The Neurobiology of the Switch Process in Bipolar Disorder: A Review

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Objective: The singular phenomenon of switching from depression to its opposite state of mania or hypomania, and vice versa, distinguishes bipolar disorder from all other psychiatric disorders. Despite the fact that it is a core aspect of the clinical presentation of bipolar disorder, the neurobiology of the switch process is still poorly understood. In this review, we summarize the clinical evidence regarding somatic interventions associated with switching, with a particular focus on the biologic underpinnings presumably involved in the switch process.

Data Sources: Literature for this review was obtained through a search of the MEDLINE database (1966–2008) using the following keywords and phrases: *switch*, *bipolar disorder*, *bipolar depression*, *antidepressant*, *SSRIs*, *tricyclic antidepressants*, *norepinephrine*, *serotonin*, *treatment emergent affective switch*, *mania*, *hypomania*, *HPA-axis*, *glucocorticoids*, *amphetamine*, *dopamine*, and *sleep deprivation*.

Study Selection: All English-language, peer-reviewed, published literature, including randomized controlled studies, naturalistic and open-label studies, and case reports, were eligible for inclusion.

Data Synthesis: Converging evidence suggests that certain pharmacologic and nonpharmacologic interventions with very different mechanisms of action, such as sleep deprivation, exogenous corticosteroids, and dopaminergic agonists, can trigger mood episode switches in patients with bipolar disorder. The switch-inducing potential of antidepressants is unclear, although tricyclic antidepressants, which confer higher risk of switching than other classes of antidepressants, are a possible exception. Several neurobiological factors appear to be associated with both spontaneous and treatment-emergent mood episode switches; these include abnormalities in catecholamine levels, up-regulation of neurotrophic and neuroplastic factors, hypothalamic-pituitary-adrenal axis hyperactivity, and circadian rhythms.

Conclusions: There is a clear need to improve our understanding of the neurobiology of the switch process; research in this field would benefit from the systematic and integrated assessment of variables associated with switching.

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The singular phenomenon of switching from depression to its opposite state of mania or hypomania, and vice versa, distinguishes bipolar disorder from all other psychiatric disorders. Although symptoms such as depressed mood, insomnia, paranoid ideation, anxiety, and appetite changes are experienced across many psychiatric disorders, the process of switching from depression to a state of mania or hypomania is a unique and core feature of bipolar disorder. Currently, no uniform definition exists to describe the switch phenomenon; herein, we have defined it as a sudden transition from a mood episode to another episode of the opposite polarity. The importance of the switch process as the hallmark of bipolar disorder was originally described in 1854 by Falret,[1] who conceptualized *circular insanity*, which he defined as a form of illness in which "depression and mania must succeed one another for a long time, usually for the whole of the patient's life, and in a fashion very nearly regular, and with intervals of rationality, which are usually short compared with the length of the episodes"[2(p1130)]

Historically, abrupt changes in mood polarity were described well before the beginning of the psychopharmacologic era. Manic features observed after a depressive episode were commonly described as "post-melancholic reactive hyperthymia," while mania that evolved into depression was referred to as "reactive depression."[3] Retrospective data obtained from patients hospitalized between 1920 and 1959 show a rate of 29% for spontaneous switching from depression to hypomania.[4] However, in modern psychiatry, the term *switch* connotes not only switches in mood polarity as a core feature of bipolar disorder but also treatment-emergent affective switch (TEAS)—often from depression to mania/hypomania. The fact that the term switch is now used synonymously to encompass both types of mood shifts has led psychiatrists to neglect the study of both spontaneous switches (ie, non–treatment related) as well as the transition from mania/hypomania to depression.

A possible reason for the dearth of modern studies addressing the neurobiology of spontaneous switches is that, presently, most patients with bipolar disorder have complex treatment regimens involving multiple drugs, so that the vast majority of clinical trials done in patients with bipolar disorder enroll patients who are already medicated. Conversely, most of the data regarding non–treatment-induced switches (spontaneous switches) derive from studies conducted 2 to 3 decades ago when the efficacy of lithium as a prophylactic agent in bipolar disorder was still debated and when monotherapy trials with antidepressants were still being conducted, at least in the United States. As a result, most of the evidence presented in this article refers to TEAS, unless otherwise specified. The issue of TEAS itself is also

one that continues to be the center of considerable controversy. There is genuine uncertainty regarding the potential benefit or harm associated with the use of antidepressants during depressive episodes of bipolar disorder. Because the depressed phase of bipolar disorder is associated with significant morbidity and increased risk of suicide, this is a significant public health challenge.

Despite the importance of the switch phenomenon, the precise mechanisms underlying the process have yet to be elucidated. Moreover, the neurobiology and long-term clinical consequences of the switch process are still poorly understood. Switching from depression to mania/hypomania can occur spontaneously over the course of the illness, but it can also be precipitated by stress, sleep deprivation, or standard treatment for bipolar depression such as electroconvulsive therapy and some antidepressants[5,6] (see below), as well as various other agents (eg, amphetamines and glucocorticoids). In addition, recent evidence suggests that genes that regulate monoaminergic transmission or circadian rhythms might increase individual susceptibility for switching.[7–9] Another key issue is that most of the research on both spontaneous switches and TEAS has observed the switch from depression into mania. Because the switch from mania to depression occurs in a relatively smaller proportion of patients with bipolar disorder than the switch from depression into mania,[10] data regarding this phenomenon are very sparse, but in this review are noted whenever possible.

Across the spectrum of bipolar disorder, there is wide individual variability in how often any given individual diagnosed with bipolar disorder will have either spontaneous switching or TEAS. Clinically, this information can be quite important, because having a pattern of switching is associated with several clinical consequences. For instance, evidence suggests that, compared to nonswitchers, switchers have a higher genetic loading for mood disorders, spend more time ill during the course of their lifetime, experience significantly more comorbidities, and are at greater risk for developing substance abuse or committing suicide.[11–14] TEAS in particular is believed to be associated with worsening clinical outcome, including cycle acceleration.[15,16] It is also unknown whether individuals switch only when exposed to particular triggers (eg, antidepressants, glucocorticoids, sleep deprivation), whether switchers have a general propensity to switch in response to any given treatment known to induce switch, or whether some individuals are genetically more likely to experience switching regardless of triggers. Understanding this unique process is crucial to our understanding of the pathophysiology of bipolar disorder. Notably, although the switch process may be involved in the phenomenon of rapid cycling and cycle acceleration, the intention of this review is to focus primarily on the switch process and not necessarily on rapid cycling and cycle acceleration or the possible long-term prognostic implications of switching. Switching is an event circumscribed to a period of time that facilitates its study and is more likely to yield information on the molecular underpinnings of the switch process per se; in contrast, rapid cycling and cycle acceleration occur over a longer period of time and are likely to be associated with distinct neurobiological correlates that may or may not be involved in switching.

In this review, we will first discuss the clinical predictors of switching and their significance. We will then discuss the clinical evidence regarding pharmacologic interventions associated with switching, with a particular focus on the individual neurotransmitter systems and the possible biologic mechanisms involved in this process.

