Achieving Expert Consensus on the Operational Definition of Treatment-Emergent Affective Switch (TEAS) Using the Delphi Method

Round 1 Feedback Report

Results of the First Delphi Round and Proposed Revisions for Round 2

Expert panel: 30 participants from 18 countries
Round 1: 27 statements

TEAS Consortium

August 2026

Study protocol: OSF Registration **https://osf.io/t6kr3/overview**

Project website: teas-consortium.com

This document summarizes the aggregated results of Round 1, anonymized expert comments, and proposed modifications for Round 2.

Contents

About this report

This report provides aggregated feedback from Round 1 of the international Delphi study on the definition of TEAS. It summarizes quantitative ratings, anonymized expert comments, and the proposed disposition of each statement for Round 2. Proposed revisions are intended to clarify the wording and address methodological issues identified by the panel while preserving the original scope of the Delphi process.

Expert panel characteristics

Of the 111 experts invited to participate, 40 registered for the study and 30 completed Round 1. The Round 1 panel represented 18 countries, most commonly the United States (n = 5, 16.7%), Canada (n = 4, 13.3%), India and Russia (n = 3 each, 10.0%), and Italy (n = 2, 6.7%); the remaining 13 countries were each represented by one expert. Most participants worked primarily in a university or academic department (n = 19, 63.3%), followed by a research institute or federal centre (n = 8, 26.7%) and an outpatient service (n = 3, 10.0%).

The median duration of professional experience in psychiatry was 29 years (interquartile range [IQR], 20–35), and the median lifetime h-index was 40.5 (IQR, 29.3-70.0). Most experts reported having authored 11 or more publications on the diagnosis and/or treatment of bipolar disorder (n = 23, 76.7%). Four participants (13.3%) reported 4-10 publications, two (6.7%) reported 1-3 publications, and one (3.3%) preferred not to disclose this information.

Twenty-one experts (70.0%) had participated in the development or adaptation of clinical guidelines for the treatment of bipolar disorder, whereas nine (30.0%) had not. The guidelines most commonly used in clinical practice were the CANMAT/ISBD guidelines (n = 18, 60.0%) and national clinical guidelines (n = 11, 36.7%). The CINP guidelines were used by six experts (20.0%), the WFSBP guidelines by five (16.7%), the NICE guidelines by four (13.3%), and the APA guidelines by three (10.0%). Six participants (20.0%) found this question difficult to answer or preferred not to disclose the guidelines they used. As multiple responses were permitted, the percentages do not sum to 100%.

Regarding clinical workload, two experts (6.7%) reported following or treating fewer than 10 patients with bipolar disorder per month, nine (30.0%) reported 10-30 patients, nine (30.0%) reported 31-60 patients, and five (16.7%) reported more than 60 patients. Five participants (16.7%) found the question difficult to answer or preferred not to disclose this information.

The proportion of patients with bipolar depression currently treated with antidepressants was below 10% for 12 experts (40.0%), 10-30% for eight (26.7%), and 31-50% for five (16.7%). None of the experts reported prescribing antidepressants to more than 50% of their patients with bipolar depression. Five participants (16.7%) found this question difficult to answer or preferred not to disclose this information. All 30 experts agreed to be contacted regarding potential participation in a future TEAS research consortium.

Statistical analysis and consensus criteria

Responses to each Delphi statement were rated on a 9-point Likert scale, where higher scores indicated greater agreement with the statement. For each item, the distribution of responses was summarized using the median and interquartile range (IQR), reported as the first and third quartiles (Q1-Q3). In addition, ratings were grouped into three predefined categories: disagreement (scores 1-3), intermediate/uncertain ratings (scores 4-6), and agreement (scores 7-9). The proportion and absolute number of responses in each category were calculated for every statement.

Consensus criteria were defined a priori in the study protocol before analysis (see https://osf.io/t6kr3). Consensus of Agreement was considered reached when the median score was between 7 and 9, at least 70% of participants rated the statement between 7 and 9, and fewer than 15% rated it between 1 and 3. Consensus of Disagreement was considered reached when the median score was between 1 and 3, at least 70% of participants rated the statement between 1 and 3, and fewer than 15% rated it between 7 and 9. All other response patterns were classified as No Consensus.

A directional tendency toward agreement was reported descriptively when the median was within the agreement range (7-9) but one or more formal consensus criteria were not met; an analogous rule was applied to disagreement. Such a tendency was not considered equivalent to consensus and was not counted as a final consensus outcome.

Open-text comments were reviewed qualitatively alongside the quantitative results. Comments were used to identify ambiguity, double-barrelled wording, unsupported operational thresholds, or other methodological issues that could affect interpretation of an item. Comments are presented using anonymous expert identification numbers and are listed in chronological order of submission. Comments were not edited for substantive content. In preparing Round 2, statements that had reached consensus were generally retained unchanged. Revisions were made only when Round 1 feedback indicated a substantive problem with wording, scope, or interpretability. Items without consensus were either retained for re-rating when disagreement appeared substantive, or revised/split when the comments suggested that the original formulation combined conceptually distinct questions. Background text could also be revised for clarification or neutrality without changing the rated statement itself.

Summary of all statements

Outcome of the first round

Item status	Items, n	Items, %
Consensus of Agreement	14	51.9%
Consensus of Disagreement	0	0.0%
No Consensus	13	48.1%

Summary table of 27 statements

Statement / topic	Median [Q1-Q3]	1-3 (disagreement)	4-6 (middle range)	7-9 (agreement)	Consensus status
01 Need for unified definition	9 [8-9]	3.3% (n=1)	0.0% (n=0)	96.7% (n=29)	Consensus of Agreement
02 DSM/ICD relevance	8 [7-8.75]	3.3% (n=1)	6.7% (n=2)	90.0% (n=27)	Consensus of Agreement
03 Guidelines and clinical practice	9 [7-9]	3.3% (n=1)	3.3% (n=1)	93.3% (n=28)	Consensus of Agreement
04 Antidepressants as triggers	8 [7-9]	6.7% (n=2)	10.0% (n=3)	83.3% (n=25)	Consensus of Agreement
05 Other therapeutic interventions	7 [5.25-8]	10.0% (n=3)	23.3% (n=7)	66.7% (n=20)	No Consensus
06 Psychoactive substances	8 [7-9]	3.3% (n=1)	13.3% (n=4)	83.3% (n=25)	Consensus of Agreement
07 Core manifestations / 8-week window	7 [5-8]	16.7% (n=5)	20.0% (n=6)	63.3% (n=19)	No Consensus
08 Post-discontinuation switches	5.5 [5-7]	10.0% (n=3)	46.7% (n=14)	43.3% (n=13)	No Consensus
09 No discontinuation requirement	8 [6.25-9]	10.0% (n=3)	16.7% (n=5)	73.3% (n=22)	Consensus of Agreement
10 Additional manifestations	7 [5.25-8]	6.7% (n=2)	26.7% (n=8)	66.7% (n=20)	No Consensus

11 Increased cyclicity	8 [7.25-9]	3.3% (n=1)	16.7% (n=5)	80.0% (n=24)	Consensus of Agreement
12 Short-duration TEAS in BD	7.5 [5-8]	23.3% (n=7)	13.3% (n=4)	63.3% (n=19)	No Consensus
13 TEAS in MDD	5 [3.25-8]	26.7% (n=8)	26.7% (n=8)	46.7% (n=14)	No Consensus
14 Rating-scale thresholds	8 [6.25-9]	13.3% (n=4)	13.3% (n=4)	73.3% (n=22)	Consensus of Agreement
15 Diagnostic interview	8 [5.25-8]	16.7% (n=5)	13.3% (n=4)	70.0% (n=21)	No Consensus
16 Rating scales as auxiliary tools	8.5 [8-9]	6.7% (n=2)	3.3% (n=1)	90.0% (n=27)	Consensus of Agreement
17 Clinical causality assessment	9 [8-9]	3.3% (n=1)	10.0% (n=3)	86.7% (n=26)	Consensus of Agreement
18 Graded causality	7.5 [6-8.75]	10.0% (n=3)	23.3% (n=7)	66.7% (n=20)	No Consensus
19 Spontaneous switches / risk factors	8 [7-8.75]	6.7% (n=2)	16.7% (n=5)	76.7% (n=23)	Consensus of Agreement
20 Treatment discontinuation	8 [6.25-9]	6.7% (n=2)	20.0% (n=6)	73.3% (n=22)	Consensus of Agreement
21 Trial-level causal inference	6.5 [3.25-9]	26.7% (n=8)	23.3% (n=7)	50.0% (n=15)	No Consensus
22 Washout period	6 [5-8]	6.7% (n=2)	50.0% (n=15)	43.3% (n=13)	No Consensus
23 Retrospective ascertainment	7.5 [7-8]	3.3% (n=1)	20.0% (n=6)	76.7% (n=23)	Consensus of Agreement
24 Subthreshold presentations in MDD	8 [7.25-9]	3.3% (n=1)	3.3% (n=1)	93.3% (n=28)	Consensus of Agreement
25 Rapid antidepressant response	5 [4-7.75]	23.3% (n=7)	40.0% (n=12)	36.7% (n=11)	No Consensus
26 Activation warning signs	7 [5.25-8]	0.0% (n=0)	46.7% (n=14)	53.3% (n=16)	No Consensus
27 Activation in youth	5 [5-7]	13.3% (n=4)	53.3% (n=16)	33.3% (n=10)	No Consensus

Proposed changes for Round 2

Statement	Proposed Round 2 disposition
1	Retain unchanged
2	Retain unchanged
3	Retain unchanged
4	Retain unchanged
5	Retain unchanged; background revised
6	Retain unchanged
7	Split into Statements 7a and 7b
8	Split into Statements 8a and 8b
9	Retain unchanged; background revised
10	Split into Statements 10a-10c
11	Retain unchanged; background revised
12	Revise; remove fixed 2-day minimum duration
13	Revise; align temporal criteria and diagnostic implications with the applicable DSM/ICD classification
14	Retain unchanged; background revised
15	Revise; include structured or semi-structured diagnostic interview and remove embedded DSM/ICD assumption
16	Retain unchanged; background revised
17	Retain unchanged; background revised
18	Revise; restrict graded causality assessment to research/pharmacovigilance and remove fixed confidence categories
19	Split into Statements 19a and 19b
20	Retain unchanged; treat as a clinical management recommendation rather than a defining criterion
21	Revise; state that randomized, double-blind, placebo-controlled trials provide the strongest evidence for causal risk

22	Revise; replace fixed 7-day washout with an intervention-appropriate washout period
23	Retain unchanged; background revised
24	Revise; replace fixed duration thresholds with reference to the applicable DSM/ICD classification
25	Retain unchanged; background revised
26	Revise; remove “soft forms of affective switching” and focus on heightened vigilance
27	Retain unchanged; background revised

Detailed item-by-item feedback

General remarks

Statement 1

A clear definition of TEAS is necessary to standardize basic science and clinical research, including trials of pharmacological and non-pharmacological interventions (including those conducted for regulatory purposes).

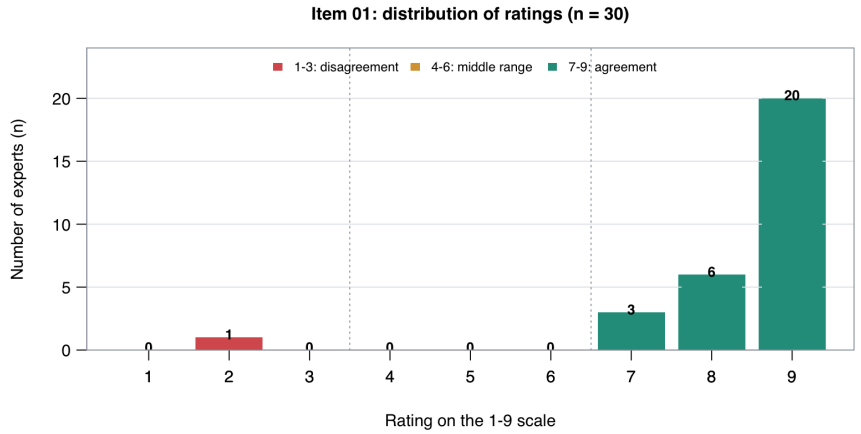
Background

Without a unified operational definition of TEAS, comparison of the results of clinical and basic research is extremely difficult. This is a key issue for the reproducibility and validity of scientific data required both by regulators (e.g., the FDA/EMA) and by developers of clinical guidelines.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	9	8	9	1

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.3% (n=1)	0.0% (n=0)	96.7% (n=29)



Consensus status: Consensus of Agreement (96.7% agreement; median 9 [8-9])

Comments (listed in chronological order of submission):

- ➔ 518904 - Affective switch is an uncommon event.
- ➔ 124685 - It is necessary to find a clear and common definition of a common phenomenon, in order to clarify the framework within which to operate.
- ➔ 126537 - There is currently heterogeneity in the definition making cross-study comparisons difficult.
- ➔ 891256 - affective 'roughening' should also be considered as well as flattening of the affect.
- ➔ 465130 - It is also necessary for standardised care.
- ➔ 597318 - TEAS is not sufficient. Antidepressants destabilize bipolar illness and increase the risk of rapid cycling, subsyndromal symptoms, and depression. TEAS is only one of the things that may occur.
- ➔ 406857 - It is important to have unified operational definition of TEAS. This will help in establishing reliability of how TEAS has been defined across studies.
- ➔ 690284 - Yes, I agree, and I have a specific comment: When a patient in an acute trial on antidepressants efficacy develops a switch it is important to obtain concensus on whether this should be considered an adverse event or a response, or both. In my opinion it should be considered a response.
- ➔ 269845 - A clear definition of TEAS should consider: 1) measurable symptomatic (rating scales) and functional (rating scales) definition of intensity AND durability; 2) a cronologically coherent relation with antidepressant start OR dose increase; 3) an aceptably short time between a.d. dose start/increase and onset of symptoms.

Round 2 action: Retain unchanged and re-rate.

Statement 2

The definition of TEAS may help refine the DSM and ICD diagnostic criteria for hypomania, mania, and mixed states emerging during treatment.

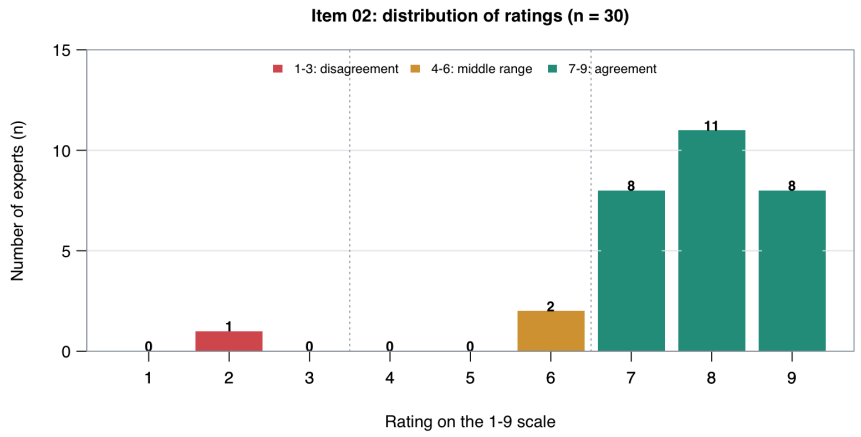
Background

Historically (DSM-IV, ICD-10), an affective episode unequivocally caused by an antidepressant or other "somatic" treatment was not considered sufficient grounds for a diagnosis of bipolar disorder. Contemporary classifications (DSM-5, ICD-11) allow such a diagnosis if symptoms of hypomania, mania, or mixed states persist at a syndromal level after discontinuation of treatment. However, authoritative organizations such as the ISBD go further and do not include treatment discontinuation as a mandatory condition in the definition of TEAS. A clear, research-based definition of TEAS is needed to resolve this controversy and establish a unified, clinically grounded standard.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	7	8.75	1.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.3% (n=1)	6.7% (n=2)	90.0% (n=27)



Consensus status: Consensus of Agreement (90% agreement; median 8 [7-8.75])

Comments (listed in chronological order of submission):

➔ 518904 - We need to know when and how TEAS occur.

