



# Combining Cognitive Behavioural Therapy and Pharmacotherapy in the Treatment of Anxiety Disorders: True Gains or False Hopes?

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## ÖZET:

Anksiyete bozuklukları tedavisinde bilişsel davranışçı terapi ve ilaç tedavisi birlikteliği: Gerçek kazanımlar mı? Gerçekçi olmayan umutlar mı?

**Amaç:** Anksiyete bozuklukları sık görülen; birey, sağlık sistemi ve toplum üzerinde olumsuz etkileri olan bir hastalık grubudur. Uygulamada anksiyete hastalarının önemli bir bölümünün tedavi gömediği, görenlerin ise çoğunlukla ya ilaç tedavisi ya bilişsel davranış terapileri (BDT) ya da kombinasyon tedavileri aldığı bilinmektedir. Bu gözden geçirme makalesi, başta panik bozukluk olmak üzere, tüm anksiyete bozukluklarının tedavisinde kullanılan kombine yaklaşımın lehine ve aleyhine olan kanıtları incelemek ve BDT ile ilaç tedavisinin olası etkileşim mekanizmalarını araştırmayı amaçlamıştır.

**Yöntem:** Makale panik bozukluğun ilaç ve BDT kombinasyonu ile tedavisine ilişkin eldeki kanıtları gözden geçirmekte ayrıca yaygın anksiyete bozukluğu (YAB), sosyal anksiyete bozukluğu (SAB), obsesif kompulsif bozukluk (OKB) ve travma sonrası stres bozukluğu (TSSB)'ndaki olası etkileşimleri metaanalitik düzeyde incelemektedir.

**Bulgular:** TSSB'de kombinasyon tedavilerinin ya da BDT'nin antipsikotik veya antikonvulsan ilaçlarla kombine edilmesinin yararlı olduğunu ortaya koyan nitelikli araştırma verisine rastlanmamıştır. Panik bozukluk, YAB, SAB ve OKB'de ise antidepressan ve benzodiyazepinlerle BDT kombinasyonunun tedavinin hem başlangıç hem de sonuç evresinde etkili olabileceği gösterilmiş olsa da kombine tedavi ile sağlanan yararların yalnızca BDT ile sağlanan yararlar kadar kalıcı olmadığı görülmektedir. Hatta bazı ilaç grupları ile kombinasyonun BDT'nin uzun dönem yararlı etkilerini olumsuz yönde değiştirdiğine ilişkin kanıtlar bulunmuştur. Psikotrop ilaçlarla BDT arasındaki karmaşık etkileşimi anlamaya çalışırken tedavinin nöronal korku ağına ve bellek işlevleri üzerine olan etkileri yanı sıra hastaların iyileşmeyi hangi tedavi yaklaşımına yükledikleri ve her bir tedavi yaklaşımına olan tutumları gibi etkenler önem kazanmaktadır.

**Sonuç:** Eldeki mevcut kanıta dayalı veriler temel alındığında uygulamada anksiyete bozukluklarının tedavisinde kombine tedavilerin kullanılması gerekenden daha fazla, yalnızca BDT'nin ise kullanılması gerekenden daha az kullanıldığı anlaşılmaktadır. Tedaviyi planlarken BDT ile ilaç tedavisi arasındaki karmaşık etkileşimler gözönünde bulundurulmalıdır.

**Anahtar sözcükler:** Bilişsel davranışçı terapisi, ilaç tedavisi, anksiyete bozukluğu

Klinik Psikofarmakoloji Bülteni 2009;19:436-446

## ABSTRACT:

Combining cognitive behavioural therapy and pharmacotherapy in the treatment of anxiety disorders: true gains or false hopes?

**Objective:** Anxiety disorders are common and have negative impact on the individual, the health system and the society. In practice a substantial percentage of patients remain untreated and those who are treated mostly receive either pharmacotherapy or CBT as monotherapy or in combination. This article aims at reviewing the available evidence for and against combination therapy in anxiety disorders with special emphasis on panic disorder and explores possible mechanisms of how cognitive behavioural therapy (CBT) and pharmacotherapy interact.

**Method:** The article reviews available evidence for combination therapy in panic disorder and putative interactions between CBT and pharmacotherapy for panic disorder as well as for generalized anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) on meta-analytic level.

