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

Round 2 Feedback Report

Results of the Second Delphi Round and Proposed Revisions for Round 3

Expert panel: 30 participants from 18 countries
Round 2: 32 statements

TEAS Consortium

September 2026

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

Project website: teas-consortium.com

This document summarizes the aggregated results of Round 2, anonymized expert comments, and proposed modifications for Round 3.

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About this report

This report provides aggregated feedback from Round 2 of the international Delphi study on the definition of TEAS. It summarizes quantitative ratings, anonymized expert comments, and the disposition of each statement following Round 2. Statements that reached consensus in Round 2 are accepted as final and will not be re-rated. Statements that did not reach consensus will be carried forward to Round 3, with revisions made where Round 2 feedback identified substantive problems with wording, scope, or interpretability.

Expert panel characteristics

Of the 30 experts who completed Round 1, 26 (86.7%) participated in Round 2. Full aggregated characteristics of the original Round 1 expert panel are presented in the Round 1 Feedback Report (https://teas-consortium.com/round-1-results.html).

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. Following Round 2, statements that met the predefined criteria for consensus were accepted as final and were not carried forward to Round 3. Only statements without consensus were considered for inclusion in Round 3. These statements may be retained unchanged for re-rating or revised where Round 2 feedback identified substantive problems with wording, scope, or interpretability.

Summary of all statements

Outcome of the second round

Item status	Items, n	Items, %
Consensus of Agreement	20	62.5%
Consensus of Disagreement	0	0.0%
No Consensus	12	37.5%

Summary table of 32 statements

Statement / topic	Median [Q1-Q3]	1-3 (disagreement)	4-6 (middle range)	7-9 (agreement)	Consensus status
01 Need for unified definition	9 [8.25-9]	3.8% (n=1)	0.0% (n=0)	96.2% (n=25)	Consensus of Agreement
02 DSM/ICD relevance	8 [6.5-9]	0.0% (n=0)	26.9% (n=7)	73.1% (n=19)	Consensus of Agreement
03 Guidelines and clinical practice	9 [7.25-9]	0.0% (n=0)	11.5% (n=3)	88.5% (n=23)	Consensus of Agreement
04 Antidepressants as triggers	8 [7-9]	11.5% (n=3)	7.7% (n=2)	80.8% (n=21)	Consensus of Agreement
05 Other therapeutic interventions	7.5 [7-8]	7.7% (n=2)	15.4% (n=4)	76.9% (n=20)	Consensus of Agreement
06 Psychoactive substances	8 [7.25-9]	0.0% (n=0)	15.4% (n=4)	84.6% (n=22)	Consensus of Agreement
07a Core manifestations	8 [7-9]	3.8% (n=1)	11.5% (n=3)	84.6% (n=22)	Consensus of Agreement
07b 8-week time window	6 [5-7]	11.5% (n=3)	50.0% (n=13)	38.5% (n=10)	No Consensus
08a Post-discontinuation switches	5 [2.25-8]	30.8% (n=8)	30.8% (n=8)	38.5% (n=10)	No Consensus

08b 7-day post-discontinuation window	5 [3-5.75]	34.6% (n=9)	50.0% (n=13)	15.4% (n=4)	No Consensus
09 No discontinuation requirement	8 [7-8]	3.8% (n=1)	15.4% (n=4)	80.8% (n=21)	Consensus of Agreement
10a Psychotic symptoms	8 [6.25-8.75]	7.7% (n=2)	19.2% (n=5)	73.1% (n=19)	Consensus of Agreement
10b Suicidal behavior	7 [5-8]	7.7% (n=2)	38.5% (n=10)	53.8% (n=14)	No Consensus
10c Paradoxical worsening of depression	7 [5-8]	15.4% (n=4)	30.8% (n=8)	53.8% (n=14)	No Consensus
11 Increased cyclicity	8 [7-9]	7.7% (n=2)	11.5% (n=3)	80.8% (n=21)	Consensus of Agreement
12 Short-duration TEAS in BD	7 [6-8]	3.8% (n=1)	26.9% (n=7)	69.2% (n=18)	No Consensus
13 TEAS in MDD	8 [7-8]	0.0% (n=0)	23.1% (n=6)	76.9% (n=20)	Consensus of Agreement
14 Rating-scale thresholds	8 [6-8]	7.7% (n=2)	23.1% (n=6)	69.2% (n=18)	No Consensus
15 Diagnostic interview	7 [6.25-8]	7.7% (n=2)	19.2% (n=5)	73.1% (n=19)	Consensus of Agreement
16 Rating scales as auxiliary tools	9 [8-9]	7.7% (n=2)	7.7% (n=2)	84.6% (n=22)	Consensus of Agreement
17 Clinical causality assessment	8 [7-9]	3.8% (n=1)	11.5% (n=3)	84.6% (n=22)	Consensus of Agreement
18 Graded causality	8 [7-9]	3.8% (n=1)	11.5% (n=3)	84.6% (n=22)	Consensus of Agreement
19a Spontaneous switches	8 [6.25-9]	11.5% (n=3)	15.4% (n=4)	73.1% (n=19)	Consensus of Agreement
19b Risk factors	8 [6.25-8]	0.0% (n=0)	26.9% (n=7)	73.1% (n=19)	Consensus of Agreement