- ➔ 124685 - Probably a correct definition of TEAS, appropriately supported by scientific references, could broaden and improve the definitions of mania, hypomania and mixed state of bipolar disorders.
- ➔ 827195 - The formal definition would allow for further research into category of TEAS and conventional affective diagnoses in terms of clinical and biological differences.
- ➔ 126537 - Changing DSM is a complicated, protracted, process and it is uncertain whether a clearer definition will result in a change in the DSM.
- ➔ 138956 - Indeed, in our research and clinical practice, even idiosyncratic reactions to antidepressants often indicate latent bipolarity.
- ➔ 763291 - Particularly pertinent to adolescents who experience an affective switch when treated for depression and where a diagnosis of bipolar disorder may be dismissed, precluding early intervention and prevention of disability.
- ➔ 597318 - Affective switch is actually too limiting.
- ➔ 276415 - If we can create an evidence informed definition of TEAS (for example, using data from acute and longitudinal placebo-controlled studies to determine the timeframe after treatment initiation when a switch is likely to be attributable to treatment; and using population-based studies to determine what proportion of people with TEAS later experience spontaneous mood elevations), this can inform diagnostic classifications.
- ➔ 406857 - Yes, that is true. It used to be called Bipolar III - switch induced. Clinically if any patient has mania/hypomania/mixed state while on treatment, we usually treat it as bipolar.
- ➔ 690284 - I agree this is an important question, but here in the case of unipolar depression we need to differentiate between TEAS as the first switch or TEAS as switch subsequent to spontaneous switch(s).
- ➔ 948206 - I am not sure whether the salient issue here is the TEAS definition or better consensus around the extent to which TEAS predict future bipolar episodes/risk
- ➔ 269845 - An excessive dose of antidepressant may induce an overactivation symptomatology which is not a TEAS and perfectly remits after adjusting to the correct (effective) dosis.

Round 2 action: Retain unchanged and re-rate.

Statement 3

A unified definition of TEAS is important for the development and updating of clinical guidelines, as well as for decision-making in real-world clinical practice.

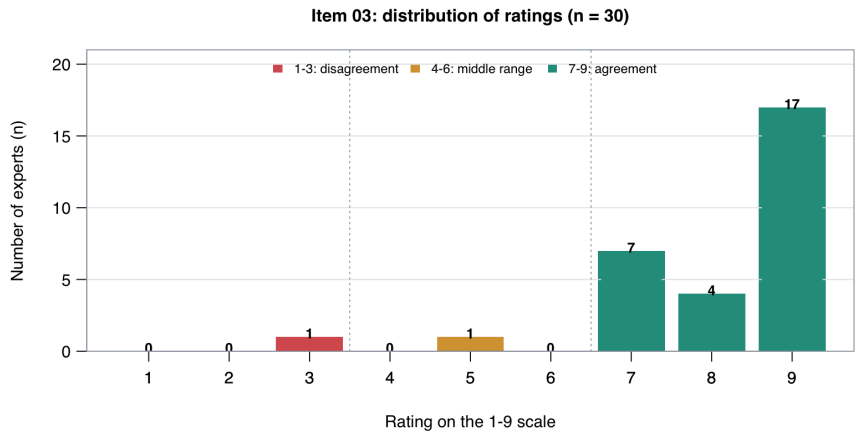
Background

The definition of TEAS is of considerable importance in many clinical guidelines for the treatment of bipolar depression. For example, some guidelines recommend against prescribing antidepressants to patients with a history of TEAS. Other guidelines propose different treatment algorithms for bipolar I depression and bipolar II depression, including on the basis that TEAS is more frequent in the former. At the same time, evidence of a higher risk of TEAS in bipolar I disorder has not been replicated across all studies. Thus, the absence of a unified definition of TEAS leads to substantial heterogeneity in the results of clinical trials, which is then reflected in the lack of concordance among international clinical guidelines.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	9	7	9	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.3% (n=1)	3.3% (n=1)	93.3% (n=28)



Consensus status: Consensus of Agreement (93.3% agreement; median 9 [7-9])

Comments (listed in chronological order of submission):

- ➔ 518904 - Studies are inconsistent about higher rates of TEAS in BD-1. Therefore, it is unclear how to unify the definition.
- ➔ 124685 - The lack of a clear and common definition limits the possible standardized interventions.
- ➔ 126537 - Not sure how many clinicians read clinical guidelines.
- ➔ 406857 - Agreed. Another thing which probably we have not discussed is antipsychotic emergent dysphoria. In clinical situations, we sometimes noticed the following: Patient has been treated with mood stabilizers and antipsychotics for mania, patient has improved and after few days/week or two, complains of dysphoria and continue despite stopping antipsychotics - Do we call it treatment emergent depression? These are common in clinical practice. When dealing with such cases, I wait for 2 weeks of complete stopping of antipsychotics (continuing mood stabilizers) and if dysphoria/depression (+other symptoms) still persists, I treat like bipolar depression. For me definition of TEAS should include Time of switch (after how much time - days/weeks of starting medications, there was switch). Effect of discontinuation. How long should be the duration. Severity and type of clinical symptoms should not be part of the criteria.
- ➔ 690284 - The problem with the thinking here is that TEAS and spontaneous switch cannot be separated in trials. In my opinion, TEAS should refer to an emergent switch no matter causality, e.g. as an outcome in trials testing prophylactic activity. See Grunze et al 2013 (WFSBPS Guidelines on maintenance treatment of bipolar disorder).
- ➔ 269845 - A consensus definition of TEAS should be systematically required in RCT researching on antidepressant drugs.

Round 2 action: Retain unchanged and re-rate.

Potential Triggering Factors

Statement 4

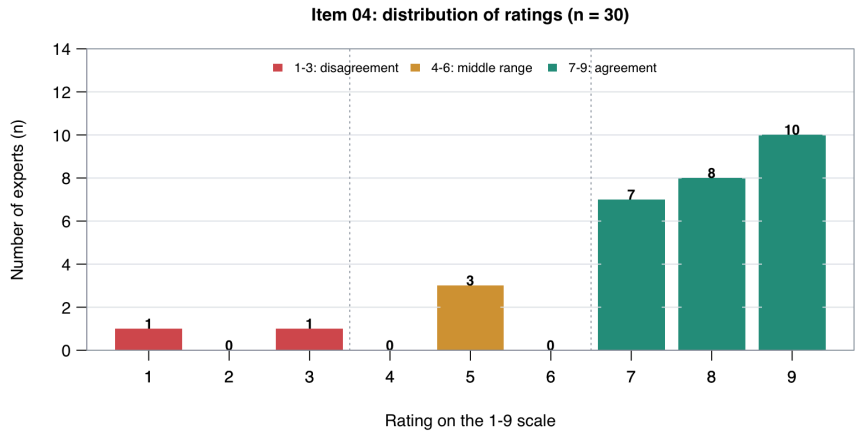
TEAS should be recognized as a potential adverse outcome of antidepressant treatment.

Background (see Statement 5)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	7	9	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
6.7% (n=2)	10.0% (n=3)	83.3% (n=25)



Consensus status: Consensus of Agreement (83.3% agreement; median 8 [7-9]).

Comments (see Statement 5).

Round 2 action: Retain unchanged and re-rate.

Statement 5

TEAS should also be considered a potential adverse outcome of other prescribed treatments or interventions with antidepressant effects (for example, antipsychotics with antidepressant properties, dopamine agonists, anti-inflammatory agents, electroconvulsive therapy, sleep deprivation, etc.), although the evidence is less extensive than for antidepressants.

Background

Historically, TEAS has been associated primarily with antidepressant treatment. However, affective switches have also been described with other interventions that have antidepressant effects, including ECT [1, 2], light therapy [3], sleep deprivation [4], as well as several other treatment classes, among them antipsychotics with antidepressant properties [5, 6, 7], dopaminergic agents [8, 9], and anti-inflammatory therapy [10, 11]. This raises the question of whether TEAS is a specific effect of antidepressants or a broader phenomenon associated with rapid reduction of depressive symptoms and/or dopaminergic stimulation. At the same time, the frequency of such switches, their mechanisms, and their clinical significance have been studied far less extensively than in the case of antidepressants, and the evidence for individual types of therapy remains limited to case series.

References:

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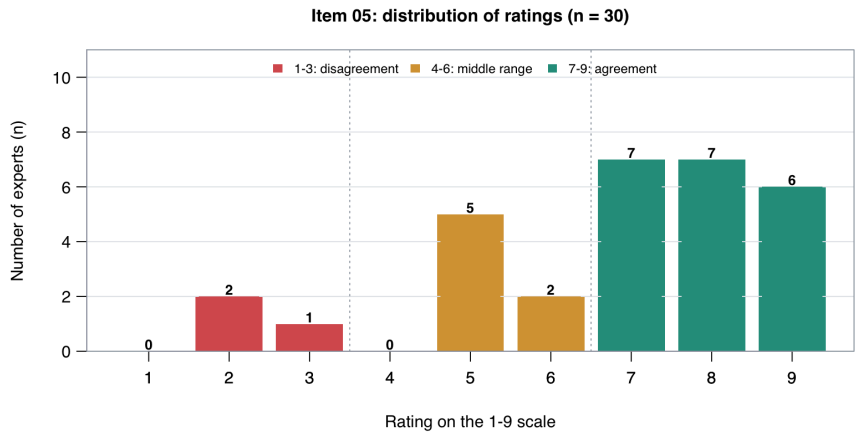
Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	7	5.25	8	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
10.0% (n=3)	23.3% (n=7)	66.7% (n=20)



Consensus status: No Consensus, with a directional tendency toward agreement (66.7% agreement; median 7 [5.25-8]).

Comments (listed in chronological order of submission):

- ➔ 485621 - TMS, especially вteta-birst stimulation, should be added to the list of probable TEAS [Miuli A, Sepede G, Stigliano G, Mosca A, Di Carlo F, d'Andrea G, Lalli A, Spano MC, Pettorruso M, Martinotti G, di Giannantonio M. Hypomanic/manic switch after transcranial magnetic stimulation in mood disorders: A systematic review and meta-analysis. World J Psychiatry. 2021 Aug 19;11(8):477-490. doi: 10.5498/wjp.v11.i8.477 and Miller B. Theta burst but not standard stimulation resulting in treatment emergent affective switching (teas): an inter- subject case-control series of two patients. Brain Stimulation 13(6):1845 DOI: 10.1016/j.brs.2020.06.026].
- ➔ 731602 - Antidepressants, dopamine agonists or stimulants are among most obvious contributors, but there other potential triggers with very little systematic data available yet "suspect" in clinical practice.
- ➔ 518904 - The problem is that TEAS occur also spontaneously.
- ➔ 351746 - TEAS should not be viewed as a "general" adverse effect, it is primarily associated with bipolar disorder.
- ➔ 124685 - The potential of different drugs to induce TEAS should be differentiated based on the category and pharmacological potency of the molecules, with particular attention to tricyclic antidepressants. It would be ideal to identify antidepressants indicated for major depressive episodes rather than MDD, such as vortioxetine. I would be more cautious with antipsychotics.

- ➔ 854317 - It may depend on the clinical purpose for which the intervention was used. For example, the definition may differ between mood changes that occur when a dopamine agonist is used as adjunctive treatment for depression and those that occur when it is used for ADHD treatment. Similarly, TEAS may be conceptualized differently when ECT is administered for its antidepressant effect compared with when it is used primarily to treat psychotic symptoms. Therefore, I think the statement would be clearer if it explicitly incorporated the clinician's therapeutic intent when defining the relevant intervention.
- ➔ 465130 - Eidence is not strong enough to include TEAS as an adverse effect for other treatment other than anti-depressants. Further large scale studies are required.
- ➔ 763291 - Also consider lamotrigine.
- ➔ 597318 - The definition of TEAS must be independent of specific agents.
- ➔ 276415 - Regarding the second question, I definitely agree that comparing rates of TEAS in antidepressants and other treatments will help inform comparisons of the risk-benefit ratios. Case reports will probably not be particularly informative. Acute phase trials may also not fully capture the relevant data, since TEAS also appears to have a low risk during acute trials with both adjunctive modern antidepressants and second-generation antipsychotics. Longer term (maintenance) placebo-controlled trials will probably be of the greatest relevance. To give an example, a meta-analysis of placebo-controlled RCTs of adjunctive antidepressants (PMID: 34483777), and Yatham's placebo-controlled maintenance RCT of adjunctive antidepressants (PMID: 37530824), showed an increased risk of hypomanic/manic switch during long-term treatment, compared to placebo. In contrast, maintenance studies of second generation antipsychotics with antidepressant properties like quetiapine show that it significantly reduces the risk of mania compared to placebo. Maintenance treatment with adjunctive lurasidone (PMID: 28689688) and cariprazine (PMID: 38609342) also non-significantly reduced the risk of mania. There is probably limited data for other treatments like ECT, ketamine, etc.
- ➔ 406857 - Whether we call it side effect of the treatment or occurrence of full fledged separate episode. Clinically I consider it the latter for management purposes.
- ➔ 690284 - Again, in individual cases it is impossible to differentiate between natural/spontaneous switch and drug-induced switch, both from depression to mania or from mania to depression (see Licht et al 2008).
- ➔ 269845 - TEAS should be systematically assessed with different treatments, pharmacological but not only. However, rather than an adverse effect, I see it as a precipitating factor of a preexisting liability.

Round 2 action: Retain unchanged and re-rate. Background revised for clarification to reflect the varying strength of evidence across different interventions.

New background: Historically, TEAS has been associated primarily with antidepressant treatment. However, affective switches have also been described with other interventions that have antidepressant effects, including ECT [1, 2], light therapy [3], sleep deprivation [4], as well as several other treatment classes, among them antipsychotics with antidepressant properties [5, 6, 7], dopaminergic agents [8, 9], and anti-inflammatory therapy [10, 11]. This raises the question of whether TEAS is a specific phenomenon associated primarily with antidepressant treatment or a broader phenomenon that may also occur with other therapeutic interventions. At the same time, the frequency of such switches, their mechanisms, and their clinical significance have been studied far less extensively than in the case of antidepressants, and the strength of evidence varies substantially across individual interventions.

Statement 6

Affective switches attributable to psychoactive substances (for example, intoxication) should be considered separately from TEAS if they are not associated with prescribed treatment, and should be coded under the heading “Disorders due to substance use or addictive behaviours”.