**Results:** There is no high-quality data that favours combination therapy in PTSD or combination of CBT with antipsychotics or anticonvulsants. In panic disorder, GAD, SAD and OCD combined treatment with antidepressants or benzodiazepines may result in greater effectiveness during the acute phase and post-treatment but treatment gains appear not to be durable compared to CBT monotherapy. Some evidence suggests that combination with some types of medication may actually be detrimental to long-term outcome. Effects on the neuronal fear network and memory function as well as attribution of improvement and patients' attitudes towards treatment are possible factors in understanding the complex interaction between psychotropic medication and CBT.

**Conclusions:** Combination therapy in anxiety disorders may be clinically over-used considering the current evidence base while CBT monotherapy appears underutilized. The complex interaction between pharmacotherapy and CBT should be considered in treatment planning.

**Key words:** Cognitive behavioural therapy, pharmacotherapy, anxiety disorder

Bulletin of Clinical Psychopharmacology 2009;19:436-446

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Kabul tarihi / Date of acceptance: 25 Kasım 2009 / November 25, 2009

## Bağıntı beyanı:

A.W.: yok.

M.Z.S.: Çok sayıda ilaç firmasından bilimsel aktiviteleri karşılığı honorarium kabul etmiştir.

## Declaration of interest:

A.W.: none.

M.Z.S.: Received honoraria for scientific activities from various pharmaceutical companies.

## INTRODUCTION

Anxiety disorders such as obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder (SAD), generalized anxiety disorder (GA) and post-

traumatic stress disorder (PTSD) are the most common of the psychiatric disorders worldwide with a prevalence of up to 18% (1). These disorders often only receive little attention by mental health services despite their great contribution to overall clinical burden and economic costs

of mental disorders (2). Anxiety disorders tend to be chronic and can be as disabling as psychotic or somatic disorders. They severely impact on the quality of life of the individual and their families and also have an economic impact through increased utilisation of medical care and prescription drugs as well as through reduced productivity and a greater number of days missed at work. Compared with those who have other psychiatric disorders, people with anxiety disorders present more frequently to general practitioners than to psychiatric professionals. Anxiety disorders often remain undiagnosed and/or untreated. In a recent American study (3) conducted in a primary care setting almost half (47.3%) of 539 primary care participants with at least one anxiety disorder were untreated. Of those patients treated nearly 21% were receiving medication alone for psychiatric problems, 7.2% were receiving psychotherapy alone, and 24.5% were receiving a combination of medication and psychotherapy. This means that about 10% of people with anxiety disorders overall received pharmacological monotherapy, only about 3.5% received psychotherapy as monotherapy and about 12% were treated with combination therapy. Merely 31.3% of anxiety patients reported treatment that met the authors' criterion for appropriate care for anxiety disorders. A comparison in the same study between care provided by primary care physicians and psychiatrists revealed that in terms of pharmacological treatment there was no great difference between the two groups although psychiatrists were more likely to prescribe benzodiazepines. Regarding psychological treatment psychiatrists were much more likely to use a combination of pharmacotherapy and psychotherapy. Seventy-seven percent of patients treated by psychiatrists with medication also received psychotherapy compared to just 33% treated by primary care physicians with medication. Although the numbers may be slightly different in different health systems and are also influenced by patients' choices and expectations the study highlights that psychotherapy is still rarely applied as monotherapy in patients with anxiety disorders whereas combination therapy (psychotherapy plus pharmacotherapy) is used comparatively often.

The article reviews the available data regarding combination therapy for anxiety disorders with a special focus on panic disorder as the most extensively researched disorder in order to better understand which factors may

influence outcome in combination therapy. The aim is also to highlight when combining these two treatments may actually be detrimental by affecting outcome negatively, increasing drop-out rates and/or driving up costs. As cognitive-behavioural therapy (CBT) is the form of psychotherapy with by far the greatest evidence base in the treatment of anxiety disorders (4-6) this article will only consider CBT-based approaches both as monotherapy and as part of a combination therapy. For example in a review of 16 meta-analyses Butler and colleagues (6) reported an effect size (ES) of CBT of 0.95 for generalized anxiety disorder (GAD), social phobia, post-traumatic stress disorder (PTSD) and panic disorder compared to no treatment, waiting list or placebo combined, which indicates high efficacy. A similar ES was reported in OCD. They same authors also concluded that in panic disorder there appears to be robust evidence that CBT produces a superior long-term outcome with relapse rates 50% lower than for pharmacotherapy alone. They furthermore reported evidence for long-term benefits in GAD, SAD and OCD although follow-up duration rarely exceeded 12 months. Hofmann et al. (5) meta-analytically reviewed the efficacy of CBT versus placebo for adult anxiety and obtained a pooled ES (Hedges' *g*) of 0.73. The strongest ES were observed for OCD and acute stress disorder. In addition to antidepressants and benzodiazepines other classes of medication such as antipsychotic and anticonvulsant substances (7,8) have found some limited application in the treatment of anxiety disorders. However, there is currently no available high-quality data that allows drawing conclusions about combining these medications with CBT in anxiety disorders so that this review can only examine the combination of CBT with either antidepressants or benzodiazepines.