DATA SOURCES AND STUDY SELECTION

Literature for this review was obtained by searching the MEDLINE database (1966–2008) using the following keywords and phrases: *switch*, *bipolar disorder*, *bipolar depression*, *antidepressant*, *SSRIs*, *tricyclic antidepressants*, *norepinephrine*, *serotonin*, *treatment emergent affective switch*, *mania*, *hypomania*, *HPA-axis*, *glucocorticoids*, *amphetamine*, *dopamine*, and *sleep deprivation*. All English-language, peer-reviewed, published studies, including randomized controlled trials, naturalistic and open-label studies, and case-reports, were eligible for inclusion.

CLINICAL PREDICTORS OF SWITCH AND THEIR SIGNIFICANCE

Few studies have tried to characterize the clinical characteristics of the switch process in bipolar disorder or its prognostic significance. To study the clinical and prognostic correlates of the phenomenon of switching in patients with bipolar disorder, Maj and colleagues[14] prospectively compared a group of patients who experienced a *mood switch* (defined as a sudden transition from a mood episode to another episode of the opposite polarity with an intervening period of no more than 1 month) to a comparison group of subjects who did not experience any switches during an observational period of at least 3 years. The study found that switchers were more likely to have a greater number of hospitalizations previous to their study index episode and to need more time to recover from their index episode. Furthermore, the time to 50% probability of recovery was significantly longer for patients who experienced more than 1 switch (ie, those having a polyphasic episode) during their index episode (44 weeks) compared to patients who had only 1 switch (ie, those having a biphasic episode) (12 weeks) or to nonswitchers (7 weeks). Likewise, patients with more than 1 switch spent more time in mood episodes during the observational period following the index episode than the other 2 groups. In this study, switching from depression to mania/hypomania was associated with a poorer prognosis as well as an increased risk of switching during subsequent episodes than switching from mania/hypomania to depression. In addition, switchers were more likely to show psychomotor retardation than nonswitchers. However, gender, a positive family history of bipolar disorder, nor age at recruitment were significant predictors of switching.[14]

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Another retrospective study found that the presence of mixed symptoms during a depressive episode was associated with an increased risk of having a manic switch.[17] In another study, Zarate and colleagues[18] found that a mixed manic presentation was a strong predictor of switch from mania to depression. They investigated clinical and demographic predictors of switch from mania to depression in 28 switchers and 148 nonswitchers. In this study, switching from mania to depression was not associated with a longer time to recovery or earlier time to relapse during the 24-month follow-up period. In these 2 studies, the treatment status at the time of switching was not controlled for, as the patients were undergoing uncontrolled treatment with multiple classes of drugs. A recent observational study[10] that investigated the switch from mania to depression noted that a history of previous depressive episodes, substance abuse, greater overall severity on the Clinical Global Impressions scale-Bipolar Version (CGI-BP), and benzodiazepine use all increased the risk of this type of switch. Conversely, the authors also identified factors associated with lower switch rates from mania to depression, including atypical antipsychotic use, lower Young Mania Rating Scale (YMRS) severity, and higher CGI-BP depression scores.[10]

Several clinical variables have been studied specifically as potential predictors of TEAS, including gender, diagnosis, age, number of previous episodes of mania, previous history of TEAS, and polarity of onset episode. Some studies have found that switchers have a higher number of past manic episodes,[19] while others found more past manic episodes in nonswitchers,[20] and still others found no differences between switchers and nonswitchers[21] on this variable. Serretti and colleagues[20] found an association between TEAS and depressive polarity of illness onset, but this was not replicated in subsequent studies.[22,23] Two studies[20,24] reported that switchers were older at intake, but the opposite association (ie, earlier age at intake) was reported in a more recent study.[22] Also, a positive past history for TEAS was found to predict current TEAS in some[22] but not all studies.[19,25] A positive history of rapid cycling has also been associated with TEAS.[20,22] However, gender, family history, age at onset, and substance abuse have not been found to predict TEAS.[20,22,23]

In addition, a number of studies have focused specifically on clinical predictors of TEAS when antidepressants are administered. Data from the Systematic Treatment Enhancement Program for Bipolar Disorder[22] suggest that a past history of multiple antidepressant trials is associated with TEAS.[22] A history of past TEAS also seems to be associated with the development of chronic dysphoria following antidepressant administration.[26] Another important question is whether patients with bipolar I disorder and bipolar II disorder differ in their risk for TEAS; while some studies[27] detected an increased likelihood of switch in patients with bipolar I disorder, others[21,28] reported no difference, or increased risk for subjects with bipolar II disorder.[20] However, a recent meta-analysis[29] that combined results from 9 different studies assessing TEAS rates in patients with bipolar I disorder and bipolar II disorder noted that patients with bipolar I disorder had a significantly higher risk of TEAS (14.2% vs 7.1%, respectively).

ANTIDEPRESSANTS AND SWITCH

The evidence regarding the likelihood that antidepressant treatment in individuals with bipolar disorder confers increased risk of TEAS has long been controversial and inconclusive, and it is beyond the scope of this review to extensively discuss this controversy (we refer the interested reader to some authoritative reviews on the topic[5,30,31]).

Virtually all antidepressants have been associated with increased risk for TEAS; studies[21] have found that antidepressant-induced TEAS ranges from 10% to 70%, depending on the methodological heterogeneity of the study design, concomitant treatment, and the type of statistical analyses conducted. Many researchers have recently discussed the methodological flaws associated with many of the studies from which this evidence was drawn.[5,30] These include investigating switch potential as a secondary aim or post hoc analysis, heterogeneity in terms of concomitant treatments administered to patients, and lack of agreement on TEAS-defining criteria. Similarly, different diagnostic criteria, such as heterogeneity of YMRS score cutoff for defining a switch, and duration of follow-up need to be considered when interpreting the results (Table 1 for an overview of switch criteria used in the studies described herein). Ideally, in order for results to be comparable across studies, a single a priori definition of switching should be provided, with fulfillment of *DSM-IV* criteria for mania or hypomania within a short time frame (eg, 6 weeks) from the beginning of antidepressant treatment in patients experiencing a depressive episode. Our present lack of a consensus definition or temporal criteria may dilute the biologic underpinnings of this phenomenon, because subjects who develop affective switch within very different time frames from the start of antidepressant treatments are considered equivalent. This methodological issue has been recently emphasized by a task force of the International Society for Bipolar Disorder, which recommended empirical testing in clinical trials of the reliability of different definitions of switch.[6]

Another critical issue is the uncertainty regarding switch rates in unmedicated patients; for instance, retrospective data obtained from patients hospitalized between 1920 and 1959 found a rate of 29% for spontaneous switching from depression to hypomania.[4] Without a clear benchmark estimating the rate at which patients are likely to switch spontaneously, it can be difficult to assess the degree to which antidepressants increase that risk. Relatedly, the fact that most patients with bipolar disorder receive antidepressants concomitantly with mood stabilizers[32] makes switch rates even more difficult to estimate accurately.

