

Impulsivity in Mania

Alan C. Swann, MD

Corresponding author

Alan C. Swann, MD
Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, 1300 Moursund Street, Room 270, Houston, TX 77030, USA.
E-mail: alan.c.swann@uth.tmc.edu

Current Psychiatry Reports 2009, 11:481–487

Current Medicine Group LLC ISSN 1523-3812

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Impulsivity, a breakdown in the balance between initiation and screening of action that leads to reactions to stimuli without adequate reflection or regard for consequences, is a core feature of bipolar disorder and is prominent in manic episodes. Catecholaminergic function is related to impulsivity and mania. Manic individuals have abnormal dopaminergic reactions to reward and abnormal responses in the ventral prefrontal cortex that are consistent with impulsive behavior. Impulsivity in mania is pervasive, encompassing deficits in attention and behavioral inhibition. Impulsivity is increased with severe course of illness (eg, frequent episodes, substance use disorders, and suicide attempts). In mixed states, mania-associated impulsivity combines with depressive symptoms to increase the risk of suicide. Clinical management of impulsivity in mania involves addressing interpersonal distortions inherent in mania; reducing overstimulation; alertness to medical-, trauma-, or substance-related problems; and prompt pharmacologic treatment. Manic episodes must be viewed in the context of the life course of bipolar disorder.

Introduction

Impulsivity is clearly a prominent part of mania. The diagnostic criteria for mania require behavior without regard to its consequences as well as specific types of financial and other indiscretions that generally are considered impulsive. One of the most severe problems faced by manic patients is the fear of a loss of control that is a pervasive part of impulsivity [1]. The challenges of treating manic patients and supporting their caregivers or allies are strongly related to the problems posed by this impulsivity.

This article focuses on results of recent work on impulsivity in mania in the context of previous key findings. We discuss impulsivity in terms of the neurobiology of mania, the behavioral mechanisms of impulsivity, the

role of impulsivity in clinical characteristics of manic episodes, and characteristics of patients that contribute to clinical problems related to impulsivity. For each topic, we briefly summarize relevant background information and then review the results of studies conducted over the past year. In considering impulsivity in mania, we take the following points into account:

- Not all problematic behavior in mania is impulsive. Some is planned but highly inappropriate because it is based on grandiosity or other affective and cognitive distortions.
- Manic episodes cannot be viewed in isolation from the lifelong illness of bipolar disorder that generates them.
- The time course of impulsivity involves an interaction between impulsivity as a stable trait and factors that influence the expression of that trait at a given time. Trait impulsivity is high in bipolar disorder, but its behavioral expression varies considerably.

Neurobiology of Mania

Mania is associated with increased turnover of dopamine and norepinephrine [2]. The increase in norepinephrine correlates with severity of mania but reverts toward normal with successful treatment of mania [2]. Noradrenergic activation, such as with severe stressors, impairs function in the prefrontal cortex, potentially leading to impulsivity [3]. Interestingly, sleep deprivation, which is prominent in mania, also increases impairment of response inhibition, a basic component of impulsivity [4]. Drugs that increase norepinephrine increase impulsivity in healthy humans in parallel with increased behavioral activation [5]. These findings are consistent with the parallel increases in impulsivity and norepinephrine also reported in manic states [2].

Dopaminergic function is also increased in mania [2]. Dopamine can increase impulsivity as a result of its role in motivation and the initiation of action [6]. Serotonin depletion in rats only increases impulsivity if dopamine is intact, so impulsivity over time may reflect a balance between dopamine and serotonin [7]. Acute changes in norepinephrine superimposed on the balance between dopamine and serotonin may therefore underlie acute changes in the expression of impulsivity during manic episodes.

The prominent increase in goal-directed activity during manic episodes may represent abnormal sensitivity of reward systems. Dopamine has a prominent role in reward systems and, through its involvement in initiation of motor activity, impulsivity. Interestingly, patients with Parkinson's disease, possibly through dopaminergic hypersensitivity, have increased susceptibility to impulse control disorders [8]. Functional MRI showed that in manic individuals, responses to receipt or to omission of rewards were abnormal in dopaminergic regions, including ventral tegmentum (expectation of reward) and nucleus accumbens (receipt vs omission of rewards), compared with individuals with schizophrenia and healthy controls [9]. These findings were consistent with behavioral characteristics of mania, in which patients pursue goals that are unrealistic and ignore evidence that they should not do so.

