needs in the therapeutics of these disorders. Worldwide, millions of people who are treated for those conditions do not obtain adequate responses to pharmacotherapy and, collectively, major depressive disorder, bipolar disorder and schizophrenia constitute the world's greatest public health problem (1), costing billions of dollars of lost human capital.

Although ongoing efforts to develop novel pharmacologic treatments will probably help to address these staggering unmet needs, at present the best strategy to improve outcomes is to combine therapies that are thought to have complementary mechanisms of action. Among the myriad of potentially adjuncts to pharmacotherapy that might be considered, cognitive behavior therapy (CBT) is arguably the most promising.

As exemplified by the model of therapy developed and refined over the last 40 years by Aaron T. Beck and colleagues, CBT is a treatment of first choice for outpatients with depressive and anxiety disorders (2,3). Beyond efficacy as a stand-alone treatment for less severe mental disorders, there have been vigorous efforts over the past 30 years to adapt CBT for treatment of more severe mental disorders. In this paper we examine the evidence pertaining to the utility of CBT for treatment of schizophrenia and the more severe, chronic or treatment resistant mood disorders. We also suggest areas where additional research would be helpful to further clarify the role of CBT for improving the lives of people with these potentially ruinous illnesses.

SCHIZOPHRENIA AND RELATED PSYCHOTIC DISORDERS

By the 1970s it was evident that, although many patients with schizophrenia obtained some symptomatic benefit from antipsychotic medications, relatively few actually fully recovered and the psychosocial functioning of many who obtained symptomatic relief left much room for improvement. The adjunctive use of psychosocial therapies, including more rehabilitative interventions and individual psychotherapies, represented one of the most obvious strategies to try to broaden the benefits of treatment and improve the quality of outcomes.

Whereas many psychosocial approaches to psychotic disorders side stepped delusions and hallucinations as appropriate targets for intervention, CBT did not, and promising findings from the first generation of randomized controlled trials (RCTs) began to emerge in the 1990s. There have been more than fifty RCTs, which have informed a number of meta-analyses and narrative reviews. These have generally been positive, and guidelines internationally have recommended the use of CBT in people with psychosis, especially medication-resistant cases (4,5). Typically, effect sizes ranging between 0.3 and 0.5 have been found (6,7).

In one of the most influential meta-analyses, Wykes et al (6) found an average effect size for target symptom (33 studies) of 0.40 (95% CI: 0.25-0.55), and significant effects (ranging from 0.35 to 0.44) for positive symptoms (32 studies), negative symptoms (23 studies), functioning (15 studies), mood (13 studies) and social anxiety (2 studies). They noted that these effect sizes were somewhat smaller in the

twelve studies that used the most rigorous methodologies – for example, a target symptom effect of 0.22 (95% CI: 0.02-0.43).

In the most recent meta-analysis, Turner et al (7) considered forty-eight RCTs examining psychological interventions for psychosis, including 3,295 participants. They concluded that CBT was significantly more efficacious than other interventions pooled in reducing positive symptoms (g=0.16). Of note, CBT was also significantly more efficacious when compared directly with befriending for overall symptoms (g=0.42) and supportive counseling for positive symptoms (g=0.23).

One limitation revealed in these meta-analyses has been a high degree of heterogeneity: the studies have been diverse and have included differing patient groups and different models of CBT of different levels of intensity. Nevertheless, even critics of CBT agree that there is a real, albeit small effect size advantage for CBT over and above medication alone (8). Notably, the investigators found no evidence of publication bias in these studies (8).

One persisting question has been the utility of CBT for the patients who may need the greatest amount of help, namely those who are resistant to multiple courses of therapy with antipsychotics. The meta-analysis of Burns et al (9) directly addressed this issue, examining the adjunctive benefit of CBT in patients with medication resistant syndromes both on completion of treatment and at follow-up. Twelve randomized controlled trials, with 639 participants, were included. Of these, 552 completed the post-treatment assessment (drop-out rate of 14%). An overall benefit for adjunctive CBT was found at post-treatment on both positive symptoms (Hedges' g=0.47) and global symptomatic status (g=0.52), and these effects were maintained at follow-up (g=0.41 and 0.40, respectively, for positive and general symptoms).