Despite these limitations, results from clinical trials may provide important clues to understanding the neurobiology of the switch process by analyzing switch rates for antidepressants that target different neurotransmitter systems (for

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Table 1. Operational Criteria for Defining *Switch* Applied in Different Pharmacologic Studies

Study	Time From Start of Antidepressant Required to Define Treatment-Emergent Affective Switch	Type of Study	Definition of Switch and Treatment-Emergent Switch
Lewis and Winokur,[38] 1982	None required	Retrospective	*DSM-III* mania while hospitalized or within 6 mo of discharge
Cohn et al,[42] 1989	6 wk	RCT	Not specified
Himmelhoch et al,[40] 1991	6 wk	RCT	Mania, research diagnostic criteria
Peet,[33] 1994	Not specified	Retrospective	Not specified
Sachs et al,[43] 1994	8 wk	RCT	*DSM-III-R* mania or hypomania
Altshuler et al,[15] 1995	8 wk	Retrospective	Mania within 8 wk of the initiation of antidepressant treatment
Boerlin et al,[34] 1998	Within 2 mo after a depressive episode	Retrospective	*DSM-IV* mania/hypomania
Bottlender et al,[37] 2001	None required	Retrospective	Mania/hypomania according to the physician's assessment based on *DSM-IV* criteria
Henry et al,[21] 2001	6 wk	Naturalistic	*DSM-IV* mania/hypomania or mixed episode within 6 wk of initiation of antidepressant treatment
Mundo et al, [9] 2001	None required	Retrospective	*DSM-IV* mania/hypomania while being treated with SSRIs for depression
Nemeroff et al,[39] 2001	10 wk	RCT	*DSM-IV* mania
Silverstone,[41] 2001	8 wk	RCT	YMRS score ≥ 10, or study discontinuation for manic symptoms
Joffe et al,[49] 2002	Not specified; switch attributed to an antidepressant based on clinical judgment	Naturalistic	*DSM-IV* mania or hypomania
McIntyre et al,[48] 2002	8 wk	RCT	Not specified
Maj et al,[14] 2002	None required	Naturalistic	One episode of mania or hypomania and 1 episode of depression (research diagnostic criteria) with an intervening period of < 1 mo
Vieta et al,[50] 2002	6 wk	RCT	YMRS score > 11 and fulfilling *DSM-IV* criteria for mania or hypomania
Rousseva et al,[56] 2003	None required/90 d	Retrospective	Broad definition: self-report of mood elevation at any time after the introduction of an antidepressant; Narrow definition: self-report of mood elevation within 90 d from the beginning of treatment
Serretti et al,[20] 2003	None required	Retrospective	*DSM-IV* mania/hypomania while being treated with SSRIs for depression
Tohen et al,[53] 2003	8 wk	RCT	YMRS score < 15 at baseline and > 15 at any time thereafter
Serretti et al,[57] 2004	4 wk	Retrospective	*DSM-IV* mania/hypomania while being treated with antidepressants for depression
Tamada et al,[24] 2004	None required	Naturalistic	*DSM-IV* hospitalized mania or mixed state; YMRS score ≥ 12 and at least 3 d of antidepressant treatment within 2 wk of hospital admission
Amsterdam and Shults,[52] 2005	8 wk	RCT	YMRS score > 8 at any visit
Fonseca et al,[54] 2006	12 wk	Open label	YMRS > 12 and *DSM-IV* criteria for manic switch; *DSM-IV* criteria for hypomania for hypomanic switch
Post et al,[25] 2006	10 wk	RCT	Two-point increase on the CGI-BP, CGI-BP score of at least 3, or YMRS score > 13
Schaffer et al,[55] 2006	12 wk	RCT	Not specified
Carlson et al,[23] 2007	None required	Retrospective	*DSM-IV* mania/hypomania while being treated with antidepressants or within 30 d of stopping treatment
Nolen et al,[45] 2007	10 wk	RCT	At least "much worse" on the CGI-BP rating of change in mania as baseline and/or YMRS score ≥ 14
Sachs et al,[19] 2007	16 wk	RCT	*DSM-IV* criteria for mania or hypomania or clinically significant mood elevation needing clinical intervention within 16 wk or before reaching durable recovery (up to 26 wk)
Truman et al,[22] 2007	12 wk	Retrospective	Non-*DSM-IV* report of mania, hypomania, or mixed episode
Amsterdam and Shults,[51] 2008	12 wk	Open label	Two different criteria: YMRS ≥ 8 or YMRS ≥ 12 at any visit

Abbreviations: CGI-BP = Clinical Global Impressions scale-Bipolar Version, DSM = *Diagnostic and Statistical Manual of Mental Disorders*, RCT = randomized controlled trial, SSRI=selective serotonin reuptake inhibitor, YMRS = Young Mania Rating Scale.

an excellent and extensive recent review of this topic, see Licht et al[5]). Below, we review what is known about the various classes of antidepressants and their propensity to cause TEAS in individuals with bipolar disorder.

TEAS Associated With the Use of Various Classes of Antidepressants

Tricyclic antidepressants (TCAs) have consistently been associated with a high risk of TEAS compared to other antidepressants; naturalistic and retrospective studies have reported TEAS incidence rates ranging from 9% to 69%.[33–38] Because much of this knowledge has been previously and extensively reviewed by others and is already familiar to the reader,[31] we offer here only a brief discussion of the evidence concerning the mood-elevating potential of TCAs; when possible, we also include data from randomized controlled trials in bipolar depression.

Bunney and colleagues[35] reviewed 80 studies involving 3,923 patients mostly treated with TCAs for depression and found that the incidence of TEAS into mania or hypomania was 9.5%. A later study by Wehr and Goodwin[36] of 26 patients with bipolar I and II disorder found that 18 experienced manic or hypomanic switches while on TCAs after an average of 21 days for those with bipolar I disorder and

35 days for those with bipolar II disorder. Pooled data have similarly shown that mood switches are considerably more frequent with TCAs (11.2%) than with selective serotonin reuptake inhibitors (SSRIs) (3.7%) or placebo (4.2%).[33] Bottlender and colleagues[37] evaluated the incidence of mania and hypomania in 158 patients with bipolar I disorder treated for depression. They describe switch rates of 34% for patients receiving TCAs. Similar switch rates were reported in a naturalistic study by Boerlin and colleagues,[34] who found that both TCAs and monoamine oxidase inhibitors (MAOIs) were associated with higher switch rates than the SSRI fluoxetine (32%, 35%, and 12%, respectively). The TCA imipramine has also been associated with TEAS (rates between 6.6% and 17.8%) in 4 studies.[39–42] These rates are considerably lower than those obtained from naturalistic and retrospective studies, but the enrollment of patients with milder forms of bipolar disorder in clinical trials compared to observational/naturalistic studies might explain this difference.

Evidence from a clinical trial in bipolar depression suggests that use of the TCA desipramine, which is a selective inhibitor of norepinephrine reuptake, was associated with a high frequency of switches into mania or hypomania (30%).[43] However, no definitive conclusions can be drawn from this study, as few patients were enrolled (n = 10); furthermore, there have been no studies evaluating desipramine's propensity to cause TEAS since 1994. One case report[44] noted that reboxetine, another norepinephrine reuptake inhibitor (though not available in the United States), induces hypomania.