In a recent study using postmortem brains of individuals with unipolar and bipolar disorder who died from suicide compared with normal controls, immunoactivity for the synthetic enzymes for norepinephrine and serotonin synthesis was lower in the locus coeruleus in those with bipolar disorder compared with unipolar suicide victims or controls [10]. Although the individuals were considered depressed at the time of death (there are no data about the possibility of mixed states) and there was no comparison group of individuals with bipolar or unipolar disorders who were not suicide victims, the results suggested abnormal serotonin–norepinephrine interactions in bipolar disorder.

Mechanisms and Time Course of Impulsivity in Bipolar Disorder

Impulsivity can be defined as a “predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences” [11]. Impulsive behavior can be destructive and include impulsive aggression [12], impulsive suicide attempts [13], and other rapid, unplanned acts with severe long-term consequences. Impulsivity reflects poor regulation of the initiation of action and involves responses to stimuli that occur before conscious awareness of the stimuli. Normal responses require a balance between initiation and inhibition of action [14]. Impulsive behavior occurs when this balance fails, with excessive spontaneous behavior or stimulation (eg, mania) or deficient screening of potential behavior (as in frontal lobe trauma [15]), thus increasing the probability of action without conscious reflection. Impulsivity, which is prominent in bipolar disorder, is increased in mania [16,17]. Impulsivity confers increased risk of rapid behavioral responses with severe consequences, including aggression, financial and social indiscretions, and suicide [13,18].

Models of impulsivity

Two models of impulsivity—derived from studies in animals—provide the basis for clinical measures of impul-

sivity and for potential pharmacologic treatments. Rapid response or response inhibition impulsivity is based on responding without “reflection” or adequate screening of the situation [19]. This model requires a filtering or screening function—served by the amygdala, prefrontal cortex, and other structures—and can be assessed with continuous performance, go–no go, or stop-signal tasks [20]. Reward delay or delay discounting impulsivity is based on preference for a small immediate reward over a larger delayed one, an exaggeration of the normal decrement in value of a future reward with increased delay [19]. Tests comparing preference for rapid versus delayed rewards are highly validated measures [20].

Complementary to these measures of response inhibition, questionnaires measure impulsivity as a stable trait characteristic integrating behavioral and cognitive aspects of impulsivity with their consequences. High “trait” impulsivity may be most likely to result in overt impulsive behavior in situations such as mania, stressors, or sleep deprivation, when catecholamine function is increased or poorly regulated. The Barratt Impulsiveness Scale (BIS-11) identifies three factors associated with impulsivity as an enduring characteristic: attentional impulsivity, or lack of cognitive persistence with inability to tolerate complexity; motor impulsivity, or acting on the spur of the moment; and nonplanning impulsivity, or lack of a sense of the future (or the past) [21]. The BIS-11 provides information on the potential for impulsive behavior [21].

Impulsivity as an enduring characteristic, with its highly variable expression depending on the situation and affective state, is especially prominent in bipolar disorder, in which impulsivity may be increased as a stable characteristic but is most prominently expressed during manic episodes. We have shown that individuals with bipolar disorder had increased BIS-11 scores whether they were euthymic or manic, but response inhibition was more impaired during mania [16] and correlated with manic symptoms in individuals not experiencing full manic episodes [22].

State-trait relationships of impulsivity are complex in bipolar disorder. BIS-11 impulsivity scores were increased differentially in different affective states, with increased motor and attentional impulsivity in mania and increased attentional and nonplanning impulsivity in depression [17]. Motor impulsivity correlated significantly with Mania Rating Scale scores, especially visible hyperactivity. These apparently state-related differences were much smaller than the very large differences between individuals with bipolar disorder and healthy controls [23], with BIS-11 scores further increased in those with a history of substance use disorders, frequent episodes, or suicide attempts.

In terms of specific mechanisms of impulsivity, response inhibition, including rapid response and delayed reward tasks, was impaired during mania [24]. These increases were most severe in individuals with a recurrent and complicated course of illness [25]. Impulsive responses were accelerated in those with severely recurrent course of illness, substance use disorders, or suicide attempts [25].

Impulsivity can short-circuit conscious decision making, and deficits in the two processes can be distinguished. A study of decision making in bipolar disorder used the Iowa Gambling Task, which was analyzed in a way that disentangled impacts of rewards, punishments, sizes of payoffs, and response consistency. As would be expected with increased impulsivity, response inconsistency was the factor that most strongly identified individuals with bipolar disorder [26].