### **Lessons to be learned from panic disorder**

Among the anxiety disorders panic disorder takes a prominent place regarding research data on the effects of combination therapy.

#### ***The combination of CBT and benzodiazepines in panic disorder***

In studies carried out in the 1990s the focus had been on the combination of benzodiazepines with CBT

treatments that emphasized exposure to feared stimuli and situations. Watanabe and colleagues (9) recently conducted a meta-analysis of available studies but only two studies met their inclusion criteria which highlights that many of the earlier studies suffer from flaws in study design. Analyzing the data from studies by Marks et al. (10) and Wardle et al. (11) the authors concluded that exposure-based CBT plus benzodiazepines is superior to benzodiazepines alone, especially at the end of acute treatment (RR = 3.39, 1.03 to 11.21). This advantage is also likely to exist during the acute phase and at long-term follow-up. The combined therapy may also be superior to exposure-based CBT alone during and at the end of the acute phase. However, the most striking outcome was that this possible superiority at the end of the acute phase of combining benzodiazepine with exposure-based CBT may not persist and possibly even invert during the follow-up 6-12 months after treatment termination. In other words, a short-term advantage on some measures of combination therapy over exposure-based CBT alone may result in a worse long-term outcome of combination therapy compared to CBT monotherapy.

#### ***The combination of CBT and antidepressants in panic disorder***

Although benzodiazepines are still being prescribed quite widely for the treatment of anxiety disorders (12) they have fallen out of favour in many treatment guidelines including guidelines for the treatment of panic disorder (e.g. published by the National Institute for Health and Clinical Excellence, United Kingdom (13)). Guidelines tend to recommend the prescription of antidepressant medication instead of benzodiazepines in anxiety disorders if pharmacotherapy is chosen as first line treatment. In 2000 Barlow and colleagues (14) conducted one of the largest trials employing a randomized controlled study design and examining the effectiveness of the tricyclic antidepressant imipramine, CBT and their combination on patients with or without mild agoraphobia. However, patients were also permitted up to 10 doses of benzodiazepine (0.5 mg of alprazolam-equivalent) in the 2 weeks before the first treatment visit and up to 20 doses during baseline and acute treatment combined, which may have influenced the outcome considering the findings described above. In Barlow's study the intention-to-treat analysis revealed a response

rate in the acute treatment phase regarding the PDSS (Panic Disorder Severity Scale) score of 45.8% for the imipramine only and 48.7% for the CBT only group. The response rate for CBT plus placebo was 57.1% and for CBT plus imipramine 60.3%. However, six months after treatment discontinuation, the response rates were 19.7% for imipramine alone, 32.4% for CBT alone, 25.0% for CBT combined with imipramine and 41.0% for CBT plus placebo. This means that in follow-up the groups having received either imipramine alone or in combination with CBT did worse than the groups having received CBT alone or combined with placebo.

Furukawa and colleagues (15) conducted a meta-analysis of 23 randomized comparisons (representing 21 trials, 1709 patients), 21 of which involved cognitive behavior therapies, some of which were exposure-based. Antidepressants included tricyclic antidepressants as well as selective-serotonin reuptake inhibitors (SSRI). In the acute phase treatment, the combined therapy was superior to antidepressant pharmacotherapy (RR 1.24) or psychotherapy (RR 1.17). Taking a closer look at combination therapy compared to psychotherapy alone at the end of acute treatment panic frequency decreased as much in combined treatment as in psychotherapy alone, whereas phobic avoidance, depression and general anxiety level reduced more in combined treatment. However, the combined therapy produced more dropouts than psychotherapy alone due to medication side-effects. The overall superiority of the combination over either monotherapy seemed to persist during drug maintenance after the acute-phase treatment. In follow-up, after termination of active treatment including stopping medication, the combined therapy was more effective than pharmacotherapy alone (RR 1.61) and was about as effective as psychotherapy alone (RR 0.96). In summary, adding pharmacotherapy to CBT did not improve long-term outcome but increased drop-out rates, whereas adding CBT to pharmacotherapy outperformed pharmacological monotherapy both during the acute phase and follow-up.

