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Review Article

Do we need to flick the switch? The need for a broader conceptualization of iatrogenic course aggravation in clinical trials of bipolar disorder

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The term 'switching' is often used in bipolar disorder when describing polarity changes in bipolar disorder, but this term is ambiguous and imprecise, and is sometimes used interchangeably with the term 'cycling'. Furthermore, polarity changes in bipolar disorder can be understood in different ways, because their clinical manifestations range from the emergence of subthreshold symptoms to a full episode of the opposite pole. Besides the need to tighten the meaning of the term 'switching', this paper also argues that switching does not adequately describe the complex phenomena that occur with course aggravation of bipolar disorder, such as alteration in episode frequency or amplitude. A more-fine grained approach to course aggravation in bipolar disorder is proposed, which incorporates trans-polar switching, index polarity aggravation, as well as alterations in episodic amplitude, episodic duration, and inter-episode length. This approach has the potential to capture a broader, more fine-grained and clinically relevant picture of the process of aggravation of the bipolar cycle.

Key words: bipolar disorder, cycling, clinical trial, course, switching.

AMBIGUITIES OF THE TERM 'SWITCHING'

SWITCHING IS PERTINENT to bipolar disorder, and is central to the contentious issue of antidepressant use in this condition.[1] In clinical parlance, the term 'switching' can be used to convey different situations, from a broader meaning of the occurrence of an episode of opposite polarity subsequent to the index episode, to a more narrow meaning of an intra-episodic change from the depressive to the manic pole, often with an iatrogenic connotation. Maj *et al.* noted that the terms 'switching' and 'cycling' are sometimes used interchangeably.[2] Illustrating this ambiguity is the DSM-IV definition for rapid cycling, which requires that 'episodes are demarcated either by partial or full remission for at least 2 months or a switch to an episode of opposite polarity'.[3] But there is no separate definition of switching. In addition to referring to polarity, 'switching' may also be used to denote a diagnostic change, usually from unipolar depression to bipolar disorder,[4] as well as the substitution of one medication with another.[5] This imprecise application of the term 'switching' is mirrored in the field of bipolar research, with variable definitions that potentially undermine the interpretation and comparability of results.

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In drug treatment trials, switches in mood have typically been defined as a swing from an index depressive pole to the manic pole within the same episode. As an example, in a head-to-head trial of antidepressants in bipolar depression, Post *et al.* operationalized this definition as a 2-point increase on the Clinical Global Impression–Bipolar Version (CGI-BP) mania severity scale, or a score ≥3 on this scale, or a Young Mania Rating Scale (YMRS) score >13 at any point during the trial.[6] The reverse principle has been applied in mania clinical trials, with Tohen *et al.*,[7] for instance, defining switching as the change from a Hamilton Depression Rating Scale score ≤8 at baseline to any score ≥15 at any time during the trial. Neither of these definitions requires the episode of opposite polarity to persist for any specified duration, or, for that matter, the presence of a minimum requisite number of symptoms associated with a manic or hypomanic syndrome. By contrast, Sachs *et al.*, in their placebo-controlled trial of adjunctive antidepressant therapy for bipolar depression, defined switching as the emergence of hypomania or mania meeting the DSM-IV criteria or requiring clinical intervention.[8] Although these clinical trials have set different operationalized criteria for switching, at the core of all these definitions is the primary focus on the transition from the index affective polarity to the opposite. Prior to speculating on the meaningfulness of this common notion of switching, the wider context of this concept must first be examined.

CONCEPT OF SWITCHING IN THE WIDER BIPOLAR CONTEXT

The essence of bipolar disorder is its innate affective cyclicity. Some authors have linked cyclicity with recurrence per se and differentiated it from polarity change,[9] reflective of Kraepelin's (1921) historical construct of manic-depressive illness as 'periodic circular insanity'. When the periodicity of mood episodes is not only frequent, but also regular, the longitudinal course of illness may be more complex and involve greater functional impairment than when patterns of recurrence are irregular.[10] Clearly, there may be distinct and identifiable characteristics within this cyclical process.