Impulsivity and brain function in mania

Recent studies have explored the time course of specific aspects of impulsivity in bipolar disorder and their relationships to brain function. A functional MRI study in mania—using a test of motor inhibition—showed that response inhibition was associated with lack of engagement of the ventrolateral prefrontal cortex, which normally suppresses irrelevant responses [27••]. These recent results, combined with earlier work, show the following:

- Bipolar disorder is associated with increased potential for impulsivity regardless of clinical state.
- This involves all major mechanisms of impulsivity, including the inability to respond to a stimulus before evaluating it and the inability to delay response for a larger reward.
- Impulsivity is more severe in patients with an extremely recurrent course of illness, early onset, or comorbid substance use or anxiety disorders.
- The behavioral expression of this impulsivity is increased during mania.

Clinical Characteristics of Episodes: Mixed States

The components of manic behavior may combine with components of depression in bipolar disorder to produce mixed states. These combinations have been reported for hundreds of years and seem to be associated with a generally severe form of bipolar disorder. Coexisting manic and depressive symptoms are associated with worse course of illness, including severity of recurrence and comorbidities [28] and whether the episode is predominantly manic [29] or depressive [22•].

Depression during mania

Mixed states are associated with increased prevalence of substance use and anxiety disorders and thus have the potential for more severe impulsivity than nonmixed mania. Efforts to classify manic episodes generally have yielded results suggesting that the current classification systems for mixed states, both the *DSM* and *ICD*, are excessively rigid. They also have found manic subtypes including “classic” mania without mixed features, mania with prominent depressive features and a generally worse course of illness, mania with prominent psychosis, and mania with prominent behavioral problems usually including irritability or hostility that even exceeds the typical severity in mania; increased impulsivity cut across all these subtypes [30,31]. In susceptible individu-

als, the risk for mixed states may increase over the course of illness [32]. Once established, however, the pattern of manic subtypes may be stable within individuals [33]. The course of illness of patients susceptible to mixed manic episodes suggests that they have increased trait-related impulsivity, with substance use disorders and similar problems even when they are not manic [28].

Mania during depression

Current diagnostic classifications omit the fact that subsyndromal manic symptoms can be present during depressive episodes. Mania is accompanied by increased impulsivity even when prominent depression is also present. During depressive episodes, impulsivity (either BIS-11 score or rapid response impulsivity) correlates with manic symptoms and a more recurrent course of illness [22•]. A recent review of mixed depressive states (primarily depressive episodes with subsyndromal manic symptoms) reported a developing consensus that patients who have more than two or three manic symptoms during a depressive episode are different from those who do not in terms of course of illness, clinical characteristics, and family history [34]. Clinicians must show increased awareness of this important clinical phenomenon when evaluating patients [35]. A recently completed study of 1380 individuals with bipolar depressive episodes confirmed that subsyndromal manic symptoms during depressive episodes could be easily overlooked and were associated with a more recurrent and complicated clinical course of illness and increased substance use disorders and other problems generally associated with increased impulsivity [36•].

Treatment-induced mania

Manic episodes can be precipitated (or can appear to be precipitated) by many pharmacologic agents, including antidepressive agents, other medical treatments, and drugs of abuse. This phenomenon even occurs in patients previously thought to have unipolar disorder [37]. Pharmacologic mania is an example of a more general phenomenon: substance-induced activation. Consistent with a correlation between manic symptoms and impulsivity during predominantly depressive episodes, this can increase the risk of suicide and other impulsivity-related behavioral problems and may be more common if a personality disorder is also present [38]. These results show the following:

- Mania can be combined with depression and/or anxiety.
- Impulsivity correlates with severity of manic symptoms, even in patients who are also depressed.
- This combination of impulsivity and depression can have serious behavioral consequences, including increased risk for suicide.
- Patients at risk for mixed states tend to have a more complicated course of illness, with comorbidities that can add to the complexity of their manic episodes and that can be associated with increased impulsivity and severe problems, even between episodes.

Complications Related to Impulsivity Violence

Manic episodes can be associated with increased aggressive behavior, much of which is impulsive. As with other psychiatric disorders, the likelihood of aggression is increased in the presence of substance use disorders and in individuals with previous—especially recent—aggressive behavior [39]. Diagnosis of personality disorder, but not of psychotic disorder, is related to increased risk of aggressive behavior [40]. A large prospective study ($n = 34,653$) confirmed that psychiatric disorder per se did not predict violent behavior but that a coexisting substance use disorder, along with other risk factors, including previous arrest, juvenile detention, or parental arrest, was associated with violent behavior [41•]. This study did not focus specifically on individuals who were manic.

Suicide

Suicidal behavior is not increased in pure mania but is increased in manic episodes with concurrent depressive symptoms [42]. Laboratory-measured impulsivity is associated with increased history of severe suicidal behavior [18]. Therefore, manic symptoms during depressive episodes may increase impulsivity and suicide risk.

