Switch Phenomenon in Bipolar Disorders: What is it?

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Abstract

The phenomenon of Affective switch process is not well understood. It is difficult to differentiate switch from natural course of emergence of Manic/Hypomanic episodes. International Society of Bipolar Disorders (ISBD) has worked out operational definition for switch. Bipolar disorder I has highest rates of switch compared to Bipolar Disorders II. Tricyclics and Tetracyclic Antidepressants and Venlafaxine have highest switch rates. Controversy exists on role of mood stabilizers protecting from switch. Switch to depression is seen in some studies but meta-analyses have not focused on this issue. Among the correlates in prediction of switch, history of a positive family history of a mood disorder, symptoms of sub threshold mania, emotional dysregulation, behavior problems, Psychotic symptoms, suicide attempt and high scores on the aggressive-disruptive behavior item of the Young Mania Rating Scale appear promising. Mechanisms of switch are yet to be understood. Cautious prescribing of antidepressants for brief periods has been suggested in Pediatric Mood disruptions.

Keywords: Switch, Bipolar disorders, Antidepressants, Mood stabilizers, Pediatric BD

Introduction

The definition of mood switching lacks consensus among experts.[1] Antidepressant emergent switch was defined by the International Society for Bipolar Disorders (ISBD) task force as a manic, hypomanic or mixed episodes occurring within 8weeks after introducing an AD treatment.[2] DSM-5 adds the note to the diagnostic criteria of manic episodes as follows: "A full manic episode that emerges during antidepressant treatment, ECT but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis". Hypomanic episodes have a similar note in DSM-5. These notes seem to widen the concept of bipolar disorder because patients developing mania or hypomania during antidepressant treatment beyond the physiological effect can be diagnosed as bipolar I or II in DSM-5 although they were diagnosed as suffering from substance-induced mood disorder in DSM-IV-TR.[3] When criteria, such as self-report or an interviewer impression of "subsyndromal hypomania" (defined as an episode lasting 3 or less days with 4 symptoms or more, or as an episode lasting 4 days or more with 3 symptoms or less) are employed, then there is evidence for an increased risk of switch. Inconsistency exists between studies regarding the definition of such a switch, including the use of different scales, such as the Clinical Global Impression for Bipolar Disorder (CGIBP) or the Young Mania Rating Scale (YMRS), or using different cutoff scores for mania or hypomania on the scale, such as a YMRS score of 16, 12, or 8.[4] This results is making data applicability to clinical practice difficult. Majority of recent studies do not demonstrate a significant risk of Manic/hypomanic switch as a result of antidepressant treatment in acute bipolar depression, both as mono therapy and with a mood stabilizer when such criteria are not used.[5]

It difficult to distinguish spontaneous from antidepressant-induced switching as the difficulty lies in attributing causality, as mood elevations and changes in cycle frequency occur unpredictably in the natural course of bipolar disorder. The ISBD reached consensus in recommending use of the term "treatment-emergent affective switch" instead of antidepressant-induced switch emphasizing association without implying causality and provides operational criteria that consider factors such as timing, duration, and severity of mood changes in attributing probable causation to antidepressant treatment.[2,6,7]

Switching in Bipolar I and II groups

In a self-reported study, 40% of subjects reported manic/hypomanic switch associated with antidepressant use but recent data suggests the placebo or course-of-illness switch rate may be as low as 4–5%.[8,9]

Recent meta analyses of combined mood groups (bipolar & unipolar) have suggested that the relative risk of antidepressant associated mood elevations in bipolar II disorder was intermediate between bipolar I and major depression and that the relative risk of mania induction was more frequent with than without antidepressants, and in bipolar as compared to unipolar patients.[10,11]

Higher risk of mood switching was seen in bipolar disorder than in unipolar depression (2.50% per week compared with 0.275% per week), even though 70% of the bipolar patients were receiving antidepressant-mood stabilizer combinations and unipolar patients received an antidepressant alone.[4,6]

The risk of switch may also vary according to bipolar type. Patients with bipolar I disorder are at higher risk of switching than those with bipolar II disorder, a finding that was supported in a post hoc analysis from the Stanley Foundation Bipolar Network study.[6,10,11,12] Studies also suggested a low risk of

switching for bipolar disorder II patients, even when treated with antidepressant monotherapy.[12-15]

