

# THE PSYCHIATRY LETTER

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## Mixed States

In this issue, PL addresses the general issue of mixed mood states, as mentioned in a number of prior issues. This topic is complex but, in the PL viewpoint, it is central to a new and powerful way of thinking about the diagnosis and treatment of so many patients with mood and anxiety symptoms. This issue presents these ideas more systematically than has been the case either in prior issues or on the PL website. Due to the complexity of the topic, it is discussed in two PL issues, part I on diagnosis now and part II on treatment next month.

In this issue, we also have a new guest columnist, Ed Mendelowitz PhD, who discusses the basic perspective of existential psychotherapy.

The Article of the Month relates to the concept of mixed states, discussing a new systematic review on the concept of psychomotor excitation, or activation, as being the core feature of mania. The Drug of the Month is ziprasidone, a unique dopamine blocker which also is a serotonin and norepinephrine reuptake inhibitor. By the Numbers provides summary numbers for clinicians to know and think about in relation to diagnosis of mixed states.

Through our collaboration with PeerPoint Inc, we continue to provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to psychiatrists and nurses and psychologists.

If you find PL helpful to you and your patients, please let others know so that more clinicians and patients may benefit.

**Nassir Ghaemi MD, Editor**

*New truths begin as heresies and end as superstitions - T. H. Huxley*

## Special Article: Mixed States - Part I: Diagnosis

### A key concept for understanding “depression”

#### Definitions

A key issue in understanding the phenomenon of depression is knowing how it contrasts with mania. One approach is the DSM approach: compare this number of criteria versus that number of criteria for this or that amount of time. This is how most clinicians are taught. What they don't realize is that the DSM definitions are based on very broad concepts of depression and very narrow concepts of mania. We'll return to this idea.

For now, let's go the classic psychopathology literature and ask the question, decades and centuries before DMS-III in 1980: How did the great thinkers of medicine and psychiatry define depression versus mania?

The answer is simple: Depression meant a slowing down of one's thinking, feeling, and moving. Mania meant a speeding up of one's thinking, feeling, and moving. Translated to current terms, depression was equivalent to psychomotor slowing and mania was equivalent to psychomotor excitation.

#### Mood is secondary

Readers will note that in this classic psychopathology, mood is not central to the definitions of depression or mania. Psychomotor slowing can come with sad mood, or it can come with normal mood. One sees this kind of depression in the classical seasonal depression of the fall/winter: patients describe loss of motivation and anhedonia but not sadness of mood. Similarly psychomotor excitation can come with euphoric mood, or it can come with

irritable mood, or with sad mood, or with anxious mood, or with none of the above.

The term “mood disorders” is false in both words. The term “disorder” is a DSM phrase that is applied to all conditions so as to produce a purposeful vagueness (in an effort to be “atheoretical”), as discussed in the May 2016 PL issue. The use of “mood” implies that a mood change is central to these conditions, whereas in fact psychomotor activity appears to be central and primary; the mood experiences is epiphenomenal and secondary. Perhaps the older term “affective” would be preferable, as it implies a larger and more complex construct as opposed to the subjective mood experience.

For our purposes, this distinction is important in understanding mixed states. In the article of the month, PL reviews a newly released systematic review that provides the empirical evidence in support of this classic psychopathology. Specifically, it shows how psychomotor excitation or activation is central to the phenomenon of mania.

If mania is thus understood, as opposed to solely accepting the DSM criteria, then some major changes follow in our understanding of affective states like depression.

#### The primacy of mania hypothesis

Athanasios Koukopoulos was a Greek psychiatrist, who practiced most of his life in Rome. He passed away a few years ago, after about 50 years of active clinical practice in a prestigious private practice in Rome. He published some of his observations and ideas over

