When Anxiety and Depression Coexist: The Role of Differential Diagnosis Using Clinimetric Criteria

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Keywords

Depression · Anxiety · Psychotropic drugs · Cognitive behavioral therapy · Clinimetrics · Medicine-based evidence · Well-being therapy

Abstract

Depressive and anxiety disorders are frequently associated. Depression may be a complication of anxiety and anxiety can complicate depression. The nature of their relationship has been a source of controversy. Reviews generally base their conclusions on randomized controlled trials and meta-analyses that refer to the average patient and often clash with the variety of clinical presentations that may occur when anxiety and depression coexist. The aim of this review was to examine the literature according to profiling of subgroups of patients based on clinimetric criteria, in line with the recently developed concept of medicine-based evidence. We critically reviewed the literature pertaining to the specific presentations of anxiety and depression, outlining the advantages and disadvantages of each treatment approach. The following prototypic cases were presented: depression secondary to an active anxiety disorder, depression in patients with anxiety disorders under treatment, anxious

depression, anxiety as a residual component of depression, and demoralization secondary to anxiety disorder. We argue that the selection of treatment when anxiety and depression coexist should take into account the modalities of presentation and be filtered by clinical judgment. Very different indications may ensue when the literature is examined according to this perspective.

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Introduction

Major depressive disorder and anxiety disorder commonly coexist [1–4], being present in up to 25% of general practice patients [5] and in 80% of drug-naïve patients [6]. Their close relationship has been a long-standing clinical observation. Depression is a frequent complication of anxiety disorders [7, 8] and, vice versa, anxiety is a common complication of depression [3, 9–11].

The nature of the relationship between anxiety and depression has been a source of controversy [3, 8, 9, 12–15]. Current clinical practice is to diagnose both disorders separately and refer to comorbidity [16]. A clear-cut op-

timal treatment strategy for co-occurring anxiety and depression is still lacking and a trans-diagnostic approach is advocated [16]. However, following the evidence-based medicine (EBM) model, reviews and guidelines refer their findings to the “average” patient and apply customary clinical taxonomy based on DSM-5 [17]. Diagnostic criteria do not include patterns of symptoms, severity of illness, effects of comorbid conditions, timing of phenomena, rate of progression of illness, responses to previous treatments, and other clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same psychiatric diagnosis [18]. Such assessment is subsumed under the rubric of clinimetrics, the science of clinical measurements [18–20].

There is no simple “average” solution to most medical problems. The question is how to put the available evidence within the context of individual, unique assets and liabilities. There is thus the need of integrating the information that derives from EBM with medicine-based evidence (MBE) [21]. MBE attempts to produce fine-grained profiling of subgroups of patients based on clinimetric criteria. The aim of this review was to provide such profiling in the setting of anxiety associated with depression.

Methods

A computerized search was carried out (from PubMed inception to March 2021) using as key words: “anxiety AND depression.” In addition, the reference lists from existing reviews and from the articles retrieved were inspected. Only English language articles that were published in peer-reviewed journals were included. The prototype diagnostic configuration of disorders [21] was used as the method of dissecting the most frequent clinical presentations of anxiety and depression in adults. It allows the clinician to compare a patient’s overall clinical presentation to a set of diagnostic prototypes and rate the extent of match of the patient’s clinical presentation to the prototype [22]. Assessment of comorbidity was based on clinimetric principles as any “additional co-existing ailment” separate from the primary disease, even in cases where this secondary phenomenon does not qualify as a disease per se [23]. Comorbidity included the unfavorable modifications in the course, characteristics, and responsiveness to treatment of an illness that may be related to previously administered therapies, i.e., iatrogenic comorbidity [24].