20 Treatment discontinuation	8 [6-9]	11.5% (n=3)	19.2% (n=5)	69.2% (n=18)	No Consensus
21 Trial-level causal inference	8 [6-9]	11.5% (n=3)	26.9% (n=7)	61.5% (n=16)	No Consensus
22 Washout period	7.5 [6-9]	7.7% (n=2)	26.9% (n=7)	65.4% (n=17)	No Consensus
23 Retrospective ascertainment	7.5 [6.25-8]	3.8% (n=1)	23.1% (n=6)	73.1% (n=19)	Consensus of Agreement
24 Subthreshold presentations in MDD	8 [8-8.75]	3.8% (n=1)	7.7% (n=2)	88.5% (n=23)	Consensus of Agreement
25 Rapid antidepressant response	5 [3-6.75]	38.5% (n=10)	34.6% (n=9)	26.9% (n=7)	No Consensus
26 Activation warning signs	8 [7-9]	7.7% (n=2)	7.7% (n=2)	84.6% (n=22)	Consensus of Agreement
27 Activation in youth	6.5 [5-8]	11.5% (n=3)	38.5% (n=10)	50.0% (n=13)	No Consensus

Proposed changes for Round 3

Statement	**Proposed Round 3 disposition**
1	accepted as final; not carried forward to Round 3.
2	accepted as final; not carried forward to Round 3.
3	accepted as final; not carried forward to Round 3.
4	accepted as final; not carried forward to Round 3.
5	accepted as final; not carried forward to Round 3.
6	accepted as final; not carried forward to Round 3.
7a	accepted as final; not carried forward to Round 3.
7b	substantially revise and split.
8a	substantially revise.

8b	substantially revise.
9	accepted as final; not carried forward to Round 3
10a	accepted as final; not carried forward to Round 3
10b	revise and re-rate.
10c	substantially revise.
11	accepted as final; not carried forward to Round 3
12	retain unchanged and re-rate.
13	accepted as final; not carried forward to Round 3
14	revise and re-rate.
15	accepted as final; not carried forward to Round 3
16	accepted as final; not carried forward to Round 3
17	accepted as final; not carried forward to Round 3
18	accepted as final; not carried forward to Round 3
19a	accepted as final; not carried forward to Round 3
19b	accepted as final; not carried forward to Round 3
20	revise and re-rate.
21	substantially revise and re-rate.
22	substantially revise and re-rate.
23	accepted as final; not carried forward to Round 3
24	accepted as final; not carried forward to Round 3
25	substantially revise and re-rate.
26	accepted as final; not carried forward to Round 3
27	revise, split, and re-rate

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).

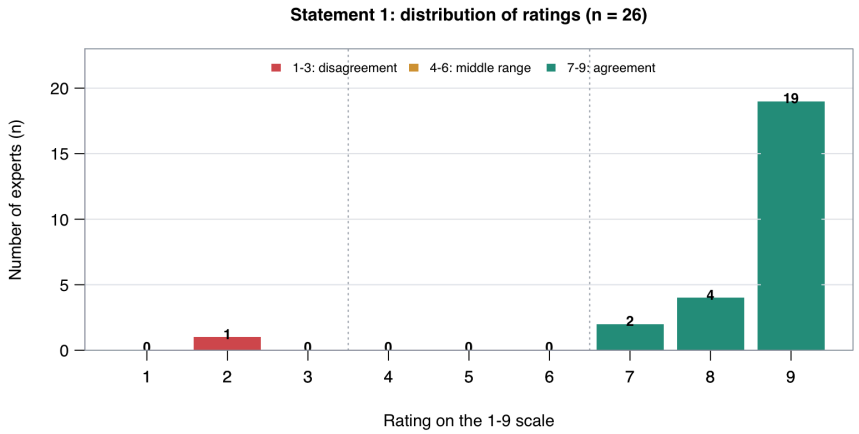
Background

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 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	9	8.25	9	0.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.8% (n=1)	0.0% (n=0)	96.2% (n=25)



Consensus status: Consensus of Agreement (96.2% agreement; median 9 [8.25-9]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

➔ 394618 - it is very important to have a clear definition of TEAS.