*“Mania meant a speeding up of one's thinking, feeling, and moving...”*

the years, and, in his last decade, he summarized his central thinking in the theory of the “primacy of mania.” On this theory, depression is the effect of mania. Mania is the cause, the primary driver, of depression. This idea turns traditional psychiatric thinking upside down in at least two ways. It has been taught for a century that mania is a “flight from depression,” that manic states are superficial reactions to not being able to acknowledge and experience the painful state of depression. As with most psychoanalytic thinking, there has never been any empirical scientific proof of this hypothesis. In current DSM-based thinking, depression (MDD) and mania (bipolar disorder) are viewed as two distinct and separate conditions. They overlap in symptoms of depression, but they are different “disorders” and are assumed by most clinicians to be different illnesses. As discussed in many PL issues and the PL website, this DSM belief contrasts with the older Kraepelinian theory of manic-depressive illness (MDI), which held that all depressive episodes and manic episodes were part of the same illness, MDI. In other words, unipolar depressive illness was the same disease as bipolar illness. Koukopoulos adds a twist to this Kraepelinian idea. He holds that depressive episodes do not happen unless they are preceded by or caused by manic episodes or symptoms. *Mania is the fire, depression is the ash.*

### Defining mixed states

Another large category of persons with depressive episodes have manic episodes during the depressive episodes, i.e., mixed states. This group of patients was of most interest to Koukopoulos. These mixed states can be defined in different ways, outside of DSM constraints. The simplest approach is the “bipolarity specifier” described by Benazzi; on this definition a mixed state would be

defined by a clinical depressive episode in which three or more DSM-defined manic symptoms occurred for any amount of time (not limited to the 4 days or longer DSM criterion of duration for hypomania or one week or longer for mania). On this definition, Angst and colleagues found that 47% of a large sample of 5635 outpatients with depressive episodes met the mixed state definition. One could also use Koukopoulos’ own definition of “mixed depression”, which is even broader than the bipolarity specifier because it goes beyond DSM criteria. In Koukopoulos’ definition, as described in more detail below, mixed depression involves the presence of a clinical depressive episode along with psychomotor excitation, which can be limited to psychomotor agitation and/or marked rage. Using Koukopoulos’ definition of mixed depression, in his own Rome clinic, 51% of 435 consecutive patients with clinical depressive episodes had mixed depressive states.

If we combine the approach of Angst and Benazzi on one hand, and Koukopoulos on the other, we can conservatively estimate that about 50% of all depressive episodes are mixed with manic symptoms, and thus are mixed states, not pure depression. The theory of the primacy of mania would apply if we accept the notion that these mixed states are driven by their manic components; in other words, one cannot separate the depressive from the manic symptoms; they come from the same pathophysiological source. Without the manic symptoms, the depressive symptoms would not occur.

So here are another 50% of depressive episodes, the largest chunk, which would not happen without mania. Combined with the 15% of classic manic-depressive cycles in bipolar illness, we account for the majority, 65%, of depressive

episodes so far, meeting the definition of the primacy of mania.

### **Affective temperaments**

What about the remaining 35%? Are they purely depressive cases, so-called “unipolar” depression? Now we turn to the concept of affective temperaments, described in detail in the June 2016 PL issue. The idea was that mild mood symptoms could occur in persons with mood illnesses, in between the severe episodes, and these mild symptoms were present all the time, as part of one’s temperament. These conditions were defined as dysthymia, hyperthymia, cyclothymia (mild depressive, manic, and manic-depressive symptoms, respectively). In various studies, it’s been found that manic temperaments - hyperthymia or cyclothymia - are present in about 1/3 of persons with recurrent unipolar depressive episodes. If so, these calculations would explain one-third or so of the 35% of remaining persons with depressive episodes (i.e., about 12%). We now have explained 77% of all persons traditionally diagnosed with severe clinical depressive episodes (50% + 15% + 12%). This would be almost 4 out of 5 of such persons.

Affective temperaments appear to predispose to a later risk of depressive episodes. Often these depressive episodes are mixed with manic symptoms, in the case of cyclothymia and hyperthymia, because the baseline manic symptoms of those temperaments remain, and are mixed with new onset depressive episodes. Sometimes, people with cyclothymia and hyperthymia have pure depressive episodes, not mixed states. Often these depressive episodes are of the melancholic type.

Thus, affective temperaments are relevant in two ways: 1) If present, patients often have mixed states when they become depressed; 2) many people with pure or melancholic depressive episodes have manic temperaments before or after their depressive states. In the latter case, Koukopoulos would argue that long-standing hyperthymic or cyclothymic temperaments predispose such persons to depressive episodes. Again, manic symptoms cause depressive symptoms.