The comorbidity profile that ensued was submitted to macro-analysis, a method developed for organizing clinical data as variables in clinical reasoning [18, 25]. Macro-analysis starts from the assumption that in most cases there are functional relationships with other more or less clearly defined problem areas and that the targets of treatment may vary during the course of disturbances [18, 25]. It was thus applied to establish a relationship between co-occurring ailments and to establish what to treat first, also taking

into account the primary/secondary distinction [26]. For instance, after months of panic disorder, an individual may become depressed; in this case depression is defined as secondary. Vice versa, if a patient develops a depressive disorder that, after a few months, becomes characterized by panic attacks, depression in this case is defined as primary. The staging method [27, 28] allowed us to analyze the longitudinal interplay between anxiety and depression, viewed as two symptomatic stages of the same affective disorder, with the ratio that assessment and treatment depend on when the observation is made [29]. Advantages and disadvantages of therapeutic approaches in the specific prototype setting were outlined, with particular reference to potential benefits, likelihood of responsiveness to the treatment option, and vulnerability to the adverse effects of treatment [30].

From Research to Clinical Practice

The following interactions between mood disorders and anxiety disturbances were selected.

A. Depression Secondary to an Active Anxiety Disorder

The occurrence of a major depressive disorder after the onset of an anxiety disorder is common [31, 32]. Noyes et al. [32] observed brief depressive episodes in 44% of patients with anxiety disorders over 6 years. Such episodes do not necessarily require specific treatment and may improve with appropriate therapy of the underlying anxiety disturbance. It is thus important to determine the type of intervention that is requested, as the clinical case illustrates.

Clinical Presentation

Julia is a 50-year-old housewife with a long-standing history of hypochondriacal fears and somatic symptoms. She always considered them as part of the way she was. In the last 5 years, after her mother’s death, she also suffered from agoraphobia with panic attacks, which she tried to manage by relying on her husband accompanying her to places. A few months after the onset of panic attacks and agoraphobia, she developed irritability, difficulties concentrating, low mood, and loss of appetite, which were followed by lack of energy and motivation. Only then did she ask for treatment.

Assessment and Diagnosis

Macroanalysis. The patient fulfilled the criteria for a major depressive episode, panic disorder, and agoraphobia. Depression occurred after the onset of panic disorder. She still had hypochondriacal fears and somatic symptoms and started having problems with her husband

Fig. 1. Macroanalysis of Julia's clinical case.

since she needed to be accompanied very often (shown in Fig. 1).

Staging. In accordance with the view of panic disorder as a stage of development of previous anxiety and mood disturbances [27], Julia was on stage 3 (online suppl. Table S1; see www.karger.com/doi/10.1159/000517518 for all online suppl. material).

Treatment Options

Cognitive behavioral treatment (CBT) of panic disorder and agoraphobia may be efficacious regardless of the baseline depression level [33]. Therefore, one option would be that of treating this patient with CBT only, with the clinical advantage of not having drug treatment, which may negatively interfere with psychotherapy regarding the long-term outcome [34]. However, patient preferences should be addressed, and she was asking for rapid control of symptomatology. In addition, the rapidity of symptom onset may herald further deterioration [27] and the impaired energy and motivation levels may hinder exposure homework, which is necessary for overcoming agoraphobic fears. The other option would be that of endorsing a sequential combination of treatment, using an antidepressant first and adding CBT when remission from depression occurs, with subsequent tapering and discontinuation of the antidepressant [35]. In the case of mild depression, another option would be a sequential combination of treatments which includes a benzodiazepine [36] first and CBT when improvement from panic attacks occurs, with subsequent tapering and discontinuation of the benzodiazepine. In the case of this patient the first sequential model was used [35], with tapering and discontinuation of the antidepressant medication. Since the patient did not reach a full recovery after

CBT, well-being therapy (WBT) [37, 38], a short-term psychotherapeutic strategy that pursues self-observation of instances of well-being, was added [39]. The sequential combination was effective in abating symptoms of agoraphobia, depression, and panic. Interpersonal frictions faded away after WBT.

B. Depression in Patients with Anxiety Disorders Under Treatment

If the patient with an anxiety disorder is under treatment (particularly if antidepressant drugs are used), the potential iatrogenic role of therapy needs to be evaluated [40]. Demoralization and mood disturbances may occur during treatment of agoraphobia and panic with CBT [41]. Depression may also ensue during antidepressant treatment [42]. The overall situation may be complicated, as this case illustrates.