Reinforcing the importance of impulsivity and activation in suicidal behavior, a study of 127 military personnel with suicidal behavior showed that severity of hypomanic symptoms—and not personality disorder—predicted subsequent suicidal behavior [43]. The presence of a substance use disorder increased the risk of suicide attempts; this risk was associated with increased aggression and impulsivity [44]. After the first manic episodes, severity of suicidal behavior was related to the presence of a mixed state [45•]. Consistent with the role of combined depression and impulsivity in suicide risk, a prospective 18-month study showed that the incidence of suicide attempts was twice as high among individuals with mixed states (combined predominantly depressive and predominantly manic) as it was in those with pure depressive episodes [46••].

Medical complications

A host of medical conditions can cause or contribute to manic episodes, including neurologic, collagen vascular, metabolic, infectious, and toxic disorders; manic episodes can also exacerbate preexisting medical problems [47].

Psychiatric disorders, especially major depressive disorder and bipolar disorder, are associated with increased cardiac morbidity and mortality stemming from a combination of increased high-risk behavior (eg, smoking) and other more disease-specific characteristics [48]. In addition, manic/hypomanic symptom burden over time, probably as a result of sympathetic nervous system activation, was significantly associated with cardiovascular mortality in a 25-year prospective study [49•]. Cardiovascular mortality in individuals with bipolar I disorder was twice that seen in those with bipolar II

disorder. Furthermore, acute behavioral changes during mania, especially impulsive behavior, are associated with increased incidence of high-risk behavior for HIV [50].

The high prevalence of substance or alcohol use disorders, especially in patients susceptible to mixed states, can add to the medical complexity of manic episodes. Even when it is not the only precipitating factor, substance intoxication or withdrawal can contribute to manic episodes and/or be masked by them.

Comorbid Conditions

Anxiety and personality disorders

Anxiety disorders are common in bipolar disorder and are associated with increased impulsivity and more severe course of illness, including greater likelihood of mixed episodes, compared with patients without comorbid conditions [51]. The increased activation and arousal of anxiety may predispose individuals to impulsivity [52].

A large epidemiologic study showed that in women, the lifetime prevalence of substance use disorders was increased in those with bipolar disorder who also had anxiety disorders [53]. Anxiety disorders were also associated with increased prevalence of mixed states and legal problems [53], increased risk of suicidal behavior [54], and poor treatment outcomes [55]. Anxious individuals with bipolar disorder had higher BIS-11 scores, which was consistent with many of the clinical problems associated with anxiety in bipolar disorder [56].

Substance use disorders

Most patients with bipolar disorder have also met diagnostic criteria for a substance or alcohol use disorder [57]. Substance use disorders carry an increased risk for mixed states [28]. Impulsivity is increased synergistically in patients with both disorders, including an increase in measures of impulsivity that are usually elevated only during manic episodes [16].

Cognitive consequences of substance use disorders and impulsivity overlap in bipolar disorder. Patients with bipolar disorder combined with an alcohol use disorder had more severe impairments in executive function, verbal and visual memory, and fluid intelligence [58]. A recent study showed that impulsivity could be distinguished from risk-taking behavior and that risk-taking behavior was increased in individuals with bipolar disorder combined with alcohol abuse or dependence [59]. These results show the following:

- Concurrent psychiatric and medical problems are common in bipolar disorder and can contribute to the onset and complexity of manic episodes.
- Manic symptoms may be associated, over time, with increased cardiac morbidity and mortality, probably as a result of increased catecholaminergic activation.
- Anxiety is a prominent problem in bipolar disorder and is associated with increased impulsivity and mixed states.

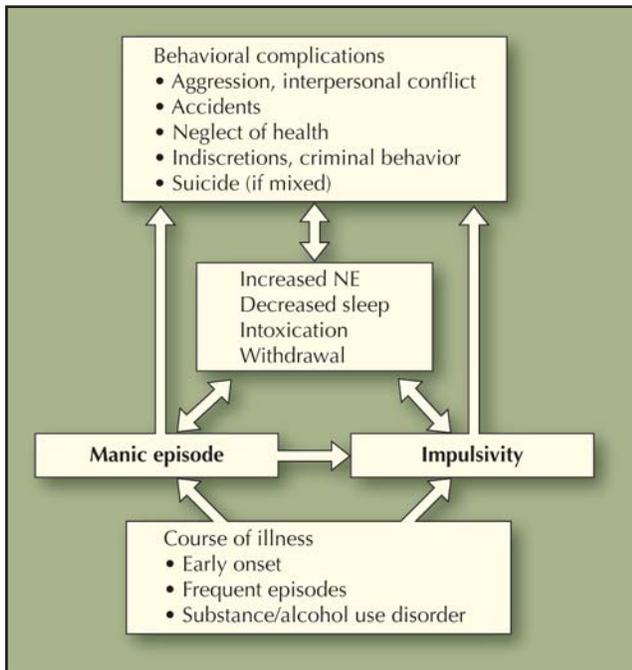


Figure 1. Summary of interactions between mania and impulsivity. Consequences of increased impulsivity in manic episodes contribute to greater impulsivity and to worsening of the episode. Previous course of illness increases impulsivity and the probability of future episodes. NE—norepinephrine.

