



THE UNDISCOVERED ILLNESSES

PSYCHIATRY

HUNDREDS OF THOUSANDS OF PEOPLE EXPERIENCE MANIA WITHOUT EVER GETTING DEPRESSED. WHY DOES PSYCHIATRY INSIST ON CALLING THEM BIPOLAR?

By Simon Makin

Photography by The Voorhes

IN OCTOBER 1997,

at the age of 58, David Ho had an unusual experience while listening to a recording of Bach. “I began to dance and pretended to conduct,” he says. “And as I practiced, instead of following the music, I felt as if I were creating it. I entered into a state of selfless oblivion, like a trance. My mind exploded. Flashes of insight rained down, and I saw beauty everywhere, in faces, living things and the cosmos. I became disinhibited, spontaneous, liberated.”

Ho was in the grips of his first episode of mania. His description sounds like an enviable burst of creative energy, but the symptoms of mania can also include inflated self-esteem, grandiosity, racing thoughts, extreme talkativeness, decreased need for sleep, increased activity or agitation, reckless behavior, delusions and other psychotic events. Severe episodes can impair day-to-day functions, sometimes enough to require hospitalization.

Perhaps the most surprising thing about such cases is that in the eyes of the psychiatric profession, mania does not exist as a distinct and unalloyed condition. Mania is usually known as the upside of bipolar disorder. For most people, it occurs alongside periods of depression, the downside. But Ho, who has had 20 manic episodes since 1997, has never suffered from depression. Thousands of people in the U.S. share that experience. Unlike those who experience only depression, however, patients with mania alone are lumped with those who have bipolar disorder. This puts psychiatry in the strange position of claiming that depression by itself is different from depression accompanied by mania but that mania by itself is not.

Most psychiatrists agree unipolar mania exists, but there is debate about whether it differs sufficiently from bipolar disorder in important enough ways to warrant a distinct diagnosis. Central to that debate is the tension in psychiatry between fewer, broader categories and more numerous, tightly defined ones. But the missing diagnosis may have consequences for patients: some studies suggest that people with unipolar mania may respond differently to certain treatments. If, as some researchers believe, unipolar mania and bipolar disorder differ in their underlying biology, classifying mania separately could speed development of new treatments that are more personalized and effective. But because unipolar mania is far less common than bipolar disorder, research into the condition has been both scant and equivocal.

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As both a patient and a clinical psychologist, Ho is well placed to advance this debate. In 2016 he published a self-study in the journal *Psychosis* cataloguing his symptoms, which include enhanced recall, increased empathy and spiritual experiences. He has suffered some ill effects, including severe fatigue, confusion and behavior that caused concern among friends and colleagues: he once burst into tears while delivering a lecture. But his professional training has helped him control his impulses and avoid delusional thinking. On balance, he believes that his madness, as he calls it, has enriched rather than damaged his life. “I’m aware my case may be atypical,” Ho says. “Precisely for this reason, it challenges prevailing psychiatric beliefs that fail to acknowledge the positive value of mental disorders.”

A MODERN ILLNESS

CREDIT FOR THE MODERN CONCEPT of bipolar disorder usually goes to 19th-century French psychiatrist Jean-Pierre Falret, who called it *folie circulaire*, or “circular insanity,” for its periods of pathologically elevated and depressed moods, usually separated by symptom-free periods of varying length. This idea became gospel in the early 20th century, when a father of modern psychiatry, Emil Kraepelin, proposed a historically significant hypothesis.

At the time, psychiatry drew a distinction between so-called reactive psychoses, which were seen as a response to outside events, and endogenous psychoses, which were innate. Kraepelin divided all endogenous psychoses into two broad classes: dementia praecox—now known as schizophrenia—and manic-depressive insanity, now known as bipolar disorder. Endogenous depression was therefore classed as a form of manic-depressive insanity. All mania also fell under the same rubric because mania was thought never to be a reaction to outside events. There were dissenters, notably the renowned German neurologist Carl Wernicke, who held that mania was related to hyperactivity of neural firing and depression to decreased neural activity. But Kraepelin’s idea dominated and persists in today’s diagnostic system.