#### ***Sequential treatment and adding-on treatment***

In a study by Spiegel et al. (16) patients with panic disorder with mild to severe agoraphobia were treated with alprazolam until they were panic-free. Then they were randomly assigned to receive either supportive drug

maintenance and slow, flexible drug taper or 12 weeks of individual cognitive behavioral treatment and slow, flexible drug taper. In the combined treatment group medication was gradually stopped before cognitive behavioral treatment ended. There was no significant difference between groups in the rate of alprazolam discontinuation that was achieved by patients (80% vs. 90%, respectively). However, during the 6-month follow-up period, half of the subjects who discontinued alprazolam without cognitive behavior therapy, but none of those who had been given concomitant cognitive behavior therapy, relapsed and restarted using alprazolam. In a follow-up study over 2-5 years 75% of the patients who had stopped medication under CBT-treatment remained abstinent of any type of treatment for panic disorder, and maintained their acute-treatment clinical gains (17). In a small study by Schmidt and colleagues (18) panic patients that had been treated with an SSRI antidepressant were randomly assigned to either continue with medication or stop medication gradually during a course of group CBT. Patients who stopped medication did as well as patients who continued maintenance SSRI treatment both at the end of the course of CBT as well as 6 months later. In a case series by Pollack and colleagues (19) 15 patients with panic disorder referred for further treatment due to incomplete response to pharmacotherapy were treated with 12-weeks of group cognitive behavior therapy. Overall, patients experienced a significant improvement in global function at the end of the cognitive behavior therapy intervention, as well as a decrease in panic attack frequency. Improvement was maintained at follow-up. However, in a recent randomized clinical trial in panic patients refractory to initial treatment with SSRI adding clonazepam or CBT resulted in small therapeutic gains ( $ES=0.24$ ) in both groups. Increasing the SSRI dose did not result in any further improvement at all (20).

Kampman and colleagues (21) published a study of patients who had not responded to 15 sessions of CBT. Forty-three unsuccessfully treated patients from this group were included in a double-blind, placebo-controlled, 'next-step' treatment study consisting of continued CBT plus adjunctive paroxetine at a dose of 40 mg/day or continued CBT plus placebo. Patients in the CBT plus add-on paroxetine condition improved on agoraphobic behaviour and anxiety discomfort significantly more than patients in the CBT plus add-on

placebo condition.

The available evidence on sequential treatment is scarce and not always methodologically satisfactory. It appears that stopping either benzodiazepine or antidepressants during CBT is possible and superior in maintaining treatment gains at follow-up compared to stopping medication outside of concomitant CBT. Adding on antidepressant medication to CBT when treatment gains are unsatisfactory during CBT alone may result in some therapeutic gains during continued CBT.

### ***Possible factors that may influence the outcome of combination therapy in panic disorder***

#### *Effects on learning and memory:*

State-dependent learning: State-dependent learning refers to the phenomenon where learning that occurs under the influence of a drug does not generalize to the drug-free state. Whereas it is a phenomenon well-demonstrated in animal experiments the evidence for state-dependent learning with benzodiazepines in humans is more limited (22). The available findings suggest, however, that learning in CBT acquired with concurrent use of benzodiazepine may not transfer to the non-medicated state, resulting in continued need for medication for durable treatment gains. While state-dependent learning has been demonstrated in humans for various substances such as caffeine (23) there is a paucity of research regarding state-dependent learning using antidepressants. A study conducted on mice (24) using the antidepressants amitriptyline, maprotiline and fluoxetine suggests that state-dependent learning may not play a substantial role in antidepressants, although the evidence is too sparse to exclude it as a factor in humans for some antidepressants.