### **Neurotic depression**

This leaves 23% of people with clinical depression. As noted on the PL website, “MDD” is not the same thing as unipolar depression. Unipolar depression was seen always as a subtype of manic-depressive illness: it was severe, episodic, recurrent, highly genetic, and biological. In contrast, neurotic depression was mild, chronic, and not highly genetic. The PL view is that the remainder of depressed persons would be of the neurotic variety, with brief severe exacerbations leading to clinical attention. This group of depressed patients does *not* have mixed states. They are notably anxious, but they are not markedly agitated, and not rageful or impulsive.

### **DSM-5: MDD with mixed features**

In DSM-5, there is acknowledgment of much of this work demonstrating that mixed states occur in depressive episodes that are diagnosed as MDD, without full DSM-based manic episodes allowing the diagnosis of bipolar illness. Thus, mixed episodes as a subtype of bipolar disorder was removed from DSM-5, and replaced with mixed features which could be applied to both bipolar disorder and MDD. MDD with mixed

*“[DSM-5 MDD with mixed features is] like excluding pain in the head from a diagnosis of headache...”*

features was limited, however, on conceptual grounds, to “non-overlapping” symptoms. Thus, if a patient has depression, they cannot be diagnosed as having mixed features according to DSM-5 if they also have psychomotor agitation, irritable mood, or distractibility. Those manic symptoms are excluded from the mixed features definition in MDD. The only manic symptoms that can be used are classic euphoric ones, such as euphoric mood, grandiosity, flight of ideas, along with evidence of increased energy, such as increased goal-directed activities. The problem with this DSM-5 approach is that it excludes the most common manic symptoms that occur in mixed states, namely: psychomotor agitation, marked anger/irritability, and distractibility. This would be like excluding pain in the head from a diagnosis of migraine. Thus, the DSM-5 mixed concept has been criticized by the primary researchers in mixed states as being, as is typical with DSM, based on conceptual concerns (a narrow definition to avoid “overdiagnosis”) as opposed to following the empirical, scientific evidence (allowing those symptoms that are most common in mixed states to be included in the diagnosis).

### **Clinical Scenarios**

So what are the clinical scenarios of these different kinds of mixed states? Here are typical examples of how patients would present:

*Bipolarity specifier (Angst and Benazzi):* These patients have brief manic periods, lasting hours to days, as part of a longer depressive episode. Thus, a person might be severely depressed for 2 months, with low sleep and appetite and interest and energy, and then suddenly for a weekend he has high energy and is sexually impulsive and talking fast, and then he has another 2 months of low sleep and appetite and interest and energy.

*Mixed depression (Koukopoulos):* These patients are markedly agitated, highly angry and rageful, and very labile in mood, alternating from angry to sad to tearful. These symptoms are constant for months on end, along with classic depressive symptoms (low energy, appetite, interest, sleep, concentration).

*Mixed hypomania (DSM-5):* MDD with mixed features excludes the classic irritability and agitation of Koukopoulos’ mixed depression. It also excludes the brief manic states of Angst and Benazzi’s bipolarity specifier. In effect, it represents a hypomanic state with some depressive symptoms, rather than a depressive state with some manic symptoms (as in the other two mixed states above). These patients are energetic and grandiose and highly active most of the time, but have dysphoric mood and some depressive symptoms like poor appetite and guilt.

### **Summary**

In summary, mixed states are an important concept to understand when thinking about “depression.” The DSM approach to life tries to force all patients into one of two categories: depression or mania. (Hypomania is just mild mania, and captured in the same category, just as mild depression -to be consistent we should speak of “hypodepression” - is part of the category of depression). Instead, a large clinical and scientific literature supports the view that most mood states are mixed states, not purely depression or mania, but both. Often the depressive features predominate but notable manic symptoms of psychomotor excitation are present. In the DSM-based ideology, mania is restricted to a very small definition, excluding the classic psychopathology of psychomotor excitation (often referred to colloquially as “agitation” or “stimulation”, but then not seen as “manic”). The classic pre-DSM tradition in psychiatry, dating to Kraepelin, can be

supported with newer research by thinkers like Koukopoulos. This literature resuscitates the concept of psychomotor excitation as being diagnostically very important, and as identifying mixed states. Further Koukopoulos' hypothesis that mania causes depression can be supported by the high frequency of manic states occurring either just before or during depressive states, as reviewed above (with the proviso, in the PL view, that neurotic depression is a different condition in which manic states are not present).