The question of what to include under the umbrella of bipolar disorder reignited in 1966. In separate investigations, psychiatrists Carlo Perris of Umeå University in Sweden and Jules Angst of the University of Zurich in Switzerland each studied some 300 patients with either true bipolar disorder or depression alone and more than 2,000 of their close relatives.

IN BRIEF

Mania usually occurs with depressive episodes as part of bipolar disorder. Yet some bipolar patients experience only mania, raising the question of whether another diagnosis is needed.

Evidence to justify separate diagnoses for unipolar mania and bipolar disorder has been elusive, but studies hinting at measurable differences are starting to emerge.

Some researchers recommend defining unipolar mania as an official subtype of bipolar disorder to raise awareness and facilitate further research into what distinguishes it.

Both researchers found that relatives of the bipolar patients had more mood disorders than those of patients with depression alone. They also discovered that although bipolar illness was common in the relatives of bipolar patients, it was no more common in relatives of depressed patients than in the general population. These findings, Perris and Angst argued, suggested that bipolar disorder and depression were genetically different conditions.

As a consequence, when the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*, or *DSM*, appeared in 1980, it included major depressive disorder as a condition distinct from bipolar disorder. Perris and Angst's studies focused only on depression and did not address mania. "There weren't enough cases of pure mania to do anything reasonable," Angst says.

Whether unipolar mania should have its own diagnosis is complicated by bipolar disorder's clinical diversity. The manic and depressive phases vary in severity and the extent that one or the other dominates. The pattern of episodes varies unpredictably and from patient to patient. Mixed states, involving aspects of opposite mood extremes simultaneously, sometimes occur, too. Indeed, many psychiatrists argue that mood disorders are best thought of as lying on a spectrum, ranging from major depression through various bipolar presentations to pure mania.

IN SEARCH OF A SUBTYPE

THE VARIABILITY OF SYMPTOMS, along with findings from large psychiatric genetics studies that implicate numerous biological factors, suggests that bipolar disorder includes a range of subtly different conditions. "One reason we still have limited understanding of bipolar disorder after 50 years of intense research is that it's treated as one entity, and it's clearly not," says psychiatrist Paul Grof of the University of Toronto.

The resistance to subtyping may be the result in part of changes in research funding over the past few decades, as the pharmaceutical industry has taken over progressively more psychiatric research from universities, Grof says. Drug companies generally just want to know if a new drug is better than a placebo, and the larger the patient group, the greater the likelihood of finding a significant difference. Subdividing bipolar disorder into smaller populations would complicate these efforts. The industry also prefers to study diagnoses recognized by the Food and Drug Administration—and unipolar mania is not on its list.

Institutional inertia can also come into play. Every rewrite of the *Diagnostic and Statistical Manual of Mental Disorders* is a laborious process. Each edition is based on the previous one, and any change must be backed by fresh evidence, with papers submitted to committees justifying the decision. The last edition, *DSM-5*, was published in 2013, and in the view of the committee tasked with reviewing mood disorders, unipolar mania was covered by the bipolar diagnosis known as BP-I, which is mania with or without associated depression. "There was very limited discussion as to whether mania should be separate because the onset and course of illness weren't seen as that different from BP-I," says psychiatrist Trisha Suppes of Stanford University, who was a member of the *DSM-5* work group for mood disorders.

The lack of a separate diagnosis may be making evidence harder to gather. The standardized clinical interview used under the *DSM* to make diagnoses for research studies has no category for unipolar mania, meaning investigating the condition would have to rely on ad hoc techniques that might not align with those used

in other studies. Unipolar mania is thus at the hub of a catch-22: the absence of a diagnosis is an impediment to research, and the paucity of research makes creation of a diagnosis less likely.

In studies that do occur, the lack of a formal designation for unipolar mania makes it difficult to compare results. "A major problem is definitions," says Allan Young, a psychiatrist at King's College London. One source of disagreement is the severity of symptoms necessary for a case to qualify as mania. Another is the frequency of episodes. Some studies include anybody who has had at least one episode of mania with no history of depression, whereas others require three or four. Still others stipulate a minimum number of years of illness. These differences have led to widely disparate prevalence estimates for unipolar mania, ranging from 1.1 to 65.3 percent of bipolar patients.

