

Diagnosis and Treatment of Mixed States

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19.1 WHAT IS A MIXED STATE?

19.1.1 THE CONCEPT OF MIXED STATE – HISTORY AND DEVELOPMENT

Mixed states are an unusual challenge in bipolar disorder. They are considered to be difficult to treat and to represent a more complicated course of illness. Perhaps the greatest challenge presented by mixed states, however, is that they force us to redefine what is meant by an episode in bipolar disorder, and to consider bipolar disorder in a manner different from its usual formulation as an illness with discrete symptomatic affective states.

The concept of mixed states is old, predating that of bipolar disorder itself. Combinations of depressive and manic behavior were described by Areteaus of Cappadocia and in the Bible (Angst and Marneros, 2001; Jackson, 1986). Case reports in the medical literature predate the formulation of recurrent affective disorders by Kraepelin (1921), much less that of bipolar disorder by Leonhardt (Angst and Marneros, 2001; Jackson, 1986).

Kraepelin realized that symptomatic states of bipolar disorder did not consist simply of affective symptom complexes, but as combinations of more fundamental behavioral disturbances, which he considered to be increased or decreased mood, thought, and activity (Kraepelin, 1921). He observed that, in his patients, these basic behavioral disturbances formed a variety of combinations, which included pure depressive (mood, action, and thought all inhibited) and manic (mood, action, and thought all disinhibited) states, but also states where aspects of depression and mania were mixed. He also observed that mixed states were, in some way, more severe, both in symptomatic state and course of illness, than nonmixed depressive or manic states (Kraepelin, 1921). As information on neurobiology has grown, the idea that more basic elements of behavior underlie affective disorders has developed to include elements with more identifiable neurobehavioral bases (Carroll, 1983; van Praag *et al.*, 1990).

Unfortunately, this formulation of mixed states was lost in the descriptive psychiatry of the late twentieth century, where mixed states were defined, in DSM-III and DSM-IV, as a variant of mania that included, essentially, a major depressive episode as well (American Psychiatric Association, 1995). This model did not allow for mixed states with hypomania, in bipolar II disorder, or with predominately depressive affect (Akiskal and Benazzi, 2005a). Largely as a result, data on treatment of mixed states is almost entirely derived from studies of manic episodes that happened to also include subjects who were experiencing full syndromal depression.

More recent data suggests a broader range of mixed states, that is, closer to the Kraepelinian model of permutations of basic behavioral disturbances (McElroy *et al.*, 1992; Akiskal and Benazzi, 2004). Salient features include the following:

1. Manic episodes with subsyndromal depressive symptoms resemble DSM-IV mixed states in their response to treatment and course of illness (Swann *et al.*, 1997).
2. Predominately depressive mixed states are at least as prevalent as predominately manic mixed states (Benazzi, 2008).
3. Predominately depressive and predominately manic mixed states are similar in their more severe course of illness (Swann *et al.*, 2001; Maj *et al.*, 2006) and in the treacherous manner in which they combine hopelessness with behavioral activation (Akiskal and Benazzi, 2005b). The resulting increase in risk for suicide was first described over 70 years ago (Jameison, 1936) and has been documented repeatedly (Dilsaver *et al.*, 1995; Strakowski *et al.*, 1996; Berk and Dodd, 2005; Goldberg *et al.*, 1998, 2009; Balazs *et al.*, 2006).
4. There may be a continuum across predominately depressive and manic mixed states, with the degree to which mixed symptoms are present being proportional to severity of the underlying course of illness (Swann *et al.*, 2007, 2009), as originally proposed by Kraepelin (1921). Accordingly, catecholaminergic activity in mixed states is substantially higher than that in nonmixed manic episodes, even though manic symptoms are not (Swann *et al.*, 1994).

Summary: the Models and Concepts of Mixed States

Mixed states combine depressive and manic features in the same episode and are a severe presentation of bipolar disorder. They were described long before the concept of bipolar disorder was developed. Current nosology calls for full superimposed syndromal depression and mania, but the historical evolution of the concept, and the clinical characteristics of the patients, are more consistent with a model where activation and depression are combined dimensionally.

19.1.2 QUESTIONS ABOUT MIXED STATES AND TARGETS FOR TREATMENT

In order to understand mixed states and their treatment, it may be necessary to depart from our accepted model where bipolar disorder is defined as depressive or manic episodes

for one in which episodes are defined by their dominant polarity and the extent to which depressive and manic symptoms are mixed. Basic questions include

1. Should there be integrated treatment, or separate treatments aimed at depression and mania? The answer to this question depends on whether one assumes the presence of a mechanism that drives the mixed episodes, or assumes that the episode consists of more independent components.
2. Should predominately depressive or manic mixed states be addressed as distinctive episode types, or as a continuum? Or, expressed otherwise, is there essentially one mixed state, or are there many?