- ➔ 913780 - Besides, research, this is also important in the routine clinical practice, from the legal perspective.
- ➔ 126537 - vague definitions allow for data manipulation therefore clear guidelines are needed
- ➔ 731602 - Not much doubt here. The main question is if there is enough and consitent data to develop such definition.
- ➔ 562407 - Agree

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

Statement 2

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

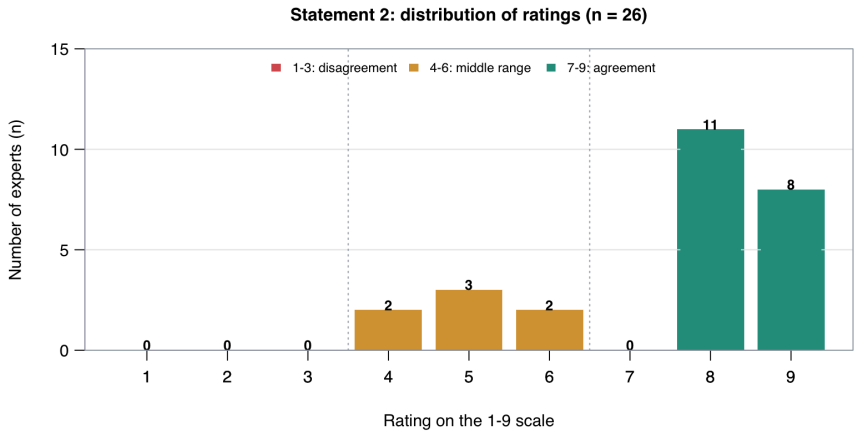
Background

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 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	6.5	9	2.5

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
0.0% (n=0)	26.9% (n=7)	73.1% (n=19)



Consensus status: Consensus of Agreement (73.1% agreement; median 8 [6.5-9]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

- ➔ 746052 - DSM and ICD are artificial and do not reflect the actual state
- ➔ 518904 - I do not understand how the clear definition of TEAS could affect the diagnosis of hypomania, mania or mix state
- ➔ 913780 - Agreed with the need for clear definition
- ➔ 731602 - Yes, this is badly needed and current DSM/ICD criteria are not very useful in this respect.

- ➔ 597318 - I do not think the DSM should be changed. Antidepressant complications should not be used to make a diagnosis
- ➔ 138956 - Not sure that discontinuation matters so much vs switch indicates latent bipolarity even if medications still used.

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

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.

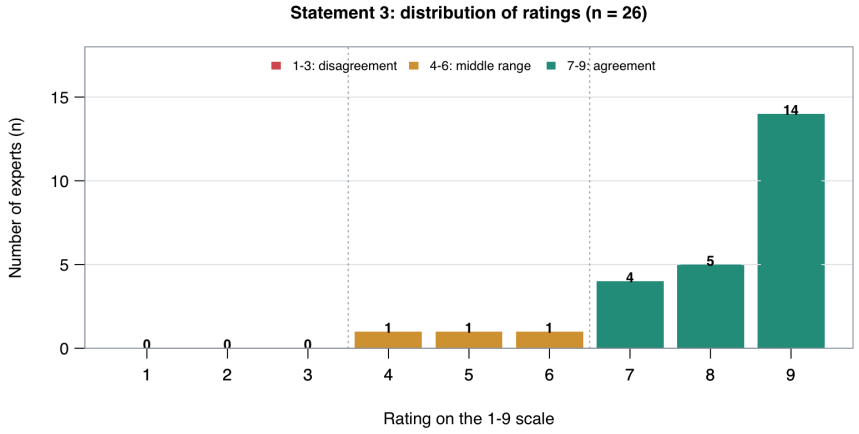
Background

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 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	9	7.25	9	1.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
0.0% (n=0)	11.5% (n=3)	88.5% (n=23)



Consensus status: Consensus of Agreement (88.5% agreement; median 9 [7.25-9]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

- ➔ 518904 - It would certainly be important to define well the TEAS but on the other hand the presence of so much uncertainty would indicate the difficult to frame the definition of TEAS.
- ➔ 126537 - not sure how much this will influence clinical practice

- ➔ 597318 - Not sure a definition is as important as the statement makes it out to be.
- ➔ 138956 - A clear definition improves reliability, but validity would still need to be tested.

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

Potential Triggering Factors

Statement 4

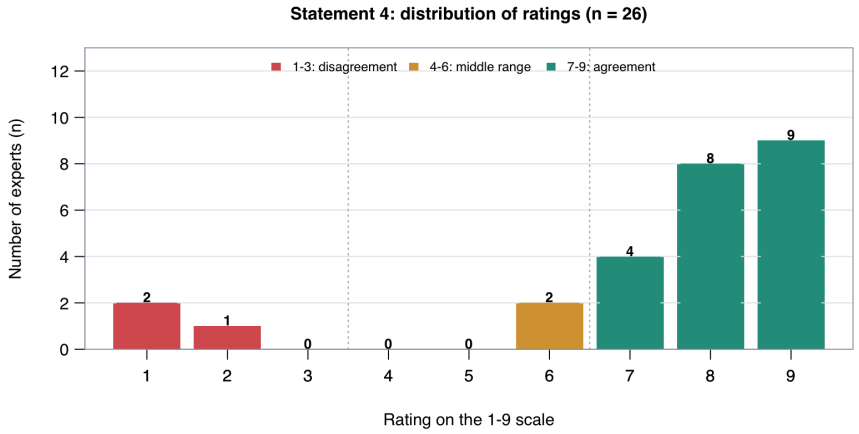
TEAS should be recognized as a potential adverse outcome of antidepressant treatment.

