Mood-stabilizing drugs slipped into the vocabulary of psychiatrists during the last 15 years without a proper discussion of their definition. Consequently, these medications have been used in ways that have no empirical justification.

Mood-stabilizing drugs slipped into the vocabulary of psychiatrists during the last 15 years without a proper discussion of their definition. Consequently, these medications have been used in ways that have no empirical justification. The original idea behind the term mood stabilizer was the apparent ability of lithium to offer antimanic qualities as well as some measure of antidepressant action. *The American Psychiatric Association's Practice Guideline for Treatment of Patients With Bipolar Disorder* (1994) defines mood stabilizers as "medications with both antimanic and antidepressive actions." From time to time, research has been contradictory about the efficacy of lithium as an antidepressant (Keck and McElroy, 1996). However, the concept was clear. This is not the case with the various anticonvulsant medications that have been labeled mood stabilizers. Despite widespread use, it is not obvious what is meant by a mood stabilizer and how anticonvulsants fit that description.

There is little if any clear-cut evidence that valproate (Depakote, Depakene), carbamazepine (Tegretol) (Kalin, 1996-1997) or gabapentin (Neurontin) are effective antidepressant agents. Yet as soon as they were shown to have efficacy in acute mania, they were quickly labeled mood stabilizers rather than antimanic agents. This is not a matter of small significance, since it is not unusual for bipolar patients with a predominantly depressive history to be exclusively put on mood stabilizers with the expectation that the depression will be treated, and that rapid cycling due to the use of traditional antidepressants will be avoided. I'm not referring to the prophylactic use of mood-stabilizing agents when it is expected that antidepressants will later be necessary so that protection against a potential manic episode seems judicious. Frequently, mood stabilizers are used as the sole antidepressant. Indeed, an expert consensus treatment protocol recommends mood stabilizers alone as a first-line approach in treating milder major depressive episodes in bipolar I disorder and as a second-line approach in bipolar II disorder (Frances et al., 1996).

Some experts such as Bowden (1996) and Keck and McElroy (1996) are so concerned about the possibility of rapid cycling that they go still further, considering the use of antidepressants as a last resort in treating bipolar depression only after multiple mood stabilizers have been tried first. While the concern about antidepressants causing rapid cycling is based on an indisputable clinical possibility, these experts have no illusions about the effectiveness (or indisputable evidence for the effectiveness) of anticonvulsant medications as treatment for acute bipolar depression. Both valproate and carbamazepine did little better than placebo in the studies they cited, but if I understand them correctly, they considered bringing relief from the torment of depression as quickly as possible a less important priority than not iatrogenically causing mood instability. According to Gary S. Sachs, M.D., the definition of the term mood stabilizer does not require antidepressant or antimanic efficacy, per se, merely that the medication "decrease vulnerability to subsequent episodes of mania or depression" and not exacerbate the current episode or maintenance phase of treatment (1996). The use of anticonvulsant medicines as mood stabilizers has become even more relevant since the expansion of the bipolar disorder (BD) diagnosis to include bipolar II patients (American Psychiatric Association, 1994). Bipolar II is a reasonable addition to the nosology of mood disorders, sometimes allowing earlier recognition and an appropriate alertness to the softer signs of the illness. However, it also has contributed to an excessive looseness in diagnosing BD. On more than one occasion, I have had patients hospitalized for severe depression and, after a three- or four-day stay, they have returned on a mood-stabilizing agent and nothing else. They have been told that they have bipolar disorder and that their anticonvulsant medication treats the basic problem.

Here is an example.
Ariel, a 16-year-old girl, had a history of repeated severe suicidal depressions punctuated by periods of a few hours, sometimes a day or two (definitely not four days as specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition for hypomania), in which she felt a bit giddy as well as more social, energetic and creative. There was no family history of manic-depressive illness. She did not feel that her "up" times were a problem. Indeed, she was able to perform at a high level academically and felt more connected to her friends and parents. There was no pressured speech, flight of ideas or a sense that her mind was racing. There was no distractibility; impulsivity; irresponsible spending, driving or sexual behavior; or loss of judgment. Insomnia was not present, and there was no history of a decreased need for sleep. Although there was an improvement in self-esteem, it was not inflated or grandiose. Ariel's parents and friends, as well as Ariel herself, considered her good moods entirely normal and delighted in them.