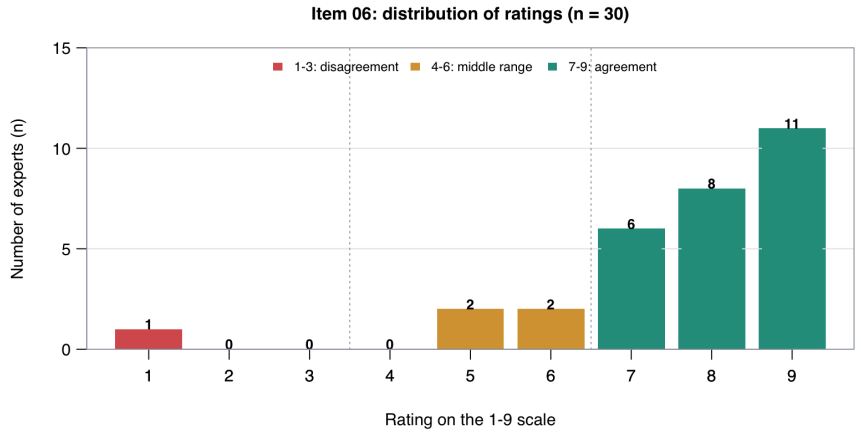
Background

TEAS as a research construct was developed to assess the safety of therapeutic interventions, rather than to explain all possible triggers of affective instability in bipolar disorder. Patients with bipolar disorder are vulnerable to a wide range of external influences, including stress, somatic illnesses, and psychoactive substance use. If all such states are incorporated into the definition of TEAS, the construct loses its specificity and ceases to be a useful instrument for regulatory decision-making and clinical trials. Distinguishing substance-induced states from TEAS (an outcome associated with prescribed treatment) helps preserve the operational clarity of the concept and avoids conflating medication-related risk assessments with risks attributable to comorbid substance use disorders.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	7	9	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.3% (n=1)	13.3% (n=4)	83.3% (n=25)



Consensus status: Consensus of Agreement (83.3% agreement; median 8 [7-9])

Comments (listed in chronological order of submission):

- ➔ 670349 - Distinguishing substance-induced states from TEAS clarifies the concept and separates medication-related risk from risks tied to comorbid substance use disorders.
- ➔ 518904 - The definition of switch associated with nonprescribed substances would be useful.
- ➔ 124685 - It is right to distinguish between drug intoxication and a prescription at therapeutic doses.
- ➔ 465130 - a different coding from “Disorders due to substance use or addictive behaviours” should be used.
- ➔ 417960 - Substance induced mood disorder is a differential diagnosis.
- ➔ 597318 - This exclusion becomes more important with the introduction of psychedelics. However one needs to define how long is reasonable for intoxication.
- ➔ 276415 - It's beyond the scope of this project, but investigating the biological mechanisms underlying switches related to all of these influences would be informative. I can envision the possibility of different mechanisms related to different antidepressant classes; and overlapping mechanisms between some substances of abuse and some antidepressants; which might over time, as these mechanisms become clearer, modify how we think about this question.
- ➔ 406857 - I think it should remain separate - the biological pathway here (due to treatment) may be similar to the biological pathway of bipolar disorder. The pathways of substance induced affective symptoms/disorders may be similar to substance dependence disorders.
- ➔ 269845 - By definition, recreational drugs are not treatment, therefore should not be included in the definition of "TEAS". This is a semantic problem, as recreational drugs may clearly induce affective episodes, and similarly to treatment-emergent ones, an acute intoxication would not fulfill the concept of an acute mood episode induced by the recreational drug.

Round 2 action: Retain unchanged and re-rate.

Main Clinical Manifestations

Statement 7

TEAS is characterized by the development of hypomania, mania, or mixed states within 8 weeks of treatment initiation or following a dose increase of antidepressants or other interventions with antidepressant effects.

Background

The reproducibility of the definition of TEAS requires alignment of three interrelated parameters, each of which carries methodological implications. First, the definition should be limited exclusively to clinically significant episodes of hypomania, mania, or mixed states, verified by means of a diagnostic interview rather than identified solely on the basis of rating scale data. Second, the 8-week time window is consistent with the ISBD consensus and ensures comparability with the main body of the literature; however, its applicability to non-antidepressant interventions remains empirically untested [1]. Third, the time count should restart not only at treatment initiation, but also after each dose increase, because patients often enter studies while already receiving ineffective treatment, and switches occurring after treatment intensification would otherwise be erroneously attributed either to the initial regimen or to the spontaneous course of disease. A potential difficulty is that this set of criteria, while increasing the internal validity of studies, simultaneously creates a gap from clinical reality: rigid reliance on an 8-week window and on dose escalation does not capture all clinically meaningful scenarios (for example, switches occurring after dose reduction of an antipsychotic or mood stabilizer, or delayed reactions in slow metabolizers). Thus, the proposed parameters represent a working agreement necessary for the standardization of research, but one that requires either empirical validation or recognition as a provisional compromise open to revision as further data accumulate.

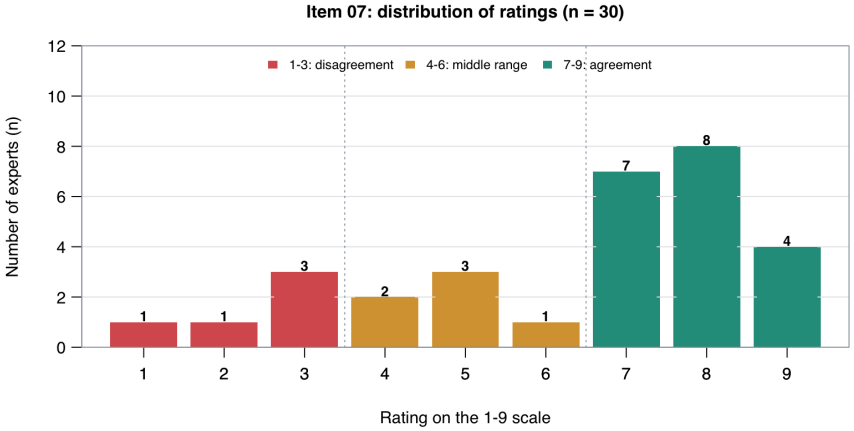
References:

1. Tohen, M., Frank, E., Bowden, C. L., Colom, F., Ghaemi, S. N., Yatham, L. N., Malhi, G. S., Calabrese, J. R., Nolen, W. A., Vieta, E., Kapczinski, F., Goodwin, G. M., Suppes, T., Sachs, G. S., Chengappa, K. R., Grunze, H., Mitchell, P. B., Kanba, S., & Berk, M. (2009). The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar disorders, 11(5), 453–473. https://doi.org/10.1111/j.1399-5618.2009.00726.x

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	7	5	8	3

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
16.7% (n=5)	20.0% (n=6)	63.3% (n=19)



Consensus status: No Consensus, with a directional tendency toward agreement (63.3% agreement; median 7 [5-8]).

Comments (listed in chronological order of submission):

- ➔ 670349 - These parameters are a useful research standard but should remain provisional pending empirical validation or revision as new data emerge.
- ➔ 518904 - The 8-week window is unproven. I have seen TEAS even after several months of treatment.
- ➔ 124685 - The definition appears adequate, I would only exclude previous states of mania prior to the prescription and the differential diagnosis with states of activation and anxiety.
- ➔ 840362 - This statement does not cover other possible changes in therapy, such as dose reduction or treatment discontinuation. I suggest replacing the phrase “dose increase” with “dose adjustment” (or “change in dose”).
- ➔ 138956 - I am getting more and more frustrated by definitions containing arbitrary elements, usually around the duration of treatment, but even symptoms. Unless we can base the 8 weeks on actual data, I would rather not include an arbitrary number.
- ➔ 240738 - 8 weeks may be too long.
- ➔ 891256 - not sure about the time frame. Also i consider other affective conditions (e.g. roughening).
- ➔ 854317 - As a general comment, I found it somewhat unclear whether this question is intended to ask whether TEAS should be limited to the current syndromal definitions of affective episodes, or whether it should also include broader clinically relevant phenomena, such as Koukopoulos' agitated depression or antidepressant-associated chronic irritable dysphoria. Because the subsequent questions address these issues separately, respondents may interpret the purpose of this question differently depending on the order in which they read the questionnaire.
- ➔ 465130 - How do you determine biologically the antidepressant effect responsible for TEAS?

- ➔ 597318 - TEAS should not be limited to switch from depression to mania. One should also consider switch from mania to depression, or euthymia to either mania or depression, or switch from a stable mood (euthymic, depressed, manic) to a different mood including rapid cycling.
- ➔ 276415 - I'm probably in the minority, but I'm going to express uncertainty/disagreement on this. The evidence regarding this is poor and not strong enough to make such a statement. For the (hopefully) most common situation - combining an antidepressant with an antimanic agent or agents - a 2021 meta-analysis found that the risk of manic/hypomanic switch didn't differ between antidepressant and placebo in trials lasting 6-12 weeks (PMID: 34483777). In other words, any switch occurring during this period is most likely due to the natural history of the illness. Although treatment emergent, there's unlikely to be a causal effect. Now, this was based on a small number of trials and patients, and they obviously met inclusion criteria for research studies (and so weren't necessarily reflective of real-world patients), but it's the best evidence we have. Conversely, this same MA found that in 2 trials lasting a year, the switch rate was significantly higher with antidepressant than placebo. The Yatham NEJM 1-year placebo controlled maintenance study similarly found a (non-significantly) higher switch rate with adjunctive antidepressant than placebo (PMID: 37530824). My own suspicion is that antidepressants increase the risk of switch for however long they're prescribed, with the effect accumulating over time (and thus best detectable over long periods). I'm not certain there's a specific high-risk period. I know this doesn't really help in terms of forming a definition of TEAS, but above all I feel like we should avoid an incorrect definition that will set things back. In the situation of antidepressant monotherapy things may be different - we've all seen patients switch almost immediately on starting an antidepressant in clinical practice - but that's less well studied. Of note, in the McElroy EMBOLDEN 2 study, paroxetine monotherapy didn't have a higher switch rate than placebo (10.7% v 8.9%) (PMID: 20122366).
- ➔ 406857 - The recommended duration to diagnose that 2 separate episodes have occurred is - 8 weeks/ 2 months. If we keep duration as 8 weeks, it would be difficult to differentiate between spontaneous affective episode or TEAS.
- ➔ 690284 - TEAS should not be confined to treatment with antidepressants and to any causality between any drug and switch. TEAS as an outcome could also be applied to a placebo arm.
- ➔ 948206 - Are you asking whether this is the accepted definition or whether this SHOULD be the accepted definition? I was a bit confused by the question itself.
- ➔ 269845 - the time cutoff should be unequivocally assessed with evidence.

Round 2 action: Revise and split into two statements for re-rating. The clinical manifestations and the proposed 8-week temporal criterion will be assessed separately, as Round 1 comments indicated that disagreement was primarily related to the time window rather than to the core clinical manifestations of TEAS.

New statement 7a
TEAS should be characterized by the development of hypomania, mania, or mixed states following treatment initiation or a dose increase of antidepressants or other interventions with antidepressant effects.

New statement 7b
An 8-week period following treatment initiation or a dose increase should be used as the operational time window for the emergence of TEAS.

New Background: Existing definitions of treatment-emergent affective switch generally focus on the emergence of clinically significant hypomanic, manic, or mixed states in temporal association with treatment. An 8-week window after treatment initiation or dose increase has been used in the ISBD nomenclature and in subsequent research, providing a practical framework for standardization and cross-study comparability [1]. However, the empirical basis for a fixed 8-week cutoff remains limited. Round 1 comments highlighted uncertainty regarding whether this interval is too short, too long, or applicable across different treatments, as well as whether the relevant time window should differ according to treatment characteristics. Therefore, the clinical manifestations and the temporal criterion are presented separately for re-rating in Round 2.

Statement 8

The 7-day period following discontinuation or abrupt reduction of an antidepressant or other intervention with antidepressant effects should be regarded as a vulnerable period for the emergence of TEAS.

Background

Traditionally, affective switches were thought to occur predominantly during the treatment initiation phase [1,2]. However, accumulating evidence indicates that TEAS may also emerge during antidepressant discontinuation or abrupt dose reduction [3]. Inclusion of the 7-day period following discontinuation in the definition of TEAS is necessary for the proper capture of these states in safety studies and real-world clinical practice, since otherwise switches occurring at the end of treatment may be erroneously attributed to the spontaneous course of illness or may be excluded from analysis altogether. A potential difficulty lies in the empirical uncertainty surrounding the time window itself: seven days is an expert-based assumption rather than a value established on the basis of prospective studies of the temporal distribution of TEAS after discontinuation. In real-world clinical practice, antidepressants are often tapered gradually, and it remains unclear whether the vulnerable period should be counted from the first dose reduction, from complete discontinuation, or from crossing some "subtherapeutic" threshold. It also remains an open question whether the same period is applicable to other interventions with antidepressant effects (for example, discontinuation of light therapy or completion of an ECT course), for which the pharmacokinetic and neurobiological mechanisms of discontinuation may differ substantially. Thus, the proposed criterion expands the clinical relevance of the definition of TEAS, but requires either validation in specifically designed studies or deliberate acceptance as a provisional operational agreement.

References:

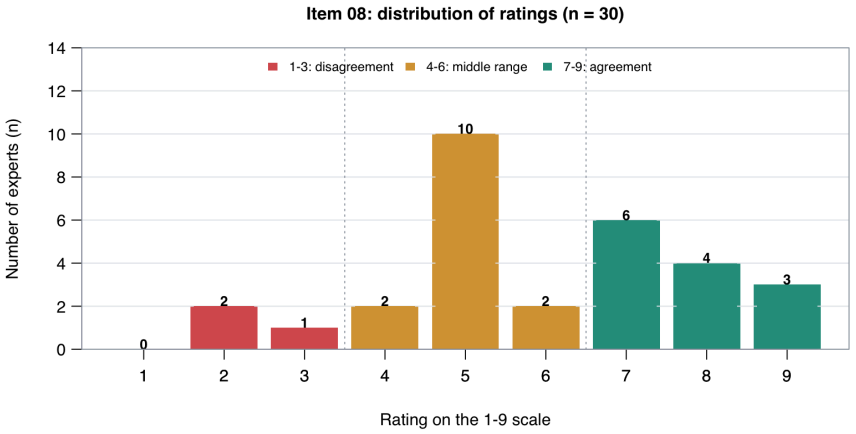
1. Tohen, M., Frank, E., Bowden, C. L., Colom, F., Ghaemi, S. N., Yatham, L. N., Malhi, G. S., Calabrese, J. R., Nolen, W. A., Vieta, E., Kapczinski, F., Goodwin, G. M., Suppes, T., Sachs, G. S., Chengappa, K. R., Grunze, H., Mitchell, P. B., Kanba, S., & Berk, M. (2009). The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar disorders, 11(5), 453–473. https://doi.org/10.1111/j.1399-5618.2009.00726.x
2. Altshuler, L. L., Suppes, T., Black, D. O., Nolen, W. A., Leverich, G., Keck, P. E., Jr, Frye, M. A., Kupka, R., McElroy, S. L., Grunze, H., Kitchen, C. M., & Post, R. (2006). Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. The American journal of psychiatry, 163(2), 313–315. https://doi.org/10.1176/appi.ajp.163.2.313
3. Ali, S., & Milev, R. (2003). Switch to mania upon discontinuation of antidepressants in patients with mood disorders: a review of the literature. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 48(4), 258–264. https://doi.org/10.1177/070674370304800410

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	5.5	5	7	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement

10.0% (n=3)	46.7% (n=14)	43.3% (n=13)



Consensus status: No consensus (43.3% agreement; median 5.5 [5-7])

Comments (listed in chronological order of submission):

- ➔ 913780 - Antidepressants like fluoxetine which has long half-life, may require longer period.
- ➔ 670349 - In clinical practice, antidepressants are often tapered gradually. This makes it unclear whether the vulnerable period begins with the first dose reduction or only after full discontinuation.
- ➔ 518904 - The 7-days after discontinuation is an arbitrary time.
- ➔ 124685 - The type of suspension should be distinguished, whether hyperbolic, or gradual according to which scheme.
- ➔ 840362 - A duration of 7 days may not be universally applicable and could, for example, depend on the antidepressant's half-life. It is possibly more appropriate for sertraline, but less so for fluoxetine.
- ➔ 138956 - Same issue as above, i.e. including arbitrary duration criteria, which are not based on evidence. Also, this gets into somewhat misleading territory, misnomers - i.e. treatment emergent effects at the time when the treatment is not present.... That may either speak to a different mechanism or simply a cumulative impact of the previous treatment, impossible to differentiate.
- ➔ 891256 - needs differentiation from antidepressant withdrawal symptoms.
- ➔ 597318 - The immediate time period after discontinuation is a period of withdrawal (not too dissimlar from intoxication).
- ➔ 276415 - As you outline well in the Background above, there is much uncertainty about this statement. It's unclear to me whether it should be considered a separate phenomenon ("treatment discontinuation emergent mania?").
- ➔ 406857 - yes.

