


A reevaluation of mixed depressive states from the DSM-5- TR perspective: a series of prototypical cases

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ABSTRACT

Mixed depressive states are defined by the co-presence of depressive and manic symptoms. They represent extremely variable conditions from the point of view of clinical expressiveness and are difficult to recognize, ranging from clear schizophrenic-like psychoses and pseudodemented pictures to subsyndromal psychopathology. At the basis of the extreme variability of depressive pictures with mixed features are the different combinations that depressive and manic symptoms can assume. Furthermore, the intensity of depressive symptoms and manic symptoms, combined, can be variable, a factor that contributes to making the picture even more variable. Each form of mixed depressive state therefore presents its own specific symptomatic characteristics and specific difficulties in differential diagnosis and each form requires a different therapeutic strategy. In this work we have distinguished four possible specific subtypes of mixed depressive states, describing their specific clinical presentation and the therapeutic options most supported by the literature with the aim of contributing to a better recognition of mixed depressive states, to avoid incorrect diagnoses at patient and treatments that are useless if not worsening.

KEYWORDS: mood disorder; depression; bipolar disorder; bipolar mixed states; depressive mixed states; mixed states

INTRODUCTION

Depressive disorders in the DSM-5 include disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder [1]. In the revised fifth edition of the DSM (DSM-5-TR), the classification of depressive disorders remained unchanged except for the addition of the diagnostic category “unspecified mood disorder” [2]. The common feature of all these disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual’s capacity to function. Among the different specifiers, the focus of this article is on the one “with mixed features”. This specifier includes [2]:

A. At least three of the following manic/hypomanic symptoms are present nearly every day during most days of a major depressive episode:

1. Elevated, expansive mood;
2. Inflated self-esteem or grandiosity;
3. More talkative than usual or pressured to keep talking;
4. Flight of ideas or subjective experience that thoughts are racing;
5. Increase in energy or goal-directed activity (either socially, at work or school, or sexually),
6. Increased or excessive involvement in activities with a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, foolish business investments).
7. Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia).

B. Mixed symptoms are observable by others and represent a change from the person’s usual behavior.

C. For individuals whose symptoms meet full criteria for either mania or hypomania, the diagnosis should be bipolar I or bipolar II disorder.

D. The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment).

Note: Mixed features associated with a major depressive episode are a significant risk factor for developing bipolar I or bipolar II disorder. As a result, it is clinically useful to

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note the presence of this specifier for treatment planning and monitoring of response to treatment.

Many bipolar illnesses begin with one or more depressive episodes, and a substantial proportion of individuals who initially appear to have major depressive disorder will prove, in time, to instead have a bipolar disorder.

This is more likely in individuals with onset of the illness in adolescence, those with psychotic features, and those with a family history of bipolar illness. The presence of a “with mixed features” specifier also increases the risk for future manic or hypomania diagnosis. Major depressive disorder, particularly with psychotic features, may also transition into schizophrenia, a change that is much more frequent than the reverse.

■ CLINICAL PRESENTATIONS OF DEPRESSIVE MIXED STATES

Chronic or resistant depression are common diagnostic labels for cases in which a mixed state presents with prevailing depressive symptoms. These depressive mixed states tend to follow a chronic course because their mild manic component is largely overlooked, so treatments are usually inadequate [3-5].

Severe forms of depressive episodes with mixed features are often psychotic, carry a high risk of suicide, and respond poorly to standard treatments [6-8]. There are nonpsychotic forms of mixed states that appear to represent the mixed phase of the bipolar II disorder, in which the tendency towards chronicity is greater than in the bipolar I disorder. These forms have a prolonged duration due to various factors, such as a high rate of comorbidity [9]. Most of these mixed features, particularly those with depressive episodes, still fail to be detected by the current nosological systems, which require a full symptomatic picture of both major depressive and manic episodes, or major depressive and hypomanic episodes [10]. Furthermore, the duration of manic and depressive symptoms and their co-occurrence are inadequately defined.

Therefore, the available diagnostic criteria favor the identification of mixed features in expansive episodes that correspond to the so-called dysphoric mania or mixed mania, which has received much attention from clinicians and researchers in the last few decades. Conversely, moderate or mild depressive mixed states have been neglected and frequently misdiagnosed as unipolar, atypical, or neurotic depression; in addition, severely psychotic mixed depressive forms have been occasionally misdiagnosed as paranoid schizophrenia.