Where specific symptoms, such as command hallucinations (10), have been targeted, meta-analyses have also given positive results. A recent study focusing specifically on negative symptoms (11) likewise demonstrated a statistically significant and clinically meaningful benefit for adjunctive CBT. There have also been successful studies in early psychosis (12), patients with a history of aggressive behavior (13) and patients who have refused to take antipsychotics (14). In one study of CBT in patients with psychosis who were abusing substances (15), adjunctive CBT significantly improved outcomes, although in a second study the combination of motivational interviewing and CBT failed to demonstrate a positive effect (16).

There has been some dissent about the degree of effect overall and in comparison with supportive therapies (8,17), although the audience at a recent debate held at the Institute of Psychiatry in London rejected the contention that CBT for psychosis had been "oversold" (18).

There is also a substantial body of psychological and social evidence underpinning the practical research into "salience" (19), which is a very useful concept in describing deficits addressed by medication and CBT. The influence of trauma and social factors, such as poverty or immigration status, have been demonstrated to be relevant to psychosis (20) and these are key foci in CBT (21), with success shown in cultural adaptations (22).

However, implementation of CBT, even in countries where guidelines have strongly advocated its use, such as the UK, has been slow. Estimates suggest that up to 90% of eligible patients are not being offered adjunctive therapy in that country. A program of work with pilot sites and outcome metrics has been commenced to address this problem with dissemination.

CBT for psychosis has developed from Beck's original work in depression, which linked thoughts, feelings and behavior and broadened our biopsychosocial perspectives on psychopathology (23). However, the use of CBT in psychosis requires a primary focus on engaging people who may not recognize and indeed may actively dispute that they have mental health problems. There is, therefore, a need to develop a shared formulation of the problems that is acceptable to the individual from the narrative that he/she can provide. This allows increasing understanding and ability to cope with hallucinations, delusions and negative symptoms as well as anxiety and depression. The aim is to reduce distress and disability by working with these experiences and symptoms. The evidence shows that symptoms such as hearing voices and the intensity of delusional beliefs may recede, but this is a subsidiary goal.

Work with delusions involves exploration of their narrative – what led up to the beliefs emerging – and then further elaboration of the feelings and behaviors that accompany these beliefs. A reasoning approach is helpful in re-examining the basis for beliefs or at least sewing doubt sufficient for behavior to shift from often quite extreme avoidance or self-defeating behaviors to more constructive actions.

Beliefs about hallucinations can be elicited – these tend to involve externalization, omnipotence and omniscience. Each can be explored and alternative explanations arrived at, often using normalizing information – e.g., discussing effects of sleep deprivation and similarities of voices with dreams may be helpful. The content of voices may be commanding and abusive – work countering voices can begin to undermine underlying beliefs of shame, guilt and general negativity. Reduction in anxiety and depression can contribute to improvements in general wellbeing. Traumatic events commonly precede onset of abusive voices and work with these directly or by cognitive restructuring of negative beliefs about the self can be very successful.

Negative symptoms often arise through demoralization, but may also protect against distress and recrudescence of positive symptoms. Social avoidance reduces stress but causes major functional disability – work in finding alternative ways of coping with distress including behavioral activation can provide positive reinforcing experiences. Understanding beliefs like delusions of reference and thought broadcasting can provide the confidence and

resilience to release motivation and combat social inactivity and isolation.

In summary, CBT for psychosis is a very promising and evolving development (24). The evidence is clear that it reduces suffering, but it is offered to very few people in very few countries. Psychiatrists (25), mental health nurses (26) and case managers (27) have all been demonstrated to be able to effectively and safely use CBT in working with their patients with schizophrenia. Training is available, and there are many mental health workers – and their patients – who could benefit from using more effective and acceptable recovery-focused ways of working. National psychiatric associations and governments need to address problems with dissemination of CBT as a matter of urgency.

MAJOR DEPRESSIVE DISORDERS

CBT is by far the best-studied form of psychotherapy for treatment of major depressive disorders (28). It is also the best studied form of adjunctive psychotherapy for use in combination with antidepressants. For ambulatory treatment of non-psychotic episodes of major depressive disorder across the severity continuum, the combination of CBT and antidepressant medication has been shown in meta-analyses to convey an about 10-20% advantage in response or remission rates (29,30).