- Substance use disorders are common in bipolar disorder, increase both state- and trait-like impulsivity, predispose individuals to mixed states, are associated with increased frequency and severity of recurrence, and can add to the complexity of manic episodes via effects of substance/alcohol intoxication or withdrawal.

Treatment Implications

Impulsivity during manic episodes is treacherous because it is combined with increased energy and goal-directed hyperactivity. The attendant fear of loss of control leads to interpersonal distortions and easy provocation to violence [1]. Little information exists about specific treatment effects on impulsivity in mania, largely because impulsivity is so pervasive in mania that it may be difficult to distinguish effects that are specific to impulsivity from those on mania in general. A factor analysis of manic behavior showed that impulsivity was reduced by successful pharmacologic treatment [60].

Management of impulsivity in manic episode requires a combination of nonpharmacologic and pharmacologic strategies. Potentially activating treatments, including antidepressive agents and stimulants, generally must be discontinued, and physicians must be alert for the possibility of stimulant intoxication or sedative or alcohol withdrawal. The potential for impulsivity can be reduced by controlling overstimulation and by maintaining consistent, structured interactions between the patient and all treatment personnel. Inconsistent behavior can exacerbate the fear of loss of control and lead to escalation [1].

Principles include the following:

- Maximizing predictability and reducing overstimulation
- Reasonable, strict, and consistent interpersonal boundaries
- Vigilance for medical problems, either preexisting or generated by the manic episode, including trauma from fights or accidents resulting from impulsivity
- Pharmacologic treatment that reduces overstimulation and hyperactivity.

Conclusions

Impulsivity, a central component of mania, is related to the increased catecholamine output that is associated with manic episodes. Impulsivity also links characteristics of manic episodes to the life course of illness. Figure 1 summarizes interactions among mania, the course of illness, and impulsivity. Manic episodes lead to increased impulsivity, largely as a result of increased catecholaminergic function. Behavior during the episode, including substance abuse, increases impulsivity further. Recurrent manic episodes are associated with increased impulsivity, even between episodes, and greater risk for subsequent episodes. In summary:

- State-dependent increases in impulsivity during mania are associated with increased norepinephrine.
- Mania, with increased norepinephrine release and impulsivity, can combine with depression.
- Both trait- and state-dependent impulsivity are increased with severe course of illness, including recurrence, early onset, and substance use disorders.
- Treatment of manic episodes requires nonpharmacologic and pharmacologic mechanisms that address impulsivity, uncontrolled goal-directed hyperactivity, and fear of loss of control.

Disclosure

Dr. Swann has served as a consultant for AstraZeneca, Pfizer, Bristol-Myers Squibb, and Sanofi-Aventis and as a speaker for Sanofi-Aventis, Abbott Laboratories, and AstraZeneca.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. Janowsky DS, Leff M, Epstein RS: **Playing the manic game: interpersonal maneuvers of the acutely manic patient.** *Arch Gen Psychiatry* 1970, 22:252–261.
 2. Swann AC, Koslow SH, Katz MM, et al.: **Lithium carbonate treatment of mania. Cerebrospinal fluid and urinary monoamine metabolites and treatment outcome.** *Arch Gen Psychiatry* 1987, 44:345–354.