The clinical heterogeneity of depressive mixed states has largely contributed to nosological and diagnostic difficulties. Historically, Himmelhoch [11] stated that the diagnosis of affective disorders cannot become a formula in which “the diagnostic categories turn into a Neoplatonic Procrustean bed into which heterogeneous affective syndromes are forced to fit”. Particularly, a diagnosis based upon a rigid categorical system does not seem adequate for mixed states.

The assessment of discrete psychopathological dimensions and clusters of symptoms, which are opposed to the main syndromic picture, results in a more effective means of identifying and/or classifying mixed depression.

In this paper, we attempt to identify distinct subtypes of depressive states with mixed features through a brief description of prototypical case studies.

■ PATHOPHYSIOLOGY

A pre-existing affective, temperamental dysregulation might play a role in the pathophysiology of a mixed state and might justify the overlapping of two theoretically opposite syndromes. For instance, in mixed mania, a depressive temperament could add some anxious depressive, irritable features to the mild manic episode [12]. This hypothesis is supported by the observation of the prevalence of mixed mania in females [13], in whom depressive temperaments are more frequent [14], and by the report of a high familial incidence of depressive disorders other than bipolar disorders [15].

Similarly, a depressive mixed state might result from either the interplay of a hypomanic episode or a bipolar temperamental dysregulation (i.e., hyperthymic or cyclothymic temperament) with a melancholic episode. These conditions may contribute to the observed increased sensitivity of these patients to irrelevant stressors. In addition, they may lead to a predisposition to common negative events, such as job loss or intrafamilial and extrafamilial conflicts, which are chronologically connected with the major episode, and may predispose towards the abuse of alcohol and sedatives.

The impact of pharmacological sedation and withdrawal symptoms on a “pure” depressive or manic state has been reported to modify it in a dysphoric and/or mixed state; similarly, abuse of sedatives has been reported to reduce tolerance to stress and favor the occurrence of other mood episodes, which are frequently associated to mixed features [16,17].

Pharmacological interventions, such as antidepressants (ADs) (e.g., tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs], etc.) and neuroleptics also may influence and/or modify the course of bipolar illness, since these drugs accelerate the natural tendency of episodes towards remission; during the depressive episode, a pharmacologically induced acceleration towards mania may give rise to the co-occurrence of both depressive and manic symptoms.

The hypothesis that mood instability may be associated with an underlying epileptic diathesis, often supported by the patient’s family and personal history and by electroencephalogram (EEG) data, places depressive mixed states along the same continuum as epilepsy of the temporal lobe [11,18]. This justifies the paradoxical reaction of mixed states to antidepressants and their positive response to anticonvulsants.

■ CLINICAL FORMS

Depressive mixed states consist of different clinical pictures with varying degrees of severity. There are psychotic and nonpsychotic major forms expressing bipolar I disorder, sometimes with pseudodemential features due to minimal brain damage or other concomitant physical disorders. There are also subsyndromal conditions, in which anxiety-agitation and temperamental dysregulations coexist with depression. These conditions are the mixed expression of bipolar II disorder and tend towards chronicity.

Each form of depressive mixed states presents its specific symptomatologic characteristics and specific difficulties in differential diagnosis and requires a different therapeutic strategy. We have distinguished four subtypes of depressive mixed states: 1. psychotic mixed state with a prevalence of

melancholia; 2. chronic depressive mixed state with pseudo-dementia features; 3. protracted mixed state with a prevalence of depression; 4. subsyndromal mixed state with prevalent and persistent depressive-anxious features.

Subtype 1: Psychotic Mixed State with Prevalence of Melancholia

In 1921, Kraepelin [19] described agitated depression, depression with flight of ideas, and depressive or irascible mania among mixed states with depressive mood. In these cases, psychotic features often complicate the clinical picture. Quality of mood, neurovegetative signs, and thought contents are usually of depressive type. However, the speed of speech, absent-mindedness, switching between thoughts, increased motricity and impulsive behavior patterns are manic. The rapid fluctuations of symptomatology may provoke a mismatch between mood and behavior (e.g., depressed mood and hypersexuality). The interaction between depressive and expansive-excited components has an important role in developing delusions.