Given the large contribution of non-specific therapeutic effects in milder depressions (see, for example, 31), it has been suggested that the cost-effectiveness of combined treatment would be greater if it were used preferentially with patients with more severe, chronic or treatment resistant depressive disorders, i.e., those who are less likely to remit with one or the other monotherapy (28).

To date, no large scale studies or meta-analyses have confirmed the hypothesis that the advantage of combining CBT and pharmacotherapy is larger for more severe depressions. However, in a meta-analysis of individual patient data from studies of major depressive disorder that utilized either CBT or interpersonal psychotherapy (IPT), either singly or in combination with antidepressants, Thase et al (32) found a modest overall advantage for combined therapy, which was moderated by a significant interaction between severity and treatment strategy. Specifically, the advantage of combined treatment over psychotherapy alone was about three fold larger for the patients with recurrent major depressive disorder and more severe depressive symptoms than for the remainder of the patients.

There have been two major studies of CBT for patients who have not responded to antidepressants. The first was conducted as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project, a large multicenter trial carried out in the U.S. (33). This particular component of the multi-stage study enrolled 304 outpatients with major depressive disorder who had not remitted after a 12-14 week trial of citalopram therapy. Patients were allocated to receive either CBT or a change in pharmacotherapy, either alone or in addition to ongoing citalopram therapy. About 40% of the participants were treated in primary care practices, with the remainder treated in ambulatory psychiatric clinics.

The statistical power of the randomized components of STAR*D was unintentionally, but adversely affected by the decision to use an equipoise stratified randomization strategy. This was a paradoxical observation, as equipoise stratified randomization was intended to minimize attrition by maximizing patient choice. As only about 30% of the eligible patients consented to the randomization strata that offered CBT, the study had much less statistical power than planned and, as a result, could only detect large group differences as statistically significant. Some have suggested that the fact that so many patients opted out of the psychotherapy arms indicates that CBT has relatively low acceptability in "real world" settings. This interpretation, while understandable, is incorrect, as comparable proportions of patients were likewise unwilling to accept randomization to either the augmentation or switch options within the pharmacotherapy alone strata.

Among those who consented to randomization, the 12-week outcomes of the patients who received CBT (either alone or in combination with ongoing citalopram therapy) were generally similar to those who received pharmacotherapy alone. There were, in fact, no statistically significant differences in symptom reduction or response/remission rates. Not surprisingly, the patients who received CBT alone had fewer side effects than those who received pharmacotherapy alone, and those who received CBT as an adjunct to ongoing citalopram therapy had a significantly longer time to remission than those who received pharmacologic adjuncts.

The second study of antidepressant non-responders, known as CoBalT, was conducted in England (34). This study, which was carried out in primary care clinics, randomly assigned 469 patients with major depressive disorder who had not responded to at least one prospective, adequate antidepressant trial in the current episode to either CBT plus "usual care" (UC) or UC alone. Importantly, the design of CoBalT differed from that of STAR*D in that no effort was made in UC to ensure that patients received adequate courses of pharmacotherapy. CoBalT also differed from STAR*D in that the primary outcome was assessed six months after randomization, rather than after three months. Thus, CoBalT studied about seven times more CBT-treated patients than STAR*D and provided a longer course of therapy in comparison to a less rigorous specified pharmacotherapy condition.

With these design differences in mind, it may not be surprising that the CoBalT trial found a strong difference favoring the group that received CBT plus UC as compared to the group that received UC alone. For example, 46% of the CBT-treated patients met the response definition after 6 months, as compared to only 22% of the group that received UC alone. Significant

differences were also found on several secondary outcomes, including measures of depressive and anxiety symptoms.

A third study evaluated the utility of CBT for relapse prevention following successful treatment with electroconvulsive therapy (ECT) (35). This is a potentially important application of CBT because, despite being the most effective intervention for severe depression, longer term outcomes following ECT are typically worse than desired because of a high rate of relapse.

In this multicenter trial conducted in Germany, 90 patients with major depressive disorder who received an in-hospital course of right unilateral ECT began a 6-month course of guideline-guided antidepressant medication and were randomly assigned to one of three conditions: one third received adjunctive CBT, one third received adjunctive ECT, and one third received no adjunctive therapy (i.e., medication alone).