In this review, we will attempt to address these questions in a practical manner.

19.1.3 DIAGNOSIS AND CLINICAL CHARACTERISTICS OF MIXED STATES

Mixed states have to be identified before they can be properly treated. Mixed states can be predominately manic or predominately depressive. Each presents its own diagnostic challenges.

19.1.3.1 Predominately Manic

This includes the mixed state, that is, defined in DSM III/IV. Its diagnosis requires a full manic episode with, essentially, a superimposed depressive episode lasting at least a week (American Psychiatric Association, 1995). Comparisons of the nature of manic symptoms in mixed compared to nonmixed manic episodes vary; generally there is less euphoria in mixed states, but grandiosity, irritability, and increased goal-directed activity are prominent (Swann *et al.*, 1986; Henry *et al.*, 2003). Depression-related symptoms include anhedonia, hopelessness, and suicidal ideation (Swann *et al.*, 1986; Henry *et al.*, 2003). Anxiety is especially prominent, to the extent that Kraepelin referred to these episodes interchangeably as anxious or depressive mania (Kraepelin, 1921).

Multivariate analyses and investigations of treatment response have shown that the DSM-IV criterion is unnecessarily narrow (Swann *et al.*, 2001; Bertschy *et al.*, 2007; Gonzalez-Pinto *et al.*, 2003). Treatment response, clinical characteristics, and course of illness are already quite different if two or more depressive symptoms are present (Swann *et al.*, 1997; Akiskal *et al.*, 1998). Several authors have suggested that a continuum or spectrum of mixed characteristics across manic episodes was a more accurate description than a dichotomy requiring full superimposed manic and depressive episodes (Swann *et al.*, 1997; Henry *et al.*, 2003; Akiskal *et al.*, 1998).

19.1.3.2 Predominately Depressive

Predominately depressive mixed states, where a depressive episode is combined with hypomania or subsyndromal hypomanic symptoms, may be more common than predominately manic mixed episodes – yet are not recognized in DSM-IV (American Psychiatric Association, 1995). Flight of ideas/racing thoughts, agitation/hyperactivity, and

irritability were the most consistent hypomanic symptoms identifying mixed depressive states (Akiskal and Benazzi, 2004; Goldberg *et al.*, 2009; Benazzi, 2003; Benazzi and Akiskal, 2006). As with mixed states based on mania, the course of illness was more severe than with nonmixed depression, including early onset, frequent episodes, suicidal behavior, and comorbidities (Akiskal and Benazzi, 2004; Goldberg *et al.*, 2009; Swann *et al.*, 2007). Clinical features including more severe course of illness emerge with modest, subsyndromal levels of hypomanic symptoms, in a manner that also resembles predominately manic mixed states (Swann *et al.*, 2007).

19.1.3.3 Mixed States and Agitated Depression: Boundaries of Bipolar Disorder

Mixed states are a subset of agitated depressive episodes, but not all agitated depressive episodes are mixed states of bipolar disorder. Agitation can be an expression of excited hyperactivity, as occurs in mania or mixed states, or painful inner tension, as occurs in depressive or mixed states (Akiskal and Benazzi, 2005b; Swann *et al.*, 1993). Noradrenergic function is higher in mixed states than in agitated depression without hypomanic symptoms (Swann *et al.*, 1994). Agitated depressive episodes that include noneuphoric hypomanic symptoms are different from those that do not, in a manner consistent with the presence of bipolar disorder: early onset, risky behaviors, addictive disorders, and family history of bipolar disorder are all increased in agitated depressed patients who have noneuphoric hypomanic symptoms compared to those who do not (Maj *et al.*, 2006; Zimmermann *et al.*, 2009; Akiskal *et al.*, 2005). It has been suggested that these episodes should be considered excited, rather than agitated, depressions (Akiskal *et al.*, 2005). The excitement can be expressed cognitively or motorically (Akiskal and Benazzi, 2004).

Some patients with agitated depression and noneuphoric hypomanic symptoms may have bipolar disorder with a predominately depressive presentation, but have not had their first hypomanic or manic episode yet (O'Donovan *et al.*, 2007). For such patients, the initial hypomanic or manic episode, and the accurate diagnosis of bipolar disorder, may be delayed by 10 years or more (Rosa *et al.*, 2008). Others, however, may have a presentation of bipolar disorder where hypomanic (or manic) episodes occur only during depressive episodes (Benazzi and Akiskal, 2008).