This form of mixed state generally manifests a tendency towards a protracted course and a chronic deteriorative evolution, often worsened by pharmacological factors. It presents most frequently in adolescence, often resulting in a misdiagnosis of schizophrenia, particularly when the expansive-excited component loses intensity and thought disturbances emerge quite openly.

Carbamazepine (CBZ) and sodium valproate are first-line drugs for acute and long-term treatment. In the acute phase, a combination with an atypical antipsychotic such as clozapine may be suitable [20,21], because of its effectiveness against agitation and psychotic symptoms. Amongst antidepressants, SSRIs with a sedative profile are preferable. In resistant cases, in which anxious excitement, psychotic symptoms and self-destructive ideation persist, electroconvulsive treatment (ECT) may be useful.

Case Study 1. Patient 1 is a 54-year-old housewife, married with two children. Her family history reveals that her mother suffered from bipolar disorder and her father from alcoholism. The patient was affected by a pharmacologically controlled hypothyroidism. The premorbid personality assessment revealed the presence of a hyperthymic temperament. At 28 years of age, the patient presented a mild post-partum depressive episode that switched into a manic phase following treatment with clomipramine. This switch resulted in involuntary admission to a psychiatric department, where she was treated with neuroleptics and BDZs.

Once the patient was discharged, she voluntarily stopped treatment.

At 36 years of age, after her second child was born, she suffered from a depressive episode with mixed features. Her husband reported that she had gradually become irritable and aggressive towards him.

She no longer took care of herself, their children, or the house, and spent most of the day in bed. She started to starve herself to lose weight, slept only 4 or 5 hours a night, and showed delusions of feeling guilty for having had sexual intercourse with one of her cousins during her adolescence. After a course of nortriptyline, and BDZs, her irritability and

aggressiveness increased, her insomnia became severe and other symptoms emerged, such as sexual hyperactivity and recriminations towards her husband's relatives with consequent murder threats. Soon afterwards, persecution and poisoning delusions materialized: "My mother-in-law put some microphones in my bedroom; she has put powders in my food to kill me slowly".

The worsening of her feelings of ineffectiveness and emptiness, her sensation of being confused, together with her inability to stop her thoughts; and her impression of being surrounded led to a suicide attempt by means of drug overdose. The patient was admitted to a specialized department and treated with amitriptyline, bromperidol, and BDZs. When she was discharged after 2 months, her psychopathological condition had only partially improved; her clinical picture was characterized by irritability, persecution ideation and rapid mood switches. The patient was treated with neuroleptics, BDZs, and TCAs when necessary, but her compliance was poor. During subsequent two years, illness took a chronic course with periodic exacerbations. She made three suicide attempts and was admitted to the hospital seven times. During her most recent hospitalization, she was diagnosed as paranoid schizophrenic and treated with depot neuroleptics.

GF was referred to our department after her third suicide attempt. We admitted the patient and treated her with ECT (eight bilateral applications)- and clozapine. BDZs were suspended gradually. Her mood improved, delusions and psychomotor abnormalities disappeared, and she recovered her normal sleep pattern. She was discharged after 6 weeks with a treatment with lithium salts, valproic acid, and clozapine. After 2 months, depressive symptoms reappeared: "I feel tired and insecure and find it difficult to cope with housework...I don't want to go out anymore". This condition required the reduction of clozapine dosage and the introduction of fluvoxamine. After 3 months of this regimen, the patient became euthymic.

Discussion of Case study 1. In this case, the persistence of delusions for 3 years, even when the manic-depressive symptomatology was meager, could have caused a misdiagnosis of paranoid schizophrenia if the entire clinical history of the patient had not been taken into consideration. The combination of different elements led to the correct diagnosis of depressive episodes with mixed and psychotic features. Important diagnostic elements included a family history of bipolar disorder, hyperthymic temperament, good premorbid social and familial adjustment, and an onset of depression in the post-partum. Additional clinical elements of the bipolar nature of the patient's illness were the marked emotional instability with rapid switching from depression to irritability and aggressiveness, increased psychomotricity and sexual hyperactivity, suicide attempts, and persistent insomnia.