Clinical Presentation

Thomas is a 35-year-old, single, white-collar worker. He has been taking citalopram for social anxiety for 2 years (20 mg at bedtime) and reported a mild improvement in anxiety. Citalopram had been prescribed by the family doctor. Recently, however, he started feeling sad, had late insomnia, loss of interest in life, and reported a decrease in appetite and energy. His anxiety considerably increased, especially when he tried to approach women, and a panic attack occurred. The family doctor increased citalopram to 40 mg per day with no results.

Assessment and Diagnosis

Macroanalysis. The patient met DSM-5 criteria for a major depressive episode and social anxiety disorder. He also reported one isolated panic attack. The loss of clinical

Fig. 2. Macroanalysis of Thomas' clinical case.

effect after 2 years of treatment with citalopram, as well as the refractoriness to dose increase, are well documented in the literature [40, 43]. The patient de facto did not respond to the first course of treatment. Thomas's macroanalysis is illustrated in Figure 2.

Staging. In accordance with the view of panic disorder as a stage of development of previous anxiety and mood disturbances [27], Thomas was moving from stage 2 to stage 3.

Treatment Options

Fux et al. [42] observed depressive symptoms in 7 out of 80 patients during the treatment of panic disorder with fluvoxamine. The symptoms abated when fluvoxamine was discontinued, and tricyclic antidepressants or clonazepam were prescribed; symptoms reappeared when fluoxetine was introduced. Similar findings were reported during the follow-up of patients receiving tricyclic antidepressants for panic disorder [44]. Furthermore, a relationship between the use of antidepressants and increased relapse risk of panic disorder was observed [45–47].

In the long-term treatment of depression, when loss of clinical effect occurs, an increase in dosage is unlikely to yield lasting remission [48], as was found to be the case with this patient. Thus, in this case, citalopram was tapered and discontinued, with the help of clonazepam [49] since withdrawal symptoms occurred despite tapering [34]. Augmenting strategies or switching to another antidepressant were not chosen, because of the potential occurrence of further behavioral toxicity [43]. In Thomas's case, his mood improved but social anxiety persisted despite use of clonazepam. CBT was thus added to the treatment and yielded an improvement; clonazepam was tapered and discontinued.

C. Anxious Depression

About half of outpatients with major depressive disorder have clinically meaningful levels of anxiety [50–52]. Such characterization must be differentiated from mixed anxiety-depressive disorder, that is subsyndromal symptoms of major depression, generalized anxiety disorder, or any other full-syndrome disorder [53]. Rickels et al. [54] observed that outpatients classified on relative degrees of depression and anxiety differed in their response to amitriptyline, chlordiazepoxide, their combination, or placebo. However, the response of patients with low levels of depression and anxiety did not differentiate active treatment and placebo [54]. The clinical case illustrates the difficulties entailed by the concept of anxious depression.

Clinical Presentation

Mary is a 46-year-old, divorced, blue collar worker who presented with high anxiety, hypochondriacal fears, worry, depressed mood, irritability, sleep difficulties, lack of appetite and energy, and sense of guilt. A few weeks earlier the man she was engaged to for many years abandoned her and the patient became single. She started to be extremely worried about not finding another life companion because of her age. Her family doctor prescribed sertraline 50 mg at bedtime with little success. It was also discontinued because of side effects such as nausea and diarrhea.

Assessment and Diagnosis

Macroanalysis. The patient met DSM-5 criteria for a major depressive episode. Her disturbances did not reach the threshold for anxiety disorder, even though she appeared to be very anxious, tense, and worried. At a more careful examination, depressive symptoms had modest

Fig. 3. Macroanalysis of Mary's clinical case.

intensity and fluctuated, which is more characteristics of cyclothymic than unipolar depression. Furthermore, the patient appeared to be under considerable stress which exceeded her coping skills (i.e., allostatic overload) [55] and spent most of the time at home chatting with family members or friends on her mobile. Mary's macroanalysis is illustrated in Figure 3.