The arguments for and against using a loose definition of BD hinge on the risk/benefit ratio of active treatment. On the benefit side, at least theoretically, is the kindling model for bipolar disorder. It is hoped that the prevention of frequent manic episodes may prevent rapid cycling that often develops later in the illness. But this is theory, not fact. Even when the diagnosis is clearly bipolar, there's no empirical documentation and no longitudinal studies that demonstrate long-term administration of medications will prevent rapid cycling later in the illness. Despite this lack of proof, when a bipolar diagnosis is unequivocal, treatment is a no-brainer. We treat vigorously with the hope there will be this eventual benefit because good acute control is desirable anyway. When the diagnosis is based on looser criteria, it is a more complicated issue. There are at least two prospective studies demonstrating that patients with major depressive disorder and a definite family history of BD have a very high risk for transformation to bipolar I disorder (Akiskal et al., 1983; Strober and Carlson, 1982). Clearly in this situation, it is advisable to monitor patients with serious depression closely for early signs, even more so when there are soft signs of hypomania. But if there is no family history, a case can be made to hold back on treating the patient's not diagnostically definable highs.

From this vantage point, if a patient such as Ariel does not have symptoms that she, her family and friends, or any layperson, would consider symptoms, what are we treating? If we believe that we are somehow correcting a fundamental chemical imbalance, there would be a rationale. But we don't know what the chemical imbalance(s) is (are) in bipolar disorder. We don't really know what mood stabilizers do for the illness. Even our guesses hint at diverse possibilities. Thus, valproate seems to have an effect on GABA receptors, and gabapentin may increase brain levels of GABA. In contrast, the proposed mechanism of action for carbamazepine and lamotrigine (Lamictal) is voltage-dependent inhibition of sodium currents. The latest speculations about lithium are that it is affecting G-proteins, that it exerts a push/pull effect on the neurotransmitter glutamate (Dixon and Hokin, 1998; Lenox et al., 1998), or that it alters sodium transport in nerve and muscle cells and effects a shift toward intraneuronal metabolism of catecholamines (Physicians' Desk Reference, 1999).

Diverse research hypotheses are a good thing, but they are not the same as hard knowledge. How can we argue that we are treating at a fundamental, etiological level of the illness when we don't know what the chemical problem is, when our best guesses about how various mood stabilizers work are that they work differently from each other, and when we don't know how these proposed mechanisms might or might not be related? Moreover, we don't have clear proof that we will prevent the eventual development of the DSM-IV illness; even in the treatment of the DSM-IV illness, we don't yet know if we are altering its long-term course. All we do know is that we have good-not great-medications that help control symptoms.

Hagop S. Akiskal, MD, makes the strongest argument for a liberal view of a very broad bipolar spectrum of abnormalities. He believes DSM-IV is far too limiting and would include a bipolar III and a variety of conditions under the bipolar umbrella (Akiskal, 1996; Akiskal and Mallya, 1987). This position is not absurd in the sense that when we eventually understand the genetics and biology of manic-depressive illness, we may discover fundamental relationships. However, DSM-IV is not a true collection of illnesses defined by etiologies. It is a collection of disorders about which committees decide certain symptoms should be clustered with the hope that someday, true etiological understanding will correlate with these clusters or future clusters as the evidence indicates. The issue here is using medications that may only be working on symptoms (and possibly or probably not etiology or pathogenesis) in patients who do not have symptoms as defined by themselves or reasonable laypeople. In Ariel's case, she was suffering from depression and was given a treatment that has not been shown to be effective for depression.
On the risk side of the equation, the danger of unnecessary medication is obvious with carbamazepine because of the possibility of aplastic anemia and agranulocytosis. While this is rare (six patients per 1 million population per year for agranulocytosis and two patients per 1 million population per year for aplastic anemia), if carbamazepine is used by enough psychiatrists over enough years for unjustifiable purposes, there will be deaths that might not have occurred. In the case of valproate, hair loss, weight gain, fatigue and, most recently, the threat of polycystic ovaries, favors caution in a patient such as Ariel. Tiredness and, sometimes, hypersomnia are not uncommon even at therapeutic levels and contribute to treatment noncompliance. A huge number of patients whom I have followed after inpatient stays with an equivocal diagnosis are sleeping 14 hours a day. Of course, it does not help that locally the standard regimen resulting from these hospitalizations seems to also include Zyprexa (olanzapine).

Ariel did have "mood swings." She would be in a perfectly good mood and then suddenly, with relatively minor provocation, switch to sadness, irritability or an outburst of anger. This was the other major justification for placement on a "mood stabilizer." There's only one problem with this. The use of the term mood swings in bipolar disorder has usually referred not to labile affect, but to relatively long stretches of depression or mania lasting weeks or months—although occasionally days—which would then swing to the opposite.