Further support to diagnosing a psychotic mixed state derived from the patient's therapeutic response. ECT, which is particularly useful in psychotic mixed states, proved to be effective towards acute symptoms. In addition, the long-term therapeutic strategy, based on the association between mood stabilizers (lithium salts and anticonvulsants) with a small dosage of an SSRI and clozapine, turned out to be effective.

Subtype 2: Chronic Depressive Mixed State with Pseudodemential Features

Agitated psychotic depression with hypomania is considered a rare condition. It is most frequent in the advanced age, when organic factors related to age may produce signs that suggest a severe cognitive impairment. In the elderly, an affective episode, especially one of mixed state, can show a peculiar combination of neurological and behavioral symptoms requiring a differential diagnosis with primary dementia.

The description of *melancholie anxieuse* by Falret in 1864 recalls this condition: "It is characterized by constant pacing and inner turmoil, which incapacitates these patients so they cannot concentrate..." [22].

Within a mood that does not appear clearly depressed but constantly anxious and dysphoric, ideation is poor and fragmentary, focused on a few, sometimes delusional, repetitive contents.

Anxiety, insomnia, and restlessness are present, while psychic retardation increases the cognitive dysfunctions.

The response to psychotropic drugs is often incomplete; thus, ECT appears more rapidly effective in treating this disorder.

Case Study 2. Patient 2 is a 66-year-old widow with one son. Her family history shows that her mother had been hospitalized frequently for recurrent depression, and her elder sister has been reported to suffer from depression and be on treatment with lithium salts. The patient has been living alone since the death of her husband which occurred when she was 58. She was described as extremely precise and competent in all she did, fastidious towards herself and others, and dictatorial. Besides these obsessive traits, the son reported that his mother exhibited some hyperthymic characteristics: dynamism, energy, high levels of achievement, and impulsiveness.

After death of her husband, the patient started to feel depressed, with polarization of ideas towards events related to his death. During the following months, the depressed mood persisted, with disturbances of her eating and sleeping patterns, and she began to refer to ruin and death. After outpatient treatment with TCAs and BDZs, the clinical picture showed a partial remission, but feelings of inadequacy, indecision, and difficulty persisted, particularly at work. One year later, after her retirement, there were no significant affective symptoms except ruminations about her money.

At the age of 63, the patient underwent surgery for a hip replacement. During convalescence she was intensely polarized towards her state of health, worried about not being able to walk anymore. It was impossible for anyone to reassure her. In the following months, affective symptomatology showed oscillations, from states of anergia, anhedonia, and sadness, to inconclusive hyperactivity with anxious restlessness, associated with difficulties in memory and concentrating, while leading to a gradual impairment of familial activities. Low doses of clomipramine and BDZs were started. In a few days, the patient presented with perplexity, severe alterations in her sleep pattern, and sub-confusional episodes, which led to her hospitalization.

When she arrived at our psychiatric ward, she was untidily dressed, unable to keep still, and twisted a corner of her dress continuously. She spoke incoherently, with frequent requests for help. Her clinical picture had worsened

in the last few days, so that her restlessness had increased to the point of agitation, with auditory hallucinations. She seemed confused and was unable to recall her son's name.

Computer tomography (CT) revealed slight atrophy of the cortex but absence of ventricular enlargement. TCAs were stopped, and the administration of fluvoxamine, carbamazepine and haloperidol was initiated to control her agitation, insomnia, and psychotic symptoms. The rapid remission of pseudodemential manifestations, but the persistence of anxious excitement and depressive thoughts after 1 month suggested to intervene with ECT. Improvement was seen after the fourth ECT session.

Treatment at discharge included carbamazepine and fluvoxamine.

Discussion of Case study 2. An important element which conducted to a diagnosis of mixed state is the history of previous mood episodes with melancholic features superimposed on a hyperthymic temperament.

The current episode was characterized by a mixture of cognitive, somatic, and affective symptoms of similar severity with protracted course. The relevant cognitive impairments (e.g., memory and attention dysfunctions, disorientation), tend to mask the affective symptoms, (e.g., dysphoric mood, anxiety, resistant sleeplessness, multiple somatizations, and delusional hypochondriac worries. Moreover, the existence of mood symptoms of opposite polarity in the psychomotor sphere (psychic retardation and motor excitement) contributes to confused-excited behavior. The soft organic comorbidity influences the pseudodemential presentation of the depressive episode with mixed features and justifies the paradoxical reaction to TCAs, and the good tolerability to SSRIs. In these cases, ECT may be effective.