### Treatment

In next month's PL issue, we will review the treatment of mixed states, highlighting the problems when these mixed states are misdiagnosed only as "depression" and treated with so-called antidepressants. It will be shown that the latter agents worsen these mixed states and that dopamine blockers and second messenger modifiers (mood stabilizers) improve mixed states. This issue emphasizes the point that these mixed states occur primarily in patients diagnosed with "MDD", not in bipolar illness. This key point is central to understanding the diagnosis and treatment of mixed states.

### The PL Bottom Line

- Mixed states are the most common type of mood states
- They occur in about one-half of depressive episodes, even in patients diagnosed with "MDD," i.e., not bipolar illness.
- Mixed states may reflect the primacy of mania, meaning that manic symptoms or episodes caused depressive symptoms or episodes.
- Neurotic depression may be an exception to the concept of the primacy of mania.
- Manic temperaments are common in persons with depressive episodes, often leading to mixed states.
- MDD with mixed features in DSM-5 is narrow on conceptual grounds, while broader mixed state definitions have stronger research evidence for them.
- Mixed states are key to the proper diagnosis and treatment of "depression."
- Treatment implications will be discussed in detail in the next PL issue.

### *PL Reflection*

We work in the dark.  
 We do what we can.  
 We give what we have.  
 Our doubt is our passion.  
 And our passion is our task.  
 The rest is the madness of art.

*Henry James*  
*The Middle Years, 1893*

## Current Study of the Month: *Agitation/activation is mania*

*Activation in bipolar disorders: A systematic review. J. Scott et al, JAMA Psychiatry. Published online December 21, 2016.*

### A confirmation of classic psychopathology

This systematic review examined 56 studies of the psychopathology of bipolar illness, using different methods, such as factor analysis (29 studies), or actigraphy (20 studies), among other methods.

Factor analysis is a statistical method used commonly to analyze symptoms. Basically, this approach quantifies if and how much certain symptoms group with other symptoms. For instance, in clinical depression, the symptom of insomnia will tend to group with the symptom of low energy. If a patient has one symptom, she will tend to have the other. Those symptoms will load onto a single factor, which might differ from other symptoms (such as suicidality) that might not occur commonly or regularly along with insomnia and low energy. The number of factors found can be added up to explain all the symptoms in a study (the “variance”, which reflects how many symptoms are observed and how much they correlate with each other).

Overall, these studies identified 2 to 7 factors in the psychopathology of mania, which explained 52% of the variance (meaning they explained about half of the observed symptoms; the other half can be seen as being extremely variable and now loading onto any factors of notable size). The top two factors in these studies were examined, and consistently, the most common or primary factor was psychomotor activation. This was a separate factor from mood (elation or depression/dysphoria), which was the second most common factor. Some studies included mixed

manic states, and reported that depressed/dysphoric mood was the primary factor, with activation being a secondary factor. In both cases (pure mania and mixed mania), activation was a separate factor from the mood state (euphoria or dysphoria).

In the actigraphy studies, which involve wearing a device that measures and records one’s physical movements, it was found that mean daytime activity was higher in manic states than in depressive or euthymic states, as one might expect. It was interesting that an even more consistent finding was that there was more variability to activity levels in manic states, compared to depressed or euthymic states. In other words, activity was more unpredictable and less rhythmic in manic states, compared to depression or euthymia. One conclusion one could make is that “goal-directed” psychomotor activity is increased in mania, but perhaps more commonly, it is agitated and unpredictable in nature.

*“...psychomotor activation is the most common and primary psychopathology in pure mania...”*

### The PL Bottom Line

- Psychomotor activation is the primary abnormality of pure mania.
- Psychomotor activation is a separate factor from mood state in mania.
- Increased “goal-directed” activity is present in mania, but unpredictable agitation is even more common.

## Drug of the Month: Ziprasidone

A combined dopamine blocker (antipsychotic) /  
monoamine agonist (antidepressant)

### Biological mechanism

Ziprasidone is a dopamine-2 and serotonin-2 receptor blocker, with potent norepinephrine and serotonin reuptake inhibitor effects. The latter monoamine reuptake effects are equivalent in potency to imipramine, a classic tricyclic antidepressant.