For instance, there are data suggesting that index polarity is predictive of the polarity of relapse, such that individuals whose index episode is depressive or mixed are more likely to have a subsequent depressive episode and, conversely, an index manic episode is predictive of a subsequent manic relapse.[11,12] A key phenomenological implication of these observations is that bipolar cyclicity may be pole-predilected. Consequently, exogenous aggravation of the core cyclical process could affect the polarity of primary individual vulnerability as much as, or perhaps even more than, the less predisposed polarity. This may provide an explanation for clinical phenomena such as the loss of antidepressant effectiveness and rapid depressive cycling. In this context the current use of switching as the sole measure of iatrogenic bipolar aggravation does not allow the investigation of this hypothesis, because it is restricted to examining polarity reversals. Notably, no clinical trials in bipolar disorder to date have included the worsening of an index episode as an outcome measure. This traditional uni-directional view may capture only one potential manifestation of bipolar cycle aggravation, when a bi-directional perspective could potentially provide more comprehensive data. Differentiating iatrogenic effects (e.g. treatment-induced worsening of mood) from the natural course of illness is often difficult to infer from non-controlled, observational studies, and may be harder to recognize if one does not account for patient-specific factors such as depression- or mania-proneness, degree of past treatment unresponsiveness, or residual symptoms that in themselves may predispose to polarity change or the exacerbation of an index mood episode.[13]

Interestingly, there is already evidence to support the utility of a bi-directional view of bipolar aggravation. In a naturalistic study of 182 patients with bipolar disorder, the primary difference between those receiving adjunctive antidepressants and those on mood stabilizers alone, was that the former more often remained in subsyndromal depression, rather than any significant differences in manic switch rates or rapid cycling.[14] In another study, these same investigators noted that bipolar individuals on antidepressants reported symptoms of depression twice as frequently as those without antidepressants.[15] Although the prescription of antidepressants may be a proxy marker of depressive vulnerability, a direct impact of antidepressants on the aggravation of bipolar depression is possible.

The hypothesis that long-term antidepressant treatment worsens the course of depression has been expounded by Fava,[16] who proposed evidence for this in phenomena that included poor long-term treatment outcomes in major depression, paradoxical antidepressant effects, antidepressant-induced

intra-episodic transpolar switching, tolerance and resistance to antidepressants. The association between antidepressant-resistant depression and undiagnosed bipolarity may also in part reflect index polarity aggravation.[17] Relating to this, Ghaemi *et al.* proposed that lack of antidepressant response in depression may be a marker of the bipolar spectrum,[18] although the very high frequency of prospectively assessed non-response to sequential antidepressant trials in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study group – for whom all subjects met DSM-IV criteria for unipolar illness – suggests that one should not assume a bipolar diathesis based solely on resistance to antidepressants.[19] Of note, there have been reports of mania induced by antidepressant discontinuation,[20,21] which may offer support for the possibility of antidepressants aggravating bipolarity in a bi-directional manner, or that acute disruptions to affective homeostasis may trigger mood destabilization.

A further issue that should be emphasized is that the notions of switching and index polarity aggravation are artificially distinguished from, and must be considered in conjunction with, other descriptive constructs, such as episodic amplitude, duration and inter-episodic length. It is feasible that exogenous aggravations to the natural bipolar cycle may affect cycle parameters other than polarity. In fact, controversial debates have surrounded the issue of antidepressant-induced cycle acceleration for some time.[22,23] For example, antidepressants have been shown to reduce the duration of the inter-episode interval.[24] Some experts believe, however, that antidepressant use is most often incidental to the emergence of mania in bipolar disorder, and that polarity switch during antidepressant treatment can be better explained purely on the basis of illness severity, irrespective of treatment.[25]

Although switching is generally viewed as a clinical syndromic change phenomenon, biological correlates of the so-called 'switch process' in bipolar disorder may include changes in total sleep time,[26] as well as a frequent familial pattern of rapid versus gradual time course to polarity change.[27] Some individuals with bipolar disorder may also be particularly vulnerable to the emergence of mania following antidepressant exposure, based on genetic[28] or other predisposing factors.[29] Agitation after selective serotonin re-uptake inhibitor initiation, for example, appears more common among individuals who have the long allele (LL-genotype) of the promoter region of the serotonin transporter.[30]

Related to the concept of polarity change is the construct of affective instability, a diagnostically non-specific phenomenon that may represent a bridge between bipolar disorder and other conditions such as borderline personality disorder.[31] There has been little study of the neurobiological correlates to mood fluctuations that may be elicited as the consequence of interpersonal or other life stresses, although limbic hyperactivity would seem core to the process. In some individuals, polarity shift is not evidenced so much by a clear 'switch' as 'affective fibrillation'. In such situations, mood dysregulation can arise in association with the qualitative experience of the environment as non-validating, or in response to interpersonal stresses. This frequently occurs in the context of a psychosocial stressor exciting the resonant frequency of the vulnerable personality; the abandoned borderline, the bruised narcissist, the betrayed paranoid, the obsessive in a mess or the rejected dependent. This is a particularly characteristic and typically dramatic reaction of the borderline construct, and overlaps with the phenomenology of mixed states and ultradian cycling.[31] Although common, this needs to be differentiated from the phasic polarity shift that characterizes bipolar disorder.