Summary: Mixed Presentations in Bipolar Disorder

Mixed states, whether predominately depressive or manic, are similar with respect to course of illness and clinical characteristics. "Mixed" characteristics emerge with modest (two or three symptoms) levels of depression during manic episodes or of mania during depressive episodes. These findings suggest that there may be a continuum of mixed states, with the degree to which symptoms are mixed being more salient than whether symptoms are mostly depressive or manic.

19.1.4 MIXED STATES ARISE FROM AN UNSTABLE COURSE OF ILLNESS IN BIPOLAR DISORDER

The course of bipolar disorder is heterogeneous in two ways. Both are related to the concept of mixed states:

19.1.4.1 Predominately Depressive versus Manic Course

Bipolar disorder can have a life course with predominately depressive or predominately manic episodes (Quitkin, Rabkin, and Prien, 1986). Bipolar I disorder can be associated with either predominately depressive or manic episodes, while the course of bipolar II disorder tends to be predominately depressive (Colom *et al.*, 2006). The first episode usually predicts the course pattern (Chaudhury *et al.*, 2007). While the course of illness appears more severe when the first episode is depressive, this may be a result of initial misdiagnosis and treatment with antidepressive agents without concurrent mood-stabilizing treatments (Rosa *et al.*, 2008).

Mixed states may occur in either depression- or mania-prone bipolar disorder, but may be more common in the depression-prone form (Perugi *et al.*, 2000). In a minority of cases, the first episode is mixed (Perugi *et al.*, 2000; Cassidy and Carroll, 2001). Usually, the first episode is not mixed (depressive more often than manic), and mixed episodes develop later (Cassidy and Carroll, 2001; Kessing, 2008). Once a mixed episode has occurred, the likelihood of further episodes being mixed is increased (Kessing, 2008); within the same patient, depressive or manic mixed episodes tend to recur true to type (Cassidy, Ahearn, and Carroll, 2001; Mitropoulou *et al.*, 2003).

19.1.4.2 Predominately Episodic-Stable versus Inherently Unstable Course

Second, the course of bipolar disorder is heterogeneous in terms of susceptibility to frequent episodes or complications. There are two basic course patterns:

1. **Episodic-stable pattern:** Episodes may be severe, but they are relatively infrequent, recovery from an episode is relatively complete, and comorbid disturbances tend to be episode-bound. This course of illness is familial and is associated with robust response to lithium treatment (Duffy *et al.*, 2002).
2. **Inherently unstable pattern:** Episodes may not be as severe as in the episodic-stable pattern (although they may be) but they are more frequent, with earlier onset, and with less opportunity for recovery between episodes. Episodes of illness can be mixed or polyphasic (changing in dominant polarity within the same symptomatic period (Turvey *et al.*, 1999). Comorbid disturbances, like substance use or anxiety disorders, are more frequent and are not necessarily episode-bound (Turvey *et al.*, 1999; Dilsaver *et al.*, 1997). This course pattern is also familial and is associated with relative lithium-resistance (Duffy *et al.*, 2002).

Susceptibility to mixed states in general is strongly related to an unstable course of illness. Individuals with mixed states have more previous episodes of illness, with greater frequency and earlier onset, than those without mixed states (Swann *et al.*, 2001; Goldberg *et al.*, 2009; Swann *et al.*, 2007; Cassidy and Carroll, 2001), regardless of whether the mixed state is predominately manic (Swann *et al.*, 2001) or depressive (Swann *et al.*, 2007). Mixed states are also associated with greater inter-episode affective lability (Benazzi, 2006). Most of the time, the first episode was not mixed, but once subjects have experienced a mixed episode, further mixed episodes become more likely (Cassidy and Carroll, 2001; Kessing, 2008; Cassidy, Ahearn, and Carroll, 2001; Sato *et al.*, 2004).

Also consistent with the inherently unstable illness course pattern, individuals who experience mixed states are more likely to have comorbid conditions (perhaps best regarded as complications of bipolar disorder) than those without mixed states (Goldberg *et al.*, 2009; Himmelhoch and Garfinkel, 1986; Goldberg and McElroy, 2007). These include substance-use disorders (perhaps especially alcohol) and anxiety disorders (Goldberg *et al.*, 2009; Dilsaver *et al.*, 1997). Presence of these disturbances complicates treatment and further worsens the course of illness.