Most of the studies completed so far also have methodological problems. The bulk are retrospective, in which researchers simply ask participants to recount past experiences—a process known to underestimate depression, perhaps inflating estimates of pure mania. Prospective studies that follow patients for years and include periodic assessments are better. "What you really want is someone who's lived their whole life, had multiple episodes of mania, and never had depression," Young says. "The first lady I saw like this died in her late 60s and had her first episode at 21, which is getting on for 50 years, so that's very convincing."

One of the longest prospective studies, led by David Solomon, now at the Warren Alpert Medical School of Brown University, began in 1978 and was published in 2003. It began as a study of 229 bipolar patients, 27 of whom had mania with no history of depression. The investigators followed those 27 patients for up to 20 years; seven of them remained free of depression throughout the period. The results suggest that of the original 229 patients, 3 percent had unipolar mania. Solomon does not advocate the creation of a separate diagnosis for unipolar mania unless future research establishes differences in genesis, prognosis or treatment response. But if the rate reported in the study held for the general population, the number of people with unipolar mania in the U.S. would be around 100,000—and hundreds of thousands more worldwide.

The stories of people with unipolar mania help to explain why some researchers are convinced that the disorder is a separate entity. Lindsey, a ski coach from Portland, Me., is one such case. She was 18 when she had her first experience of mania. At 36, she has never been depressed, yet she still has a diagnosis of bipolar disorder. "I'm the happiest person I know," she says. "I never accepted my diagnosis." As a result, she rejected treatment and continued to have episodes. She has been hospitalized five times and has landed in jail more than once.

Lindsey's episodes start with euphoria but can spiral into delusions and difficulty speaking. While manic, she feels no fatigue, hunger or pain. One such episode, in her late 20s, began on a hike in New Mexico when she was overcome by a vision that the world was coming to an end. Lindsey called her father, who flew out to meet her and drive her home to Maine. "She had medication," her father says. "She just wasn't taking it." Early in the morning on an overnight stop in Nashville, Lindsey started playing the piano in the hotel lobby. An employee called the police, and Lindsey fled in the car.

In the adventure that followed, she deliberately got lost, buried her possessions near a railroad track and abandoned the car. She then hopped a freight train, got off in the middle of rural Tennes-

see, climbed out of a rock-walled valley and wandered into a chapel, where the pastor was able to glean enough information to contact her family. Shortly after resuming the drive home, Lindsey ran away from her father at a highway rest stop and started picking daisies in a fenced-off electrical area. The police were called again, and although the officer urged her to leave with her father, she insisted on being arrested.

In her cell, a guard pepper-sprayed her, and she ended up in the office of the jail's counselor. Lindsey was barely able to speak at this point, but she wrote "unipolar" repeatedly on a blackboard. The counselor then read Lindsey a description of mania. She credits this encounter as the moment she accepted the need to take medication. The counselor gave her Zyprexa (olanzapine), an antipsychotic. She recovered and takes it to this day, though not without reservations. "My medication is like a dose of sadness, hunger, fatigue and pain," she says. Lindsey was euphoric throughout her ordeal, even while being pepper-sprayed. Only the people around her suffer. "I feel like I've been blessed with this illness that makes me so happy," she says, "but I feel selfish because of how it affects my family."

Lindsey married Andy, a journalist, in 2015, not long after he witnessed her last hospitalization. "It made the relationship stronger in the end," he says. "I got to see her as she clawed her way back to sanity. It was impressive." The most important factor in her treatment is whether a physician accepts that she is not bipolar. "When that's ignored, she no longer trusts that person," Andy says.

IT ALL GETS REAL

A CURIOUS QUIRK in the tale of this neglected disorder is that prevalence estimates vary worldwide and are consistently higher in non-Western countries. After qualifying in South Africa in 1997, psychiatrist Christoffel Grobler worked in an inpatient unit in Ireland, where his bipolar patients were mostly in depressed states. When Grobler returned to South Africa in 2009, he noticed the opposite pattern: his patients were mostly in manic states. To investigate, in 2010 he and his colleagues interviewed 103 bipolar patients in three hospitals, using a standard diagnostic questionnaire. They found that 32 percent of patients qualified as unipolar, defined as having at least five manic episodes over four or more years. "When I present this at conferences, people come up and say, 'We see this all the time,'" Grobler says.