3. Arnsten AF: Stress impairs prefrontal cortical function in rats and monkeys: role of dopamine D1 and norepinephrine alpha-1 receptor mechanisms. *Prog Brain Res* 2000, 126:183–192.
 4. Acheson A, Richards JB, de Wit H: Effects of sleep deprivation on impulsive behaviors in men and women. *Physiol Behav* 2007, 91:579–587.
 5. Swann AC, Birnbaum D, Jagar AA, et al.: Acute yohimbine increases laboratory-measured impulsivity in normal subjects. *Biol Psychiatry* 2005, 57:1209–1211.
 6. Evenden JL: The pharmacology of impulsive behaviour in rats II: the effects of amphetamine, haloperidol, imipramine, chlordiazepoxide and other drugs on fixed consecutive number schedules (FCN 8 and FCN 32). *Psychopharmacology (Berl)* 1998, 138:283–294.
 7. Harrison AA, Everitt BJ, Robbins TW: Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. *Psychopharmacology (Berl)* 1997, 133:329–342.
 8. Weintraub D: Dopamine and impulse control disorders in Parkinson's disease. *Ann Neurol* 2008, 64(Suppl 2): S93–S100.
 9. Abler B, Greenhouse I, Ongur D, et al.: Abnormal reward system activation in mania. *Neuropsychopharmacology* 2008, 33:2217–2227.
- This investigation of brain activation in response to anticipation, receipt, and omission of rewards, which compared individuals with mania or schizophrenia with healthy controls, showed that manic patients did not exhibit the normal pattern of brain activation upon receipt versus omission of rewards compared with healthy controls. The results were consistent with abnormal function of the dopamine system in mania, especially nucleus accumbens, contributing to disinhibition and abnormal goal pursuit regulation.
10. Wiste AK, Arango V, Ellis SP, et al.: Norepinephrine and serotonin imbalance in the locus coeruleus in bipolar disorder. *Bipolar Disord* 2008, 10:349–359.
 11. Moeller FG, Barratt ES, Dougherty DM, et al.: Psychiatric aspects of impulsivity. *Am J Psychiatry* 2001, 158:1783–1793.
 12. Virkkunen M, Linnoila M: Brain serotonin, type II alcoholism and impulsive violence. *J Stud Alcohol Suppl* 1993, 11:163–169.
 13. Mann JJ, Waterman C, Haas GL, Malone KM: Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry* 1999, 156:181–189.
 14. Barratt ES, Patton JH: Impulsivity: cognitive, behavioral, and psychophysiological correlates. In *Biological Basis of Sensation-Seeking, Impulsivity, and Anxiety*. Edited by Zuckerman M. Hillsdale, NJ: Lawrence Erlbaum Associates; 1983:77–116.
 15. Bechara A, Damasio H, Tranel D, Damasio AR: Deciding advantageously before knowing the advantageous strategy. *Science* 1997, 275:1293–1295.
 16. Swann AC, Dougherty DM, Pazzaglia PJ, et al.: Impulsivity: a link between bipolar disorder and substance abuse. *Bipolar Disord* 2004, 6:204–212.
 17. Swann AC, Steinberg JL, Lijffijt M, Moeller FG: Impulsivity: differential relationship to depression and mania in bipolar disorder. *J Affect Disord* 2008, 106:241–248.
 18. Swann AC, Dougherty DM, Pazzaglia PJ, et al.: Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. *Am J Psychiatry* 2005, 162:1680–1687.
 19. Evenden J: Varieties of impulsivity. *Psychopharmacology* 2000, 146:348–361.
 20. Dougherty DM, Bjork JM, Marsh DM, Moeller FG: A comparison between adults with conduct disorder and normal controls on a continuous performance test: differences in impulsive response characteristics. *Psychol Rec* 2000, 50:203–219.
 21. Stanford MS, Mathias CW, Dougherty DM, et al.: Fifty years of the Barratt Impulsiveness Scale: an update and review. *Pers Individ Dif* 2009, 47:385–395.
- This comprehensive review discusses the development of the BIS-11, data on psychometric properties of the subscales, and a review of essentially all clinical and personality literature using the BIS-11 subscales.
22. Swann AC, Gerard MF, Steinberg JL, et al.: Manic symptoms and impulsivity during bipolar depressive episodes. *Bipolar Disord* 2007, 9:206–212.
- In patients with bipolar depressive episodes, impulsivity (questionnaire and response inhibition) and history of substance abuse, head trauma, or suicide attempt increased with increasing Mania Rating Scale scores. Even modest manic symptoms (score > 6) during bipolar depressive episodes were associated with greater impulsivity and increased alcohol abuse and suicide attempts. Manic symptoms during depressive episodes suggest the presence of a potentially dangerous combination of depression and mania-associated impulsivity.
23. Swann AC, Lijffijt M, Lane SD, et al.: Increased trait-like impulsivity and course of illness in bipolar disorder. *Bipolar Disord* 2009, 11:280–288.
 24. Strakowski SM, Fleck DE, DelBello MP, et al.: Characterizing impulsivity in mania. *Bipolar Disord* 2009, 11:41–51.
- This article investigated three specific impulsivity mechanisms—response disinhibition, inability to delay gratification, and inattention—in 70 bipolar manic and 34 healthy individuals. Manic individuals were impaired in all three tasks. Inability to delay gratification seemed not to be simply a result of the speed of decision making or inattention but to reflect differences between manic and healthy individuals in the ability to delay response for a larger reward.
25. Swann AC, Lijffijt M, Lane SD, et al.: Severity of bipolar disorder is associated with impairment of response inhibition. *J Affect Disord* 2009, 116:30–36.
- The authors investigated impulsivity in bipolar disorder in terms of deficiencies in attention or response inhibition (attention based and reward based) relative to course of illness, medicine, affective state, age, education, and gender in 112 individuals with bipolar disorder and 71 healthy controls. Those with bipolar disorder had substantial deficits in all tasks, even after correction for effects of medication or current affective state. Response inhibition was impaired further with more severe course of illness.
26. Yechiam E, Hayden EP, Bodkins M, et al.: Decision making in bipolar disorder: a cognitive modeling approach. *Psychiatry Res* 2008, 161:142–152.
 27. Mazzola-Pomietto P, Kaladjian A, Azorin JM, et al.: Bilateral decrease in ventrolateral prefrontal cortex activation during motor response inhibition in mania. *J Psychiatr Res* 2009, 43:432–441.
- This study used event-related functional MRI combined with a response inhibition task in manic and control individuals. Impaired response inhibition in mania was associated with a lack of engagement of the bilateral ventrolateral prefrontal cortex, which is involved in the suppression of irrelevant responses and potentially related to the pathophysiology of disinhibition and impulsivity in mania.
28. Himmelhoch JM, Mulla D, Neil JF, et al.: Incidence and severity of mixed affective states in a bipolar population. *Arch Gen Psychiatry* 1976, 33:1062.
 29. Swann AC, Janicak PL, Calabrese JR, et al.: Structure of mania: depressive, irritable, and psychotic clusters with different retrospectively-assessed course patterns of illness in randomized clinical trial participants. *J Affect Disord* 2001, 67:123–132.
 30. Azorin JM, Kaladjian A, Adida M, et al.: Toward the delineation of mania subtypes in the French National EPIMAN-II Mille Cohort. Comparisons with prior cluster analytic investigations. *Eur Arch Psychiatry Clin Neurosci* 2008, 258:497–504.
 31. Cassidy F, Yatham LN, Berk M, Grof P: Pure and mixed manic subtypes: a review of diagnostic classification and validation. *Bipolar Disord* 2008, 10:131–143.
 32. Kessing LV: The prevalence of mixed episodes during the course of illness in bipolar disorder. *Acta Psychiatr Scand* 2008, 117:216–224.
 33. van Rossum I, Haro JM, Tenback D, et al.: Stability and treatment outcome of distinct classes of mania. *Eur Psychiatry* 2008, 23:360–367.
 34. Benazzi F: Reviewing the diagnostic validity and utility of mixed depression (depressive mixed states). *Eur Psychiatry* 2008, 23:40–48.
 35. Dilsaver SC, Benazzi F: Diagnosing depressive mixed states in bipolar disorders. *J Clin Psychiatry* 2008, 69:e19.