Only 3 randomized clinical trials have evaluated TEAS in MAOIs. In the first trial,[41] 3.7% of patients experienced manic/hypomanic symptoms leading to study withdrawal. Also, a YMRS score ≥ 10 was described in 9.3% of all patients taking moclobemide. In the second study,[40] the MAOI tranylcypromine caused manic or hypomanic switches in 11% of patients. Finally, Nolen and colleagues[45] reported no manic switches in 8 patients with bipolar disorder openly randomly assigned to tranylcypromine for 10 weeks as an add-on to mood stabilizers. Interestingly, a recent retrospective analysis of Systematic Treatment Enhancement Program for Bipolar Disorder data suggests that TEAS is less likely to occur when MAOIs are administered in conjunction with mood stabilizers compared to other classes of antidepressants.[22]

Bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI), is associated with low TEAS potential, and its lower mood-elevating potential compared to TCAs has been described since the 1980s.[46,47] Five clinical trials have evaluated its switch-inducing potential in patients with bipolar depression, with a frequency of mood episode switches ranging from 0% to 17.9%.[19,25,43,48,49] Notably, all the patients enrolled in bupropion trials were concomitantly treated with mood stabilizers, a factor that may have contributed to the low TEAS rates observed. The highest TEAS rates were reported in the trial with the longest temporal operational criteria for defining TEAS[19] (see Table 1).

Two clinical trials have evaluated the switch-inducing potential of the serotonin-norepinephrine reuptake inhibitor venlafaxine, which is a double inhibitor of serotonin and norepinephrine reuptake, in patients with bipolar depression (both bipolar I disorder and bipolar II disorder) and reported TEAS rates ranging between 13.3% and 29%[25,50]; these rates were higher than TEAS rates reported for the other treatment arms (which used the SSRI paroxetine or sertraline, and the NDRI bupropion), thus suggesting that the perturbation of 2 monoaminergic systems is more likely to induce TEAS than when a single SSRI is used. The study by Post and colleagues[25] also showed that different operational criteria are likely to account for the variability in TEAS rates associated with antidepressant treatment across the different trials. In fact, switch rates varied from 15% to 31% for venlafaxine, from 4% to 14% for bupropion, and from 7% to 16% for sertraline, depending on the criteria used to define the switch (a 2-point increase at any point in the trial on the CGI-BP, a CGI-BP manic severity score of at least 3 [ie, at least mildly manic], or a YMRS score above 13 at any visit). In addition, this trial was 1 of the largest to define the study of TEAS as one of its primary aims. The fact that the vast majority of the subjects enrolled in the studies by Post[25] and Vieta[50] had a diagnosis of bipolar I disorder (73% and 67%, respectively) might explain the apparent discrepancy in these findings; for instance, a recent study[51] of patients with bipolar II disorder showed low TEAS rates only for venlafaxine (2.4%), even when it was administered as monotherapy.

Post hoc analyses of data from randomized controlled trials (RCTs) in bipolar depression usually show low switch rates associated with SSRIs. For example, no TEAS was reported in 2 trials[42,52] of fluoxetine in bipolar depression. However, the pooled number of patients who received fluoxetine was low (n = 38), and most of the patients came from a study[42] that also detected low TEAS rates for the TCA imipramine. Another major limitation of the study was the low completion rate: 43% of the patients randomly assigned to fluoxetine dropped out of the study. Moreover, 18 of these patients (20%) concomitantly received lithium. Another study[52] found no difference in mood episode switch between patients randomly assigned to receive either olanzapine (an atypical antipsychotic) plus fluoxetine or placebo. Five patients (15%) participating in this trial were also receiving lithium or valproate. Another study[53] that compared the efficacy and TEAS rates for olanzapine monotherapy, placebo, or a combination of olanzapine plus fluoxetine found a TEAS rate of 6% in the latter group; however, this switch rate did not differ from the placebo group. Consistent with these findings, analyses[33] of pooled data from databases of pharmaceutical industry research show that mood switches occur in 3.7% of patients treated with SSRIs.

Slightly higher TEAS rates were reported for the SSRI escitalopram in an open study led by Fonseca and colleagues,[54] in which 15% (3/20) of the patients who received add-on escitalopram to their current mood stabilizer regimen dropped out of the study because of manic/hypomanic symptoms. Recently, Schaffer and colleagues[55] reported that

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1 of 10 patients (10%) developed a manic switch during an open-label trial of citalopram added on to mood stabilizers. Similar TEAS rates were described in 2 uncontrolled retrospective studies[34,37]; Bottlender and colleagues[37] reported a switch rate of 12% when SSRIs were administered, despite the inclusion of patients who were currently taking mood stabilizers. Notably, no significant differences in switch rates were found between patients on SSRI monotherapy and patients who took SSRIs as an add-on to mood stabilizers; however, only 8 patients received SSRIs without mood stabilizers.[37] The TEAS rate of 12% observed in this study during treatment with SSRIs was higher than the 1 reported from the RCTs[42,52,53] described above or from the pooled data[33] from pharmaceutical companies, but it is possible that the less stringent inclusion criteria used in these naturalistic/observational studies (eg, inclusion of rapid cyclers, patients with comorbidities) might explain this discrepancy. Furthermore, it is interesting to note that both of these 2 naturalistic studies found a significantly lower rate of TEAS when patients were treated with SSRIs than with TCAs.[34,37]

Finally, a recent meta-analysis of randomized placebo-controlled trials by Gijsman and colleagues[32] concluded that available evidence suggests that antidepressants other than TCAs do not induce significantly more TEAS than placebo (4.7% vs 3.8%); however, it is important to note that 75% of the subjects were receiving a concurrent mood stabilizer or atypical antipsychotic. The authors also recommended that TCAs not be used as first-line treatment in patients with bipolar depression, because they were associated with higher switch risk (in that study, 10%). Thus, the evidence suggests that TCAs—for which particularly high switch rates have been described—are more likely to trigger TEAS in patients with bipolar disorder. In contrast, relatively low switch rates have been reported for SSRIs and MAOIs. The data also indirectly suggest that the concomitant perturbation of more than 1 monoaminergic system might carry a higher risk of TEAS.

THE ROLES OF THE SEROTONERGIC, CATECHOLAMINERGIC, NORADRENERGIC, AND DOPAMINERGIC SYSTEMS IN THE SWITCH PROCESS

As the preceding section emphasized, antidepressants targeting the serotonergic, noradrenergic, and dopaminergic systems have been associated with various degrees of propensity to induce TEAS, providing valuable clues regarding the underlying mechanisms of the switch process.