While state-dependent learning is an effect on retrieval of memory, psychotropic agents can influence memory also at the stage of encoding new information. Benzodiazepines are well known to cause anterograde amnesia, i.e. they impair acquisition of new memories by action on subtypes of the GABAA-receptor (25). In a functional MRI study lorazepam has been shown to cause significant decreases both in the extent and magnitude of activation within hippocampal, fusiform, and inferior prefrontal areas, which are important parts of the memory network (26). Although some interference with retrieval

of information learned prior to exposure to benzodiazepine has been described, retrograde amnesia seems to be negligible in humans compared to the anterograde amnesic effects (25). Regarding CBT benzodiazepine-induced anterograde amnesia may mean that new information that is presented to the patient in therapy or between sessions (e.g., during homework, such as exposure tasks) will be less well remembered. As old information, such as maladaptive beliefs, continue to be fully retrieved due to the lack of substantial effects of benzodiazepines on memory retrieval, the formation of novel memory associations could be affected negatively. This could result in poorer integration of new, belief-challenging information essential for modification of preexisting catastrophic beliefs and interpretations (27). Consequently, this effect of benzodiazepines on memory may reduce the efficacy of a treatment, such as CBT, which emphasizes ‘cognitive change’, i.e. learning and subsequent integration of new, more adaptive material (28). Effects that seem to support this assumption have been demonstrated in healthy individuals after a single dose of lorazepam (28). It should be pointed out that benzodiazepines, in addition to explicit memories, such as consciously held beliefs and interpretations of a situation, also affect the implicit memory system, such as procedural learning (25). Worryingly, Curran and colleagues (29) have demonstrated in a study with panic disorder patients that the negative effects of benzodiazepines (in this case alprazolam) on some memory tasks such as a word recall task can continue for more than 5-8 weeks after medication has been stopped.

Regarding antidepressants the neurocognitive effects seem to be more subtle and varied. Gualtieri and colleagues presented preliminary data (30) from depressed patients on seven different antidepressants using, among others, tests for verbal and visual memory, symbol digit coding and attention. All tested antidepressants (Citalopram, Sertraline, Bupropion, Fluoxetine, Paroxetine, Trazodone and Venlafaxine) had some effect compared to the control groups of depressed but unmedicated patients and healthy volunteers, but the extent of the negative effect differed from substance to substance. A study by Rose et al. (31) investigated if the effect of escitalopram, a SSRI antidepressant, on signal intensity of medicated, depressed individuals is large enough to be a confounding factor in neuroimaging

studies. Employing a working memory and a reaction time task during functional MRI, there was no difference in memory-load-dependent activation between escitalopram and drug-free conditions although some effects of escitalopram on the signal intensity of thalamus, anterior cingulate and inferior frontal gyrus existed. The differential effect on attention and working-memory and event-related brain potentials became also apparent in a study testing the effects of amitriptyline, nefazodone, paroxetine and placebo on day 1 and day 8 of drug-administration (32). Compared to the pronounced effects of amitriptyline as sedative and anticholinergic tricyclic antidepressant on the employed measurements and tasks nefazodone (5-HT<sub>2</sub> receptor antagonist) and paroxetine (SSRI) exerted no or only minor effects. Harmer and colleagues (33) reported that immediate recall on the verbal memory test was unaffected by intravenous citalopram administration compared to placebo. Long-term memory performance in terms of delayed recall and recognition was even enhanced relative to those participants receiving placebo. In depression suppressed neurogenesis in the hippocampus is thought to be a contributing factor (34). Recent research has indicated that both tricyclic and SSRI antidepressants can increase neural progenitor cells in the human hippocampus (35). Brain-derived neurotrophic factor (BDNF) has been assumed to play a role in the pathogenesis of stress-induced depression and the delayed efficacy of antidepressant drugs. Alme et al. (36) recently demonstrated that chronic, but not acute, fluoxetine administration lead to upregulation of these BDNF, long-term-potential-associated genes in a brain region-specific pattern. The authors conclude that chronic effects of antidepressant treatment influence molecular mechanisms underlying BDNF-induced synaptic plasticity. It appears reasonable to assume that both an increased rate of neurogenesis within the hippocampus as well as upregulation of BDNF-related neuroplasticity can have some influence on how well new information presented during a course of CBT can be integrated into memory networks.

While the pronounced effect of benzodiazepines on acquisition of new memories point to possible negative influences on the efficacy of CBT, the situation for combination between CBT and antidepressants is more complex. Direct neurocognitive effects differ between

individual antidepressant agents and possible negative effects of some agents may be attenuated or off-set by chronic treatment that influences neurogenesis and BDNF-related neuroplasticity. This may part of the explanation why the results of individual studies combining specific antidepressants with CBT such as the study by Barlow mentioned above (14) which combined imipramine (tricyclic antidepressant with anticholinergic properties) with CBT in panic disorder may show a worse long-term outcome for combination therapy. A meta-analysis such as the study by Furukawa and colleagues (15) that included a multitude of studies using different types of antidepressants may not demonstrate the same effect on long-term outcome due to the differential neurocognitive effects of the various antidepressant agents that were used in the included studies.