### Clinical efficacy

Ziprasidone is FDA indicated for schizophrenia and mania. It has been shown to be effective in mixed depression, but it was found to be ineffective in two randomized trials of acute bipolar depression. Many clinicians have the experience that it is not effective enough for severe psychosis or mania, but can be effective for moderate cases. It seems to have benefit for depressive states based on the mixed data above, but the negative bipolar depression studies should be noted. Its large dosing range, along with varying biochemical effects based on dose, as described below, have made it complicated to use. It has an intramuscular injectable formulation for acute agitation.

### Dosing

Like most dopamine blockers, its dopamine blockade is dose-related in a curvilinear fashion, reaching classic antipsychotic thresholds of 80-90% dopamine blockade at 80-160 mg/d. In

contrast, its potent norepinephrine and serotonin reuptake inhibition is present at all doses. Thus, at low doses, it has more antidepressant-like, and less anti-manic or antipsychotic, properties.

### Side effects

The most common side effect is akathisia, which is dose related. Other parkinsonian side effects also can occur. Ziprasidone does not have any cardiovascular or diabetes harms, nor does it cause weight gain. In the CATIE study, it was the agent with the best profile on lipid and diabetes parameters and in weight. It does increase QT length, which can increase the risk of cardiac arrhythmias. Due to its monoamine reuptake effects, it has been reported to cause manic episodes in some persons, and it may have some risk of serotonin withdrawal syndrome.

#### Fast Facts: Ziprasidone

*Typical dose:* 80-160 mg/d

*Biological mechanism:* Dopamine/serotonin blockade plus norepinephrine/serotonin reuptake blockade

*Typical side effects:* akathisia

*Medically important side effects:* cardiac arrhythmia

### The PL Bottom Line

- Ziprasidone has norepinephrine and serotonin reuptake blockade, like tricyclic antidepressants.
- It isn't effective for severe psychosis or mania, but can help moderate states.
- It works in mixed depressive states.
- It has no metabolic harm or weight gain, but it can cause cardiac arrhythmia.



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## Guest Column

### *Existential Psychotherapy: The uses of adversity*

Edward Mendelowitz PhD

Clinical Psychologist, Quincy MA

#### *A Consultation*

*Dr. Reilly:* You have reason to believe that you are very ill?

*Edward:* I should have thought a doctor could see that for himself. Or at least that he would enquire about the symptoms. Two people advised me recently, almost in the same words, that I ought to see a doctor. They said—again, in almost the same words—that I was on the edge of a nervous breakdown. I didn't know it then myself—but if they saw it I should have thought that a doctor could see it.

*Dr. Reilly:* “Nervous breakdown” is a term I never use. It can mean almost anything.

T. S. Eliot, *The Cocktail Part*

According to existential perspectives in psychology and psychiatry regularly considered in the *Psychiatry Letter*, it may be suggested that the greatest proportion of human strife fundamentally relates to our existential predicament, whether in terms of the inherently overwhelming nature of this predicament or in terms of the constriction necessitated by too rigid an attempt at its suppression. This basic premise is implicit throughout the works of the late existential psychologist and author Rollo May, who observed that we defend much more vehemently against thoroughgoing existential awareness than, for example, instinctive drives. The psychoanalyst Allen Wheelis wrote in this regard of “problems of being,” suggesting further that the typical doctor/patient arrangement does

not entirely apply to the psychotherapist's consulting room. Clinically speaking, it makes sense to view the individual, insisted Freud's erstwhile colleague and confidant Otto Rank, as a “suffering being” rather than as merely instinct-ridden or determined exclusively by her or his past, present distress, or otherwise clinically disordered mind. Our problems reside in our very arrival on the planet.