Subtype 3: Protracted Mixed State with Prevalence of Depression

Among bipolar patients with alcohol and sedative abuse, Himmelhoch [3] described a nonpsychotic, agitated depression with a high level of excitement persisting without progressing towards the full-blown picture of psychotic agitated depression. In such patients, the illness falls into an "interminable residual state". A careful history of these patients usually reveals a bipolar familial background; hyperthymic or cyclothymic temperament, prior to spontaneous or drug-induced manic "switches"; as well as symptoms of anergia and hypersomnia in previous depressive episodes. In the cross-sectional examination, irritability, insomnia, and dysphoria are often observed. States of intense suffering and hypersexuality are openly manifested. Obsessive ideas with suicidal content, which can lead to impulsive self-destructive behavior, are dominant within anxious agitation. A chronic or subacute course may be due to a prolonged TCA treatment that had been effective during previous episodes of inhibited depression [12].

Treatment with typical ADs would worsen insomnia as well as psychic and motor agitation. In contrast, an excellence response to sodium valproate, and carbamazepine is generally noted; in cases characterized by severe anxiety, SSRIs represent the first choice ADs.

Case Study 3. Patient 3 is a 44-year-old car salesman, separated with two children. He described his mother as

chronically anxious with recurrent episodes of depression. His father, a building contractor, had committed suicide 10 years earlier. The patient's older brother was undergoing treatment for panic disorder. The day before our visit, the patient had been admitted to the orthopedic clinic for multiple fractures following a car crash he had caused after taking a no specified amount of BDZs and alcohol. As he reported, he drove off the road at high speed with the intention of doing himself harm.

Since his youth, he had gone through good and bad periods. The bad ones, during which he became introverted, with asthenia, indifference, low self-esteem, and inability to concentrate, did not last long since symptoms often disappeared suddenly. During the good periods, he was full of energy with excessive self-confidence, impulsiveness, tendency to be quarrelsome, highly productive, enterprising, and intuitive. After secondary school, he got a degree in economics despite irregular attendance because he stopped his studies to join the military service. This period was critical: he could not put up with unfairness and started to abuse alcohol to calm himself down and pluck up his courage. A banal quarrel with some conscripts triggered an uncontrolled emotional reaction, which resulted in his hospitalization and discharge following a few days of treatment with an unspecified medication.

During the next years (until 34 years of age), mild mood changes and prevalently depressive mood became chronic; he had many repeated extramarital relationships, which led to his separation from his wife and repeated quarrels with his father. This induced him to change jobs several times, and he finally set up his own business. Although his phase with prevalently depressed mood caused him considerable personal discomfort, it reversed spontaneously with a sudden switch of mood to the opposite polarity. Use of alcohol also followed a nondependent, episodic pattern.

At the age of 34, when his father died, the patient had a major depressive episode with feelings of guilt and self-destructive thoughts, necessitating admittance to a psychiatric ward. He was treated with TCAs, neuroleptics, and BDZs.

He developed a hypomanic phase that disappeared with the rapid withdrawal of ADs and the addition of lithium salts. One year after his discharge, the patient interrupted his regular visits and medications, instead used different dosages of anxiolytics, as he felt the need, with or without alcohol.

When he was 38, following stressful events (ie, separation from his wife and serious car crash), the patient had a second major depressive episode again with guilty feelings and self-destructive thoughts. Ideas of ruin and death were associated with inhibited depression (asthenia, adynamism, anhedonia, and hypersomnia). He was hospitalized and treatment with ADs, NLs, and lithium, which resulted in remission of symptoms after 4 months. A short time after discharge, the patient gave up specific treatments.

In the next few years, the patient's mood shifts gradually worsened, and his abuse of alcohol and anxiolytics increased. His psychopathological picture was characterized by a subsequent, rapid alternation of deep apathy, inertia, and feelings of inadequacy with bursts of irritability and rapid thought and speech. Mood instability had become too intense to tolerate, giving rise to his suicide attempt: "I hardly realized what I was doing" he said.