While it is true that mixed episodes are not rare and may be characterized by very rapid shifts in mood over the course of a day, mixed episodes may also consist of a vague blending of both euphoric and dysphoric themes. In any case, until recently, the term, mood swings, did not refer to volatile moods.

Apparently, however, without a discussion in the literature of this changed definition, mood swings have come to mean labile affect. Similarly, rapid cycling-defined in the DSM-IV as four or more switches in a year—not infrequently appears in clinical summaries when what is being described are labile moods.

At first, I thought the problem was our local inpatient unit and a mistaken reading of DSM-IV by one doctor in particular. If that were the case, there would be no reason for this article. It soon became apparent that similar diagnoses were being made at three other inpatient units that I have contact with, including two prominent academic centers. I have questioned several nurses on these wards and learned that most misbehaving, impulsive teen-agers (once characterized as rebellious) are now being diagnosed as bipolar. At an outpatient alcohol rehabilitation center, a counselor told me the same thing was happening there. Erratic moods and behavior were being called mood swings, and thus had become bipolar symptoms. Moreover, the new use of the term mood swings had been embraced by the other psychiatrists in town who were doing strictly outpatient work. Social workers and psychologists were asking, as never before, for medication evaluations for bipolar disorder on the basis of mood swings, and many patients were self-referring themselves for mood swings, having read about them on the Internet.

The typical story I heard when I questioned a patient with mood swings was something like the following: "I'd be in a perfectly good mood at a party but then would feel like going home. When my boyfriend gave me a hard time, I'd let him have it." Or, "I would be doing fine shopping at the supermarket. Suddenly, someone would cut in front of me in line, and I'd go ballistic." Or, "I'd be getting along with my parents at home. Then my father would say something, and I'd go stomping off to my room." Sometimes, there would be no external event at all, but the patient would notice a dramatic shift in mood from when they woke up feeling fine to later in the day when they were feeling down.

Generally, in all of these cases the patients had almost no introspective capacity. They had never attempted on their own, or been encouraged by their psychiatrist, to make sense of the personal meaning of their father's comment, or why their boyfriend made them so angry by refusing to come home from the party and so forth. As far as they were concerned, their behavior was totally incomprehensible and beyond their control. They were relieved to hear that the explanation for their difficulty was a chemical imbalance because, not only would it no longer be their fault, but just as importantly, it could now be fixed.

Undoubtedly, over time, some of the impulsive and/or moody adolescents now being diagnosed bipolar II on the basis of their mood swings will later prove to be suffering from manic-depressive illness. This may turn out to be true of Ariel.

Kramlinger and Post (1996) described clear-cut bipolar patients who were followed on a ward and rated for mood every two hours during the course of a day. They found a group of five patients who went up and down throughout the day and wondered whether these represented "ultra-ultra rapid cycles or ultradian cycling." However, this interesting observation is a far cry from the routine
labeling of volatile patients as bipolar. There is another contributing issue to what I believe is the overdiagnosis of BD. In addition to "mood swings" being used as the basis for diagnosis, irritability has gained new status. It has always been appreciated that irritability, rather than euphoria, can be part of a manic episode. But one would assume that irritability by itself would not be the basis for diagnosing bipolar disorder in an unhappy teen-ager or depressed individual, especially since irritability is found much more commonly in depression than in mania. However, I am discovering that many psychiatrists are using this criterion quite freely, especially with patients who have labile affect, and are basically making the diagnosis on a hunch.

Although the considerations above regarding risk/benefit ratio still apply, ordinarily I would have no difficulty with a clinician following a clinical intuition and diagnosing atypical BD now and again when full criteria were not met. The problem is, if my observation of local practice patterns hold elsewhere, such hunches have become routine, especially in the rapid-turnover inpatient wards that now characterize our mental health system. It has become the diagnosis du jour. Observing practice patterns in Penn Valley, Pa., psychiatrist David Behar, MD, in a letter to Clinical Psychiatric News (1998) described bipolar disorder as being absurdly overdiagnosed. "Any overreacting patient now gets the label and a mood stabilizer," he said.

If this is the case nationally and not just in the Northeast, it is reasonable to look for an explanation. We also must include the pressure on outpatient psychiatrists from referring therapists who themselves are under pressure from health maintenance organizations and mass media articles that foster patient expectations of rapid results. The psychiatrist is placed in a situation not dissimilar to some family doctors who would prescribe antibiotics for the common cold so the patient would feel the doctor "did something." Pressure also comes from the occasional therapist who doesn't like their diagnostic acumen questioned and will refer elsewhere if the patient doesn't receive medication for mood swings. This can be likened to schoolteachers who want their unruly students labeled as having attention-deficit/hyperactivity disorder and Ritalin (methylphenidate) prescribed.