- ➔ 948206 - I don't necessarily agree with the assertion that patients are at risk for TEAS in the setting of AD cessation.
- ➔ 269845 - The reliability of this inclusion, as well as its threshold, should be univocally assessed before its inclusion.

Round 2 action: Revise and split into two statements for re-rating. Round 1 comments indicated separate uncertainty regarding whether affective switches following treatment discontinuation or abrupt dose reduction should be included within TEAS and whether a fixed 7-day temporal window is appropriate.

New statement 8a

Affective switches emerging following discontinuation or abrupt reduction of an antidepressant or other intervention with antidepressant effects may be classified as TEAS.

New statement 8b

A 7-day period following discontinuation or abrupt reduction of an antidepressant or other intervention with antidepressant effects should be used as the operational time window for the emergence of TEAS.

New background: Affective switches have been reported not only after treatment initiation or dose escalation, but also following antidepressant discontinuation or abrupt dose reduction [1–3]. However, it remains uncertain whether such events should be considered part of TEAS or regarded as a distinct treatment-discontinuation phenomenon. An additional unresolved issue concerns the appropriate temporal window. A fixed 7-day period has practical advantages for operational standardization, but its empirical basis is limited and its applicability may vary according to the pharmacokinetic properties of the treatment. Round 1 comments also highlighted the need to distinguish affective switches from antidepressant withdrawal phenomena and the difficulty of applying a fixed window when treatment is tapered gradually. For Round 2, the inclusion of post-discontinuation switches within TEAS and the proposed 7-day temporal criterion will therefore be assessed separately.

Statement 9

Hypomania, mania, or mixed states emerging during treatment with antidepressants or other interventions with antidepressant effects should be classified as TEAS, even if the antidepressant treatment was not discontinued.

Background

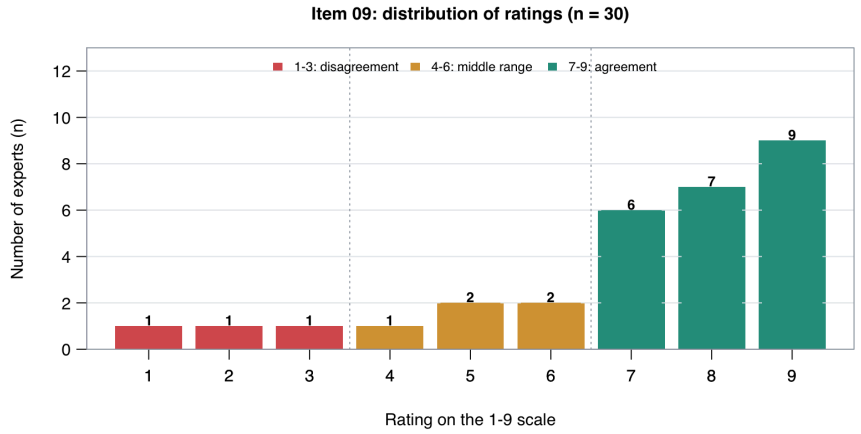
A key methodological issue in the ICD and DSM frameworks remains whether treatment discontinuation is necessary to demonstrate TEAS. The traditional approach, which requires confirmation that syndromal symptoms persist after discontinuation of the medication, creates a number of inherent limitations. First, it introduces a temporal delay between the event and its ascertainment, which runs counter to the logic of intervention safety assessment: the decision to modify treatment is made at the moment symptoms emerge, not after an experimental discontinuation. Second, the requirement for discontinuation is ethically problematic in the context of severe affective episodes and is difficult to implement in designs intended to model routine clinical practice, where discontinuation may be gradual, accompanied by the addition of mood stabilizers, or may not occur at all because outpatients do not return for consultation after a change in mental state. Third, there are no empirical data demonstrating that switches which remit after antidepressant discontinuation differ qualitatively, in terms of mechanisms, predictors, or prognostic significance, from switches that persist after discontinuation. The very concept of "persistence after discontinuation" has not been operationalized: neither the required duration of observation nor the degree of symptom reduction needed to consider an episode "fully induced" is clear.

On this basis, it appears justified to define TEAS exclusively on the basis of its temporal association with a therapeutic intervention and the attainment of full syndromal criteria for hypomania, mania, or mixed states, regardless of whether the symptoms persist after discontinuation of the medication. This approach ensures the internal coherence of the construct: TEAS is regarded as an outcome reflecting the risk inherent in the treatment itself at the time of its use, rather than as the result of a hypothetical test of the state's "endogeneity." At the same time, the question remains open as to the threshold duration of symptoms required for an episode to be ascertained (for example, whether hypomania must meet criteria for 4 days even if all 4 days occurred during treatment), as well as how to classify cases in which discontinuation was nevertheless carried out and symptoms remitted within 24-48 hours. Nevertheless, removing the requirement for mandatory discontinuation is a necessary condition for bringing the research construct of TEAS closer to clinically meaningful events and for improving the external validity of safety studies.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	6.25	9	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
10.0% (n=3)	16.7% (n=5)	73.3% (n=22)



Consensus status: Consensus of Agreement (73.3% agreement; median 8 [6.25-9])

Comments (listed in chronological order of submission):

- ➔ 731602 - This point needs to clarify the time frame. New onset (hypo)mania or mixed symptoms after several months of treatment may not qualify.
- ➔ 518904 - Discontinuation as a requirement is not necessary.
- ➔ 124685 - The definition should not be affected by discontinuation, but rather should be supported by continued use and the counter-evidence is a new TEAS in case of new exposure.
- ➔ 827195 - TEAS should take into account change in affective switch after treatment discontinuation as empirical proof of relationship with treatment to delineate a more homogeneous group.
- ➔ 840362 - Even though the required duration to validate TEAS while continuing antidepressant treatment is not clearly defined, it would still be preferable for the statement to specify something like “Hypomania, mania, or mixed states of sufficient duration to meet diagnostic criteria for an episode...”
- ➔ 138956 - Emphasis here is to not call side effects of AD, especially those more stimulating ones, a hypomanic episode!
- ➔ 597318 - I agree since most clinicians actually miss a mixed state and continue the antidepressant. If we limit the definition to agents that have antidepressant effects we may miss agents that can induce mania without an antidepressant effect.
- ➔ 406857 - agreed.
- ➔ 690284 - At this point in the survey, I see a major problem: When using the term TEAS here above, it already relates to causality, which I find problematic. First, we

need a prober definition of affective switch and then we could reach consensus about whether specific treatments are associated more or less with this.

- ➔ 269845 - there is a strong risk of overdiagnosing TEAS, therefore bipolar disorders, by excluding the need for the episode to persist after reduction/discontinuation. Also, a simple excessive dose prescription of antidepressants might induce a presentation that the untrained eye, such as an investigator in a trial, might confuse with a TEAS by dully applying rating scales. Therefore, I believe it is fundamental to retain the idea of mood episode persisting after reduction/discontinuation.

Round 2 action: Retain unchanged and re-rate. Background revised to present the competing considerations regarding persistence after treatment discontinuation more neutrally.

New background: A key methodological issue in DSM and ICD frameworks is whether persistence of hypomanic, manic, or mixed symptoms beyond the physiological effects of treatment is required for the episode to be regarded as a clinically meaningful affective episode rather than a transient treatment-related state. Requiring persistence after treatment discontinuation may improve specificity and help distinguish TEAS from short-lived activation or other direct treatment effects. At the same time, this approach has practical limitations: treatment may not always be discontinued, discontinuation may be gradual, and additional treatment may be introduced immediately after the emergence of symptoms, making persistence difficult to assess. Moreover, the duration of observation required to establish persistence has not been clearly operationalized. Round 1 comments reflected both positions: some experts considered discontinuation unnecessary for identifying TEAS, whereas others regarded persistence after dose reduction or discontinuation as important for avoiding overdiagnosis and for strengthening causal attribution. The statement is therefore retained unchanged for re-rating.

Additional Clinical Manifestations

Statement 10

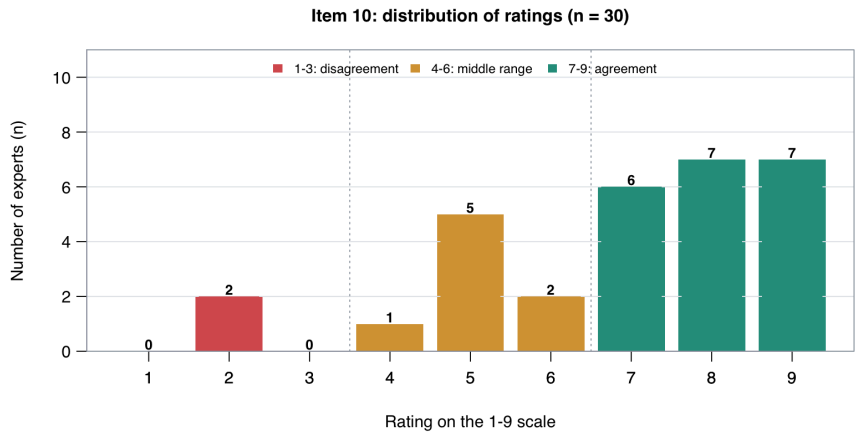
TEAS may be accompanied by psychotic symptoms, suicidal behavior, or paradoxical worsening of depression occurring shortly after the initiation or intensification of treatment with an antidepressant or other interventions with antidepressant effects.

Background (see Statement 11)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	7	5.25	8	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
6.7% (n=2)	26.7% (n=8)	66.7% (n=20)



Consensus status: No Consensus, with a directional tendency toward agreement (66.7% agreement; median 7 [5.25-8]).

Comments (see Statement 11)

Round 2 action: Split into three statements and re-rate. Round 1 comments indicated that psychotic symptoms, suicidal behavior, and paradoxical worsening of depression represent distinct clinical phenomena that may warrant separate consideration.

New statement 10a

TEAS may be accompanied by psychotic symptoms occurring shortly after the initiation or intensification of treatment with an antidepressant or other intervention with antidepressant effects.

New statement 10b

TEAS may be accompanied by suicidal behavior occurring shortly after the initiation or intensification of treatment with an antidepressant or other intervention with antidepressant effects.

New statement 10c

TEAS may be accompanied by paradoxical worsening of depression occurring shortly after the initiation or intensification of treatment with an antidepressant or other intervention with antidepressant effects.

Statement 11

TEAS may also include an increase in the cyclicity of bipolar disorder, namely the development during treatment of rapid or ultra-rapid cycling in a patient in whom such patterns had not been observed during the preceding 12 months.

Background

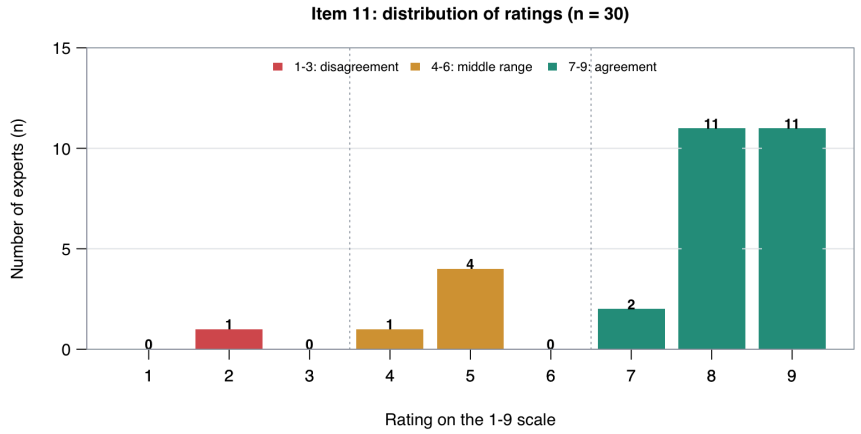
Existing definitions of TEAS have focused predominantly on polarity switch – mania, hypomania, and mixed states – as the only outcome relevant to the assessment of antidepressant treatment safety. However, the spectrum of clinically significant adverse phenomena arising in temporal association with the initiation or intensification of an antidepressant intervention is substantially broader. The literature describes cases of the emergence of psychotic symptoms, suicidal behavior, paradoxical worsening of depressive symptoms, the appearance of atypical or inverted affective syndromes, as well as the induction of rapid cycling and chronic dysphoric states persisting throughout the period of medication use. From a methodological perspective, ignoring these phenomena in the operational definition of TEAS creates a risk of systematic underestimation of the adverse consequences of treatment: the research construct becomes narrower than the clinical reality it is intended to reflect. If mood switching is regarded as a surrogate marker of treatment-induced "affective instability," there is no conceptual basis for excluding from this construct other forms of clinical deterioration that may likewise result from the same pathophysiological reaction.

At the same time, expanding the definition of TEAS beyond polarity switch entails a number of methodological difficulties. First, the causal relationship between antidepressant treatment and outcomes such as suicidal behavior or psychotic symptoms is considerably more difficult to verify than in the case of mania: these phenomena may reflect the depressive episode itself, comorbid pathology, or psychosocial factors, creating a high risk of false-positive attributions. Second, for most of the listed conditions, there are no validated threshold criteria analogous to the syndromal criteria for hypomania, which complicates their standardized registration in clinical research. Third, including in the definition of TEAS phenomena that are heterogeneous in their mechanisms and prognosis may lead to dilution of the construct and loss of its specificity as an indicator of affective destabilization per se. Thus, the decision to include, within the operational definition of TEAS, additional clinical manifestations not limited to polarity switch requires a careful compromise between clinical comprehensiveness and methodological rigor, as well as empirical verification of the extent to which these phenomena are united by a common pathophysiological mechanism and predictability in the context of similar interventions.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	7.25	9	1.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.3% (n=1)	16.7% (n=5)	80.0% (n=24)



Consensus status: Consensus of Agreement (80% agreement; median 8 [7.25-9])

Comments (listed in chronological order of submission):

- ➔ 670349 - Expanding TEAS beyond polarity switch poses challenges. Unlike mania, links between antidepressant treatment and outcomes such as suicidal behavior or psychotic symptoms are harder to verify, as these may be due to the depressive episode itself, comorbid or psychosocial factors, increasing the risk of false-positive attribution.
- ➔ 518904 - True, But TEAS may be the beginning of change of illness course including rapid cycling.
- ➔ 124685 - I would tend to distinguish affective symptoms, increased energy and activity from psychotic, depressive symptoms or suicidal ideation.
- ➔ 840362 - I would rather say that TEAS may trigger or mark the onset of rapid cycling, rather than that it "includes" rapid cycling.
- ➔ 138956 - While I have certainly seen this in clinical practice, i.e. chronification of depression on antidepressants, which resolves upon discontinuation of antidepressant, I acknowledge that differentiating treatment non response and hence worsening depression, from medications actually contributing to this is tricky. Also worsening of depression is no longer a switch so the terminology again gets misleading.
- ➔ 240738 - i think the issue is that there are differences between older tricyclics and MAOIs and the newer SSRIs and other antidepressant treatments. So, lumping all of them together is problematic.
- ➔ 597318 - Again, we should not limit definition to antidepressants. This is especially important if these definitions are going to be used for research.