Data from genetic studies that investigated polymorphisms involved in the homeostasis of the serotonergic system suggest it has a negligible role in the switch process, with 1 exception. Mundo and colleagues[9] found that the short allele polymorphism of the serotonin transporter (5-HTTLPR) was overrepresented in patients who developed treatment-emergent hypomania/mania after receiving SSRIs. However, this association was not confirmed in a subsequent study[56] that applied both a broad and a narrow definition of TEAS; failure to replicate the association between the switch pattern and the short variant of the serotonin transporter might be due to higher age at onset in the second study compared to the first. Another study[57] investigated other potential candidate genes that regulate serotonergic system homeostasis and switch, such as 5-HTTLPR, 5-HT_{2A}, and tryptophan hydroxylase, but no association was found. Tryptophan depletion, a procedure that depletes serotonin, does not generally cause mood changes in lithium-treated euthymic patients with bipolar disorder,[58] while catecholamine depletion evokes a rebound hypomania in patients with bipolar disorder (see below).

The role of the noradrenergic and dopaminergic systems in the switch process is not clearly defined or well studied. Some historical studies tried to investigate the potential role of the noradrenergic and dopaminergic systems in TEAS in bipolar disorder by measuring peripheral metabolites of monoaminergic systems activity. Most of these case reports or case series were carefully conducted with inpatients studied across sequential episodes of switches. With the exception of 3 studies,[35,59,60] all other reports described here are single case studies of patients with rapid or ultrarapid cycling. The data summarized here generally refer to drug-free patients, with few exceptions.[35,61] Higher urinary cyclic adenosine 3′,5′ monophosphate,[59,62] urinary norepinephrine,[35,63,64] and dopamine[35,63] have all been associated with mania and, more relevant to the present discussion, the switch to mania. Increased urinary 3-methoxy-4-hydroxyphenylglycol has also been described in this context.[60,65] Increased postsynaptic receptor sensitivity interacting with high levels of catecholamines has also been hypothesized to trigger manic switches in some patients with bipolar disorder.[60,66]

Several genetic polymorphisms in the catecholaminergic system (D_4 receptor, D_2 receptor, catechol-*O*-methyltransferase, monoamine oxidase A) have been proposed as putative risk factors for TEAS in bipolar disorder, but no polymorphism was specifically found to be associated with the switch process.[57] Interestingly, this study analyzed genetic polymorphisms that had previously been associated with antidepressant response,[67] thus suggesting that the process associated with spontaneous switching might have a very different mechanism from that associated with antidepressant response.

Evidence from rodent studies further supports a putative role for the catecholaminergic system in the switch process. Drugs that deplete norepinephrine in the central nervous system (reserpine-like drugs) produce depression-like symptoms (eg, locomotor hypoactivity) in animal models, whereas drugs that increase norepinephrine levels, such as MAOIs and TCAs, are associated with antidepressant-like effects.[68] One hypothesis is that these antidepressant-like effects may occur through delayed postsynaptic receptor desensitization, leading to increased receptor responsivity.[69] This is theorized to be a critical physiologic protective mechanism against acute and chronic receptor overstimulation that, in turn, might be associated with an increased

risk for switching in bipolar disorder. Also, receptor supersensitivity, altered internalization of cell surface receptors, and changes in critical messenger ribonucleic acid (mRNA) expression might result in altered monoaminergic activity in the prefrontal areas, leading to manic-like behavioral changes.[70]

THE GLUTAMATERGIC SYSTEM AND SWITCH

Abundant evidence now implicates glutamatergic system dysfunction in the pathophysiology and treatment of unipolar depression and bipolar disorder (reviewed in Zarate et al[71]). For instance, animal models of bipolar disorder suggest that the glutamatergic system plays a major role in manic-like behaviors. Du and colleagues[72] found that inhibition of glutamate receptor type 1/2 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor significantly attenuates amphetamine-induced hyperactivity in rodents. In addition, disruption of glutamate receptor type 6, a subunit of the kainate receptor (kainate receptors, along with AMPA receptors, are glutamatergic non–*N*-methyl-D-aspartate [NMDA] ionotropic receptors), produces a complex set of symptoms in mice that resemble the behavioral symptoms of mania, including increased risk-taking behaviors and aggressiveness, hyperactivity, and less despair-type manifestations.[73] Whether and how these findings might be related to the switch process will need to be addressed in future studies.

Although the study of glutamatergic drugs in the treatment of mood disorders is still in its infancy, preliminary evidence from small trials and case reports suggests that drugs that modulate the glutamatergic system have low risk of inducing TEAS. For example, lamotrigine—a US Food and Drug Administration–approved mood stabilizer that inhibits glutamate release through sodium and calcium channel blockage,[74] is not associated with significant risk of switch in patients with bipolar depression.[75] In another study[76] of 14 patients with bipolar depression, riluzole, another inhibitor of glutamate release, was not associated with increased risk of switching; in that 8-week study, patients received riluzole as an add-on to lithium.

The switch-inducing potential of glutamatergic drugs that act by blocking NMDA receptors (ie, ketamine, memantine) is essentially unknown, as the clinical evidence for their use in bipolar disorder is small.[77] Studies in healthy volunteers found that individuals who received intravenously administered ketamine showed significantly more euphoria than those who received amphetamine or placebo,[78] possibly indicating some switch-inducing potential. However, it is unclear whether ketamine or memantine elicits core manic symptoms in addition to euphoria in bipolar disorder patients. Clinical trials conducted with these agents have not noted any increased risk of switch associated with their use (see Zarate et al[71] for review). While no conclusions can yet be drawn about the propensity of these agents to induce mood switches in bipolar disorder, this is nevertheless an important new avenue of research that will undoubtedly further our understanding of the molecular underpinnings of the switch process.

DOPAMINERGIC AGONISTS (PSYCHOSTIMULANTS) AND SWITCH

Selective dopaminergic drugs, such as psychostimulants, have long been associated with high rates of TEAS and have been empirically tested in preclinical studies. Murphy and colleagues[79] studied the effects of L-dopa, and L-dopa + peripheral decarboxylase inhibitor α-methyl dopa hydrazine (MK-485) in a double-blind, randomized, placebo-controlled study in bipolar depression. Six out of 7 subjects treated with L-dopa developed hypomanic symptoms after an average of 7.8 days. Interestingly, the symptoms decreased within 24–48 hours of discontinuing L-dopa. These results suggest that, at least for some patients, the switch into mania or hypomania is associated with increased functional brain norepinephrine and dopamine.

Similarly, amphetamines that promote dopamine release and inhibit its reuptake have been shown to either precipitate hypomania in patients with bipolar disorder or induce a "hypomanic-like" state in healthy subjects.[80,81] Consistent with these findings, a chart review[82] of depressed, medically ill patients found several cases of hypomania 1 to 5 days after dextroamphetamine was initiated at doses as low as 5–10 mg/d. Another study found a significant increase in subjective measures of thought processing speed and irritability in healthy volunteers who received 25-mg oral dextroamphetamine, 2 symptoms often associated with mania.[80] However, whether amphetamine can trigger other core manic symptoms (eg, grandiosity, aggressive behaviors, pressured speech) has yet to be demonstrated. Amphetamine has been shown to trigger euphoria in healthy volunteers, mostly due to increased dopamine levels in the anteroventral striatum.[83] Polymorphisms in the dopamine (DAT1) and norepinephrine (SLC6A2) transporters are known to modulate the mood-elevating effects of amphetamine.[84,85]

Pharmacologic evidence supports the notion that manipulating the dopaminergic system can mimic the symptoms of bipolar disorder. Investigators have used a catecholamine depletion strategy employing the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine (AMPT) in lithium-treated, euthymic patients with bipolar disorder to study the pathophysiology of the disorder.[86] Intriguingly, AMPT was not associated with any mood-lowering effects, but was associated with "rebound" hypomanic symptoms. Although preliminary, these results are compatible with the theory of a dysregulated signaling system wherein the compensatory adaptation to catecholamine depletion results in an "overshoot" due to impaired homeostatic mechanisms. Most recently, McTavish and colleagues[87] found that a tyrosine-free mixture lowered both subjective and objective measures of the psychostimulant effects of methamphetamine or amphetamine, as well as manic symptom scores. These preliminary findings suggest that decreased tyrosine

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availability to the brain attenuates pathological increases in dopaminergic neurotransmission following methamphetamine administration and, putatively, in mania.