Summary: Mixed States and Course of Illness

In terms of illness course pattern, mixed states appear to be associated with an inherently unstable course of illness. Whether the mixed state is predominately depressive or manic may depend on whether the individual has a predominately depressive or manic course pattern.

19.1.5 INDIVIDUALS EXPERIENCING MIXED EPISODES ARE UNUSUALLY SUSCEPTIBLE TO BEHAVIORAL ACTIVATION AND AFFECTIVE INSTABILITY

19.1.5.1 Mixed States and Mood Instability

Rather than sporadic events, mixed states are part of a lifetime pattern of susceptibility to mood instability. Susceptibility to mood instability is a hallmark of mixed states. Models for mixed states have tended to emphasize them as a stable entity, with simultaneous depressive and manic symptoms, or as rapidly alternating symptoms, or both (Maggini *et al.*, 2000). Frequently, mixed states appear polyphasic (Turvey *et al.*, 1999), with syndromal shifts during the symptomatic period (Goldberg *et al.*, 2000). Kraepelin (1921) proposed that the pathophysiology of mixed states involves a more severe underlying illness, with greater hyperarousal, than is present in nonmixed states. This is consistent with the disproportionate increase in noradrenergic activity (both central and peripheral) in mixed states (Swann *et al.*, 1994), the strong relationships between mixed states and anxiety (Swann *et al.*, 1993; Dilsaver *et al.*, 1997; Barbee, 1998) or emotional excitability

(Henry *et al.*, 2007a, 2007b), and the relationship between mixed states and interepisode affective lability (Benazzi, 2006).

19.1.5.2 Susceptibility to Behavioral Activation in Mixed States

This susceptibility to affective instability can predispose to treatment-induced behavioral activation. Behavioral activation by antidepressive agents is associated with illness-course characteristics resembling those of mixed states, including presence of a substance-use disorder (Goldberg and Whiteside, 2002) and unstable illness course (O'Donovan *et al.*, 2007), and can precipitate mixed states in susceptible individuals (Dilsaver and Swann, 1995). Morning light therapy also induced mixed states in similar patients (Sit *et al.*, 2007). This susceptibility to behavioral activation may be related to treatment-emergent suicidal behavior in mixed depressive patients (Berk and Dodd, 2005).

19.1.5.3 Anxiety in Mixed States

Kraepelin described “frantic anxiety” in mixed states as a manifestation of the severe over-arousal experienced by these patients (Kraepelin, 1921). Anxiety, and comorbid anxiety disorders, are prominent in mixed states, regardless of the predominate polarity (Swann *et al.*, 1993; Dilsaver *et al.*, 1997): anxiety correlates with depression in manic episodes, and with mania in depressive episodes (Swann *et al.*, 2009). Patients with bipolar disorder and severe anxiety have increased overall severity, including poor lithium response, addictive disorders, suicide attempts, early onset, and increased family history of bipolar disorder (Keller, 2006).

19.1.5.4 Mixed States and Suicidal Behavior

The combination of depression and excitation is conducive to suicidal behavior. Patients who are susceptible to mixed states appear susceptible to behavioral activation even during nonmixed depressive episodes, where environmental or pharmacological stimulation can lead to excitation superimposed on depression (Berk and Dodd, 2005; Akiskal *et al.*, 2005; O'Donovan *et al.*, 2007). Two routes whereby mixed states or their emergence can increase risk for suicidal behavior are:

- In manic patients, depressive symptoms, especially hopelessness, can lead to emergence of suicidality (Dilsaver *et al.*, 1995; Goldberg *et al.*, 1998). Accordingly, Strakowski *et al.* reported a correlation between suicidality and depressive symptoms in manic patients (Strakowski *et al.*, 1996).
- In depressed patients, activated symptoms, such as racing thoughts, hyperactivity, and mood lability, are associated with increased suicidality (Akiskal and Benazzi, 2005b), as part of the natural history of their illness (Bronisch *et al.*, 2005; Swann *et al.*, 2005), or from treatment with antidepressive or other potentially activating agents (Colom *et al.*, 2006). This phenomenon is especially treacherous in depressed patients who have not yet been diagnosed as bipolar (Akiskal *et al.*, 2005; O'Donovan *et al.*, 2007).