Although this preliminary study only had the statistical power to detect extremely large effects, trends strongly favored the patients who received CBT. For example, after 6 months of continuation treatment, 77% of the CBT-treated group met criteria for a sustained response, as compared to 40% and 44% of the patients in the groups that did not receive adjunctive psychotherapy. After 12 months, 65% of the patients who received CBT, as compared to only 28% and 33% of those in the ECT and pharmacotherapy continuation arms, had sustained responses.

These results suggest that, among a group of patients that was prone to relapse despite continuation treatment with antidepressants and/or ECT, a relatively large proportion obtained sustained responses with CBT. Moreover, given the problem with relapse following ECT, these results suggest that the potential value of CBT as an alternate means to improve longer term outcomes warrants further study.

The large, multi-center study of Keller et al (36) evaluated the utility of an intervention called cognitive behavioral analysis system of psychotherapy (CBASP) in more than 600 outpatients with chronic forms of major depressive disorder. This multi-stage RCT compared outcomes of a group treated with CBASP alone and the antidepressant nefazodone alone versus a group treated with the combination of both therapies. The results at the end of the 12 week acute phase strongly favored the combination strategy, within an advantage in intent-to-treat response and remission rates of approximately 20% (36).

A more detailed secondary analysis of the temporal sequence of symptom change demonstrated that the overall advantage of the combined group was attributable to sharing both the earlier onset of benefit seen in the nefazodone alone group and the later-emerging benefit seen in the CBASP alone group (37). Combined treatment was particularly more effective than pharmacotherapy alone for patients with a developmental history of physical or sexual abuse (38) and, as compared to CBASP alone, among the subset of patients with severe sleep disturbances (39). In a crossover phase that was delimited to patients who did not respond to an initial course of treatment with either of the monotherapies (40), sequential delivery of the alternate modality resulted in eventual outcomes that, at 24 weeks, matched those of the combined group at 12 weeks.

The value of sequential combined treatment of chronic forms of major depressive disorder was not confirmed in a subsequent multicenter trial (41). In this study, 491 outpatients with chronic forms of major depressive disorder who had not remitted following a prospective trial of antidepressant medication (primarily sertraline) received a second course of antidepressant medication and, in addition, were randomly assigned to receive 12 weeks of adjunctive CBASP, adjunctive supportive therapy (i.e., a "warm" contact/expectancy control condition), or no psychotherapy. No significant advantages – neither specific nor non-specific – were observed for the groups receiving adjunctive psychotherapy (41). To date, the investigators have not been able to identify any factors to explain the discrepancy in findings between this negative study and the much more positive first study of CBASP.

In summary, the promise of CBT to improve upon the outcomes of pharmacotherapy for patients with more difficult to treat depressive disorders has been partly supported by controlled studies conducted over the past decade. Although the evidence is generally supportive, there are several studies in which the predicted additive benefits of CBT were not observed (e.g., 33,41).

BIPOLAR DISORDER

Given the unmet need for better rates of sustained recovery in patients with bipolar depression who do respond to pharmacotherapy, the field has witnessed new interest in the possible role of CBT as an adjunctive treatment in bipolar disorder.

To date, six RCTs have tested the efficacy of adjunctive CBT. They included three studies that evaluated acute phase therapy of depressive episodes (42-44) and three studies that focused on relapse/recurrence prevention as the outcome of greatest interest (45-47).

In the initial study, which was a relatively small (n=52) single site trial conducted in Australia (42), the patients who received adjunctive CBT obtained a significantly greater reduction in depressive symptoms at the 6-month assessment (the primary endpoint) than did the patients who received pharmacotherapy alone. The advantage of CBT was not statistically significant at the one-year follow-up, although the trend continuing to favor the CBT group was large enough to be clinically meaningful if confirmed in a larger study.