Evidence from animal models shows that decreased dopaminergic activity and receptor binding in the mesolimbic cortex and nucleus accumbens is associated with depression-like states that can be reversed by diverse antidepressants that potentiate dopaminergic activity.[88–91] In contrast, stimulants with dopaminergic properties (such as amphetamine and cocaine), lead to both manic-like effects and increased sensitization in diverse animal models of bipolar disorder.[92] Intriguingly, quinpirole, a D_2/D_3 agonist, induces a biphasic motor activity response, characterized by initial inhibition followed by hyperactivity, which resembles the switch process in bipolar disorder.[93,94]

Furthermore, psychostimulants exert opposite effects than mood stabilizers on major intracellular signaling cascades, which might also be relevant for the switch process. For example, increased striatal dopaminergic activity—either in dopaminergic transporter knock-out mice or following amphetamine administration—is mediated by the activation of glycogen synthase kinase 3 (GSK-3) α and β, whose inhibition is pivotal for the therapeutic actions of lithium and valproate.[95] Psychostimulants also activate protein kinase C (PKC), a family of enzymes that have been associated with the pathophysiology of bipolar disorder (reviewed in Einat and Manji[96]). Recent evidence shows that the integrity of the PKC pathway is critical for amphetamine-induced behavioral responses[97] and that PKC inhibition has robust antimanic effects in patients with bipolar disorder.[98,99]

These data are intriguing, as they show converging evidence from clinical and preclinical models regarding the major involvement of the dopaminergic system in mania and mood stabilization. However, whether activation of GSK-3 and PKC pathways is necessary for producing mood switching in patients with bipolar disorder is a topic that requires further investigation.

THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND SWITCH

Since the early 1950s, the administration of hypothalamic-pituitary-adrenal (HPA) axis exogenous hormones has been reported to produce psychiatric symptoms in some patients with no pre-existing psychiatric disorders. In particular, adrenocorticotropic hormone and cortisone have been associated with mood elevation.[100,101] A review of the literature prior to 1983 reported that the incidence of psychiatric symptoms in patients receiving corticosteroids ranged from 5.7% to 27.6% in uncontrolled studies, and 6.3% to 32% in controlled studies.[102] All of these cases were medically ill patients whose onset of psychiatric symptoms occurred within 1 day to several weeks of initiating treatment with glucocorticoids, and most of the patients developed mania/psychosis.[103] These psychiatric symptoms were clearly induced in a dose-response fashion, with a higher proportion of manic symptoms occurring in patients who received higher doses (> 80 mg/d).[104] Recent studies have also confirmed this association between corticosteroid administration and psychiatric symptoms. For example, glucocorticoids elevate mood in patients with multiple sclerosis,[105] ophthalmologic diseases,[106] asthma,[103,107,108] and also in healthy volunteers.[109] Notably, higher rates of bipolar disorder–like symptoms were usually associated with a positive personal or family history of psychiatric disorders.[107,109]

Patients suffering from bipolar disorder are particularly susceptible to developing hypomanic/manic symptoms after receiving steroids. A recent study reviewing clinical charts from patients referred for a psychiatric consultation found 9 patients with bipolar disorder whose psychiatric symptoms were precipitated by the use of corticosteroids (prednisone, betamethasone, methylprednisolone); 7 of the 9 (77%) rapidly developed manic/hypomanic symptoms.[110] Patients with bipolar disorder using a beclomethasone inhaler,[111,112] as well as those using the androgen hormone dehydroepiandrosterone,[113] also developed mania. In addition, the single administration of triamcinolone in a celiac plexus block produced manic episodes in 2 patients with bipolar disorder,[114] confirming that susceptible patients can develop manic symptoms after the administration of even a single dose of glucocorticoids, and within a short period of time.[114] This relationship between the administration of glucocorticoids and the switch process is more striking when one considers that the administration of prednisone 40–60 mg on alternate days (in an on-off fashion) induced rapid-cycling symptoms in 3 patients.[115] These patients developed manic symptoms on the days they received prednisone; the opposite—a relapse into depression—occurred on the days they did not receive the drug.

In addition, hyperactivity of the HPA axis is 1 of the most replicated biologic finding in major depression. Although the evidence for HPA dysfunction in bipolar disorder is not as well validated, several authors have reported abnormalities in urinary and cerebrospinal fluid cortisol levels and decreased dexamethasone test suppression in patients with bipolar disorder (see Daban et al[116] for a review). In contrast, this finding is not observed in pure mania.[117,118] However, this association does not necessarily implicate a causal relationship, as HPA axis hyperactivity might be an epiphenomenon of mounting mood elevation.

Converging evidence from small studies with rapid cyclers or ultrarapid cyclers in patients with bipolar disorder suggest that HPA hyperactivity is critical for the switch from mania to depression in most of these patients[63,119–121]; however, the role of the HPA axis in switching from depression to mania is more controversial. Notably, transgenic mice overexpressing glucocorticoid receptors in the forebrain displayed enhanced depressive-like behaviors and increased sensitization to cocaine and antidepressants.[122] They also had a wider range of reactivity to stimuli that trigger both negative and positive emotional responses, which might be relevant for the neurobiology of the switch process in bipolar disorder. Findings from other rodent studies, albeit not

always consistent, further support the role of glucocorticoid receptors in affective-like behaviors (reviewed in Einat and Manji[96]).

SLEEP DEPRIVATION AND SWITCH

Sleep deprivation has historically been proposed as a final common pathway prior to the onset of mania, and it can be triggered by diverse environmental, psychological, interpersonal, or pharmacologic factors associated with the onset of mania.[123] Studies have consistently shown that sleep deprivation produces an acute antidepressant response in as many as 80% of subjects with bipolar depression and 60% of patients with unipolar depression.[124] Spontaneous switch rates after sleep deprivation vary from 10%[125] to 30%[123,126] across studies, and this wide range is likely due to sample heterogeneity and the different treatment status of the patients. The fact that sleep deprivation acts quickly makes it an ideal tool to study the molecular basis of the switch process. However, it remains unclear why sleep deprivation causes temporary recovery in some patients but triggers manic switches in others and whether these 2 phenomena share the same neurobiological mechanism.