Summary: Mixed States, Over-Arousal, and Affective Instability

Consistent with the underlying course of illness, mixed episodes of bipolar disorder are marked by hyperarousal and by combinations of depression (most notably hopelessness and anhedonia), activation (most notably motor hyperactivity and racing thoughts), and behavioral arousal (most notably emotional lability and anxiety). Individuals with mixed states are susceptible to excessive activation, whether pharmacological or environmental. This combination of depression and stimulation increases risk for suicidal behavior, whether spontaneous or treatment-emergent.

19.2 GENERAL CONSIDERATIONS FOR TREATMENT STRATEGIES IN MIXED STATES

19.2.1 TARGETS OF TREATMENTS

Because clinical trials and diagnostic criteria have focused on depressive and manic syndromes, we will initially classify treatment studies in terms of effects on depressive or manic states. Treatment can address the depressive and manic components of a mixed episode. Treatments aimed at mania, however, can predispose to depression (Vieta, 2005); as discussed above, treatments aimed solely at depression can produce problematic behavioral activation (Colom *et al.*, 2006). Alternatively, treatments can address the underlying affective instability that presumably gives rise to the combination of depression and activation.

Therefore, our overall aim will be to understand integrated treatment of mixed states. Treatments optimal for mixed states may be different from those that are effective for manic or depressive syndromes in other contexts.

19.2.2 GENERAL MEDICAL CONSIDERATIONS

Perhaps even more than with other episodes of bipolar disorder, mixed states require general medical alertness. Patients with mixed states are more likely to have other illnesses that can complicate the episode:

- Substance-use disorders, with potential for intoxication, withdrawal, drug toxicity, and pharmacokinetic interactions with treatments.
- Other medical disorders, including either diagnosed or undiagnosed neurological, endocrine, or cardiovascular illnesses.
- Trauma
- Pharmacokinetic considerations: individuals with mixed episodes are likely to be taking more psychotropic agents than are other patients with bipolar disorder, in addition to treatments for other medical problems.

19.2.3 ENVIRONMENTAL AND NON-PHARMACOLOGICAL CONSIDERATIONS

Successful treatment of mixed states requires the precautions that are necessary for both manic and depressive episodes, regardless of dominant polarity. These include

- Environmental and interpersonal consistency and protection against overstimulation
- Vigilant attention toward risk for suicide, aggression, or escalation, being mindful of the potential for affective and behavioral lability,
- Ascertainment of environmental, legal, family, financial, and medical factors that might be contributing to or complicating the episode.

19.3 TREATING MANIA IN MIXED STATES

19.3.1 PREDOMINATELY MANIC

19.3.1.1 What Treatments Work According to Randomized Controlled Trials?

Most controlled studies of treatment in mixed states has focused on mixed states as a subset of manic episodes, and have therefore focused mainly on how effectively treatments reduce manic symptoms (Kruger, Trevor, and Braunig, 2005). Divalproex (Swann *et al.*, 1997; Bowden *et al.*, 1994), carbamazepine (Weisler, Kalali, and Ketter, 2004), olanzapine (Baldessarini *et al.*, 2003), ziprasidone (Keck *et al.*, 2003), aripiprazole (Suppes *et al.*, 2008), and asenapine (McIntyre *et al.*, 2009) all reduced mania rating scale scores similarly in mixed and nonmixed manic episodes. Antimanic effects of lithium were significantly less in mixed than in nonmixed episodes (Swann *et al.*, 1997; Freeman *et al.*, 1992). The initial trials with quetiapine excluded patients in mixed episodes, but did include subjects with significant subclinical depressive symptoms (Weisler *et al.*, 2008).

19.3.1.2 Lithium in Mixed Manic States

In uncontrolled studies, Himmelhoch reported that lithium treatment was less effective in outpatients with mixed, compared to nonmixed, episodes (Himmelhoch *et al.*, 1976). The NIMH Collaborative Study on the Psychobiology of Depression (Biological Studies) also found lithium to be relatively ineffective in mixed states (Swann *et al.*, 1986). In a controlled study comparing lithium, divalproex, and placebo, response to divalproex and lithium was similar overall but lithium was not effective in mixed episodes or in manic episodes with subsyndromal depression (Swann *et al.*, 1997). Similarly, in a double-blind comparison of lithium and valproate, response to valproate was better than response to lithium in subjects with depressive symptoms (Freeman *et al.*, 1992). Response to lithium was also reduced in patients who had experienced mixed episodes in the past (Backlund *et al.*, 2009), consistent with the fact that these patients were more likely to have experienced the inherently unstable course pattern, which appears relatively resistant to lithium monotherapy (Duffy *et al.*, 2002).