A systematic meta-analytic review of 13 prospective studies[16] supported the impression that bipolar I patients have a higher antidepressant-associated switch rate than bipolar II patients (relative risk=1.78, p=0.002). These findings suggest greater clinical safety with use of antidepressants in patients with bipolar II disorder as even hypomania can be problematic.[17,18]

Sidor et al[19] in his study and Tondo et al[20] in a meta-analysis synthesized data from 25 cohort studies and RCTS containing 7915 patients with bipolar I or II, reported no increased risk of switch with antidepressants when given as monotherapy or as co-treatment with mood stabilizers. The rate of overall antidepressant-induced switch was 15.3% compared to 13.8% for those not receiving an antidepressant.

Reason according to them was switch rates were higher in cohort studies and lower in RCTs. Switch rates from all high quality double-blind RCTs reporting on antidepressant use for acute bipolar depression is 8% for both antidepressant and placebo treatment arms. For cohort studies, double this rate. A prospective examination of 2166 bipolar I and II depressed patients enrolled in the STEP-BD longitudinal cohort reported an overall switch rate of 21.3%, regardless of treatment, with a median time to transition of 74 days. Of those taking an adjunctive antidepressant, 19.6% switched vs. 24.6% of patients not receiving an antidepressant. The highest switch rate, regardless of treatment, was observed in patients with rapid-cycling (44% switch rate). Retrospective analysis of a longitudinal study reported a significantly elevated risk of antidepressant-induced switch of 220 bipolar I and II patients with acute antidepressant use of 25.8% vs. 3.5% in patients not receiving an antidepressant. A meta-analysis that synthesized data from all RCTs, open-label and naturalistic studies reporting on antidepressant-induced mood elevations in bipolar I and II patients separately, found a switch rate of 14.2% and 7.1%, respectively, for acute trials (less than 16 weeks) and for maintenance trials 23.4% and 13.9%, respectively.

MEDLINE and Cochrane Collaboration Library search for papers published between 2005 and 2011 on the subject of antidepressant treatment of bipolar depression showed that the risk of manic switch following the use of SSRIs was 3.2%, not significantly greater than placebo; however, the low incidence of manic events over a short follow-up period of four to ten weeks limits the power to detect a significant difference. The rate of manic switch following the use of TCAs was demonstrated to be as high as 10%, an absolute risk difference of 6.8% (95% CI = 1.7%–11.9%); however, no valid scales were used to assess manic symptoms, causing a problem with data interpretation.

Switch to Depression

It is really difficult to distinguish whether a depressive switch is part of the natural course of the illness or should be considered as treatment-emergent. Rate of depressive switch has been estimated at 13% in first episode patients. In European study (EMBLEM) the rate of switch to depression was low (5.0%, 120/2390), probably due to olanzepine in half of the patients that could have lowered the rates. Factors associated with greater likelihood of switching to depression included previous depressive episodes, substance abuse, greater CGI-BP overall severity, mixed episodes and benzodiazepine use.[21]

Rates of depressive switch showed some variability among the different treatment arms ranging from 2.9% with quetiapine to 17.7% with haloperidol when definitions for depressive switch: MADRS score >18, HAMD-21 >15; CGI-BP depression subscale worsened by 42 points was used. Typical antipsychotics have been linked to a higher risk of depressive switch. Chlorpromazine and haloperidol are the best studied typical antipsychotics in the treatment of bipolar mania. Chlorpromazine in one small, placebo- controlled trial and a few comparative, randomized studies. Haloperidol has been compared as monotherapy to placebo, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, and as add-on treatment to lithium.

A Cochrane meta-analysis on haloperidol in acute mania (Cipriani et al)[22] showed that there was no evidence to show that haloperidol could worsen depressive symptoms in manic patients or promote switch into depression, compared to placebo. Conversely, in other studies, the rate of depressive switch was lower with olanzapine (9.4%) vs haloperidol (16.8%). Olanzapine was significantly better in prolonging time to depression. In a head-to-head comparison between and haloperidol and aripiprazole, haloperidol showed a trend to higher risk of switch (11.0% vs.17.7%). Comparison with Quetiapine, Ziprasidone did not reach statistical significance. In the observational EMBLEM study, treatment with atypical antipsychotics was significantly associated with lower rates of switch to depression. Treating acute mania with atypical antipsychotics was associated with a 42% lower risk of switch to depression than treatment with haloperidol.[23]

Globally, rates of depressive switch in these randomized controlled trials are low, ranging between 1% and 16%. Meta-analysis has not looked into the problem of depressive switch. Given this conflicting data, several clinical guide lines, British Association of Psychopharmacology (BAP) and World Federation of Societies of Biological Psychiatry (WFSBP) state there is not enough evidence yet to support the superiority of atypical over haloperidol regarding protection from switch to depression.