- ➔ 276415 - To be picky, I wonder if it should be specified that emergent psychotic symptoms should be accompanied by other mood symptoms to "count" toward the definition of TEAS. I'm not sure if treatment-emergent psychosis, in the absence of mood symptoms, can be considered a treatment emergent AFFECTIVE switch. (That said, I suspect it's rare; I don't know that I've ever seen it.).
- ➔ 406857 - Research does not really show increase of psychotic and other symptoms in TEAS which is supported by our own clinical observation. Cyclicity probability increases - should be included not for defining but as impact of TEAS.

Round 2 action: Retain unchanged and re-rate. Background revised for clarification to reflect uncertainty regarding the relationship between TEAS and increased cyclicity.

New background: Existing definitions of TEAS have focused predominantly on polarity switch, particularly hypomania, mania, and mixed states. However, other clinically significant phenomena have been described in temporal association with antidepressant treatment, including psychotic symptoms, suicidal behavior, paradoxical worsening of depressive symptoms, chronic dysphoric states, and increased cycling. It remains uncertain whether these phenomena should be considered manifestations or consequences of TEAS, separate treatment-emergent adverse outcomes, or events related primarily to the underlying mood disorder rather than to treatment.

Expanding the TEAS construct beyond polarity switch therefore presents several methodological challenges. The causal relationship between treatment and outcomes such as suicidal behavior, psychotic symptoms, or worsening depression may be difficult to establish, and standardized threshold criteria are lacking for several of these phenomena. Round 1 comments also suggested that these outcomes may differ substantially in their clinical meaning and should not necessarily be considered together. Accordingly, psychotic symptoms, suicidal behavior, and paradoxical worsening of depression will be assessed separately in Round 2, while the proposed relationship between TEAS and increased cyclicity will be retained as a separate statement.

Temporal Criteria for Clinical Manifestations

Statement 12

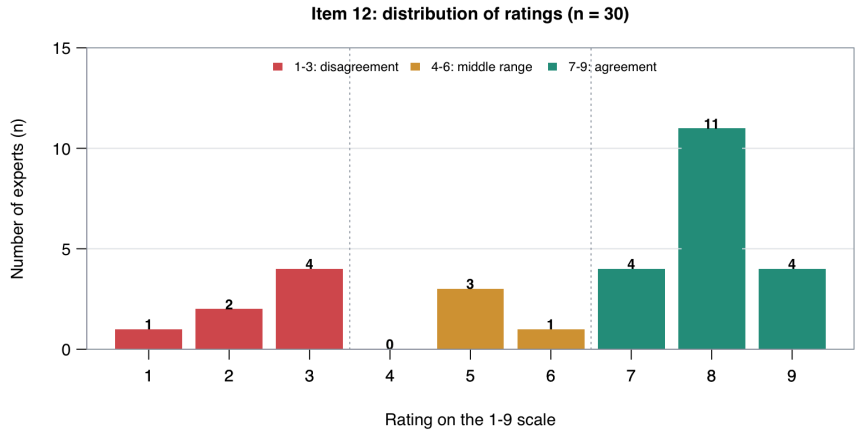
In patients with bipolar disorder, TEAS may be ascertained in the presence of hypomanic, manic, or mixed symptoms even if they do not meet the minimum duration required by DSM-5/ICD-11, provided that they are observed for at least 2 days.

Background (see Statement 13)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	7.5	5	8	3

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
23.3% (n=7)	13.3% (n=4)	63.3% (n=19)



Consensus status: No consensus (63.3% agreement; median 7.5 [5-8])

Comments (see Statement 13)

Round 2 action: Revise and re-rate. The proposed 2-day minimum duration was removed because Round 1 comments indicated insufficient empirical support for a specific temporal threshold. The revised statement focuses on whether clinically significant TEAS may be ascertained despite not meeting the minimum duration criteria of DSM-5/ICD-11.

New statement 12

In patients with bipolar disorder, TEAS may be ascertained in the presence of clinically significant hypomanic, manic, or mixed symptoms even if they do not meet the minimum duration required by DSM-5/ICD-11.

Statement 13

In patients with major depressive disorder,* the ascertainment of TEAS during a depressive phase should be based on full compliance with all DSM-5/ICD-11 temporal criteria for hypomania, mania, and mixed states, which is sufficient to warrant a change in diagnosis to bipolar disorder. *depressive episode/recurrent depressive disorder in ICD-11

Background

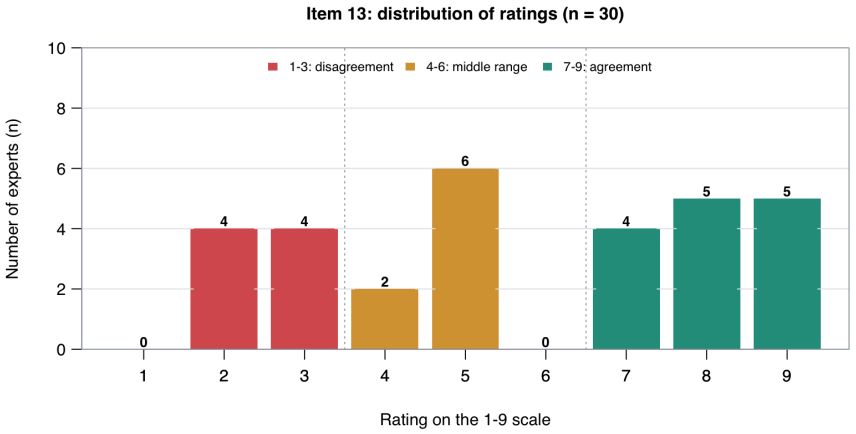
The proposed statements introduce a fundamentally different threshold for the ascertainment of TEAS depending on the baseline diagnostic context, reflecting a fundamental difference in the purpose of recording this phenomenon in the two populations. In patients with an already established diagnosis of bipolar disorder, lowering the required symptom duration to two days is justified by several considerations. First, the formal temporal criteria of DSM-5 and ICD-11 (four days for hypomania) were developed for differential diagnosis and for minimizing overdiagnosis of bipolar disorder at the population level, rather than for assessing the safety of therapeutic interventions. Second, in clinical research and real-world practice, switches lasting less than four days often require immediate therapeutic adjustment (dose reduction, discontinuation, or addition of a mood stabilizer) and therefore represent clinically significant events that cannot be ignored when evaluating the safety profile. Third, limiting the registration of TEAS only to episodes meeting full temporal criteria creates a systematic bias toward underascertainment of switches in patients whose hypomanic symptoms are rapidly terminated by prompt therapeutic intervention – an outcome that should be regarded as favorable, but not as evidence that the event itself did not occur.

In contrast, in patients with a baseline diagnosis of major depressive disorder, application of the full DSM-5/ICD-11 temporal criteria is a necessary condition for the ascertainment of TEAS, because in this population the switch event serves not only as the recording of an adverse event, but also a diagnostic function – namely, as grounds for revising the diagnosis in favor of bipolar disorder. Relaxing the temporal requirements in this group would inevitably lead to overdiagnosis of bipolar disorder in patients with transient, subsyndromal, or purely treatment-emergent mood fluctuations that have no prognostic significance for the long-term course of illness. Thus, the proposed asymmetry of criteria is not a methodological inconsistency, but a deliberate adaptation of the research construct to different clinical and diagnostic tasks. A potential difficulty of this approach is that it creates a situation in which the same phenomenological state (for example, a two-day hypomania during antidepressant treatment) would be classified as TEAS in a patient with known bipolar disorder, but would not be recognized as such in a patient with major depressive disorder, which may complicate comparisons across studies including mixed samples. Nevertheless, the alternative is either overdiagnosis of bipolar disorder in the major depressive disorder group or systematic underascertainment of clinically significant switches in the bipolar disorder group – both outcomes appear less acceptable than an asymmetrical but clinically justified definition.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	5	3.25	8	4.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
26.7% (n=8)	26.7% (n=8)	46.7% (n=14)



Consensus status: No Consensus (46.7% agreement; median 5 [3.25-8]).

Comments (listed in chronological order of submission):

- ➔ 731602 - The first question - it depends not only on duration but also severity. A short mild syndrome that might be also seen outside of AD treatment may be less convincing as TEAS. The second question is not clearly formulated.
- ➔ 670349 - Overdiagnosing bipolar disorder in major depressive disorder, or underdetecting clinically significant switches in bipolar disorder are less acceptable. An asymmetrical definition should be clinically justified.
- ➔ 518904 - Any duration of mood elevation/mixed features should help to make a diagnosis of BD.
- ➔ 124685 - Since TEAS is an iatrogenic effect, I would tend to distinguish it, or at least have broader temporal parameters than the classic episode of mania, hypomania or mixed state.
- ➔ 138956 - Considering that hypomania/mania usually occurs much later in the course of bipolar disorders than depression, I am not sure that the second argument is warranted. While I certainly would be less surprised if this happens in someone with previous diagnosis of BD, I would not take it lightly even in someone with UD and if the switch is of sufficient amplitude, I would certainly not wait longer prior to discontinuing the AD, just to meet the duration criteria for hypomania/mania.

- ➔ 891256 - these two questions try to formulate duration and quality of symptomatology in a too narrow way.
- ➔ 465130 - duration of at least 2 days should be reviewed to less than 24 hours
- ➔ 597318 - For the second question, you may have an exclusion for treated manic symptoms.
- ➔ 276415 - I'd suggest subdividing TEAS into treatment emergent mania, hypomania, mixed depression or mania, and subthreshold hypomania, and applying it to both BD and MDD. In BD, as you say, it helps avoid under-diagnosis. In MDD, it will increase the suspicion of an underlying BD to a greater or lesser degree, which I think is more realistic than a dichotomous Y/N distinction.
- ➔ 690284 - The question above is a bit awkward since mixed features in DSM-5 do not necessarily lead to a bipolar diagnosis.
- ➔ 948206 - I think the two day threshold is as empirically supported as the 4 day threshold so it should be consistent across mood disorders subtypes.

Round 2 action: Revise and re-rate. The statement was reformulated to retain the link between treatment-emergent hypomanic, manic, or mixed presentations and reassessment for bipolar disorder, while leaving the specific diagnostic implications to the applicable diagnostic classification (DSM or ICD).

New statement 13

In patients with major depressive disorder,* the ascertainment of TEAS during a depressive phase should require fulfillment of the temporal criteria for the corresponding hypomanic, manic, or mixed presentation according to the applicable diagnostic classification (DSM or ICD), and should prompt diagnostic reassessment for bipolar disorder in accordance with that classification.

*depressive episode/recurrent depressive disorder in ICD-11

New background: Statements 12 and 13 address whether the temporal requirements for TEAS should differ according to the baseline diagnostic context. In patients with an established diagnosis of bipolar disorder, clinically significant treatment-emergent hypomanic, manic, or mixed symptoms may be relevant even when their duration is shorter than that required for a formally defined episode. In patients with major depressive disorder, however, the same treatment-emergent presentations may also have implications for the underlying diagnosis and therefore require a more conservative approach to ascertainment.

Round 1 comments highlighted concerns about applying different temporal thresholds across diagnostic groups, but also emphasized the risk of both underdetecting clinically significant treatment-emergent states in bipolar disorder and overdiagnosing bipolar disorder in patients with major depressive disorder. The comments also underscored that the diagnostic implications of hypomanic, manic, and mixed presentations are not identical across DSM and ICD. For this reason, the revised statement does not impose a single universal diagnostic consequence. Instead, it requires fulfillment of the temporal criteria for the corresponding presentation according to the applicable diagnostic classification and links the ascertainment

of TEAS to subsequent reassessment for bipolar disorder in accordance with that same classification.

Method of Assessment

Statement 14

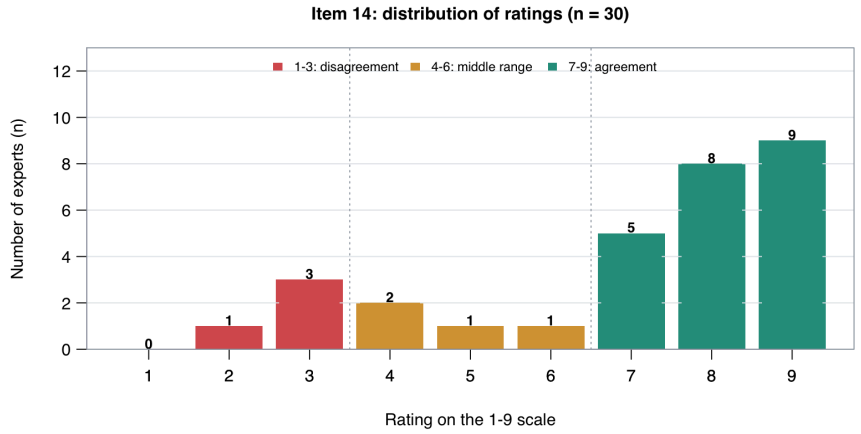
For the ascertainment of TEAS in bipolar depression, reaching a threshold score on rating scales (e.g., YMRS) is insufficient, since such scales are not fully valid for the diagnosis of hypomania and mixed states according to DSM-IV,5 / ICD-10,11 criteria.

Background (see Statement 16)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	6.25	9	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
13.3% (n=4)	13.3% (n=4)	73.3% (n=22)



Consensus status: Consensus of Agreement (73.3% agreement; median 8 [6.25-9])

Comments (see Statement 16)

Round 2 action: Retain unchanged and re-rate. Background revised to present the respective roles and limitations of rating scales and diagnostic interviews more neutrally.

Statement 15

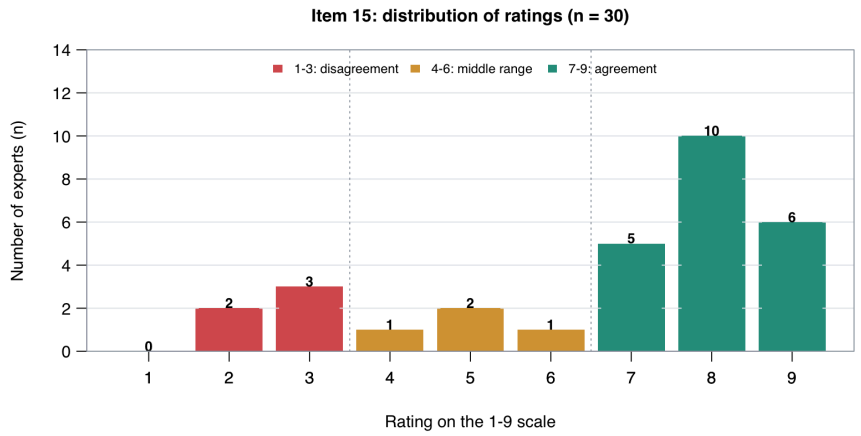
For the ascertainment of TEAS, a structured diagnostic interview based on DSM-5/ICD-11 criteria is sufficient.

Background (see Statement 16)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	5.25	8	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
16.7% (n=5)	13.3% (n=4)	70.0% (n=21)



Consensus status: No Consensus, with a directional tendency toward agreement (70% agreement; median 8 [5.25-8]).

Comments (see Statement 16).