The relative ineffectiveness of lithium (at least as monotherapy) in mixed episodes may be related to greater severity of illness in mixed states (Himmelhoch and Garfinkel,

1986). Substance-use disorders (Goldberg *et al.*, 1999) and histories of early onset and/or frequent episodes (Goldberg *et al.*, 2009; Backlund *et al.*, 2009; Swann *et al.*, 1999), both increased in mixed states, are related to reduced response to lithium (Duffy *et al.*, 2002). However, in each case, these factors are negatively related to lithium response regardless of episode subtype (Goldberg *et al.*, 1999; Swann *et al.*, 1999), so differential effects of lithium in mixed states are not solely related to comorbidities or recurrence of illness.

Mixed states are more likely than other affective episodes to require multiple treatments (Dilsaver *et al.*, 1993; McIntyre, 2008). Lithium may be less effective as monotherapy than some other treatments are, but in patients not responding to a single agent, lithium can be an extremely useful augmenting agent in a combined treatment strategy. This is especially the case considering the high lifetime risk of suicidal behavior in patients with mixed episodes (Goldberg *et al.*, 1998, 2009; Swann *et al.*, 2007). Even when it is not effective in reducing depressive or manic symptoms, lithium appears to reduce the lethality of suicide attempts (McIntyre *et al.*, 2008), possibly as a result of its anti-aggressive effects (Sheard *et al.*, 1976).

19.3.1.3 Problems with RCTs in Mixed Mania

Few randomized clinical trials have focused on mixed manic episodes. Generally studies included both mixed and nonmixed episodes and analyzed effects on mixed states as a subgroup, comparing them to nonmixed manic subjects. Statistical power for detecting differences between mixed and nonmixed subjects was potentially inadequate, since the studies were generally powered for differences between active drug and placebo for the overall group.

In general, mixed states were categorically defined according to DSM-IV. A study that investigated alternative definitions of mixed states found lithium response to be sensitive to the number of depressive symptoms, being reduced with subsyndromal symptoms (Swann *et al.*, 1997).

Patients experiencing mixed states are more likely to have other complications of illness, like substance-use or medical disorders, or to be more severely ill (Goldberg *et al.*, 2009; Cassidy and Carroll, 2001). Therefore, they may be less likely to be included in placebo-controlled studies than other patients with bipolar disorder, and those who are included are likely to be less severely ill than patients with mixed episodes in general (Licht, 1998).

19.3.2 PREDOMINATELY DEPRESSIVE: MIXED HYPOMANIA OR MIXED DEPRESSION

Recent studies describing patients with combined hypomanic and depressive syndromes, or mixed hypomania, have found them to resemble patients with mixed mania in terms of course of illness (Swann *et al.*, 2001, 2009; Goldberg *et al.*, 2009; Azorin *et al.*, 2009). These patients can have either bipolar I or bipolar II disorder (Akiskal and Benazzi, 2005a; Maj *et al.*, 2003). As is the case with hypomania in general, there is little information about pharmacological effects on hypomanic symptoms in these patients. It is generally assumed that these symptoms will respond to effective antimanic treatments.

19.4 TREATING DEPRESSION IN MIXED STATES

19.4.1 PREDOMINATELY MANIC

19.4.1.1 Independent Treatment of Depression and Mania

Effective treatment of mixed states may result in improvement of both depressive and manic symptoms. Alternatively, depressive and manic symptoms may have a more parallel and independent response to treatment.

Some early data suggested at least partial dissociation of depressive and manic symptom response. In the NIMH Collaborative Study noted above, lithium appeared to improve depressive symptoms even when mania did not improve, though the number of subjects was too small for definitive conclusions (Swann *et al.*, 1986). More recently, Brown *et al.* investigated effects of an added antidepressive agent (bupropion) in subjects whose mania had responded to multiple treatments (usually at least two of an anticonvulsant, and antipsychotic agent, and lithium) but who had persistent depressive symptoms two weeks after resolution of mania. These depressive symptoms improved after addition of bupropion (Brown *et al.*, 1994). These results support the use of antidepressive agents, but only after antimanic treatment has reduced behavioral activation.

19.4.1.2 Combined Treatment of Depression and Mania

In apparent contrast to these earlier studies, most randomized controlled trials of second generation antipsychotic agents and anticonvulsants have shown depressive symptoms to improve with the same treatments that were effective in reducing mania rating scores (Kruger, Trevor, and Braunig, 2005; McIntyre, 2008). This would support the idea that treatment of the underlying affective episode can resolve both depressive and manic symptoms in mixed states. Two factors to be taken into account are that (i) the general severity of illness is likely to have been lower in these randomized clinical trial participants than in the general population of manic patients (Licht, 1998) and (ii) in the randomized clinical trials, changes in depressive symptoms were not always reported separately in mixed and nonmixed subjects, although, when they were, subjects in mixed states did generally have significant reductions in depressive symptoms (Kruger, Trevor, and Braunig, 2005).