*Effects on processing of emotion:*

Panic disorder (PD) is a multidimensional anxiety disorder that involves the activation of a complex brain fear-network. Within this network amygdala, hippocampus and the prefrontal cortex have been suggested to play a prominent role (37,38). One current hypothesis in both depression (39) and anxiety disorders (37,40) is that amygdala activity is increased and prefrontal activity is reduced compared to healthy individuals. CBT may work by strengthening the ability of the prefrontal cortex to inhibit firing of amygdala neurons under the modulation of the hippocampus. Some data from neuroimaging studies support this hypothesis. Sakai and colleagues (41) compared the regional glucose utilization in patients with panic disorder before and after cognitive-behavioral therapy using positron emission tomography with (18)F-fluorodeoxyglucose. In 11 out of 12 patients who had improved after CBT, reduced glucose utilization was detected in the right hippocampus, left anterior cingulate, left cerebellum, and pons, whereas increased glucose utilization was seen in the bilateral medial prefrontal cortices. Hofmann et al. (42) re-analysed the data-set from Barlow's CBT+imipramine study mentioned above (14) and concluded that the multilevel moderated mediation analyses provided preliminary support for the notion that changes in panic-related cognitions mediate changes in panic severity in treatments that included CBT but not medication-only treatments. In an fMRI study eliciting amygdala

activation in healthy volunteers by exposure to emotional facial expression Hariri et al. (43,44) have demonstrated that cognitive evaluation (e.g. interpreting and labeling) of these same stimuli was associated with attenuation of the elicited amygdala response and was correlated with an increase in response of the right prefrontal cortex and the anterior cingulate cortex. This attenuating influence was also reflected in changes in skin conductance.

While this evidence supports the model of CBT strengthening the ability of the prefrontal cortex to inhibit amygdala activation, both benzodiazepines and antidepressants seem to work directly on the amygdala within the fear network. Single-dose lorazepam significantly attenuated the BOLD-fMRI signal in a dose-dependent manner in the amygdala and insula bilaterally but not in the medial prefrontal cortex in a study on healthy subjects using an emotional face assessment task (45). In a facial recognition task citalopram, an SSRI antidepressant and reboxetine, a selective norepinephrine reuptake inhibitor, taken for 7 days reduced the identification of the negative facial expressions of anger and fear (46). The same research group demonstrated that a single oral dose of citalopram in healthy volunteers resulted in a significantly reduced amygdala response to fearful facial expressions compared with placebo (47). Harmer and colleagues (48) point out that this shift in the relative balance of negative to positive emotional processing caused by antidepressants may play an important role in the treatment of depression and is compatible with the cognitive model of depression of biased information-processing. In anxiety disorders the shift in the relative balance of fearful to non-fearful emotional processing may be important.

Taking these findings into account CBT and antidepressants or benzodiazepines appear to act synergistically during continued combination treatment. Benzodiazepines and antidepressants down-regulate amygdala activity directly while CBT seems to do so by inhibiting its activity via prefrontal activation. This would explain while most studies in panic disorders find a superior effect, at least on some measures, during the acute treatment phase. Emotional-processing theory proposes that for long-term therapeutic fear reduction activation of the fear with its cognitive and behavioural components is necessary during therapeutic interventions (4). Following this line of thought lasting fear reduction

may not be achieved if, during therapeutic interventions, fear is not fully activated during psychotherapeutic interventions because amygdala activity is down-regulated by pharmacological agents. On the other hand, in very severe anxiety disorders, extreme fear activation may impede CBT because high stress levels lead to highly increased amygdala activation and disturbed hippocampus function and can interfere with encoding and consolidation of emotional material (49). Down-regulating extreme amygdala activation pharmacologically may actually facilitate CBT in the initial stages of therapy.