Treatment with a combination of an SSRI (paroxetine), a low dosage of neuroleptic (perphenazine), and carbamazepine led to the complete remission of symptoms in 2 months.

Discussion of Case study 3. The patient's family history shows a heavy genetic loading for psychiatric disorders, with familiarity of bipolar disorders and a specific inheritance for suicide and panic disorder. The shifts in mood and energy level, which are typical of the cyclothymic temperament, preceded the overt disease. These subsyndromal mood changes predisposed the patient towards substance abuse, and conditioned the instability of his life-style, with phases of adjustment and maladjustment marked by negative events and intense emotional responses. With his background of "constitutional cyclothymia", the major episodes became overt; the first two episodes had features of melancholic depression and were resolved with TCAs and lithium.

The poor compliance to treatments and the abuse of substances, had a negative impact on the course of the illness into a protracted mixed state, with the disappearance of euthymic phases.

The current episode did not include the motor retardation and inhibition characterizing previous cases; by contrast, anxiety, sleeplessness, psychic and motor agitation, and emotional instability were particularly evident, while thoughts acceleration within depressive mood, which is typical of this subtype, acted as the "engine" for the obsessive suicidal thoughts.

Treatment with an SSRI, small dosages of a neuroleptic and CBZ, led to a complete and long-lasting remission.

Subtype 4: Subsyndromal Mixed State with Prevalent and Persistent Depressive-Anxious Features

A subsyndromal depressive picture is sometimes associated with irritability, inner tension, and dysphoria; and at other times with agitation, anxiety, and outbursts of anger. The long-term effects of mood lability and instability on psychosocial adjustment emerge in "characterological" manifestations: patients are demanding, manipulative, and explosive. Maladjusted behavior and functional impairment, such as discontinuity in studying or job performances, sentimental restlessness, and a tumultuous lifestyle, may lead to a diagnosis of borderline or antisocial personality disorder. The anxiety comorbidity, especially with panic-agoraphobic spectrum, may justify a "neurotic" aspect to the clinical picture and lend to a diagnosis of personality disorder. The differential diagnosis between the long-lasting emotional instability of mixed states and the brief episodes of affective instability, mainly depressive, associated with the borderline personality disorder should be based on the observation that the latter maintains environmental reactivity and would rapidly change with appropriate stimulation and intervention. In addition, neurovegetative symptoms, such as the irregularity of the sleep/wake cycle and eating habits, are generally absent. This distinction, difficult to determine in clinical practice, strengthens the criticisms directed towards the nosological autonomy of the borderline disorder category. An understanding of this link and recognition of the borderline disorder as belonging to the bipolar spectrum would permit the adoption of more appropriate treatments.

Case Study 4. Patient 4 is a 49-year-old housewife with one son. She has a positive family history for panic disorder in her mother's family and for mood disorders in her father's

family (her father had two depressive episodes, and her aunt died because of suicide). When she was 23, the patient experienced a postpartum depression characterized by overeating, difficulty in falling asleep, concerns about caring for her child, irritability with outbursts of anger, and panic symptoms. She described a variety of gastrointestinal and respiratory complaints. She received no treatment for this episode. Mood instability, intense reactivity and avoidance behavior continued after the episode and caused conflicts with her husband and work impairment leading to the loss of her job. She began using BDZs and alcohol chronically.

At the age of 42, when her father died, the patient lost interest in everything; nothing gave her pleasure anymore. She was able to fall asleep but woke up repeatedly during the night. She had multiple complaints of pain including black ankles, painful knots in her neck, headaches that radiated all over her body, and pelvic and abdominal pain. The acute phase of this disorder remitted spontaneously after 1 year, although the patient still complained of worries about her health and reported a tendency to avoid crowded places when alone. When she was 48, her son married and her panic disorder reappeared, together with a rapid development of anticipatory anxiety and multiple avoidance behavior, as well as persistent depressive symptoms. We observed the patient about 1 year after the onset of these symptoms. She appeared anxious, and was very tense. Her speech was rapid and her voice was loud. She used dramatic expressions, saying that she felt deeply depressed and hopeless, without a future. She was often irritable and occasionally had outbursts. A psychiatrist consulted 8 months earlier had diagnosed anxious depression caused by separation from her son and had prescribed BDZs and advised psychotherapy.