The study of Miklowitz et al (43), which was a large, multicenter trial conducted as part of the Systematic Treatment Evaluation Program for Bipolar Disorder (STEP-BD), randomly assigned 293 depressed patients to receive either an intensive psychosocial intervention or three sessions of

psychoeducation. All participants were taking a mood stabilizer and/or a second generation antipsychotic, and most were also treated with an antidepressant. In addition to studying CBT, the STEP-BD investigators studied family focused therapy (FFT) and an alternate individual therapy, interpersonal-social rhythms therapy (IPSRT). The study consisted of a 6-month acute phase and a one-year follow-up. At the end of the acute phase, results strongly favored the group receiving adjunctive psychotherapy, both in terms of symptom reduction and remission rates: the group that received adjunctive psychotherapy was about 15% more likely to remit/recover than the one who received pharmacotherapy alone. Benefits were also sustained during follow-up. The outcome of the patients who received adjunctive CBT was similar to those who received IPSRT or FFT.

A third study, which was carried out in Spain (44), enrolled 40 patients with bipolar depression who had not responded to mood stabilizers and antidepressants. The CBT protocol lasted 6 months; the durability of treatment effects was assessed across a 5-year follow-up. Although the study was small, the results were clear: patients who received adjunctive CBT obtained significantly greater improvements in depressive symptoms at the end of the acute treatment protocol. At the 5-year follow-up, 89% of the patients who had received adjunctive CBT were recovered, as compared to only 20% of the group that had received pharmacotherapy alone.

The three RCTs that have examined the utility of adjunctive CBT for prevention of relapse/recurrence in bipolar disorder have produced more conflicting results. In the first trial, Lam et al (45) found a very strong effect favoring adjunctive CBT during the first year of follow-up, with the risk of relapse or recurrence reduced by about 50%. However, subsequent larger, multicenter trials found no advantage for adjunctive CBT as compared to either pharmacotherapy alone (46) or a briefer psychoeducational intervention (47).

A secondary analysis of the study of Scott et al (46) yielded an unexpected result that, if replicated, might explain the discrepancy in findings. Specifically, Scott et al found that patients who had suffered relatively few lifetime illness episodes (e.g., roughly 5 or fewer prior episodes) benefited from adjunctive CBT, whereas those who had experienced more numerous episodes (roughly 10 or more prior episodes) actually did worse when therapy was added to their treatment regimen.

As the value of routinely treating episodes of bipolar depression with antidepressant medications has still not been established definitively, the promising – albeit preliminary – findings about the use of CBT as a focused acute phase therapy for bipolar depressive episodes certainly engender optimism and suggest an important avenue for further research. It would be particularly worthwhile to examine the effectiveness of CBT – both alone and as a monotherapy – for patients with bipolar disorder II, for whom mood stabilizers have uncertain benefit, and only one medication – the second generation antipsychotic quetiapine – has received Food and Drug Administration approval.

CONCLUSIONS

Although many important questions still remain to be answered, the current state of the evidence suggests that adjunctive CBT conveys a clinically and statistically significant benefit for patients with schizophrenia and severe and/or treatment resistant mood disorders. Overall, these effects tend to be modest in grouped data – on the order of 10-20% increases in response or remission rates as compared to pharmacotherapy alone.

Such findings underpin the arguments of some who continue to assert that the additive effect of CBT for patients with severe mental disorders has been "oversold". To this we reply that we agree that there is much work to still be done and that we need other strategies to help those who do not respond to pharmacotherapy and CBT. We also note, however, that the effects of CBT in RCTs are comparable to the drug-placebo differences observed in contemporary RCTs of new generation pharmacotherapies for the same conditions. Thus, whereas there is room for further improvement, we are glad to be able to offer our patients a non-pharmacologic adjunct that may indeed help to reduce their symptoms, improve the quality of their response, or increase the amount of well time after achieving a response to treatment.

In an era of scarce resources, it cannot be said that all patients with severe mental disorders should receive adjunctive CBT. In fact, if replicated, the findings of Scott et al (46) might point to some subgroups who should not receive this type of adjunctive intervention.

Changes in the delivery of CBT are reducing the cost and slowly increasing the accessibility of treatment, which will eventually shift the cost-effectiveness equation such that combined treatment may be recommended for "most patients" who do not rapidly respond to first-line interventions. In the future, it may be possible to further refine the selection of patients who are likely to benefit from adjunctive CBT by use of neuroimaging techniques to gauge the activity of relevant circuits, as suggested by some recent findings (48-51).

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