*Effects of attribution of success and attitude towards treatment:*

Medication adherence in both mood as well as in anxiety disorders is as low as 50% or less (50,51). In controlled studies drop-out rates for combination treatment are usually higher than for CBT alone (with the exception of social anxiety disorder) (15,52). Pompili and colleagues point out that attitudes and beliefs are at least as important as side-effects in predicting adherence (51). In a systematic review of 71 studies Prins and colleagues explored patients' attitudes towards psychotherapy and pharmacotherapy in anxiety and mood disorders. Their results indicate that the vast majority of anxiety patients prefer psychological treatment forms to medication and that majority of patients view antidepressants as addictive (53).

In cognitive models of anxiety disorders the way people think about themselves in fearful situations (e.g. I can cope vs. I cannot cope) has received increasing attention. In panic disorder, for example, Casey et al. (54) proposed an 'integrated cognitive model' that emphasizes the role not only of catastrophic misinterpretations of fear-induced bodily sensations but also the role of what the author's call 'panic self-efficacy', i.e. the perceived ability to cope with assumed threatening situations. Successful CBT of anxiety disorders provides patients with exercises that provoke anxiety that the patient learns to overcome. In addition to challenging catastrophic misinterpretations patients can also experience themselves as being able to cope with difficult situations, such as exposure tasks or behavioural experiments, and can attribute therapeutic gains to their own efforts. Başoğlu (50) re-analyzed the data-set generated by Marks et al. (10) of combining

exposure-based CBT with either alprazolam or placebo in patient in panic disorder. At the end of treatment at week 8, 40 patients who had become either much or very much improved rated how much they attributed their gains to medication or to their own efforts. During the tapering-off and treatment-free follow-up, patients who, at week 8, had attributed their gains to medication and felt less confident in coping without it had more severe withdrawal symptoms and greater loss of gains than did patients who, at week 8, had attributed their improvement to their own efforts. Illness severity, older age, higher expectancy from drug treatment, and more side-effects of drugs during treatment all predicted more attributions of improvement to medication but did not independently predict relapse. Patients on alprazolam attributed improvement more often to medication than did patients on placebo. Attributions to medication predicted relapse in both alprazolam and placebo groups, but this effect was stronger in the alprazolam group. This study suggests that attribution of improvement to taking medication instead of one's own efforts in therapy can negatively influence longer-term outcome by failing to increase the patient's sense of self-efficacy.

### **Available Evidence across other anxiety disorders**

For the other anxiety disorders (OCD, GAD, PTSD, SAD) all authors of recent reviews (4, 55-57) point out the scarcity of the evidence available.

As we have highlighted above treatment gains of combination therapy during the acute phase of treatment may not be maintained or may even be inverted at follow-up. From this perspective the meta-analysis of 24 studies by Bandelow et al. (58), which does not include data at follow-up, does not provide an answer to whether clinical improvement is durable. In the meta-analysis the authors concluded that, in addition to panic disorder, combination therapy of CBT with either antidepressants or benzodiazepines appears effective during the acute treatment phase of SAD. The authors also stated that for GAD the data was insufficient which made it impossible to draw any firm conclusions.

Hofmann and colleagues (57) included 11 high-quality studies in their meta-analysis and focused on studies that compared CBT plus pharmacotherapy to CBT plus

placebo. They included trials on panic disorder ( $n = 4$ , including the studies by Marks and Barlow discussed above (10, 14)), SAD ( $n = 3$ ), OCD ( $n = 2$ ), and GA ( $n = 2$ ). The total number of patients for the analyses ranged between 236 (response rate analyses at follow-up) and 471 (response rate analyses at post-acute) participants. The analysis was limited to completer data as only two included studies had reported intent-to-treat data. Hofmann and colleagues concluded that, based on the available evidence, combined therapy appears to be effective among completers in the short term. The pooled ES for the main outcome measures at the post-acute assessment for anxiety disorder severity was Hedges'  $g = .59$ , and the pooled odds ratio was 1.95, indicating that CBT plus pharmacotherapy is more effective than CBT plus placebo in the short-term. Although the overall effect of CBT plus pharmacotherapy over CBT plus placebo was medium at post-acute treatment, no difference between these two treatment modalities was found at 6-month follow-up. Hofmann and colleagues also highlight a significant publication year bias, suggesting that more recent studies reported smaller effects than older studies. This finding might be due to more appropriate assessment methods and study designs in newer studies. The transient superiority of combined therapy during and directly after acute treatment was different for the various anxiety disorders. Large average ES were found for panic disorder (Hedges'  $g = .99$ ) and medium to large ES were found for GA (Hedges'  $g = .81$ ), but only small and non-significant ES were found for OCD and SAD. Hofmann and colleagues' conclusion confirms conclusions drawn both by Foa (4) and Black (59) in their reviews. A drawback of current meta-analyses and reviews is that they are forced to include trials of combinations between CBT and various types of psychotropic medication. In Hofmann's meta-analysis (57), for example, combination included CBT plus benzodiazepines, tricyclic antidepressants, SSRI or buspirone. Given the differential effects on memory and fear networks these members of different classes of psychotropic medication possess meta-analyses may fail to show that combinations between specific drugs and CBT may be more advantageous than others.