Staging. Based on the staging model of unipolar depression [27] (online suppl. Table S2), the patient was at stage 2.

Treatment Options

The patient had already been treated with an antidepressant with little success. One could, of course, change antidepressant, but the chances of a response would be low [50–54]. Low-dose temporary use of a benzodiazepine (e.g., clonazepam 0.5 mg twice per day) may attenuate the patient's symptoms, but it is not likely to address the depressive symptomatology. One may also give priority to anxiety disturbances (despite being subthreshold) and address them as a primary target of a CBT treatment. This was the approach used in Mary's case. CBT included suggesting lifestyle modification (e.g., stop chatting on mobile, maintain a scheme of daily life activities, actively pursuing social activities). The patient progressively recovered, regaining possession of her own daily life and depressive symptoms faded over time.

D. Anxiety as a Residual Component of Depression

Anxiety disturbances may characterize the residual phase of major depression (stage 3 in online suppl. Table S2) [27], which favor residual disability [56, 57] and increase the risk of relapse, up to 60% after 5 years [58, 59], as the following case illustrates.

Clinical Presentation

Mark is a 43-year-old building contractor, married with no children. He had a major depressive episode 3 years earlier, which was treated by the family doctor with fluoxetine for 4 months. After the end of this first depressive episode, moderate fear of having another depressive episode or health problems and mild agoraphobia persisted as residual symptoms. Mark recently had a diagnosis of spondylarthrosis which immediately triggered one isolated panic attack, followed by severe fear and worry for his health. A few weeks later, a second major depressive episode occurred. He wanted to know which treatment was right for him at that point.

Assessment and Diagnosis

Macroanalysis. The patient satisfied the DSM-5 criteria for major depressive illness, but careful evaluation disclosed hypochondriacal fears, worry for health, and marital crisis (as a result of a busy working life which created a distance with his spouse). In the macroanalysis (Fig 4a), the clinician could give priority to pharmacotherapy of major depressive disorder, leaving the other components to post-therapy assessment (i.e., hypochondriacal fears, worry for health, and the relationship between working life and marital crisis). If the clinical decision of tackling one syndrome may be taken during the initial assessment, the subsequent steps of macroanalysis require a reassessment after the first line of treatment has terminated (shown in Fig. 4b).

Staging. Based on the staging model of unipolar depression [27] (online suppl. Table S2), the patient was first at stage 3 and went back to stage 2 after the diagnosis of spondylarthrosis.

Fig. 4. Macroanalysis of Mark's clinical case before (**a**) and after (**b**) first-line treatment.

Treatment Options

A sequential strategy based on the use of pharmacotherapy in the acute phase of depression and a psychotherapeutic approach in its residual phase has been developed [60] (online suppl. Table S3) and was found to be a viable strategy for preventing relapse in major depressive disorder in a number of randomized controlled trials [35]. In this model, psychotherapy addresses problems

and symptoms that were unaffected by the drug treatment and is often different from first-line approaches (e.g., WBT, mindfulness-based cognitive therapy) [35]. An alternative option would be to provide additional pharmacotherapeutic strategies that may address symptoms such as worry and fears. A potential disadvantage in the latter case is the risk of activating clinical manifestations of behavioral toxicity, which might include extend-

Color version available online

Fig. 5. Macroanalysis of Liza's clinical case.

ed withdrawal phenomena, resistance to the same treatment, and increased vulnerability to relapse [40].

Sequential treatment, that is drug treatment of the acute episode of depression followed by psychotherapy in the residual phase [61], was applied to Mark's case. Fluoxetine was reintroduced at time 1; as soon as the acute symptoms remitted a second macro-analysis was run and, at time 2, the therapist used cognitive restructuring to intervene on residual symptoms (i.e., hypochondriacal fears, need for control). The daily working life that led to communicative difficulties with his partner was approached by proposing lifestyle modifications in the setting of WBT [37, 38]. The patient was in full remission and drug free at a follow-up of 3 years.