Because the identification of broad syndromal patterns remains the dominant nosological method in psychiatry and is crucial to the elucidation of etiopathology, a narrow construct of aggravation of the core cyclical process of the illness, focusing on pole-specific switch, may be disadvantageously restrictive. In order for the full spectrum of permutations in the innate bipolar cyclicity to be captured, broader constructs are clearly desirable.

PROPOSED CONTEXTUALIZATION OF SWITCHING

As previously argued, the current concept of switching provides only a 'unipolar' view of one aspect of the bipolar cycling course, which can be likened to a narrow-angle lens. We propose that the study of illness course in bipolar disorder could be enhanced by, first, a wide-angle bipolar view that incorporates the notion of bi-directional polarity modulation, and, second, consideration of additional cycle parameters. The dominant focus on switching as an adverse outcome in bipolar disorder may misleadingly emphasize polarity reversal and intra-episodic

Table 1. Parameters of cyclicity

Parameter	Description of the parameter
Trans-polar switching	The emergent symptoms are of the opposite polarity to the index episode
Index polarity aggravation	The symptoms of the index episode are of the same polarity, but have become more severe
Alterations in episode amplitude	The severity of the episode is different (more or less) than those usually experienced by the person having the episode
Alterations in episode duration	The duration of the episode is different (shorter or longer) than those usually experienced by the person having the episode
Alterations in inter-episode length	The length of time between episodes is different (shorter or longer) than those usually experienced by the person having the episode

change as the primary adverse clinical events, when the natural bipolar course may also be amplified and/or accelerated. A broader concept of exogenous cycle modulation would be more useful in this regard. We propose a standardized inventory of parameters of bipolar cyclicity (Table 1) that incorporates trans-polar switching, index polarity aggravation, as well as alterations in episodic amplitude, episodic duration, and inter-episode length, to build a multi-dimensional picture of modulations to the bipolar cyclic course. Many of these parameters are already used as standard measures of treatment outcomes, such as reduction in episodic amplitude and duration, and lengthening of inter-episodic interval. It would be logical to use the same measures to explore adverse treatment outcomes.

In the context of clinical trials we suggest that all these parameters be incorporated into study designs to provide broader measures of both desired and adverse impact of treatment on the bipolar course. In the example of bipolar depression, pertinent measures of cycle modulation would include not only the emergence of a clinically significant hypomanic, manic or mixed episode, but also worsening of the index depressive episode, which may manifest as increased symptomatic severity (paradoxical treatment response),[16] symptomatic aggravation following initial response, or loss of efficacy during the index episode. Although differentiation between aggravation of the index polarity and treatment resistance is difficult, clearer understanding will hopefully emerge in the context of aggregate cohort changes in clinical trials. Severity measures such as the YMRS, Montgomery–Asberg Depression Rating Scale, Bipolar Depression Rating Scale[12] and CGI-BP mania and depression severity scales should serve to identify individuals who experience increased depressive severity or emergent manic, hypomanic or mixed state symptoms, as well as estimate the durations of various levels of symptomatic severities. Alternatively, DSM criteria could be used to define emergent episodes of either pole, as Sachs *et al.* have done in their trial,[8] which incorporates the notion of duration. The DSM duration criteria for mania, hypomania and depression, however, have been criticized for their length, which may not detect a large number of brief affective episodes in bipolar disorder,[32,33] and any increase in cycling frequency beyond DSM-IV defined limits. Similarly, subthreshold symptoms may also be clinically significant. Ideally, these cyclicity parameters would eventually be operationally defined based on parameters captured in prospective life charting, such as deviations from euthymia or the number of occasions upon which mood states cross the midline within a given timeframe.[13]

The overlap between individual cycle parameters may compromise the specificity of each, but this may be an unavoidable imperfection in the current nosology. Clearly, at present we do not know what causes switching and bipolar course aggravation, and indeed how best to capture these phenomena that manifest commonly in clinical practice. But greater attention to the breadth of cycle metrics in research, and the standard reporting of results, are important in enhancing detection and will ultimately facilitate documentation of treatment effects in greater detail and with more accuracy.

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