It is striking that in both PTSD and specific phobia there are no studies that meet the quality criteria outlined by Foa and colleagues (4) and thus no conclusion regarding the relative efficacy of combined treatment

versus monotherapy can be drawn. This fact has not changed since a literature review by Black in 2006 (59).

## CONCLUSION

CBT and pharmacotherapy have both proven that they can be of value in the treatment of anxiety disorders (5,6,60). However, pharmacotherapy has higher relapse rates after discontinuation of medication (6). Longer-term continuation treatment with medication may therefore be required which has been shown to result in a higher rate of side-effects such as weight gain and in non-adherence (61,62). For both pharmacotherapy and CBT treatment approaches few trials have investigated the long-term outcome 2 or more years after treatment completion. However, the greatest dearth of evidence is in the combination of pharmacological treatments with CBT although it is widely used in clinical practice. In addition, a high proportion of people suffering from anxiety disorders receive no appropriate treatment at all (3).

There is no high-quality data regarding combination treatment of CBT plus mood-stabilizers or antipsychotics or regarding multi-combination treatments such as CBT plus antidepressants plus antipsychotics. In specific phobias and in PTSD no research studies exist that allow any conclusions regarding benefits of combination therapy. Many guidelines such as the guidelines issued by the National Institute for Health and Clinical Excellence, United Kingdom, recommend trauma-focused psychotherapy alone as first-line treatment for PTSD (63). Despite this combination therapy is still widely used in the treatment of PTSD in clinical practice. In this article we have highlighted that in panic disorder, OCD, GA and SAD combination therapy using CBT with antidepressants or benzodiazepines may be beneficial in the acute phase and post-treatment, but that this superiority of combined treatment may be lost or even reversed in follow-up after end of active treatment. Preliminary data suggests on the other hand that CBT can be helpful to maintain treatment gains for patients who need or want to stop medication by reducing medication slowly during a course of CBT. Also, introducing antidepressants in a second step after initial CBT has not been successful may be effective if both CBT and medication are continued.

It is generally believed that two effective treatment modalities that target different mechanisms should be



more effective than either modality alone. However, CBT and pharmacotherapy act on the same neuronal networks, e.g. the fear network, and successful CBT relies on intact learning and memory functions, which are affected by different pharmacotherapeutic agents in different ways (e.g. state-dependent learning, anterograde amnesia). In addition patients' attitudes towards treatment and attributions of improvement will influence treatment adherence and long-term outcome and need to be considered in treatment planning. From this perspective, improving communication between the clinician prescribing medication, the clinician providing CBT and the patient plays an important role in treatment planning and deciding on any changes of type and dose of medication.

It would be valuable if future research on combination therapy could focus on combinations of specific classes of medication such as SSRI compared to antidepressants with other mechanisms of action to come closer to an understanding if combinations between CBT and specific medications may be more beneficial than others. It has to be acknowledged that also the type of CBT (e.g. more exposure focused vs. more cognitive) may play a role in

combination effectiveness. It would further be of importance to understand better patients' attitudes towards treatment and agency of change and the resulting influence on outcome.

Combining treatments without improving long-term outcome is, in addition to risking a higher rate of side effects and patients' drop-outs from treatment, also a matter of cost. Considering cost, a recent study by McHugh (64) is of particular interest. Their study on panic disorder within the American health system demonstrated consistently greater cost-efficacy for individual over combined treatments, with imipramine representing the most cost-efficacious treatment option at the completion of the acute phase and CBT representing the most cost-efficacious option at the end of maintenance treatment and 6 months after treatment termination. Since CBT monotherapy has at least equal long-term efficacy compared to combined treatment, which has poorer cost-efficacy, and a more durable effect than pharmacotherapy alone CBT should be considered the first-line treatment of choice for panic disorder. However, CBT monotherapy unfortunately remains underutilized in the treatment of anxiety disorders in many health systems.

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