Regional variations are tricky to interpret because cultural differences come into play: depression is more likely to be considered part of normal life in Africa, for example. The quality and procedures of health care systems differ, and other causes, including infection or intoxication, may be a factor. But Grobler is convinced the geographical differences are genetic in origin and that unipolar mania therefore represents a distinct condition.

Getting to the bottom of this question will require large, multicultural international studies. In the meantime, scientists are try-

Psychic Fuel for the Creative Brain

The mad genius may be more than a cliché

Of all the tropes of artists and mental afflictions, the most enduring is the one of a genius in the throes of mania. Iconic figures ranging from William Blake to Ernest Hemingway to Kurt Cobain were known or believed to be bipolar. The association has intuitive appeal: the euphoria, abundant energy and racing thoughts of mania are credible fuel for creativity.

Scientific evidence for the association has mostly been inconclusive. Much of the data comes from historical sources, and most accounts are anecdotal. Modern investigative techniques have revealed surprisingly little about what happens in the brain during mania, partly because brain imaging requires minimal head movement, so scanning someone in a floridly manic state is a challenge. As a dynamic process involving the interplay of multiple brain networks, creativity is also difficult to research.

But comparing findings from research into bipolar disorder with certain studies of creativity reveals hints of a link: cognitive "disinhibition" seems to be a feature of both the creative state described as being in the "flow" and altered brain circuits in bipolar disorder.

Brain-imaging studies have found reduced activity in a part of the prefrontal cortex that helps to regulate emotion, which may be linked to impaired impulse control and extremes of mood in bipolar patients. (The prefrontal cortex is the brain's "orchestra conductor" responsible for directing various mental processes.) Some of these studies have also found diminished activity in an area involved in suppressing the kind of spontaneous thought that appears to well up from the unconscious, seemingly out of nowhere.

These results are reminiscent of a 2008 study of improvising jazz musicians and a 2012 study of freestyling rappers, conducted by the team of speech neuroscientist Allen Braun, then at the National Institutes of Health, which found reduced activity in the part of the prefrontal cortex that inhibits spontaneous cognition. They also found an increase in activity in a section of the prefrontal cortex that is part of the so-called default mode network, which revs up when a

ing to compensate for a shortage of data. One reason most early studies failed to find differences between mania and bipolar disorder may be that they are so slight that they can be reliably detected only in large samples. Although he is now in his 90s, Angst has recently tried to address this problem by consolidating data from nine epidemiological studies conducted in the U.S., Germany, Switzerland, Brazil and Holland. That study, published online last November in *Bipolar Disorders*, found that people with unipolar mania were more likely to be male but less likely to have attempted suicide or to suffer from anxiety, drug use and eating disorders. Angst and his colleagues claim these findings suggest unipolar mania "should be established as a separate diagnosis."

Some of these studies align with three reviews of research on unipolar mania published in the past five years. All three found that unipolar mania is less likely to co-occur with anxiety (which often accompanies depression) but more likely to come with psychotic symptoms. Unipolar mania also seems to confer less social impairment and involve fewer recurrences and better remission rates than bipolar disorder.

Perhaps most important, people with unipolar mania show subtle differences in their response to drugs administered as part

person is not focusing on a task but is rather imagining things or ruminating on the past. The researchers believe what they observed reflects relaxation of focused attention and control, making way for a creative thought process in which inspiration bubbles up from the unconscious. Other studies have found reduced thickness of certain cortical regions in both creative and bipolar brains, which may be linked to altered brain activity and disinhibited cognition.

Another element in the thinking patterns of creative and manic people is the ability to make mental connections that elude others. Neuroscientist Nancy Andreasen of the University of Iowa has found that creative people show greater activity in the so-called association cortices, which are regions tasked with linking related elements of cognition. These brain areas are not devoted to processing specific sensory or motor functions but instead with tasks such as tying together a written word with its sound and meaning. Andreasen believes creative ideas probably occur when these types of associations occur freely in the brain during unconscious mental states, when thoughts become momentarily disorganized—not unlike psychotic states of mania.