Although this perspective may be more or less implicit in the literature of existential psychiatry/psychology, it contrasts significantly with clinical perspectives that view psychological problems as deviations from some standard of presumed normalcy. It differs, too, from perspectives that seek to locate the source of conflict exclusively in historical events or distorted thoughts. These are very likely to be aspects of the problem, yet the fundamental problem may well be life itself. An examined life presses the individual into an encounter with existence (from the Latin *ex sistere*: “to stand forth,” “to emerge”) and demands a worthy response. Psychotherapy today not infrequently is presented with less clear-cut symptoms than was once the case. The finding that individuals frequently embark on psychotherapy out of feelings of purposelessness, boredom, diffuse anxiety, and vague feelings of dissatisfaction points to the existential bases of a great deal of psychological disturbance. Those who are honest with themselves (the most common lie, observed Nietzsche, is the lie that we lie to ourselves) will be aware of such feelings, and in this regard we must conclude that there is more similarity than difference between therapist and patient. Psychotherapy clients do not necessarily present with explicitly existential agendas but, rather, embark upon therapy with all manner of “everyday,” as opposed to “ontological,” concerns. From an existential vantage point, the therapist is attentive to the manner in which even these

normative foci may manifest presentations of deeper confrontations with life and the world. “Psychotherapy,” writes May, “reveals both the immediate situation of the individual’s sickness and the archetypal qualities and characteristics which constitute the human being as human.” Effective psychotherapy is attuned not only to clients’ stated complaints but also to underlying bedrock existential themes.

Existential psychotherapy is attentive to what everyday life attempts so vehemently to ignore. Through struggle and fortitude, we are capable of fashioning something uniquely meaningful out of our unique sufferings and shared fleeting, finite selves. Although the “theory” of existential psychotherapy may appear abstrusely philosophical (or, conversely, conceptually lean) as contrasted with more conventionally formulaic approaches, we may understand such an approach is more an attitude than a circumscribed system of knowledge or thought. Existential psychotherapy is interested in all the extant theories, but these are nonetheless bracketed and left behind upon entering the consulting room. Theory, though important, is secondary to the phenomenological moment and to the real encounter between client and therapist. Otto Rank once remarked, provocatively, that all theory was essentially dead, referring as it did to something found in the past and thereby occluding what was unforeseen—the moment unfolding in the here and now. Technique can be a protection from consciousness just as easily as an extension of the same. Fanatical attention to theoretical conjecture, from this point of view, may well be a flight from that which is most essential: the immediacy of experience and the anxiety and possibility that inhere in the acceptance of

responsibility for the turbulent creation of a more conscious self.

“But I do urge that we not let the drive for [objectivity] put blinders on us and cut off our range of vision so that we miss the very thing we set out to understand—namely, the living human being. We must go beyond the naiveté of the faith that if we can only get somehow and ultimately to the ‘bare empirical facts’ we shall at last have arrived safe and sound in the harbor.” Rollo May, *Psychology and the Human Dilemma*

*PL Commentary:* Dr. Mendelowitz studied under Rollo May, whose ideas he describes here, back in the 1980s. May was a psychologist who is acknowledged as the leading American thinker in the field of existential/humanistic psychology and psychiatry. May himself had studied under the existential theologian Paul Tillich, an emigre from Germany in the 1930s. Beginning in the 1950s, May introduced the German and French existential literature to American clinicians. He wrote a number of well-received books throughout the following decades, all of which, especially *Man’s Search for Himself*, are recommended to PL readers. After May’s death in 1994, his legacy has been carried on by Ed Mendelowitz, whose expertise in literature and film theory produce his unique take on existential psychology. Widely published in psychology journals, Ed Mendelowitz was the recipient of the American Psychological Association’s 2016 Rollo May award, given for lifetime achievement in humanistic psychology. PL appreciates Dr. Mendelowitz’ essay and hopes share more of his columns with PL readers in the future.

*“Existential psychotherapy is attentive to what everyday life attempts so vehemently to ignore...”*

## By the Numbers

### *Mixed States - Diagnosis*

Frequency of mixed states defined as a full clinical depression with some manic symptoms (“mixed depression” or the “depressive mixed state”), as discussed in the Special Article. Percentages refer to frequency of all “major” depressive episodes (MDEs; percentages are rounded):

In DSM-defined “MDD”: 50%

In DSM-defined bipolar disorder type I: 50%

In DSM-defined bipolar disorder type II: 60%

Most common manic symptoms in mixed depression:

Psychomotor agitation: >90%

Marked anger/rage/irritability: 80%

Flight of ideas/racing thoughts: 50%

Distractibility: 50%

Grandiosity: 20%

Euphoric mood: 10%

Frequency of DSM-5 defined “MDD with mixed features,” as percentage of all MDEs: 10%