Round 2 action: Revise and re-rate. The reference to DSM-5/ICD-11 criteria was removed to separate the method of assessment from the question of which clinical criteria should define TEAS. The statement was also broadened to include both structured and semi-structured diagnostic interviews.

New statement: For the ascertainment of TEAS, a structured or semi-structured clinical diagnostic interview is sufficient.

Statement 16

YMRS and other scales should be regarded as auxiliary instruments that do not replace a diagnostic interview.

Background

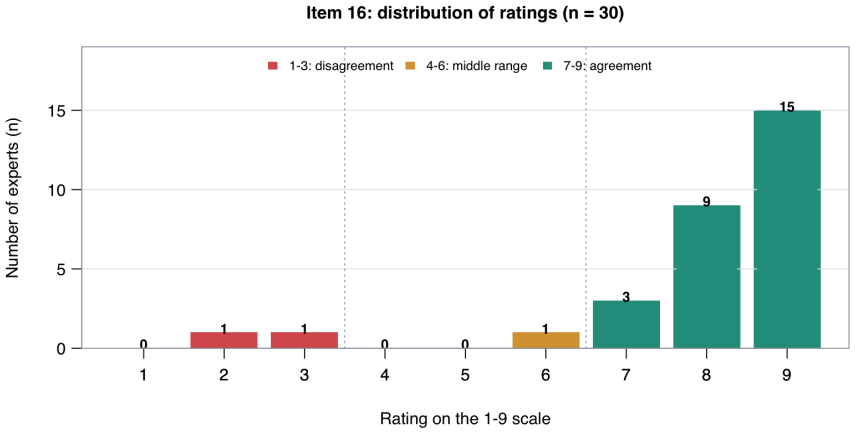
The use of rating scales, primarily the YMRS, as a standalone instrument for the ascertainment of TEAS creates inherent methodological limitations related to the mismatch between the constructs embedded in the scale and the diagnostic criteria of DSM-5/ICD-11. The YMRS was developed for the quantitative assessment of the severity of manic symptoms in the context of an already established diagnosis, rather than for the identification of hypomania or mixed states as a binary outcome. Threshold values on the scale do not have established validity for the differential diagnosis of hypomania, do not capture the duration criterion, and do not allow distinction between fully syndromal episodes and subsyndromal affective fluctuations. In addition, the YMRS is not sufficiently sensitive to the specific phenomenology of mixed states, in which high subjective ratings of depressive symptoms may coexist with objectively observable signs of activation, leading to false-negative results. Reliance exclusively on scale-based indicators inevitably generates heterogeneity across studies using different cutoff thresholds.

In this context, a structured diagnostic interview based on DSM-5/ICD-11 criteria is the necessary and sufficient method for the verification of TEAS, because only such an interview makes it possible to establish the presence of the full syndromal pattern, the required duration of symptoms, and the clinical significance of the condition. The use of an interview ensures the content validity of the outcome and the comparability of data with the nosological system adopted in clinical practice and regulatory documents. At the same time, YMRS and similar scales retain their value as auxiliary screening instruments, allowing standardized tracking of symptom dynamics over the course of a study and helping to justify the timing of the diagnostic interview. However, they cannot substitute for the interview itself in the ascertainment of the endpoint. A potential limitation of this approach is its resource intensity: conducting structured interviews requires time and personnel resources, which may be difficult to achieve in some clinical settings. Nevertheless, compromises in outcome validity for the sake of operational convenience appear unacceptable when the event being recorded may lead to regulatory decisions and changes in clinical guidelines.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8.5	8	9	1

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
6.7% (n=2)	3.3% (n=1)	90.0% (n=27)



Consensus status: Consensus of Agreement (90% agreement; median 8.5 [8-9]).

Comments (listed in chronological order of submission):

- ➔ 731602 - One should use all available information.
- ➔ 670349 - Structured interviews require time and trained personnel, resources that may be limited in some clinical settings and can make diagnosis more difficult.
- ➔ 518904 - Clinical observation may be helped by rating scales.
- ➔ 124685 - Once the problem has been defined, a specifically validated scale is needed.
- ➔ 891256 - again, the problem is that TEAS could include a variety of affective states not included in classification systems.
- ➔ 854317 - This question appears to address two separate issues simultaneously. First, it asks whether a structured diagnostic interview is sufficient for the ascertainment of TEAS. Second, it implicitly assumes that TEAS should be defined according to the DSM-5/ICD-11 definitions of hypomania, mania, and mixed states. A respondent may agree with the first proposition while disagreeing with the second. In my view, the conceptual issue of whether TEAS should be restricted to DSM-5/ICD-11 syndromal definitions has already been addressed in the preceding questions. Therefore, this item would more accurately assess expert opinion if it focused solely on whether a structured diagnostic interview is sufficient for TEAS ascertainment, without embedding the assumption that TEAS must be defined according to DSM-5/ICD-11 criteria.
- ➔ 276415 - IMHO the YMRS with appropriate cutoffs (>/= 20 for mania, 12-19 for hypomania, 8-11 for subthreshold hypomania), done by an experienced rater, should be sufficient.
- ➔ 406857 - This question ignites the debate of emphasis on interview vs on scale. Reliance on interview is better than reliance only on a scale. Scale only tells about the severity not about comprehensive assessment - say impact on functioning.

Round 2 action: Retain unchanged and re-rate. Background revised to present the respective roles and limitations of rating scales and diagnostic interviews more neutrally.

New background: Rating scales and diagnostic interviews provide complementary information for the ascertainment of TEAS. Instruments such as the YMRS are useful for standardized assessment of symptom severity and for monitoring changes over time, but threshold scores alone do not establish several clinically relevant features, including symptom duration, change from baseline, functional impact, and the broader clinical context. In addition, rating scales were not developed as stand-alone diagnostic tools for the full range of hypomanic, manic, and mixed presentations that may be relevant to TEAS.

Structured and semi-structured clinical diagnostic interviews allow a more comprehensive assessment of symptom pattern, duration, severity, functional consequences, and clinical context, while preserving a standardized approach to ascertainment. However, such interviews require trained personnel and may be more resource-intensive than rating scales. Round 1 comments also indicated that TEAS assessment may benefit from integrating all available clinical information rather than relying on a single instrument.

Accordingly, Round 2 distinguishes between three related questions: whether reaching a threshold score on a rating scale is sufficient for TEAS ascertainment, whether a structured or semi-structured clinical diagnostic interview is sufficient, and whether rating scales should be regarded as auxiliary instruments rather than substitutes for diagnostic assessment.

Causality Assessment

Statement 17

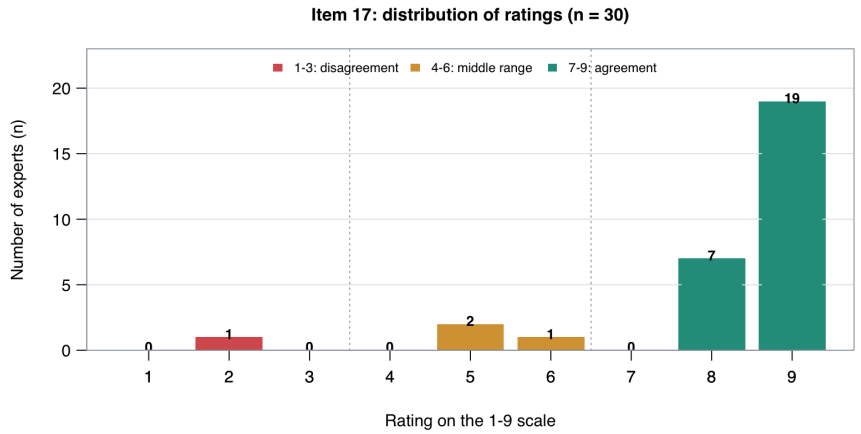
For clinical practice, a structured approach is recommended for determining the causal relationship between an intervention and the development of TEAS (temporal association, dose-response relationship, disappearance and re-emergence of symptoms following treatment modification, and exclusion of alternatives).

Background (see Statement 21)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	9	8	9	1

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.3% (n=1)	10.0% (n=3)	86.7% (n=26)



Consensus status: Consensus of Agreement (86.7% agreement; median 9 [8-9])

Comments (see Statement 21)

Round 2 action: Retain unchanged and re-rate. Background revised to clarify that causality assessment may incorporate additional clinical information and alternative explanations.

Statement 18

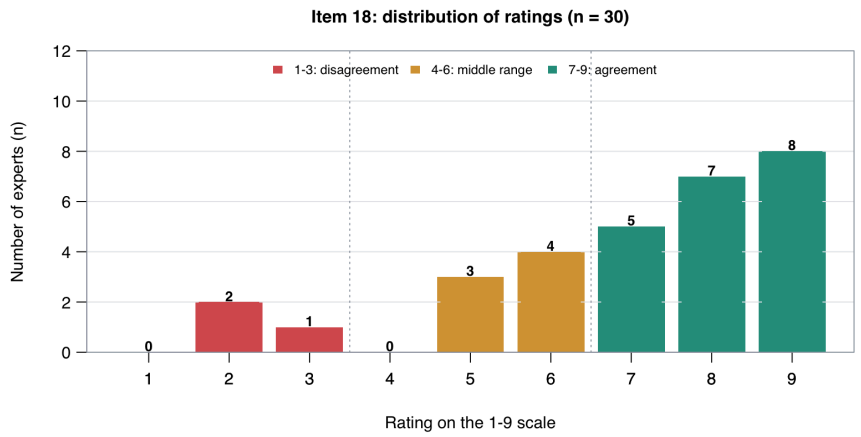
In cases of ambiguity, it is preferable to indicate the degree of confidence in the relationship with the intervention (high/moderate/low/very low), rather than make a binary determination.

Background (see Statement 21)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	7.5	6	8.75	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
10.0% (n=3)	23.3% (n=7)	66.7% (n=20)



Consensus status: No Consensus, with a directional tendency toward agreement (66.7% agreement; median 7.5 [6-8.75]).

Comments (see Statement 21)

Round 2 action: Revise and re-rate. The statement was restricted to research and pharmacovigilance contexts and reformulated to assess the principle of graded, rather than binary, causality assessment without prescribing specific confidence categories.

New statement 18

For research and pharmacovigilance purposes, when the causal relationship between an intervention and TEAS remains uncertain, the degree of confidence in this relationship should be graded rather than expressed solely as a binary determination.

Statement 19

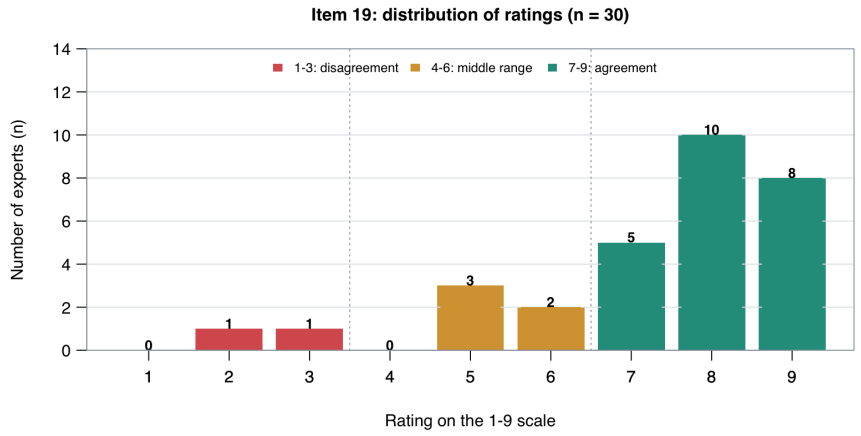
A spontaneous (natural) switch occurring in the course of bipolar disorder should be distinguished from TEAS by the absence of a temporal association with treatment initiation. At the same time, the following constellation of features may represent risk factors for TEAS: the presence of subthreshold manic symptoms during depression, the presence of rapid cycling and spontaneous switches during the preceding 12 months, and marked mood reactivity.

Background (see Statement 21)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	7	8.75	1.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
6.7% (n=2)	16.7% (n=5)	76.7% (n=23)



Consensus status: Consensus of Agreement (76.7% agreement; median 8 [7-8.75])

Comments (see Statement 21)

Round 2 action: Revise, split into two statements, and re-rate. The distinction between spontaneous switching and TEAS and the proposed clinical risk factors for TEAS will be assessed separately.

New statement 19a

A spontaneous (natural) affective switch occurring in the course of bipolar disorder should be distinguished from TEAS by the absence of a temporal association with treatment initiation or modification.

New statement 19b

Subthreshold manic symptoms during depression, rapid cycling or spontaneous affective switches during the preceding 12 months, and marked mood reactivity may represent risk factors for TEAS.

Statement 20

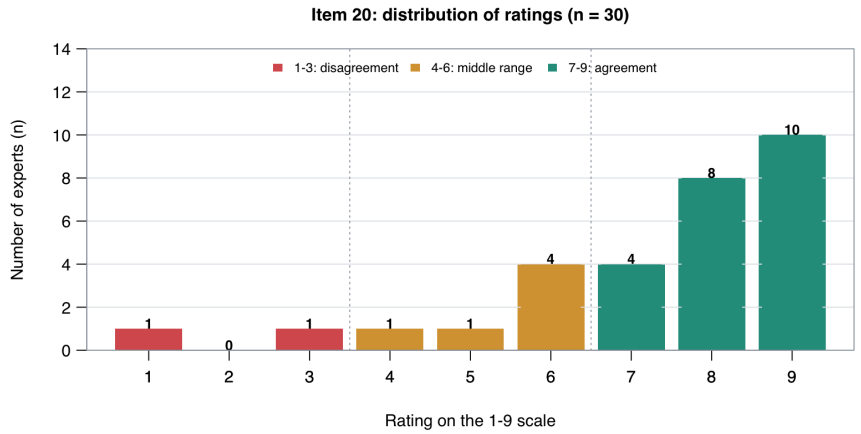
Regardless of the cause of the mood switch, in the event of the development of hypomania, mania, or mixed states, antidepressants or other interventions with antidepressant effects that may potentially have contributed to it should be discontinued.

Background (see Statement 21)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	6.25	9	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
6.7% (n=2)	20.0% (n=6)	73.3% (n=22)



Consensus status: Consensus of Agreement (73.3% agreement; median 8 [6.25-9]).

Comments (see Statement 21).

Round 2 action: Retain unchanged and re-rate. The statement will be treated as a clinical management recommendation rather than as a defining criterion for TEAS.

Statement 21

In clinical trials of a drug with established or potential antidepressant effects and an unknown risk of TEAS, determination of a causal relationship with that drug is possible only by means of a randomized, double-blind, placebo-controlled design.