Atypicals have different efficacy profiles in the treatment of bipolar depression. D2 affinity is likely to be the related factor. D2 affinity has been shown to be linked to the Polarity Index. The Polarity Index indicates the relative antimanic versus antidepressive preventive efficacy of drugs. Higher Polarity Index scores are related to higher antimanic prevention and to higher D2 affinity. Among the atypicals assessed in a meta-analysis, risperidone shows the highest polarity index followed by aripiprazole (a partial agonist). Three antipsychotics that show a trend to a lower risk of switch to depression (quetiapine, ziprasidone and olanzapine) are the ones with a lower polarity index. In a randomized clinical trial comparing quetiapine and paliperidone in acute mania, supports the idea of most powerful D2 blockers being more prone to depressive switch. In this trial, a higher percentage of paliperidone treated patients (13.9%) switched to depression compared to the quetiapine group (7.5%).

Anti-depresssants use and discontinuation in switch

In BRIDGE study, Angst et al.[24] showed the significant relationship between mood lability with an antidepressant in BD. They reported that antidepressant-induced mania/ hypomania is significantly more prevalent in BD than in MDD using the univariate analysis.

A 6-year Retrospective study of 37 patients,[20] manic/hypomanic switch was most frequently observed between 2 and 3 weeks after the antidepressant increase. Antidepressants were decreased in 13 patients and discontinued in 23. Manic/hypomanic episodes lasted from 1 to 8 weeks. The higher frequency of manic/ hypomanic switch occurred around the period when antidepressants begin to show clinical effects and the higher frequency of family history of bipolar disorders might suggest a biological susceptibility to antidepressants in patients of the switch group. Once manic or hypomanic switch develops, discontinuation or dose reduction of antidepressants should be considered. Most patients improved after discontinuation of ongoing antidepressants and after several patients received short-term antipsychotic treatment.

Type of Antidepressants and their association with Switch

Randomized trials evaluating the risk of switches with antidepressant treatment with and without a mood stabilizer are few and difficult to interpret, due to methodological limitations

A consistent finding from randomized controlled trials on antidepressants in bipolar patients is that of differences among types of antidepressants in their association with mood switches.[4,25] Several meta-analyses have evaluated antidepressant-associated switch risk which showed the rate of treatment emergent switch occurred substantially more often with tri- and tetracyclics (11.2%) than with SSRIs (3.7%) or placebo (4.2%). Sidor[19] in a meta-analysis found that, with the exception of tri- and tetracyclics and venlafaxine, switching was uncommon with other SSRIs and MAOIs. Rates of spontaneous switching were in BD I 15.3% and BD II 13.8%, with or without antidepressants. Several placebo-controlled randomized controlled trials did not find elevated switch rates with SSRIs or bupropion, either as adjuncts to mood stabilizers or as monotherapy.

In a 6-month double-blind placebo-controlled trial,[4][26] rates of mood elevations were indistinguishable (10.1% compared with 10.7%) between subjects receiving a mood stabilizer plus an antidepressant (bupropion or paroxetine, N=179) and those receiving a mood stabilizer plus placebo (N=197).

Monotherapy, with SSRIs,[4,27] paroxetine (20 mg/day) was not associated with more mood switching than placebo. In a 12-month trial the risk of antidepressant associated switching ranked was 9% for sertraline, 10% for bupropion, and 29% for venlafaxine. A short-term (6–week) study also found more mood switching with venlafaxine than with paroxetine in depressed bipolar I and II patients. Most studies of SSRIs have involved sertraline or paroxetine, and effects of MAO inhibitors are virtually unknown.