Sleep deprivation produces several behaviors in rats that suggest it may be a useful model for mania, including insomnia, hyperactivity, irritability,[127,128] aggressive behavior,[129] novelty seeking preference,[130] and hypersexuality.[131] Moreover, rats exposed to serial sleep deprivation display behavioral sensitization, with worse manic-like symptoms emerging over repetition of the procedure, which parallels clinical findings of increased severity of illness over cumulative relapses in patients with bipolar disorder.[132] Sleep deprivation induces few effects at adrenergic or serotonergic receptors,[133] but it directly regulates brain dopaminergic receptor sensitivity.[134] Increased plasma norepinephrine and norepinephrine metabolites have also been found in responders to sleep deprivation.[135,136] Decreased 3-methoxy-4-hydroxyphenylglycol levels have also been found in the cerebrospinal fluid of sleep deprivation responders compared to nonresponders.[137,138] More recent studies have demonstrated that the expression of selected critical genes varies dramatically during sleep and waking,[139] which likely plays a major role in regulating long-term neuroplastic events related to the antidepressant effects of sleep deprivation. A number of mRNA differential display, microarray, and biochemical studies have also shown that short-term sleep deprivation is associated with both increased phosphorylated cyclic AMP response element-binding protein levels (pCREB, the active form of this transcription factor) and increased expression of brain-derived neurotrophic factor (BDNF) (and its receptor tyrosine kinase B [TrkB]) (reviewed in Tononi and Cirelli[140]).

In an extension of these gene expression studies, Cirelli and Tononi[139] hypothesized that the level of activity of the neuromodulatory noradrenergic and serotonergic systems is a key factor in the induction of plasticity genes. Both of these systems project diffusely in the brain, where they regulate gene expression, and are quiescent only during rapid eye movement (REM) sleep. To delineate the putative roles of the noradrenergic and serotonergic projections in regulating the expression of plasticity genes, a series of lesioning studies was undertaken. These studies showed that the expression of these molecules was regulated by the noradrenergic system, and that lesions in the locus ceruleus abolished the up-regulation of their expression. In contrast, lesions of the serotonergic system had no effect on the level of expression of these genes (reviewed in Payne et al[141]), thus implying a negligible role for the serotonergic system in the neurobiology of response to sleep deprivation.

It has been suggested that sleep deprivation may bring about its rapid antidepressant effects by activating the locus ceruleus noradrenergic system at a time when it would normally be quiescent (ie, during periods of REM sleep at night). This would then allow the interaction of released norepinephrine with a primed, sensitized postsynaptic milieu in critical circuits, resulting in the rapid and robust expression of plasticity genes such as cyclic AMP response element-binding protein (CREB), BDNF, and TrkB and, consequently, a rapid antidepressant response, as well as a switch into mania/hypomania.[141] Notably, an early case report by Gillin and colleagues[142] documented nocturnal electroencephalogram recordings in a rapid-cycling patient who experienced 4 manic switches while asleep and showed that on every occasion the last sleep stage recorded was REM; a possible role of increased locus ceruleus firing rate during REM was hypothesized as 1 of the pathophysiological mechanisms underlying the switch process.

Supporting the importance of neuroplasticity in manic-like behaviors, studies have shown that BDNF gene mutations are associated with increased spontaneous locomotion and aggression in response to acute amphetamine and chronic cocaine in rodents, symptoms that often characterize manic episodes.[143]

OTHER NEUROBIOLOGICAL FACTORS IMPLICATED IN THE SWITCH PROCESS: ROLE OF CIRCADIAN RHYTHMS

Observational studies conducted as early as the 1970s hypothesized that a disruption in circadian rhythms in bipolar disorder was a core feature of this illness. For example, an early report of patients hospitalized at the National Institute of Mental Health showed that switches into mania were more likely to happen in the morning than at night, suggesting a possible role for circadian factors in this process.[144] Marked alterations in body temperature, sleep patterns, cortisol secretion, thyroid-stimulating hormone secretion, and motor activity have been described during episodes of bipolar disorder (reviewed in Hasler et al[7]). Increased motor activity and decreased REM sleep, in particular, were found to strongly predict an imminent manic switch.[35,59,64] According to some researchers,[123] sleep loss might be the final common pathway triggering switches into mania. According to this model, the interaction between sleep reduction and a

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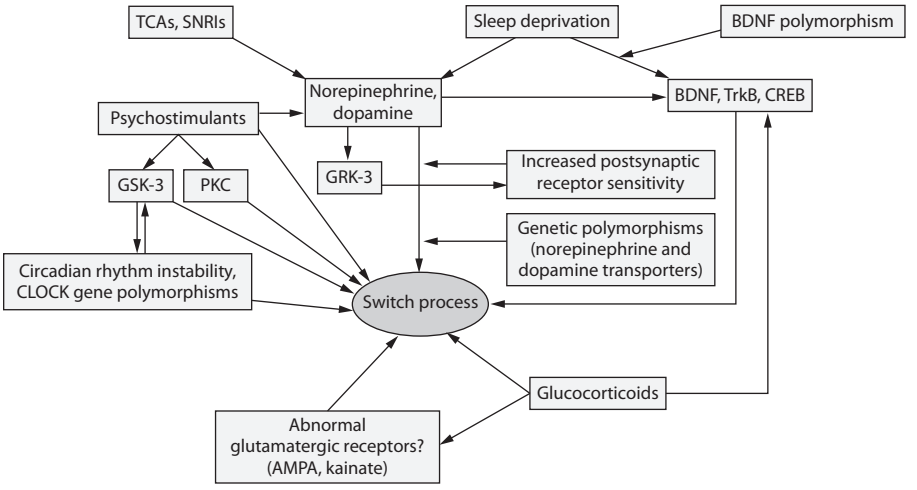
sleep-sensitive circadian phase interval could promote switches from depression. However, sleep disruption might also be the sign that the manic process is already mounting, rather than the specific trigger.

Both genetic and environmental factors might act as susceptibility factors through circadian rhythm regulation, increasing the desynchronization between the central pacemaker (ie, the suprachiasmatic nucleus) and other internal oscillators. Increased external desynchronization between the timing of body rhythms and the light-dark cycle has been also hypothesized as a predisposing factor for mood episodes.[145] Interestingly, different mood stabilizers modulate the circadian clock, controlling the expression of genes involved in circadian rhythm regulation. For example, the mood stabilizer lithium inhibits glycogen synthase kinase-3 (GSK-3), and through this mechanism increases circadian period length.[7,146] Studies conducted in Drosophila have shown that the ortholog of GSK-3, a protein called SHAGGY, is an important regulator of circadian cycles.[7] However, studies that have investigated GSK-3 polymorphisms as a putative susceptibility gene for bipolar disorder have produced conflicting results.[147–149]

Figure 1. Neurobiology of the Switch Process: A Comprehensive Overview of the Current Evidence[a]