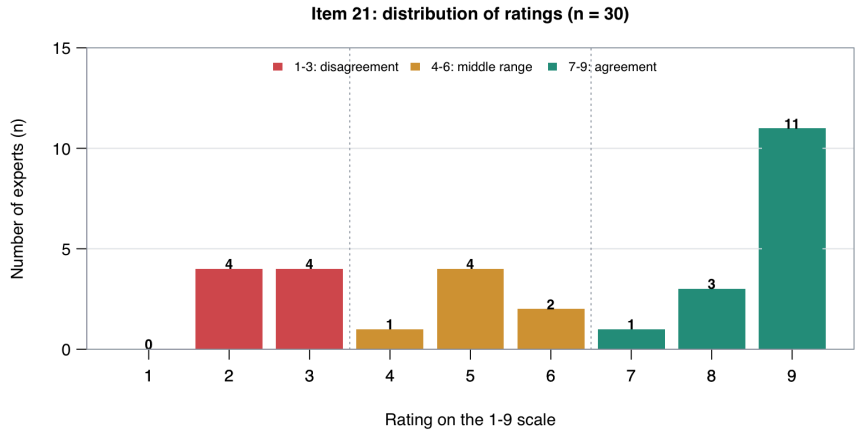
Background: The proposed statements operationalize the concept of causality as applied to TEAS, and of fundamental importance here is the distinction between the logic of clinical decision-making and the logic of research inference. In clinical practice, establishing a causal relationship between an intervention and an affective switch is always probabilistic in nature and is based on a set of criteria: temporal association, response to dose modification, effects of discontinuation and re-exposure, and exclusion of alternative explanations. Because in real-world clinical settings these criteria are rarely fulfilled in full, a binary classification of "caused" versus "not caused" is often artificial and fails to reflect the degree of uncertainty. The proposal to use a graded assessment of confidence in the causal relationship represents an attempt to bring the research construct closer to clinical reality, where the physician always acts under conditions of incomplete information, and the degree of confidence in the event's etiology influences management no less than the binary conclusion itself.

At the same time, the statements establish an important distinction between TEAS and spontaneous switching as two phenomena that may be phenomenologically indistinguishable but are separated on temporal grounds. It is further emphasized that a history of rapid cycling, spontaneous switches, or subthreshold opposite-polarity symptoms not only does not preclude a diagnosis of TEAS when an episode emerges during treatment, but also constitutes a risk factor for its development. In other words, TEAS does not arise de novo, but on the background of pre-existing affective instability, which nevertheless does not negate the role of the therapeutic trigger. Regardless of whether the switch is classified as TEAS or as spontaneous, the clinical action remains unchanged: the potentially responsible agent should be discontinued. This is an important pragmatic emphasis, distinguishing the task of safety assessment (where TEAS is an outcome requiring registration) from the task of clinical management (where the switch is a condition requiring treatment regardless of its etiology).
In the research context, however, the requirements for establishing causality are fundamentally different. For drugs with an unknown or unproven risk of TEAS, the only acceptable method for verifying a causal relationship remains a randomized, double-blind, placebo-controlled trial, because only such a design makes it possible to eliminate the influence of confounding factors – spontaneous course of illness, effects of prior therapy, regression to the mean, and systematic biases related to the expectations of both the investigator and the patient. Observational studies, case series, and clinical impression may generate hypotheses and signal a potential risk, but they cannot provide a quantitative estimate of the causal effect while controlling for alternative explanations. Thus, the proposed approach reflects an understanding that the causality assessment cannot be universal: it must differ depending on the purpose – clinical decision-making, pharmacovigilance, registration research, or scientific classification of phenomena – and each of these purposes requires its own threshold of evidence and its own degree of reduction of the complexity of real-world clinical reality.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	6.5	3.25	9	5.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
26.7% (n=8)	23.3% (n=7)	50.0% (n=15)



Consensus status: No consensus (50.0% agreement; median 6.5 [3.25-9]).

Comments (listed in chronological order of submission):

- ➔ 670349 - In ambiguous cases, a binary determination is often clinically easier than assigning confidence in the intervention relationship across graded levels: high, moderate, low, or very low.
- ➔ 124685 - The assessment of the causal relationship between antidepressants and TEAS should be evaluated like any other side effect in pharmacovigilance, therefore on the basis of temporal criteria, probability, and with exposure and re-exposure to the drug (challenge-de challenge-rechallenge).
- ➔ 840362 - Comment on item 18: this approach is not applicable to current real-world clinical practice in the context of existing diagnostic classifications. It may, however, be appropriate for research purposes. We suggest explicitly stating this in the explanatory notes. Comment on item 21: registry-based studies might also be able to address this question, provided that TEAS is systematically recorded in such databases.
- ➔ 854317 - For third question, this item appears to combine two distinct concepts into a single question. The first concerns the differentiation of spontaneous (natural) affective switches from TEAS based on their temporal relationship to treatment,

whereas the second concerns clinical risk factors that may predispose patients to TEAS. These are conceptually different issues, and it is therefore difficult to provide a single response that accurately reflects agreement with both. I believe these concepts would be better evaluated as separate items.

- ➔ 597318 - Determining a definition does not involve treatment recommendations. No definition will adequately differentiate induced versus spontanous switch.
- ➔ 276415 - As I've said in response to previous items, I feel the temporal relationship between treatment initiation / dose change and emergence of TEAS is relatively unlikely to be informative vis-a-vis causality. Other factors could be, though - e.g. is the affective switch out of keeping with the person's prior illness course? (One random example, a treatment emergent affective switch occurring in the winter, in someone who's previously experienced only spring / summer mood elevations.) Does it occur in the absence of other triggers, especially triggers for mania/hypomania that have been previously identified for the given individual? Does it occur during treatment with an agent known to be high risk? E.g. venlafaxine > bupropion. Regarding the recommendation to discontinue the agent, I fell that decision should take into account 1) the likelihood of a causal relationship between the agent and the TEAS, and also 2) the severity and duration of prior depressions, especially depression following TEAS. I have seen patients switch out of a TEAS pretty quickly on stopping an antidepressant, but switch into a severe depression. As nice as it would be to have a pat definition of TEAS, I think these statements come closest to what is currently possible - i.e. providing clinicians/researchers with guidance for how to assess the relationship between the agent and the TEAS.
- ➔ 690284 - Since an antidepressant drug in a placebo-controlled trial may induce more switches than the placebo it may be due to the increased antidepressant efficacy since switches may follow remission from depression as a spontaneous event. Therefore, in such trials the ratio between remission from depression and switch should be compared.
- ➔ 269845 - it is possible that the antidepressant be uniquely reduced, not discontinued (e.g. bipolar depression and onset of TEAS mixed features).

Round 2 action: Revise and re-rate. The statement was reformulated to avoid the categorical claim that causal inference is possible only in randomized, double-blind, placebo-controlled trials. The revised wording emphasizes that such a design provides the strongest evidence for determining whether an intervention causally increases the risk of TEAS.

New statement 21

For an intervention with established or potential antidepressant effects and an unknown risk of TEAS, a randomized, double-blind, placebo-controlled trial provides the strongest design for establishing whether the intervention causally increases the risk of TEAS.

New background: Assessment of causality in TEAS requires different approaches depending on whether the objective is clinical decision-making, pharmacovigilance, or research

inference. In clinical practice, the relationship between an intervention and an affective switch is usually probabilistic rather than directly demonstrable. A structured assessment may therefore consider the temporal relationship to treatment initiation or modification, dose-response patterns, improvement after dose reduction or discontinuation, recurrence after re-exposure when such information is available, and alternative explanations related to the natural course of illness or other potential triggers. Additional clinical information, including the patient's previous pattern of affective episodes and exposure to interventions with a known risk of switching, may further inform this assessment.

Because these elements are rarely present simultaneously, causal attribution at the individual level often remains uncertain. For research and pharmacovigilance purposes, expressing this uncertainty as a graded level of confidence may therefore be more informative than a purely binary classification. At the same time, such graded assessments should be distinguished from the diagnostic classification of the affective episode itself and from treatment decisions made in routine clinical practice.

A further challenge is the distinction between TEAS and a spontaneous affective switch. The two may be phenomenologically indistinguishable, and temporal association with treatment alone does not establish causality. Clinical characteristics such as subthreshold manic symptoms during depression, recent rapid cycling or spontaneous switches, marked mood reactivity, and other features of pre-existing affective instability may increase the probability of switching, but they do not by themselves determine whether a particular episode was treatment-emergent. For this reason, the distinction between spontaneous switching and TEAS and the assessment of risk factors for TEAS should be considered separately.

Clinical management should also be distinguished from causal classification. When hypomania, mania, or a mixed state emerges during treatment, modification or discontinuation of a potentially contributing intervention may be clinically appropriate even when the causal relationship remains uncertain. Such recommendations concern management rather than the operational definition of TEAS itself.

At the group level, research aimed at determining whether an intervention causally increases the risk of TEAS requires comparative evidence. Randomized, double-blind, placebo-controlled trials provide the strongest protection against confounding and bias and therefore offer the strongest evidence for causal attribution. Other study designs may identify associations, generate safety signals, or contribute supportive evidence, but their interpretation is more dependent on assumptions about confounding and the natural course of the disorder. Accordingly, causal assessment of TEAS should distinguish individual clinical attribution from estimation of treatment-related risk at the population level.

Statement 22

In clinical trials in which the assessment of TEAS risk is a primary or secondary endpoint, administration of a drug with known or potential antidepressant effects to patients with bipolar disorder should occur 7 days after discontinuation of antidepressants or other interventions with antidepressant effects.

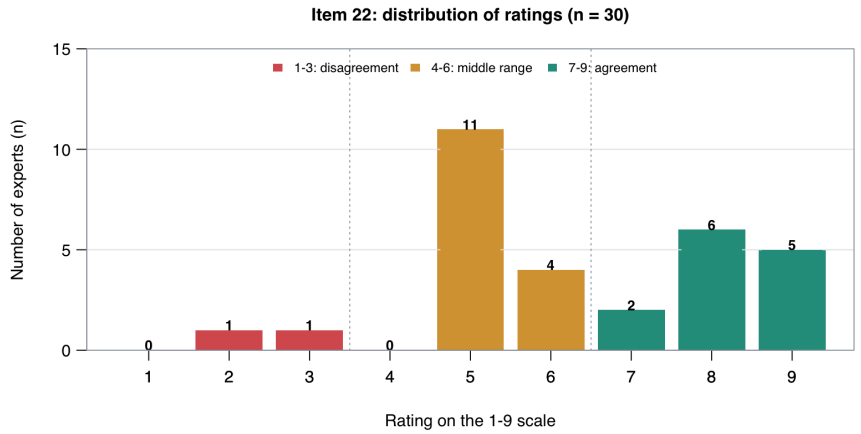
Background

A one-week washout period in TEAS clinical trials is intended to minimize confounding of the effects of the investigational drug with the consequences of prior antidepressant therapy and to ensure a comparable baseline background. This interval represents an empirical compromise between the need to eliminate the effects of prior interventions and ethical constraints. However, it remains conventional, does not account for the pharmacokinetic diversity of drugs, and creates a systematic selection bias toward less severely ill patients who can safely tolerate discontinuation. A strict washout requirement increases the internal validity of studies but limits the generalizability of the findings; accordingly, a necessary condition for the interpretation of such trials is transparent documentation of the proportion and characteristics of patients excluded because discontinuation of prior therapy was not feasible.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	6	5	8	3

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
6.7% (n=2)	50.0% (n=15)	43.3% (n=13)



Consensus status: No Consensus (43.3% agreement; median 6 [5-8]).

Comments (listed in chronological order of submission):

- ➔ 731602 - At least 7 days, also depends on pharmacokinetic parameters of the discontinued treatment.
- ➔ 351746 - That depends on the drug pharmacokinetics, half-time.
- ➔ 124685 - This could improve the quality of research, but I don't know if it would be ethically acceptable.
- ➔ 138956 - Longer half life or IMAO make such one size fits all suggestions difficult.
- ➔ 465130 - this should depend on the half life of the antidepressant. wash out period of 2 weeks is safer.
- ➔ 417960 - 7 days is arbitrary.
- ➔ 597318 - I feel more comfortable with 10 days.
- ➔ 276415 - I agree with the reservations raised in your Background. Also, if treatment discontinuation raises the risk of affective switch (as you suggested in previous statements), the discontinuation could have the opposite of the desired effect.

Round 2 action: Revise and re-rate. The fixed 7-day washout period was removed because Round 1 comments consistently indicated that an appropriate washout interval should depend on the characteristics of the discontinued intervention, particularly its pharmacokinetic properties, rather than on a universal time threshold.

New statement 22

In clinical trials in which the assessment of TEAS risk is a primary or secondary endpoint, administration of a drug with known or potential antidepressant effects to patients with bipolar disorder should occur only after an appropriate washout period following discontinuation of prior antidepressants or other interventions with antidepressant effects, taking into account the pharmacokinetic properties of the discontinued treatment.

New background: In clinical trials assessing the risk of TEAS, residual effects of previous antidepressant treatment may complicate attribution of an affective switch to the investigational intervention. A washout period before initiation of the study treatment may therefore improve internal validity by reducing overlap between the effects of previous and current interventions and by establishing a more comparable baseline.

However, Round 1 comments indicated that a fixed washout period is unlikely to be appropriate across different treatments. The duration required to minimize residual effects may depend on pharmacokinetic characteristics such as elimination half-life and active metabolites, and may differ substantially between antidepressant classes. For non-pharmacological interventions, the relevant period may need to be determined according to the expected duration of their biological effects rather than pharmacokinetic parameters.

Washout requirements also involve important methodological and ethical trade-offs. Patients who cannot safely discontinue ongoing treatment may be excluded from trials, potentially reducing generalizability and selecting for less severely ill participants. In addition, treatment discontinuation itself may produce withdrawal phenomena or affect mood stability, which

could complicate the assessment of subsequent TEAS. Accordingly, the revised statement focuses on the principle of an intervention-appropriate washout period rather than a universal 7-day threshold.

Retrospective Assessment

Statement 23

TEAS meeting all agreed criteria may be ascertained retrospectively in a patient based on a sufficiently detailed patient report.

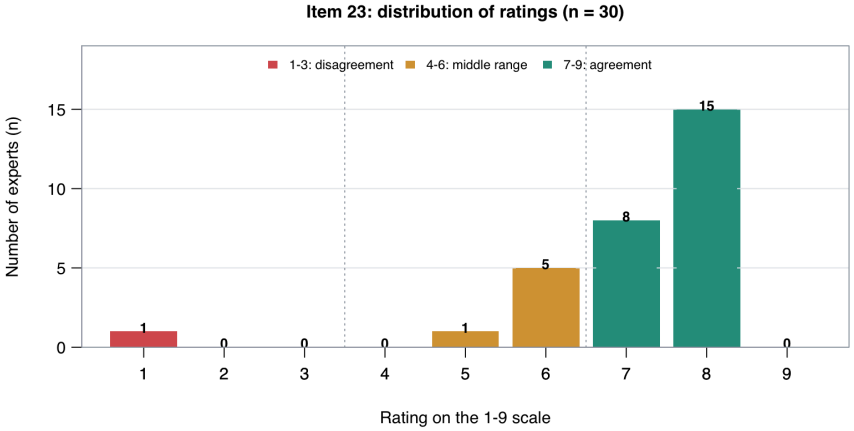
Background

The possibility of retrospective ascertainment of TEAS is of substantial importance both for clinical practice and for research using real-world clinical data or retrospective cohort designs, since not every affective switch is recorded prospectively at the time of its occurrence. A fundamental condition for the validity of retrospective assessment is sufficient detail in the information reported by the patient, allowing verification of compliance with all agreed TEAS criteria: temporal association with the therapeutic intervention, duration and full syndromal expression of the episode, and exclusion of more likely alternative explanations. When this condition is met, a retrospectively reported event has no less clinical significance than one recorded prospectively, since in real-world practice decisions to change therapeutic strategy are often made precisely on the basis of such reports. A potential limitation of this approach lies in the inevitable distortions associated with patient memory, especially in the assessment of brief hypomanic states, which may retrospectively either be omitted from recall altogether or, conversely, reinterpreted through the lens of subsequent experience. In addition, retrospective assessment does not allow application of such causality criteria as dechallenge and rechallenge effects, and it complicates differentiation of TEAS from spontaneous switches in patients with a rapid-cycling course. Therefore, retrospective ascertainment of TEAS is acceptable provided that standardized diagnostic instruments adapted for retrospective use are employed and that the degree of confidence in the reliability of the patient-reported information is formally documented.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	7.5	7	8	1

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.3% (n=1)	20.0% (n=6)	76.7% (n=23)



Consensus status: Consensus of Agreement (76.7% agreement; median 7.5 [7-8]).