Ultimately, the problem may be language itself. Even when a bipolar diagnosis, per se, is not considered, having a category of drugs called mood stabilizers lends itself quite well to a belief that it is a valid approach to moodiness. In this case, the issue is not whether anticonvulsant, antimanic medications deserve to be called mood stabilizers in bipolar disorder, but rather that the term mood stabilizers conveys the impression that they are a perfect fit for volatile, overemotional patients.

As noted, alcohol and drug abusers are now very often being diagnosed with bipolar disorder, once again because labile affect, a common finding in alcohol and drug abusers, is being called mood swings. One factor contributing to this is our better appreciation of how many bipolar patients abuse alcohol and drugs. However, in the absence of a clear-cut history, I don't know how a bipolar diagnosis can be made until the patient has been off intoxicants for a reasonable period of time. Rapid shifts in mood have always characterized the behavior of alcohol- and drug-abusing patients as well as those recovering from addiction. What is gained by the bipolar label? Some alcoholic patients like it because it "explains" their lack of control. Like genetic theories of alcoholism, it shifts blame and gives an external enemy to fight against. However, these should not be the reasons for us to make the diagnosis.

Mood lability is also an important component of borderline personality disorder (BPD) and here, too, an unusual number of patients are being diagnosed bipolar on the basis of their mood swings. Granted one can legitimately make a case, as Akiskal does, that borderline personality disorder is fundamentally an affective disorder and possibly a variant of bipolar disorder (1996). In the case of BPD, the ravages of this diagnosis are so extreme, and so many of our treatments are ineffective, that I see nothing wrong with trying one of the anticonvulsant medications on an empirical basis. However, in my experience, high doses of selective serotonin reuptake inhibitors seem to work far better for labile affect, probably because of their ability to alleviate frustration and dull passions rather than from an antidepressant action, per se.

To summarize, there are three important questions:
1) Are rapidly shifting moods (now mislabeled as mood swings) particularly diagnostic of bipolar disorder?
2) Are mood-stabilizing medications useful in patients with rapidly shifting moods whether or not they are truly bipolar?
3) What is the mechanism of action of the anticonvulsant medications that make them useful in psychiatric conditions?

Question 1: I do not know if rapidly shifting moods are a typical feature of manic-depressive illness. My clinical impression, after close to 30 years of practice, is that they are not uncommon, both
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Before other symptoms have become manifest and afterward. But rapidly shifting moods are far more common in the instances already discussed: unhappy or rebellious adolescents, alcoholics and drug abusers, and those with borderline personality disorder. Whether the mood changes during the course of a day seen in mixed episodes of bipolar patients constitute ultradian cycling or are simply what typically constitutes mixed episodes has to be settled (Kramlinger and Post, 1996).

Regardless of the outcome of that issue, I think we have to address the separate issue of whether the presence of mood lability should raise our index of suspicion for manic-depressive illness in moody adolescents, borderlines, alcoholics and others with short fuses. (It should be emphasized that Kramlinger and Post's ultradian cycling referred to ratings of mood systematically made every two hours and not sudden mood shifts.)

Questions 2 and 3: Ironically, despite the unfocused use of the term mood stabilizer described earlier in this article, I think clinicians may have found a legitimate use for anticonvulsant medications in psychiatric practice. The literature includes theories that GABAergic mechanisms may play a role in depression (Petty, 1995; Petty et al., 1996). From time to time, various benzodiazepines have been claimed to have antidepressant efficacy. This might be due to the hypothesized fundamental chemical relationship between GABA and mood. Or, it might be an indirect result of their tranquilizing function. After all, patients with panic disorder often develop depression secondary to their lost sense of control and have an improvement in mood once benzodiazepines have put out the fires. Similarly, some patients with agitated depressions experience anxiety as the most distressing part of their syndrome and find their mood improves, even before antidepressants kick in, when benzodiazepines have provided relief from their anxiety.