The patient's psychopathological condition worsened, particularly her agitation, irritability, and insomnia, and self-injuring proposals appeared. When admitted to the psychiatric department, she was treated initially with BDZs and CBZ. In a few days, agitation was controlled, and BDZs were decreased with complete suspension of BDZs after 45 days. The subsequent administration of trimipramine and paroxetine permitted a complete control of both depressive and panic symptoms.

Discussion of Case study 4. The characterizing elements of this case are the presence of persistent panic-agoraphobic symptoms, unremitting depressive symptoms, and physical complaints. Cross-sectionally, this clinical picture had simply led to a diagnosis of anxious depression with some features of an Axis II disorder (dramatic presentation of symptoms). However, a careful evaluation of the familiarity and patient's personal history oriented the diagnosis toward a subsyndromal mixed state with comorbid panic attacks. In this case the indicators of bipolarity were the post-partum onset, mood reactivity, extreme loquacity, thought acceleration, manipulativeness and tendency to explosiveness. In addition, the presence of a hypomanic component was confirmed by the worsening of symptoms, in particular psychomotricity, after intake of TCAs.

The correct diagnosis was confirmed by treatment response. Anticonvulsants, initially given by BDZs, controlled the elated mood quickly. The subsequent administration of an AD with sedative and antipanic activities permitted the resolution of the entire clinical picture.

■ GENERAL DISCUSSION

The difficulty to detect depressive mixed states can result from various combinations of opposite manic and depressive symptoms, and from the circumstance that the symptoms of one polarity may be fully expressed, while those of the opposite polarity may be weak. Systematic clinical observation has led to recognition of depressive mixed forms that present a variety of psychopathological conditions, ranging from clear schizophrenic-like psychoses and pseudodemential pictures to subsyndromal psychopathology. The recognition of depressive mixed states and knowledge of the precise diagnostic boundaries are essential elements in choosing the correct treatment. The variability of the clinical picture, with manifestations belonging traditionally to other nosological categories, can make it difficult to recognize depressive mixed states during cross-sectional examination [23]. As stated by Winokur [24]: "It is this panoply of varying and contrasting emotions which makes these patients difficult to diagnose".

The case reports discussed in this paper are indicative of different subtypes of depressive mixed states with chronic course, which may require different treatments.

Antipsychotic agents are recommended in the acute treatment of psychotic mixed states. A good response to clozapine has recently been observed in a group of patients with psychotic mixed states, who had been resistant to conventional treatments [20]. ECT seems to be useful in patients with psychotic mixed states resistant to drugs, with persistent suicidal ideation and anxious excitement [25]. This may be the first-line treatment in chronic depressive mixed state with pseudodemential features, which are likely to be observed more frequently in elderly patients. TCAs may worsen restlessness and inner tension in these patients. Conversely, SSRIs are usually more effective and safer.

In mixed state with prevalence of depression and subsyndromal mixed state with prevalent and persistent depressive-anxious features, alcohol or sedatives are often taken by the patient to alleviate his/her subjective suffering and anxiety. Correct treatment calls for the tapering of drug and abuse substances.

Although the presence of a mixed state is widely recognized as a predictor of a poor response to lithium, a combination of lithium and anticonvulsants has proven effective with some patients. Besides prophylaxis of manic recurrences, lithium appears to attenuate the "anergic depressive state" which follows treatments with CBZ or valproate alone [26,27].

■ CONCLUSION

The descriptive clinical approach indicates that depressive mixed states belong to manic-depressive illness, a viewpoint that has important heuristic, diagnostic, prognostic, and therapeutic consequences. As discussed, these clinical conditions tend strongly to camouflage themselves with the most varied diagnoses based on virtually endless combinations of manic polarity symptoms and depressive polarity symptoms that can give rise to extremely clinical pictures different from each other.

The authors' opinion is that mixed depressive states must be taken into strong consideration during the primary

diagnostic process or during the re-evaluation of previous diagnoses that have not responded adequately to therapies.

It can be deduced that a lack of diagnosis of a mixed depressive state can represent a factor of resistance to therapy.

Informed Consent

Written informed consent was obtained from the patients for publication of their cases.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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