Treatment of Predominately Manic Mixed States

Most, but not all, treatments that are effective for mania also reduce depressive symptoms in manic episodes, including valproate, second generation antipsychotic agents, and carbamazepine. Monotherapy with lithium is an exception, but lithium is a valuable second treatment. Mixed episodes are more likely than nonmixed episodes to require multiple treatments for an optimal response.

19.4.2 PREDOMINATELY DEPRESSIVE

19.4.2.1 Mood-Stabilizing Treatments

Consistent with the case for bipolar depression in general, there is little information on treatment response of depression in predominately depressive mixed states. Randomized controlled trials suggest that quetiapine may be effective (Calabrese *et al.*, 2005). Other nonantidepressant treatments with suggested effectiveness in bipolar depressive episodes, including lithium (Swann *et al.*, 1986), valproate (Ghaemi *et al.*, 2007), or lamotrigine (Geddes, Calabrese, and Goodwin, 2009), have potential promise.

In the case of lamotrigine, five randomized controlled trials in bipolar depressive episodes were negative for the primary end point (Calabrese *et al.*, 2008) (one was positive for a secondary end point (Calabrese *et al.*, 1999)), but meta-analysis showed an overall positive effect, especially for patients with relatively severe depression (MADRS > 24) (Geddes, Calabrese, and Goodwin, 2009).

19.4.2.2 Antidepressive Agents

It is tempting to use antidepressive agents in treating these patients, and the incidence of antidepressive treatments is high (Azorin *et al.*, 2009; Ghaemi, 2008). However, there is little evidence for effectiveness of antidepressive agents even in bipolar disorder as a whole (Ghaemi, 2008), much less in patients experiencing mixed states, who appear to be unusually sensitive to mood destabilization and behavioral activation. The STEP-BD, in 380 patients given antidepressants in depressive mixed states, reported increased manic symptoms with limited or no benefit for depression (Goldberg *et al.*, 2007).

Treatment of Predominately Depressive Mixed States

In these episodes, it is necessary to recognize the importance of the underlying mood instability. Antimanic agents that are also effective against mixed states are primary treatments, especially those like quetiapine and valproate that also have evidence suggesting effectiveness against bipolar depression. Favored second treatments are lithium or other potentially mood-stabilizing treatments, including lamotrigine. Because these patients are susceptible to pharmacological mood destabilization, it is prudent to defer unimodal antidepressive treatments until after mood stabilizing treatments have been instituted and determined not to elicit an adequate response.

19.5 NONPHARMACOLOGICAL TREATMENTS

Nonpharmacological treatments, including electroconvulsive treatment (ECT) and transcranial magnetic stimulation, can be aimed at either depressive or manic syndromes. Vagal nerve stimulation is a potential treatment for depressive episodes. ECT is the only

nonpharmacological treatment with substantial supporting data for mixed states. It has the advantages of potential effectiveness for either depression or mania, many years of experience, and recent technical advances. Most evidence is from case series. A meta-analysis supported its effectiveness in full bipolar mixed states (Valenti *et al.*, 2008), as have other studies where it was effective in patients who had not responded to vigorous conventional treatment (Gruber *et al.*, 2000). In a randomized study, ECT was superior to lithium in acute mania; the difference emerged from the superior effectiveness of ECT in subjects with mixed features (Small *et al.*, 1988).

19.6 AN INTEGRATED MODEL FOR TREATING MIXED STATES

19.6.1 PROVISIONAL, OPERATIONALIZED DEFINITION OF MIXED STATE

For the purpose of recommending practical treatment, we will define mixed states in a manner that reflects the combination of activation and depression, the similarity in course of illness between predominately depressive and manic mixed states, and the apparently continuous nature of mixed symptoms, ranging from mania with modest depressive symptoms or depression with modest manic symptoms to full manic and depressive syndromes (Swann *et al.*, 2009). Our definition is based on evidence that differences in course of illness and treatment response emerge in manic episodes with two or more depressive symptoms, and in depressive episodes with two or more manic symptoms (Swann *et al.*, 1997; Maj *et al.*, 2006; Swann *et al.*, 2009; Akiskal *et al.*, 1998; Benazzi and Akiskal, 2001).