36. Goldberg JF, Perlis RH, Bowden CL, et al.: **Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD.** *Am J Psychiatry* 2009, **166**:173–181.

This large, prospective study of illness course and treatment response in bipolar disorder showed that subsyndromal manic symptoms were widespread in bipolar depression. Presence of subsyndromal mania was associated with an unfavorable course of illness.

37. Benvenuti A, Rucci P, Miniati M, et al.: **Treatment-emergent mania/hypomania in unipolar patients.** *Bipolar Disord* 2008, **10**:726–732.
38. Harada T, Sakamoto K, Ishigooka J: **Incidence and predictors of activation syndrome induced by antidepressants.** *Depress Anxiety* 2008, **25**:1014–1019.
39. Amore M, Menchetti M, Tonti C, et al.: **Predictors of violent behavior among acute psychiatric patients: clinical study.** *Psychiatry Clin Neurosci* 2008, **62**:247–255.
40. Colasanti A, Natoli A, Moliterno D, et al.: **Psychiatric diagnosis and aggression before acute hospitalisation.** *Eur Psychiatry* 2008, **23**:441–448.
41. Elbogen EB, Johnson SC: **The intricate link between violence and mental disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions.** *Arch Gen Psychiatry* 2009, **66**:152–161.

This was a longitudinal study of 34,653 individuals representative of the community who were interviewed twice, about 3 years apart. Incidence of violence was higher for people with severe mental illness, but only significantly so for those with co-occurring substance abuse and/or dependence. Other predictors included historical, demographic, and contextual factors, which were more common in major psychiatric illness.

