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Advice for Clinicians on How to Treat Comorbid Anxiety and Depression

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Depressive and anxiety disorders frequently co-occur. It is widely known that the outcome of comorbid anxiety and depressive disorder together is more negative than each single counterpart. Clinically, comorbidity is associated with greater severity of symptoms, with an increased risk of suicide, a more reduced quality of life, and a more limited level of functioning.[1] Although it can be questioned whether it is best to view depression and anxiety as a single condition or distinct conditions, current clinical practice is to diagnose both disorders separately and refer to comorbidity. However, a clear-cut optimal treatment strategy for comorbid anxiety and depression is lacking. Should we treat the disorders sequentially (treating one and subsequently the other) or parallel (treating both disorders simultaneously)? Should we start a single treatment focusing on both disorders (integrated treatment) or a transdiagnostic treatment focusing on underlying mechanisms present in both anxiety and depressive disorders?[2]

Most clinical guidelines do acknowledge the frequent occurrence of comorbidity. However, they are disorder specific, because they are based on randomized clinical trials that usually target single disorders. Moreover, these randomized clinical trials frequently exclude severe comorbidity to obtain optimal effect sizes in homogeneous patient samples. As a result, disorder-specific guidelines cannot appropriately advise on comorbidity treatment.

In this article, we question the optimal treatment strategy in cases of comorbidity. We summarize the evidence from recent research on how best to treat comorbid depression and anxiety and arrive at practical advice for clinicians. We limit ourselves to the most prevalent depressive and anxiety disorders according to the *DSM-5*.

What Is the Association of Comorbidity of Anxiety and Depressive Disorder With Treatment Outcome?

Two recent meta-analyses[3,4] demonstrated that comorbid symptoms decreased during treatment of the more clinically significant disorder. This holds true for treating depression with psychotherapy with regard to anxiety symptoms[3] and treating anxiety disorders with cognitive behavioral therapy with regard to depressive symptoms.[4] However, in these meta-analyses, the comorbid condition was assessed at the symptom level rather than the disorder level. While meta-analyses at the disorder level are lacking, it has been frequently shown that directing treatment at the more clinically significant disorder also improves the comorbid disorder, although the level of evidence is higher for anxiety disorders with comorbid depressive disorder[5] than depressive disorders with comorbid anxiety disorders.[6]

Comorbid disorders appear to improve at a similar pace during treatment as noncomorbid, or single, disorders.[3,4] This explains why the treatment response percentages (defined as a percentage decrease of baseline symptom severity) are comparable for single and comorbid disorders. However, comorbid disorders appear to have higher pretreatment symptom severity.[1] This explains why comorbid disorder remission percentages (defined as posttreatment severity below a specific threshold) are frequently lower than those seen in single disorders.

Is Transdiagnostic Treatment a Better Alternative?

Transdiagnostic treatment may be an alternative for patients with comorbidities. Antidepressants targeting both anxiety disorders and depression can be viewed as transdiagnostic. Reviews for pharmacologic treatment suggest serotonergic antidepressants, such as the selective serotonin reuptake inhibitors and selective serotonin and noradrenalin reuptake inhibitors, as the first-line pharmacological options for treating anxiety-depression comorbidity.[7]

A transdiagnostic psychological treatment targets common underlying psychological mechanisms of anxiety and depressive disorders. Research on the efficacy of transdiagnostic approaches for anxiety and depression is emerging in recent years. This is demonstrated by a systematic review, including 16 randomized clinical trials examining transdiagnostic psychological treatments.[8] The authors conclude that transdiagnostic psychological treatment is more effective than a control condition. Moreover, they report that transdiagnostic treatment may have comparable outcomes with no clinically significant differences compared with disorder-specific treatment but may be even more efficacious for individuals with a depressive disorder. However, as only 4 studies were included that compared transdiagnostic treatment with disorder-specific treatments, these results are preliminary. As a result, more research into the efficacy of transdiagnostic treatment is needed.

Implications for Clinical Practice

Contrary to the commonly held pessimistic view on treatability of comorbidity, we conclude that such pessimism is unnecessary; treatment for comorbid anxiety and depressive disorder is efficacious. With regard to psychotherapy, it seems more rational to focus on the more clinically significant disorder than to focus on both disorders simultaneously, because according to current knowledge, focusing on the more clinically significant disorder results in simultaneous improvement of the comorbid disorder. Two practice-based options have been proposed to determine the more clinically significant disorder in patients with comorbidities. The first option is to examine which disorder presented first. A disadvantage of this approach is that this may not be the disorder that affects the patient most or for which they are seeking treatment. From a clinical viewpoint, it may be difficult, if not impossible, to start treatment focusing on anxiety symptoms while the patient is seeking treatment for depressive symptoms or vice versa. According to the second option, the more clinically significant disorder is the most severe disorder at the time of the examination or the disorder that requires attention first according to the patient and clinician. Determining the more clinically significant disorder thus

depends on clinical aspects as well as patient preferences. It requires a process of shared decision-making with the patient.

In our opinion, to define the more clinically significant disorder as the most severe disorder for which the patient seeks treatment is most reasonable in most patients, given the importance of patient preferences with regard to motivation and level of treatment adherence and hence the feasibility of treatment. There is no clear advice for the best choice of psychotherapy in case of comorbidity. There is only evidence for the efficacy of cognitive behavioral therapy in comorbid disorders with anxiety as the primary disorder.[4] If depression is the primary disorder, also other types of psychotherapy seem to be efficacious to treat comorbidity without a preference for specific type.[3]

With regard to pharmacological treatment, a transdiagnostic approach is appropriate, given the amount of evidence supporting the efficacy selective serotonin reuptake inhibitors and selective serotonin and noradrenalin reuptake inhibitors in comorbid depressive and anxiety disorders. In the first phase of antidepressant treatment, anxiety symptoms may deteriorate. Usually, psychoeducation about a possible increase in anxiety is sufficient for patients to cope. Otherwise, benzodiazepines may be used temporarily in this initial phase. Another possibility is to incrementally increase the dosage of antidepressants slowly, dependent on the experienced adverse effects.

However, in treating patients with comorbidities, the course of psychopathology requires more attention. Therefore, after achieving remission for the primary disorder, an assessment should be made as to whether the comorbid disorder needs additional treatment. If so, treatment focusing on the comorbid disorder should commence, this being a form of sequential treatment. Likewise, in case of nonimprovement of the more clinically significant disorder, a reevaluation of diagnosis and treatment is necessary. Either redefining the more clinically significant disorder or simultaneously treating both disorders with a transdiagnostic psychological treatment may be suitable in such situations. Additionally, we must realize that treating comorbid conditions, which generally are more severe, requires longer treatment durations to achieve remission. Moreover, treatment engagement might require attention. Thus, throughout treatment, there is a continuing need to evaluate both the treatment process as well as the severity and course of the comorbid disorder.

To conclude, treatment of patients with comorbid anxiety and depression is effective on its own. However, further research may lead to a more efficient approach of treating comorbidity.

ARTICLE INFORMATION

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