E. Demoralization Secondary to Anxiety Disorder

Demoralization is a feeling state characterized by a patient's perception of impotence and inability to deal/cope with pressing problems and receive adequate support from others [55]. A feeling of having failed to meet their own or other expectations and lack of hope that problems will be solved are also present [55]. It can be encountered with anxiety disorders [62, 63], particularly in agoraphobia and panic [64]. It can be associated with major depression or occur independently, as in the case here illustrated.

Clinical Presentation

Liza is a 45-year-old, single, architect. She has suffered from generalized anxiety since she was 20 years old; the family doctor managed anxiety by prescribing alprazolam 0.25 mg, when needed. In the last 2 months, she perceived to be unable to cope with pressing problems at

work, when she had tight deadlines and inadequate support from others. In addition, she had the feeling of having failed to meet her own expectations (e.g., having a family, having children) and believed there were no solutions for these problems and difficulties.

Assessment and Diagnosis

Macroanalysis. The patient satisfied DSM-5 criteria for generalized anxiety disorder; she also suffered from demoralization, according to the Diagnostic Criteria for Psychosomatic Research [55] (shown in Fig. 5). Due to demoralization, Liza tended to avoid social situations and spent her spare time on the sofa taking naps or watching TV, although she felt highly dissatisfied by her lifestyle.

Treatment Options

Demoralization is frequently subsumed under the rubric of minor depression. However, demoralization has specific features [55], which allow its differentiation from major depression, minor depression, and adjustment disorder.

It is conceivable, even though yet to be tested, that demoralization occurring during CBT may improve during the continuation of therapy [33] or respond to specific cognitive strategies, whereas depressive features may require pharmacological treatment. Unfortunately, there has been insufficient research on the characteristics of demoralization in the setting of anxiety disorders [64] and its response to psychotherapy [65, 66]. A recent randomized controlled trial on the treatment of demoralization and depression in acute coronary syndrome [67] indicated the efficacy of the sequential combination of CBT and WBT.

Liza was engaged in cognitive and behavioral strategies which resulted in a partial remission of her symptoms.

Conclusion

Reviews generally base their conclusions on randomized controlled trials and meta-analyses (e.g., Saha et al. [68]) that refer to the average patient [69] and may thus clash with the variety of clinical presentations. Very different, if not diverging, indications may ensue when the literature is examined based on the modalities of clinical presentations and when therapeutic options are evaluated in light of potential benefits, likelihood of responsiveness, and vulnerability to adverse events.

There is no simple "average" solution to most psychiatric problems, such as comorbid anxiety and depression,

and the solution is not represented by overdiagnosing [70]. The question is how to put the available evidence within the context of individual, unique assets and liabilities. There is thus the need for integrating the information that derives from EBM with MBE [21]. A clinimetric approach that includes repeated assessments, macroanalysis, staging, broadening of clinical information, and consideration of iatrogenic comorbidity [20, 27, 43] appears to be necessary when anxiety and depression coexist. Similar considerations may be extended to depression with psychotic features [71] or in the setting of psychotic disorders [72].

Such an approach calls for a renaissance of psychopathology (observation, interviewing, classification and differential diagnosis of signs and symptoms) as the basic neglected method of clinical psychiatry, which may lead to an overdue critical scrutiny of current conceptual models that clash with clinical reality. It might also override the limits of the existing guidelines in the literature, with recommendations referring to a hypothetical “average” patient, shedding some light on “real” patients in naturalistic settings. This approach also seems syntonetic with the perspective of a dimensional psychopathology, which is in need of been integrated into the diagnostic process [73].

Psychiatrists, who in their clinical practice use sophisticated forms of clinical judgment and master techniques of interviewing and history taking, are ready to reveal something that has not vanished, but that is simply buried under inadequate conceptual models.

Statement of Ethics

Original data were not collected, thus ethical committee approval was not needed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There are no funding sources to declare.

Author Contributions

The authors contributed equally.

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