Provisional Definition of a Mixed State

- Mania, hypomania, or depression is present, and
- There are two or more symptoms of the opposite polarity. This excludes symptoms that overlap between depressive and manic states, including insomnia, and agitation as defined broadly (McElroy *et al.*, 1992). Decreased need for sleep and increased goal-directed activity, however, are considered mixed symptoms in depressive episodes.

19.6.2 INTEGRATED PHARMACOLOGICAL TREATMENT STRATEGY

These general guidelines depend on the individual’s previous history of psychopharmacological response and toleration. Because of the complexity of mixed states, treatment will need to be individualized (Dilsaver and Benazzi, 2008):

1. **Initial treatment:** If the patient is not receiving treatment, institute treatment with one or two of the following medicines, which have been reported to be effective, in placebo-controlled studies, for mania and for mixed mania, and not to worsen depression or cause mood destabilization:
 - (a) Valproate (Swann *et al.*, 1997; Bowden *et al.*, 1994)
 - (b) A second-generation antipsychotic agent: Olanzapine (Baldessarini *et al.*, 2003), risperidone (Khanna *et al.*, 2005), quetiapine (initial mania studies excluded mixed states but did include subsyndromal depression (Weisler *et al.*, 2008), and efficacy against depression in bipolar I and II disorders has been demonstrated (Calabrese *et al.*, 2005)), ziprasidone (Keck *et al.*, 2003; Vieta *et al.*, 2008) (initially IM or with at least 500 kcal of food (Citrome, 2009)), aripiprazole (Suppes *et al.*, 2008), or asenapine (McIntyre *et al.*, 2009)
 - (c) Lithium (not as monotherapy (Swann *et al.*, 1997))
 - (d) Lamotrigine (efficacy against mania has never been demonstrated and evidence against depression is limited, so only in depressive mixed state, and not as monotherapy)
 - (e) Carbamazepine (Weisler, Kalali, and Ketter, 2004) or oxcarbazepine, allowing for potential pharmacokinetic interactions in patients receiving multiple treatments.
2. **Second treatment:** If the patient is already receiving one of the treatments above (McIntyre, 2008),
 - (a) Maximize the dose, and
 - (b) Add another treatment from (1), but not a second antipsychotic agent
3. **Additional treatment:** If the patient is already receiving, or has not responded to two treatments from (1)
 - (a) Add a third treatment from the list in part 1, or
 - (b) Add clozapine if predominately manic (Suppes *et al.*, 1992), or
 - (c) Institute bilateral ECT (Valenti *et al.*, 2008)
4. **Residual depression:** If the patient has experienced improvement in manic symptoms using the above strategy, but is still depressed after two weeks:
 - (a) Add lithium or lamotrigine if they are not already being given, or, if the patient is not receiving an antipsychotic agent, consider quetiapine (Calabrese *et al.*, 2005); or
 - (b) Add a nontricyclic antidepressive agent with a relatively low incidence of mood destabilization, such as bupropion (Brown *et al.*, 1994); or
 - (c) If depression or history of treatment-emergent mood instability is severe, consider ECT (Valenti *et al.*, 2008).
5. **Long-term treatment:**
 - (a) As for other episodes of bipolar disorder, treatments considered essential for resolution of the episode should be adjusted for tolerability and continued.

- (b) Due to the relative lack of long term prophylactic efficacy of antidepressive agents (Ghaemi, 2008), their gradual taper and discontinuation should be considered, generally after the patient has had time to recuperate from the episode and to recover pre-episode functionality, unless the specific patient's past history shows consistent relapse into depression after antidepressant discontinuation.
- (c) In patients who had poor responses to pharmacological treatments and responded to ECT, maintenance ECT should be considered.
- (d) Because of these patients' susceptibility to a severe and unstable course of illness, additional measures to preserve affective and behavioral stability are vital, including symptom monitoring, management of substance-use disorders and other complications of bipolar disorder, and protection of social and sleep-activity rhythms.

19.7 CONCLUSIONS

Mixed states are a serious manifestation of bipolar disorder, where symptoms are not limited to depressive or manic syndromes, and substantial affective and behavioral instability occurs in the specific episode and in the course of illness. They are characterized by a course with early onset and frequent recurrences, poor response to conventional treatments, substance use disorders, and susceptibility to suicidal behavior. Their treatment requires identification of the mixed state, and vigorous treatment of the underlying severe bipolar disorder that generates the episode.

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