Efficacy of antidepressants in bipolar II depression remains uncertain as mostly they are open-label or small RCTs involving Paroxetine, fluoxetine, sertraline, bupropion, venlaflaxine and citalopram. The authors are of the opinion that antidepressant monotherapy with SSRIs should be considered as a second-line treatment option for bipolar II depression if alternative treatments have failed. In a double-blind continuation study of 81 bipolar II fluoxetine responders which found that long-term (up to 50 weeks) monotherapy with fluoxetine was superior to lithium or placebo for prevention of depression-relapse. However, patients that originally responded well to fluoxetine progressed to the continuation phase with fluoxetine. [18] Contrast to these findings with results from large randomized placebo controlled trials, such as the STEP-BD and EMBOLDEN II trials, report no advantage of acute SSRI treatment to placebo in terms of clinical response or remission, regardless of bipolar sub-type, highlighting the importance of study design to the results and conclusions obtained. It appears that maintenance therapy for up to 3 years with an adjunctive antidepressant provides no enhanced clinical response or benefit for bipolar II depression.

Among other drugs, Ziprasidone was most likely to be ranked first for switch to mania (i.e. has the lowest risk of switch) and lamotrigine most likely to be ranked last. Olanzapine+ fluoxetine and quetiapine can be said to have the most optimal balance of efficacy and safety with respect to switching.[28]

Does adding Mood stabilizer to antidepressant change the picture?

Tondo et al[29] in a comprehensive review found a lack of evidence that treatment with mood stabilizers protects against mood elevation in bipolar patients, with or without antidepressant co-treatment, but noted a lack of appropriate controls or randomization with which to make an adequate assessment.[4]

They found that mood stabilizers did not protect against treatment-emergent mania during antidepressant treatment. Their meta-analysis included several studies adding up a large number of patients, but could not control for confounding factors. Patients treated with a mood stabilizer in combination with an antidepressant had a more severe disorder than patients treated with a mood stabilizer alone, which is likely to obscure any potential protective effect that a mood stabilizer has on the switch rate.

In Swedish national registry study[30] on 3240 BD patients, adopting within individual design (which reduced confounding caused by differences in disorder severity) patients on antidepressant monotherapy was associated with an increased risk of mania (hazard ratio=2.83, 95% CI=1.12, 7.19) compared to group on antidepressant with mood stabilizer during the 3 months after the start of antidepressant treatment (hazard ratio= 0.79, 95% CI=0.54, 1.15), and a decreased risk was observed during the period 3–9 months after treatment initiation (hazard ratio=0.63, 95% CI=0.42, 0.93).

Electro Convulsive Therapy(ECT) and Switching

Pathogenesis of the depressive relapse or switching to mania during ECT is not clear, although evidence shows the involvement of BDNF and GDNF in both processes. Peripheral BDNF levels were repeatedly reported to be low in depressive disorders and in depressive and manic episodes of bipolar disorder but findings related to GDNF levels are contradictory. Impaired glial cell functions in mood disorders resulted in decreased synaptic glutamate uptake and extracellular glutamate toxicity, which has a role in the pathogenesis of manic switch.[31]

Studies are needed to verify the mechanisms that initiate manic switch; whether higher GDNF levels are a compensatory up-regulation against glutamate toxicity or increased release due to the activation of the extracellular signal-regulated kinase/mitogen-activated protein kinase and/or dopaminergic systems.

rTMS and Switch

A review of 53 RCTs of rTMS in unipolar and bipolar depression, Treatment Emergent Mania occurrence rate was 0.84% for active treatment group, and 0.73% for sham group, which was not statistically different. In total of 65 bipolar patients, the switching rate in the active rTMS group was 3.1% and for unipolar depression was 0.34% indicating that rTMS does not have a higher risk of manic switch than antidepressants pharmacotherapy.[32]

In a parallel crossover study on 130 patients with 1 and 2 Hz stimulation, only one manic switch occurred (again, in patient with bipolar depression). There is a report of transient hypomanic symptoms in a period of a day during high frequency rTMS given at the left prefrontal cortex (PFC) in 3 of 50 healthy volunteers. It is hypothesized that rTMS in combination with antidepressant medications might modulate kindling and sensitization phenomena, which enhance cycle acceleration in bipolar spectrum patients. Use of mood stabilizers during rTMS treatment of bipolar depression was proposed to maximize safety, but that also did not completely stop switches during rTMS, similar to use of mood stabilizers during antidepressant pharmacotherapy.