This observation resonates with clinical psychologist David Ho, who has experienced racing thoughts and extraordinarily enhanced recall during manic episodes, letting him write without inhibition or self-doubt. “With repression vanished, my mind functioned with holistic oneness,” he says. “Creative ideas rained down faster than I could cope.” Researchers do not know if the association cortices are more active in mania, but all these findings suggest that at key moments of the creative process, our thought processes flow more freely, with novel combinations of sights, sounds, memories, meanings and feelings producing insight and originality in creative work akin perhaps to what happens during mania.

Of course, mental illness is neither necessary nor sufficient for creative talent, and severe manic episodes most likely are too debilitating for any kind of sustained activity. But researchers have found that family members of people with bipolar disorder also tend to be more creative than average, supporting the idea that mild manifestations of the disorder may furnish cognitive benefits.

It is important not to romanticize conditions that mainly cause suffering, but evidence that mania can enhance creativity in some people may help reduce the stigma of a diagnosis. “It is possible to retain a measure of madness in dignified living,” Ho says, “and of dignity even in a state of madness.” —S.M.

of preventive treatment. Three studies have found that unipolar mania patients respond less well to lithium (a mood stabilizer and first option for bipolar) than true bipolar disorder patients do.

The most recent of these studies, published in 2012 by Olcay Yazici and Sibel Cakir, both at Istanbul University, also examined the question of whether unipolar mania is merely bipolar disorder weighted to the manic end of the spectrum—so-called dominant manic polarity. They divided 121 patients into two groups, 34 with unipolar mania and 87 with classic bipolar disorder. As the earlier studies found, the unipolar group had a lower response rate to lithium, and their response to another frontline bipolar treatment, the anticonvulsant Depakote (divalproex sodium), was no different.

The researchers next grouped all 121 patients according to whether the majority of their episodes were manic or depressive and then created a further division of patients whose manic episodes accounted for at least 80 percent of the total. A smaller percentage of patients who had at least a majority of manic episodes responded to lithium than patients who had more depressive episodes did, and this difference was greater for patients whose mania put them in the 80 percent group. Most tellingly, when those

with unipolar mania were excluded from this analysis, these differences disappeared, suggesting the treatment difference relates to unipolar mania, not to dominant manic polarity, implying that unipolar mania is its own entity.

THE WAY AHEAD

THOSE WHO OPPOSE a separate diagnosis sometimes point out that the mania in unipolar mania is indistinguishable from that in bipolar disorder. But the same is true of depression, and many studies have found differences in the brains of people with major depression and those with bipolar disorder. Future work that compares brains of people with unipolar mania and bipolar disorder might be just as revealing.

Biological and brain-imaging studies of unipolar mania are rare. But one from a quarter of a century ago gives clues to differences in physiology. A 1992 CT scan study led by Sukdeb Mukherjee of the Medical College of Georgia at Augusta University found that unipolar mania patients had smaller third ventricles (one of four interconnected cavities in the brain that let cerebrospinal fluid flow) than bipolar patients did. This result is intriguing because subsequent studies found that bipolar patients who experienced multiple episodes have larger ventricles than people experiencing their first episode or healthy control subjects, a hint that enlarged ventricles may be linked to pathology. The implication that unipolar mania may not cause as much damage in the brain tallies with the better outcomes associated with the condition.

Creating a separate diagnosis for unipolar mania remains controversial. An interim step would be to recognize it as an official subtype of bipolar disorder. Such a move might encourage

research and raise awareness among clinicians. “There’s a mystery here we don’t understand: Why do some people get mania and then depression, whereas others stay unipolar manic?” Suppes asks. “It’s deserving of more research than it’s gotten so far.” Further investigation might also benefit patients who do not identify with other labels. Lindsey pleads, “The most important thing my doctor could do for me is say, ‘I’m sorry, we were wrong—you’re not bipolar, you’re unipolar.’” ■

MORE TO EXPLORE

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