Frequency of “mixed depression,” as defined in Special Article (using bipolarity specifier or Koukopoulos’ criteria), as percentage of all MDEs: 50%

Frequency of mood episodes in unipolar depression and bipolar illness combined:

Pure depression: 20%

Pure mania: 20%

Mixed states (mixed depression and dysphoric mania): 60%

## Curbside Consults

### *Questions and cases from you*

*Question:* Is there sufficient evidence to recommend lithium, divalproex, carbamazepine, or a dopamine blocker as the first drug of choice in a particular bipolar patient? For example, divalproex/ziprasidone over lithium for a mixed, dysphoric bipolar depression or lithium for the MDI pattern (mania, M, followed by depression, D, followed by a normal interval, I) patient with euphoric mania?

*PL:* In general the PL view is that if we were to generalize to the average patient with bipolar illness with the most common types of symptoms, all other things being equal (i.e., proneness to side effects, medical illnesses), lithium is the most proven and most effective second messenger modifier overall.

*All other things being equal, the PL view is that lithium is the “drug of choice” for bipolar illness.*

The reasons for this general preference for lithium are as follows: Lithium is the most proven agent for prophylaxis, both for depression and mania. No agent is proven more effective than lithium for prevention of either pole, including lamotrigine for depression (see the prior PL issue, January 2017). Unlike other second messenger modifiers lithium has the added benefit of being the only agent proven to prevent completed suicide. Further, unlike other agents in this class, lithium is the only agent with notable evidence of dementia prevention and of biological neuroprotection benefits in animals and humans in replicated studies. Lithium also is the only agent proven to reduce overall mortality, extending the average lifespan in bipolar illness by a decade (due to reduced cardiovascular mortality as well as suicide prevention). Many of these lithium benefits occur at low doses, as discussed

on the PL website, and thus low-dose lithium (300 mg/d or less) can be considered for all patients with bipolar or unipolar mood illness, for these proven or likely mortality reduction and dementia prevention benefits.

However, there are some provisos to this general recommendation, and there are some specific situations where other agents might be preferred to lithium. In the acute mixed manic episode, divalproex and carbamazepine are proven more effective than lithium. In rapid-cycling bipolar illness, lithium alone is proven ineffective (as is divalproex alone and lamotrigine alone), but lithium should be combined with divalproex or carbamazepine. Regarding other patterns of course (mania followed by depression or depression followed by mania), that literature is mostly observational and PL would not draw strong conclusions. With active severe substance abuse comorbidity, divalproex has somewhat more evidence of benefit than lithium.

Perhaps the most important issue with lithium is its long term renal impairment. The risk is about 1% at 20 years of treatment, as reviewed on the PL website. This risk can be lowered by giving lithium once daily, which reduces constant renal exposure to lithium levels, and by keeping the overall level as low as possible. Many people, especially with non-type I bipolar illness, will respond to levels below 0.6. That said, in choosing to use lithium, another factor to take into account is when to start the clock, so to speak, on its renal effects. In a 50 year old, 1% at

20 years is not as much of a concern, as opposed to a 20 year old, who will only be 40 years old with potential renal impairment, and who will have more likelihood of renal impairment by his/her 60s, when they still will have many years of life ahead of them in most cases. Thus, the PL preference is to use lithium less, all other things being equal, in adolescents and twentysomethings, and to use it more in middle age. Obviously, there is also higher risk of toxicity with lithium in the elderly, especially at standard levels. Very low doses of lithium, specifically for suicide prevention in the young (300 mg/d or less), or for dementia prevention in the elderly (150 mg/d or less), would still be feasible and recommended where either suicide risk or dementia risk was notable. But, as the primary "mood stabilizer" for prevention of full mood episodes, if all other things were equal, PL would lean away from lithium in adolescents and young adults, and toward lamotrigine or carbamazepine (neither of which cause weight gain) or divalproex (in males, due to PCOS risks in young women). Similarly, in those above age 70, PL would lean way from standard dose lithium and towards lamotrigine preferably, and divalproex secondarily (if manic states are more prominent). Divalproex is secondary in the elderly because it has been shown to cause cortical atrophy in that age group. Carbamazepine should be avoided in this age group due to notable hepatitis risk as well as the many unavoidable drug interactions in most persons at this age who will need medications for other common medical conditions.

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