If there is a fundamental relationship between GABAergic mechanisms and mood, then the use of valproate and gabapentin might eventually be empirically shown to have antidepressant action, and my earlier denigration of the term mood stabilizers would be misplaced. The term would legitimately apply to these anticonvulsant medications in its traditional sense. However, since carbamazepine and lamotrigine are not believed to work through GABAergic mechanisms, and they are mentioned in the same breath with the other mood stabilizers, my best guess is that the quality that anticonvulsant medications have in common is that they are calming agents or tranquilizers. They may represent the long-sought effective, nonaddicting tranquilizers. (There is some support for valproate's anxiolytic-like function in animal research [Dalvi and Rodgers, 1996; de Angelis, 1995].) On an intuitive level, it makes sense that anticonvulsant medicines, whatever their mechanism of action, are calming. Indeed, if we picture seizures as "a massive discharge of neurons," it is not much of a stretch to think of the various psychiatric conditions where anticonvulsant mechanisms are finding particular usefulness-explosive disorder, mania, panic disorder, borderline personality disorder-as conditions that may possibly have analogous massive discharges of nerve impulses. And one step down from that, one could imagine that mood swings, as the term is being used today for those with fiery temperaments, or those caught in the storms of adolescent turmoil, might be attenuated by calming agents, with or without a bipolar diagnosis. In other words, mood stabilizers help mood swings, as the terms are being misused today. Eliminate calling the patients bipolar and not that much harm is done. Valproate may deserve its widespread usage.

We are still left with the question of whether anticonvulsant medications' calming action is necessarily working directly on mood. This question is of some relevance because of the kind of backward reasoning that seems to accompany the effective use of anticonvulsant medications. For example, Stephen J. Donovan, M.D., has proposed that a new diagnosis-explosive mood disorder (EMD)-be created and replace the diagnoses of conduct disorder or oppositional defiant disorder in one subset of patients-children with irritable mood swings-"because these are sociological not psychological constructs. They do not identify what is 'disordered,' suggest etiology or guide treatment" (Sherman, 1998). And what was Donovan's basis for suggesting that the primary difficulty is mood? Adolescents meeting the EMD criteria improved on the mood stabilizer divalproex. Similarly, because such agents as valproate and carbamazepine have been found useful in recovering alcoholics does not necessarily support a view that these patients are probably bipolar. Rather, the patients' improvement might be the result of these agents' tranquilizing function. This kind of thinking is entirely separate from whether or not anticonvulsant medications have an antidepressant action.

Going out on a limb, I would argue that even in bipolar disorder, the various anticonvulsant medications being used to control mania may not be directly treating the elevated mood, per se, but rather treating the intensity of mania, the exuberance of energy, racing thoughts and the like. Just as patients with panic disorder often feel less dysphoric when they regain control through the use of benzodiazepines, it is possible that mood stabilizers could, with chronic administration, be...
demonstrated to have an indirect antidepressant action by returning a measure of self-control, rather than through a direct antidepressant action. Certainly, many patients with BD rue the foolishness of their mania, not to mention the broken marriages, lost friendships and jobs, depleted bank accounts, and sheer havoc left in the wake of their exuberance. Over a period of time, less havoc would serve as one less stressor to precipitate dysphoria and depressive episodes. Also, I have treated several bipolar I (mixed) patients who resembled agitated depressives in their level of anxiety. Although admittedly a small anecdotal sample, my personal impression is that these are the only patients who have shown an antidepressant effect from divalproex. My guess would be that it is the calming effect of the divalproex that was helpful here rather than the antidepressant effect. Otherwise, from pure chance, I would have seen more cases in which the divalproex worked as an antidepressant. Moreover, considering the amount of research done, one would expect by now to see good double-blind evidence of divalproex antidepressant action (rather than the usual "soon to be published" impression) if the effect were a robust one. I am also curious if, within the studies showing that anticonvulsants have an acute antidepressant action (in the range of 30% to 40%), there are data that could be teased out regarding agitation. Did the responding patients have greater amounts of agitation than other depressed patients?

Finally, before we get too excited about "better living through chemistry," a word about mood swings of the adolescent variety. Classic psychoanalytic concepts are more relevant than ever. The vicissitudes of self-esteem regulation in many adolescents are closely linked to the loss of an idealized authority figure (and accompanying culture) from whom they can feel protection and confirmation. As they leave the cocoon of their own family's world and values, they must replace it with a stark and uncertain court governed by peer approval. It is a faddish, unforgiving universe of shifting gurus and uncertain alliances that plays havoc with mood until, with maturity, a more stable identity can be established. This is not to mention the effect of changing hormones, astonishing physical growth and emergence of sexual passion. Medication may have a role to play during this transitional period. But I would hope that psychiatrists have the wisdom to guide parents and children appropriately through this difficult time, and not confuse matters with scary diagnoses such as bipolar disorder and the use of chemicals that work in ways that are poorly understood.

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