Further controlled studies of rTMS in mania are needed to answer about manic switch.

Mechanisms of switch

In Biological Factors, Meta-analyses of studies of 5HTTLPR and antidepressant induced mania did not demonstrate a significant association between genotypes at the 5HTTLPR polymorphism and antidepressant induced mania.[33]

Kindling refers to a progressive decline in the strength of electrical current required to elicit seizure activity. Post (1992) postulated the kindling hypothesis of mood disorders, whereby major psychological stressors play a greater role in the initial episodes of a mood disorder. Only 1 in 3 retrospective human studies have provided support for such a hypothesis.[34]

Altered HPA function, or hypersensitivity to glucocorticoids, may represent a trigger related to switching between mood states. Manipulation of the HPA axis could induce switching of mood states in 30–80% of cases in a dose-related fashion. Prednisone treatment can induce manic episodes in BD sufferers. About pharmacological treatments that can induce switching to a depressive state, Physostigmine, an acetylcholinesterase inhibitor indirectly elevates acetylcholine. Physostigmine treatment can reduce mania symptoms in BD patients Elevated acetylcholine levels are observed in patients with BD and unipolar depression as well as altered cholinergic receptor levels in BD.

Environmental factors that induce switching between states in BD:

Disturbed sleep patterns have been observed at the time of the switch to mania in euthymic unmedicated patients with BD. Full sleep deprivation can induce a manic episode in up to 30% of BD patients and mania-like behavior in healthy subjects. Sleep deprivation-induced changes in mood supports the social rhythm disruption (SRD) theory of affective disorders. According to SRD theory a disruption in social/biological rhythm can induce changes in mood in

vulnerable individuals. Disruption can be stressful live events, or even positive events. Disruption in daily rhythm during summers or spring high can also induce switches into a manic episode associated with elevated TH levels. The triggers that switch to a depressed state appear less clear at present.

Clinical correlates of Switch and Predictors

Most of the information regarding clinical correlates of risk of mood switching during antidepressant treatment is from retrospective or post hoc analyses.[4]

Sub-syndromal manic symptoms at the start of antidepressant with mood stabilizer treatment were associated with an increased risk of switching into hypomanic or manic episodes, worsening of manic symptoms, and higher rates of unsatisfactory response to antidepressants. Also, a history of suicide attempt and high scores on the aggressive-disruptive behavior item of the Young Mania Rating Scale, were associated with a higher risk of mood switching among antidepressant-treated depressed bipolar patients.

A large long-term study found that among patients in a major depressive episode, those meeting criteria for bipolar features showed a higher risk of later episodes of hypomania or mania and greater mood lability during antidepressant treatment. A history of antidepressant-associated mood switching, lower rates of previous clinical benefit from antidepressant treatment, and multiple previous antidepressant trials have been associated with subsequent mood switches, generally more severe illness, and worse long term outcomes. Depressed bipolar patients first exposed to antidepressant monotherapy had higher switch rates and more suicide attempts than those treated with antidepressant- mood stabilizer combinations.

The picture regarding genetic characteristics as predictors of mood switching in bipolar patients treated with antidepressants is still unclear.

Patients with continuous cycling BD are more likely to be depressive than mixed at onset and a higher rate of switch and a lower rate of response to treatment regimens. Antidepressants should be avoided in mixed depressive episodes may increase manic symptoms severity and switch and suicidality.[35]

In a review of 7 studies,985 pediatric depression followed up for 1–11 years showed significant risk factors for manic switches as, a positive family history of a mood disorder, symptoms of subthreshold mania, emotional dysregulation, behavior problems and Psychotic symptoms. The rate of manic switching in youth with MDD ranged between 9–49%.[9]