[a]Several factors have been associated with the switch process in bipolar disorder, but little is known about how these neurobiological variables are interconnected. Psychostimulants, TCAs, SNRIs, and sleep deprivation, 4 interventions that trigger manic switches in a significant proportion of individuals with bipolar disorder, are all known to increase catecholamine levels. Increased catecholamine levels lead to up-regulation of factors involved in neuroplasticity cascades and to increased postsynaptic receptor sensitivity, which might ultimately increase the liability to switch. Psychostimulants also act by activating GSK-3 and PKC, 2 major proteins whose inhibition is important in the mechanism of action of mood stabilizers.
Other major determinants of this complex phenomenon include glucocorticoids, which increase cellular vulnerability to different physiologic stressors (eg, glutamatergic-mediated excitoxicity), abnormal glutamatergic transmission, and circadian rhythm instability.
Some genetic polymorphisms that regulate catecholaminergic transmission (norepinephrine and dopamine transporters), neuroplasticity (BDNF), circadian period length (GSK-3), and GRK-3 may also be important mediators of the switch phenomenon.
Abbreviations: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, BDNF = brain-derived neurotrophic factor, CREB = cyclic AMP response element-binding protein, GRK-3 = G protein receptor kinase 3, GSK-3 = glycogen synthase kinase 3, PKC = protein kinase C, SNRI = serotonin-norepinephrine reuptake inhibitor, TCA = tricyclic antidepressant, TrkB = tyrosine receptor kinase B.

The CLOCK gene is another major determinant of circadian cycles and might be involved in the switch to mania in patients with bipolar disorder; indeed, such evidence has arisen in animal models of bipolar disorder.[150] Disruption of the CLOCK gene produces manic-like behaviors in mice, such as hyperactivity, increased reward-value for cocaine and sucrose, and medial forebrain bundle stimulation.[150] In humans, CLOCK gene polymorphisms were shown to be associated with illness recurrence but not with diurnal variation in individuals with bipolar disorder.[8] Thus, it appears that polymorphisms in genes that regulate the circadian clock (eg, CLOCK), along with sleep disruption and consequent increase in neuroplastic factor expression (pCREB, TrkB, BDNF) might have a substantial impact on mood destabilization leading to manic switch.

CONCLUSIONS AND FUTURE PERSPECTIVES

Despite the fact that the switch phenomenon is a core aspect of the clinical presentation of bipolar disorder, as well as fundamentally relevant to its therapeutics, it is still poorly understood. The studies conducted on this issue are unfortunately associated with several methodological limitations and are often retrospective in nature or the result of secondary analyses. For example, different definitions of TEAS have been used throughout these studies and may produce dramatically different results in terms of both clinical and biologic findings. In order for a systematic study of this topic to be successful, the criteria and threshold of rating scales used will need to be uniform across studies. Agreement is also needed regarding how long after the beginning of drug treatment a manic episode should be considered as TEAS. Another major limitation in our understanding of the switch process is the lack of appropriate animal models for manic behaviors; preliminary evidence linking glutamate receptor abnormalities with manic-like behaviors in rodents[73] are encouraging in this sense and might provide new evidence about the role of the glutamatergic system in the switch process.

For these reasons, results from clinical trials that have investigated the switch potential of different classes of antidepressants are difficult to interpret and subject to controversy among researchers. Even considering these caveats, it appears that drugs that "perturbate" more than 1 monoaminergic system, such as TCAs and, possibly,

venlafaxine, confer a higher risk for TEAS than SSRIs or other second-generation antidepressants. A putative role for the monoaminergic system in the switch process has been suggested by clinical[35,64] and preclinical studies[140] but needs further systematic investigation. Increased catecholamine levels lead to up-regulation of factors involved in neuroplasticity cascades and to increased postsynaptic receptor sensitivity, which might ultimately increase the liability to switch (Figure 1).

Other pharmacologic and somatic interventions reviewed here include exogenous corticosteroids, dopaminergic agonists, and sleep deprivation. These interventions are particularly interesting because, in contrast to antidepressants, when they do induce switch, it generally occurs within a short time frame and is seen even in healthy volunteers. Also potentially relevant to the switch process are data from preclinical studies linking the HPA axis, the dopaminergic system, and sleep deprivation to intracellular signaling pathways that have been extensively investigated in bipolar disorder, as well as in the mechanisms of action of mood stabilizers; these include BDNF, GSK-3, and PKC cascades. Other factors that have been linked to this complex phenomenon include abnormal glutamatergic transmission and circadian rhythm instability.

To date, the most convincing evidence suggests that BDNF may play a major role in the switch process, as suggested by preclinical models of the antidepressant effects of sleep deprivation. Human genetic studies further suggest that BDNF plays a key role in bipolar disorder and, perhaps, switch.[151] For instance, a valine(66) methionine variant associated with increased BDNF stimulated release in vitro,[152] was found to be excessively transmitted in patients with bipolar disorder,[153] and was associated with earlier age at onset.[154] These preliminary data raise the intriguing possibility that individuals with bipolar disorder with the val/val BDNF genotype may be at greater risk for spontaneous and antidepressant- or sleep deprivation–induced switches into mania. However, future studies are clearly needed to investigate this possibility. Furthermore, BDNF has been already implicated in other facets of bipolar disorder, including rapid cycling,[155] response to lithium,[156] and suicidality.[157] Figure 1 highlights the factors and pathways that may be putative determinants of the switch process and warrant further study.

In summary, there is a clear need to refine our understanding of the neurobiology of the switch process. Research with patients who experience mood switching during the course of clinical trials in bipolar disorder is not likely to be very informative in terms of understanding the neurobiology involved in this process, given the relatively rare occurrence of switch, the time until a switch occurs, and the multiple confounding factors associated with such investigations. In order to better understand the neurobiology of the switch process, it might be more illuminating to investigate interventions that more consistently produce switch, typically within a short period of time, such as sleep deprivation. In addition, the phenomenon could be studied in distinct groups, such as healthy subjects receiving switch-inducing interventions and individuals with bipolar disorder not receiving concomitant medications. Furthermore, a large sample size would allow investigating whether healthy subjects or individuals with bipolar disorder with certain "risk polymorphisms" (eg, homozygous subjects for the BDNF Val66 allele or with certain CLOCK genetic variants) have a higher risk of switch compared to those without this vulnerability. Such group comparisons would also permit the systematic evaluation of neurobiological factors associated with switching (eg, plasma catecholamines and hormones, sleep parameters, brain imaging data). Finally, preclinical studies conducted in appropriate animal models might provide important hints about the molecular and cellular mechanisms of this understudied but key phenomenon.

Drug names: amphetamine (Adderall and others), beclomethasone (Qvar and Beconase), betamethasone (Celestone, Diprolene, and others), bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa and others), desipramine (Norpramin and others), dexamethasone (Ozurdex, Maxidex, and others), dextroamphetamine (Dexedrine and others), escitalopram (Lexapro and others), fluoxetine (Prozac, Sarafem, and others), imipramine (Tofranil and others), ketamine (Ketalar and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), memantine (Namenda), methamphetamine (Desoxyn), methylprednisolone (Medrol, Depo-medrol, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), riluzole (Rilutek and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), triamcinolone (Azmacort, Kenalog, and others), tyrosine (Demser), venlafaxine (Effexor and others).

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