42. Dilsaver SC, Chen YR, Swann AC, et al.: **Suicidality in patients with pure and depressive mania.** *Am J Psychiatry* 1995, **151**:1312–1315.
43. Bryan CJ, Johnson LG, David RM, Joiner TE Jr: **Hypomanic symptoms among first-time suicide attempters predict future multiple attempt status.** *J Clin Psychol* 2008, **64**:519–530.
44. Elizabeth SM, Carballo JJ, Moreno C, et al.: **Substance use disorders and suicide attempts in bipolar subtypes.** *J Psychiatry Res* 2009, **43**:230–238.
45. Khalsa HM, Salvatore P, Hennen J, et al.: **Suicidal events and accidents in 216 first-episode bipolar I disorder patients: predictive factors.** *J Affect Disord* 2008, **106**:179–184.

A total of 216 DSM-IV bipolar I disorder patients were studied prospectively for 4.2 years from first-lifetime hospitalization. Suicidality was strongly associated with initial mixed state, proportion of follow-up weeks in mixed states or depression, and prior suicide attempts; accidents were associated selectively with initial mania or psychosis, later mania or hypomania, and alcohol abuse.

46. Valtonen HM, Suominen K, Haukka J, et al.: **Differences in incidence of suicide attempts during phases of bipolar I and II disorders.** *Bipolar Disord* 2008, **10**:588–596.

This was a prospective, naturalistic, 18-month life-chart study of suicide attempts versus phase of illness in 176 psychiatric inpatients and outpatients. Incidence of suicide attempts was 37-fold higher during combined mixed and depressive mixed states—twice the elevation seen in major depressive episodes.

47. Krauthammer C, Klerman GL: **Secondary mania: manic syndromes associated with antecedent physical illnesses or drugs.** *Arch Gen Psychiatry* 1978, **35**:1333–1339.
48. Sowden GL, Huffman JC: **The impact of mental illness on cardiac outcomes: a review for the cardiologist.** *Int J Cardiol* 2009, **132**:30–37.
49. Fiedorowicz JG, Solomon DA, Endicott J, et al.: **Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder.** *Psychosom Med* 2009, **71**:598–606.
- Individuals in the National Institute of Mental Health Collaborative Depression Study ($n = 435$ bipolar I and II disorder patients) were observed prospectively for up to 25 years. Bipolar I disorder had more than double the cardiovascular mortality risk of bipolar II disorder, and the burden of clinically significant manic/hypomanic symptoms predicted cardiovascular mortality independent of diagnosis, treatment, age, gender, and cardiovascular risk factors at intake; depressive symptom burden did not.
50. Meade CS, Graff FS, Griffin ML, Weiss RD: **HIV risk behavior among patients with co-occurring bipolar and substance use disorders: associations with mania and drug abuse.** *Drug Alcohol Depend* 2008, **92**:296–300.
51. Young LT, Cooke RG, Robb JC, et al.: **Anxious and non-anxious bipolar disorder.** *J Affect Disord* 1993, **29**:49–52.
52. Barratt ES: **Perceptual-motor performance related to impulsiveness and anxiety.** *Percept Mot Skills* 1967, **25**:485–492.
53. Goldstein BI, Levitt AJ: **The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder.** *Bipolar Disord* 2008, **10**:67–78.
54. Hawgood J, De Leo D: **Anxiety disorders and suicidal behaviour: an update.** *Curr Opin Psychiatry* 2008, **21**:51–64.
55. Lee JH, Dunner DL: **The effect of anxiety disorder comorbidity on treatment resistant bipolar disorders.** *Depress Anxiety* 2008, **25**:91–97.
56. Taylor CT, Hirshfeld-Becker DR, Ostacher MJ, et al.: **Anxiety is associated with impulsivity in bipolar disorder.** *J Anxiety Disord* 2008, **22**:868–876.
57. Regier DA, Farm ME, Rae DS: **Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study.** *JAMA* 1990, **264**:2511–2518.
58. Levy B, Monzani BA, Stephansky MR, Weiss RD: **Neurocognitive impairment in patients with co-occurring bipolar disorder and alcohol dependence upon discharge from inpatient care.** *Psychiatry Res* 2008, **161**:28–35.
59. Kathleen HM, Bearden CE, Barguil M, et al.: **Conceptualizing impulsivity and risk taking in bipolar disorder: importance of history of alcohol abuse.** *Bipolar Disord* 2009, **11**:33–40.
60. Swann AC, Bowden CL, Calabrese JR, et al.: **Pattern of response to divalproex, lithium, or placebo in four naturalistic subtypes of mania.** *Neuropsychopharmacology* 2002, **26**:530–536.