Comments (listed in chronological order of submission):

- ➔ 518904 - Retrospective assessment could be quite helpful.
- ➔ 124685 - The retrospective reconstruction loses too many details to be considered valid, suspect at best.
- ➔ 406857 - Retrospective ascertainment is a clinical need for deciding what kind of treatment will be offered to patient.
- ➔ 690284 - It is impossible to answer this question since we have no agreed criteria on TEAS.

Round 2 action: Retain unchanged and re-rate. Background revised to clarify that retrospective ascertainment is contingent on the ability to verify the TEAS criteria agreed upon through the Delphi process.

New background: Retrospective ascertainment of TEAS may be relevant in both clinical practice and research using real-world data or retrospective designs, because affective switches are not always assessed prospectively at the time they occur. For a retrospectively reported event to meet the definition of TEAS, the available history would need to be sufficiently detailed to assess the criteria agreed upon through the Delphi process, including the characteristics and timing of the affective change in relation to treatment.

Retrospective assessment has important limitations. Recall of the onset, duration, and severity of symptoms may be inaccurate, particularly for brief hypomanic or mixed presentations, and subsequent experiences may influence how earlier episodes are interpreted. Information relevant to causal assessment, treatment changes, or alternative explanations may also be incomplete. These limitations may reduce confidence in retrospective ascertainment compared with prospectively documented events.

Round 1 comments reflected both the clinical usefulness of retrospective assessment and concern about the loss of information inherent in retrospective reconstruction. The statement

therefore asks whether TEAS may nevertheless be ascertained retrospectively when the patient report is sufficiently detailed to determine that the event meets the criteria agreed upon in this Delphi process.

High-Risk Groups

Statement 24

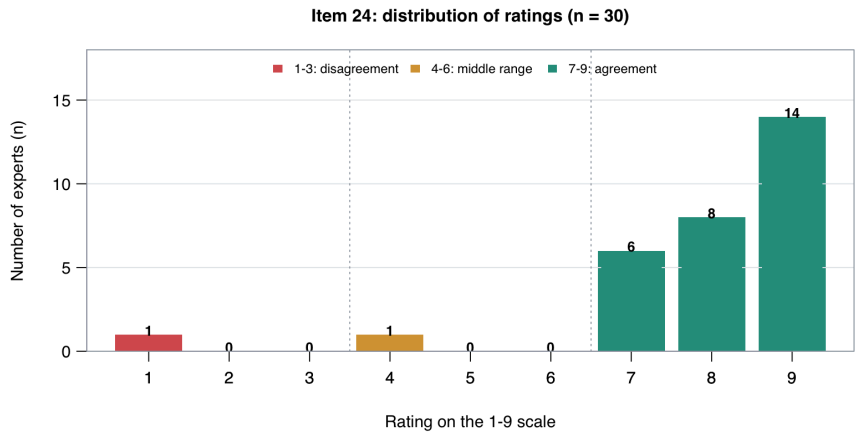
If a patient with a confirmed diagnosis of major depressive disorder develops hypomanic (<4 days), manic (<7 days), or mixed symptoms lasting <14 days that do not reach the minimum duration threshold, they should be considered part of a high-risk group for TEAS and bipolar disorder, requiring additional and more frequent clinical monitoring.

Background (see Statement 27)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	8	7.25	9	1.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.3% (n=1)	3.3% (n=1)	93.3% (n=28)



Consensus status: Consensus of Agreement (93.3% agreement; median 8 [7.25-9]).

Comments (see Statement 27).

Round 2 action: Revise and re-rate. Specific duration thresholds were replaced by reference to the applicable diagnostic classification (DSM or ICD), while retaining the Round 1 consensus that clinically significant subthreshold-duration hypomanic, manic, or mixed presentations identify a group requiring closer monitoring for TEAS and bipolar disorder.

New statement 24

Patients with major depressive disorder who develop clinically significant hypomanic, manic, or mixed presentations that do not meet the minimum duration criteria of the applicable diagnostic classification (DSM or ICD) should be considered at increased risk of TEAS and bipolar disorder and warrant closer clinical monitoring.

Statement 25

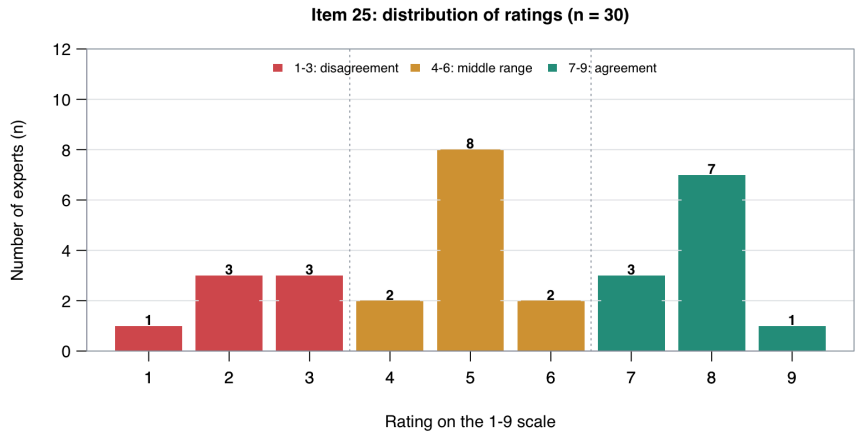
If a patient with any mood disorder shows rapid reduction of depressive symptoms within 1-2 weeks, with the development of euthymia after initiation of an antidepressant or other interventions with antidepressant effects, they should be considered part of a high-risk group for TEAS, requiring additional and more frequent clinical monitoring.

Background (see Statement 27)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	5	4	7.75	3.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
23.3% (n=7)	40.0% (n=12)	36.7% (n=11)



Consensus status: No consensus (36.7% agreement; median 5 [4-7.75]).

Comments (see Statement 27)

Round 2 action: Retain unchanged and re-rate. Background revised to emphasize the uncertainty regarding whether rapid antidepressant response represents a clinically meaningful predictor of TEAS.

Statement 26

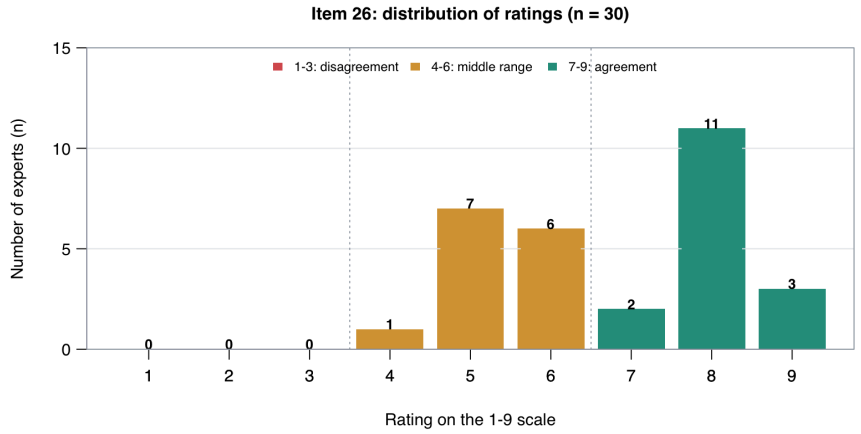
Conditions such as marked agitation, mood instability, abrupt worsening of anxiety, panic attacks, or significant insomnia/hypersomnia arising during treatment with an antidepressants or other interventions with antidepressant effects in patients with mood disorders should be regarded as potential predictors or "soft" forms of affective switching and should warrant heightened vigilance for the detection of hypomania.

Background (see Statement 27)

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	7	5.25	8	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
0.0% (n=0)	46.7% (n=14)	53.3% (n=16)



Consensus status: No Consensus, with a directional tendency toward agreement (53.3% agreement; median 7 [5.25-8]).

Comments (see Statement 27).

Round 2 action: Revise and re-rate. The term "soft forms of affective switching" was removed because the listed symptoms are nonspecific and may have alternative explanations. The revised statement focuses on whether their emergence during treatment should prompt heightened vigilance for hypomanic, manic, or mixed symptoms.

New statement 26

In patients with mood disorders, marked agitation, mood instability, abrupt worsening of anxiety, panic attacks, or significant sleep disturbance emerging during treatment with an antidepressant or other intervention with antidepressant effects should warrant heightened vigilance for the emergence of hypomanic, manic, or mixed symptoms.

Statement 27

In children and adolescents, antidepressant-related activation symptoms such as restlessness, insomnia, impulsivity, irritability, or behavioral disinhibition, in the absence of a distinct clinically significant hypomanic/manic or mixed episode, should not be classified as TEAS.

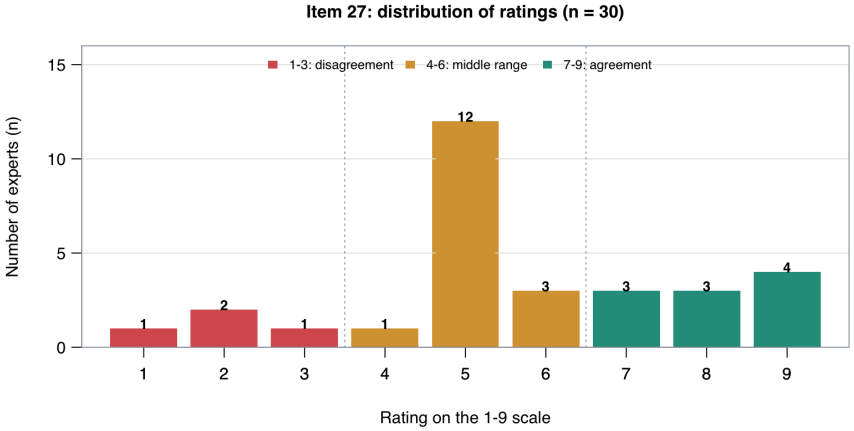
Background

The proposed statements broaden the focus of the TEAS construct from the ascertainment of an already completed switch to the proactive identification of high-risk groups, thereby shifting the paradigm from reactive event registration to preventive clinical monitoring. Patients with major depressive disorder who develop, in the context of antidepressant treatment, hypomanic, manic, or mixed states that are subthreshold in duration but meeting full syndromal criteria, represent a diagnostically uncertain yet clinically vulnerable population in whom the formal criteria for TEAS have not yet been met, but in whom the risk of subsequent polarity switch and conversion to bipolar disorder is substantially increased. Similarly, an ultra-rapid reduction in depressive symptoms within one to two weeks, culminating in euthymia, is traditionally regarded as a favorable therapeutic outcome, but may in fact indicate affective lability and high sensitivity to antidepressant effects, thereby creating conditions for a subsequent switch if treatment is continued or the dose is modified. Finally, a broad range of activation symptoms – agitation, affective instability, paroxysmal anxiety, panic attacks, and sleep inversion – is often ignored or interpreted as adverse effects or manifestations of comorbid pathology, whereas in the context of bipolar vulnerability they may represent subclinical equivalents of hypomanic activation preceding the full clinical picture of a switch. Integration of these three categories into a unified system of early detection requires reconsideration of thresholds for clinical vigilance and implementation of more frequent structured monitoring in at-risk groups. However, it is also associated with the danger of overdiagnosis and unjustified discontinuation of effective antidepressant therapy in patients in whom such phenomena are transient. A key direction for further research should be the empirical validation of the proposed predictors and the development of differentiated monitoring algorithms that distinguish states requiring heightened attention alone from those warranting immediate therapeutic correction.

Round 1 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
30	5	5	7	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
13.3% (n=4)	53.3% (n=16)	33.3% (n=10)



Consensus status: No consensus (33.3% agreement; median 5 [5-7]).

Comments (listed in chronological order of submission):

- ➔ 731602 - Q2: in some cases a rapid antidepressant response does not have to represent a risk factor. The main question would be how long the antidepressant should continue in such cases. Q4: The adverse response to antidepressants in adolescents is especially problematic and one should be careful to avoid it - often with a high risk of suicide.
- ➔ 670349 - Future research should validate the proposed high-risk groups and develop monitoring algorithms that distinguish cases needing closer observation from those requiring immediate therapeutic intervention.
- ➔ 124685 - Risk stratification based on personal, family, and pharmacological history, as well as a specific assessment, would be essential.
- ➔ 891256 - to my knowledge there are no real data to rely on and answer the above questions. The natural course of the illness is not a predictor of TEAS; anxiety caused by antidepressants could be an isolated idiosyncratic reaction also in unipolar patients (see STAR-D) etc.
- ➔ 597318 - For the 3rd question above, multiple (>2) subsyndromal symptoms of mania should be sufficient. For the 4th question, children frequently have chronic or mixed symptoms that may vary independently of any treatment.
- ➔ 276415 - Strongly agree with: "A key direction for further research should be the empirical validation of the proposed predictors and the development of differentiated monitoring algorithms that distinguish states requiring heightened attention alone from those warranting immediate therapeutic correction."
- ➔ 406857 - What are the factors that are important to detect and prevent a switch - is important. 1. Full syndrome - retrospectively or prospectively. 2. Subsyndrome (because not meeting the duration criteria) - So presence of classical symptoms > presence of duration criteria. 3. Certain features that increase the risk to develop TEAS - persons should be under heightened observation/vigilance. I think 1 and 2 should be together (clinically 2 behaves like 1 eventually - becomes bipolar)and 3.

should be separate. So making 2 categories - present and risk of recurrence - will be better.

Round 2 action: Retain unchanged and re-rate. Background revised to clarify that classification of antidepressant-related activation as distinct from TEAS does not imply that such symptoms are clinically benign or do not require intervention.

New background: Identification of patients at increased risk of TEAS may allow closer clinical monitoring before a full affective switch develops. Several clinical phenomena have been proposed as possible markers of increased risk, but they differ substantially in their specificity and empirical support.

In patients with major depressive disorder, clinically significant hypomanic, manic, or mixed presentations that do not meet the minimum duration criteria of the applicable diagnostic classification may indicate increased vulnerability to TEAS and bipolar disorder. Round 1 showed strong agreement that such presentations warrant closer monitoring. The revised statement therefore retains this principle while avoiding fixed duration thresholds that may not apply uniformly across DSM and ICD classifications.

Other proposed markers are less well established. A rapid reduction of depressive symptoms after initiation of an antidepressant or another intervention with antidepressant effects may represent either a favorable therapeutic response or, in some patients, a marker of increased affective instability. Likewise, marked agitation, mood instability, abrupt worsening of anxiety, panic attacks, and significant sleep disturbance arising during treatment are nonspecific phenomena that may reflect treatment-related activation, the underlying mood disorder, comorbidity, or other adverse effects. Their presence may therefore be more appropriately considered a reason for heightened clinical vigilance than as evidence of TEAS itself.

Antidepressant-related activation in children and adolescents presents an additional challenge. Restlessness, insomnia, impulsivity, irritability, and behavioral disinhibition may be clinically significant and may require treatment modification, but their relationship to hypomania, mania, mixed presentations, and subsequent bipolar disorder remains uncertain. Distinguishing such activation from TEAS does not imply that these symptoms are benign; rather, it addresses whether a distinct clinically significant affective episode should be required before the event is classified as TEAS.

Accordingly, the statements in this section distinguish between clinical features that may identify patients requiring closer monitoring and the criteria used to ascertain TEAS itself.