In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) analyses of 2,154 patients who completed one follow-up with depressive episode during the study, a switch to a manic, hypomanic or mixed state prior to recovery from the index episode of depression was observed in 21.2% which was significantly greater in those with current or past drug or alcohol use disorder.[36] 4.8% of them experienced antidepressant-emergent manic switch (AEMS) after 4 weeks of antidepressant treatment in depressed bipolar patients receiving mood stabilizers in everyday practice. The mean time from antidepressant initiation to induction of mania or hypomania was 11.4 to 9.0 days and was frequently associated with lifetime manic, depressive, and total mood episodes and with past AEMS. A higher score at two items of MADRS, pessimistic and suicidal thoughts were significantly associated with AEMS. Number of life time manic episodes and past AEMS were the two most factors associated with an AEMS. More than 4 past manic episodes was associated with a 2.84 fold increased risk of AEMS with the attributable risk being 47.5%. For more than 9 past depressive episodes (OR=1.97) and for more than 8 mood episodes of any type (OR=2.18). Several studies have demonstrated impairing effects on brain function with more frequent, long, or chronic states of depression advocating the possibility of a neurotoxic effect of mood episodes.[37]

In a Survival analysis study for time to transition to mania, hypomania, or mixed state among 2166 bipolar I and II individuals in a major depressive episode, (21.3%) transitioned to a manic/hypomanic or mixed state before remission, 19.6% of those treated with antidepressants for the episode. Clinical features associated with greatest transition hazard (HR=1.23) were greater number of past depressive episodes, recent or lifetime rapid cycling, alcohol use disorder, previous suicide attempt, and history of switch while treated with antidepressants. Lifetime history of suicide attempt and the disruptive behavior item on the YMRS were associated with significantly greater switch risk only among antidepressant-treated patients.[38]

Study on 217 bipolar disorder type I and II, whose first episodes were depression, with a history of antidepressant treatment-induced mania, compared to recurrent (unipolar) major depressive disorder had similar clinical features suggest that antidepressant-induced switching may represent an acceleration of the natural course of bipolar disorder.[39]

Paediatric BD switch

In a retrospective cohort study, aged 6–18 years of bipolar disorder and depression, treatment groups were 179 antidepressant monotherapy, 1047 second-generation antipsychotic (SGA) monotherapy, 570 mood stabilizer monotherapy, 445 antidepressant polytherapy, and 1906 SGA–mood stabilizer polytherapy users. Manic switch was defined as having received a diagnosis of mania within 6 weeks after the initiation of bipolar depression treatment. Study findings indicated a higher risk of manic switch associated with antidepressant monotherapy than with SGA (Hazard Ratio = 2.63) in pediatric patients with bipolar depression. The finding supported the clinical

practice of cautious prescribing of antidepressants for brief periods.[40,41]

Emotional dysregulation and subthreshold forms of BD-I disorder whether they increase the risk for BD switches in ADHD youth with non-bipolar MDD was done in a prospective study. Profile of the Child Behavior Checklist (CBCL) with (2SD) elevations in the Anxiety/Depression, Aggression, and Attention (A-A-A) scales was used.The rate of conversion to BD-I disorder at follow up was higher in MDD subjects with subthreshold BD-I disorder at baseline compared to those without (57% vs. 21%; OR=9.57, 95%CI=1.62–56.56, p=0.013) and in MDD subjects with deficient emotional self-regulation (OR=3.54, 95%CI=1.08–11.60, p=0.037).[42]

Conclusion

Affective switch process criteria at present has to reach a global consensus, however, operational guidelines recommended by International Society for Bipolar disorders (ISBD) would be a starting point. If the operational criteria are accepted, then differentiation of switch from natural course of emergence of Manic/Hypomanic episodes would not be too difficult theoretically. Recording of events and recall bias as in most of the Psychiatric diagnosis is definitely not an easy task practically. Bipolar disorder I has highest rate of switch compared to BD II. In fact, BD II switch does not appear to be different from Placebo group. In well conducted studies, BD I switch rates are less compared to prevalence or open labeled studies. While SSRIs appear mostly safe, tricyclics, tetracyclic antidepressants and venlafaxine have highest switch rates. Mood stabilizers protecting from switch is a matter of debate and scope for research. Switch to depression is seen in some studies but meta-analyses have not focused on this issue. While looking for correlates in prediction of switch, history of a positive family history of a mood disorder, symptoms of subthreshold mania, emotional dysregulation, behavior problems, Psychotic symptoms, suicide attempt and high scores on the aggressive-disruptive behavior item of the Young Mania Rating Scale appear promising. Underlying mechanisms of switch are yet to be understood. Pediatric Mood disruptions is an active area of research and cautious prescribing of antidepressants for brief periods has been suggested as behavioural activation and impulsivity are seen frequently.

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