Background

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	7	9	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
11.5% (n=3)	7.7% (n=2)	80.8% (n=21)



Consensus status: Consensus of Agreement (80.8% agreement; median 8 [7-9]). The statement is supported by the expert panel.

Comments (see Statement 5).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

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 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.

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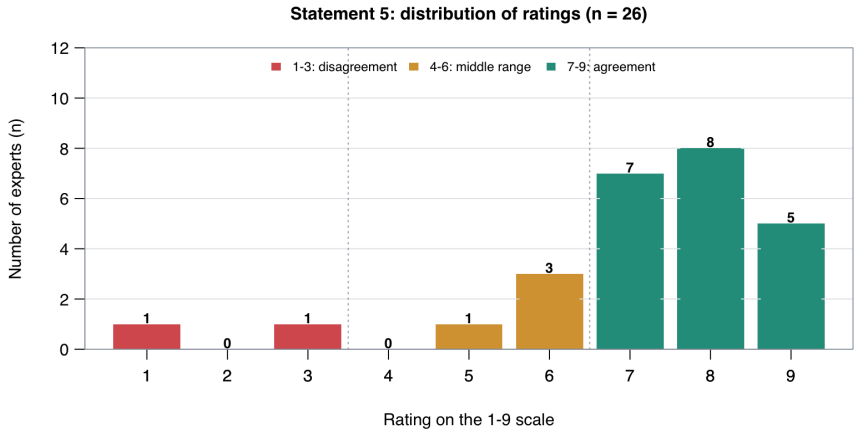
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Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	7.5	7	8	1

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
7.7% (n=2)	15.4% (n=4)	76.9% (n=20)



Consensus status: Consensus of Agreement (76.9% agreement; median 7.5 [7-8]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

- ➔ 518904 - I certainly agree with the idea that many therapeutic agents or strategies can cause TEAS which should be considered an adverse effect
- ➔ 731602 - Agreeed. The caveat is in the word "potential"
- ➔ 597318 - This could dilute the importance of TEAS
- ➔ 690284 - The evidence is weak, not only for other agents but also for antidepressants, and even in those cases that antidepressants may cause switch it could be considered a positive outcome in the context of an acute trial since in that case the depression has ended. And as stated, earlier there is no way to distinguish spontaneous switch from antidepressant-caused switch.
- ➔ 138956 - The list of non-antidepressant medications is perhaps too broad. Am yet to see a switch after an antipsychotic with antidepressant properties.

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

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”.

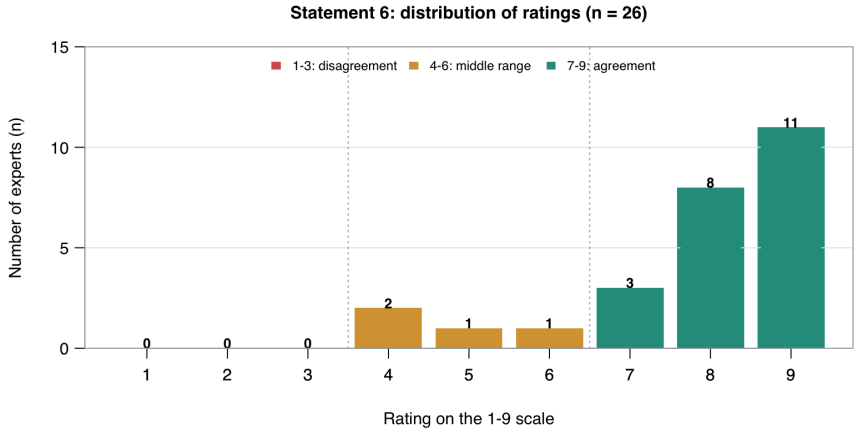
Background

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 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	7.25	9	1.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
0.0% (n=0)	15.4% (n=4)	84.6% (n=22)



Consensus status: Consensus of Agreement (84.6% agreement; median 8 [7.25-9]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

- ➔ 518904 - I agree that substance induced states should be considered differently from TEAS
- ➔ 731602 - The dividing line here is less clear. In both cases the issue is that "a substance" alters the course of illness

➔ 597318 - The T in TEAS is treatment.

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

Main Clinical Manifestations

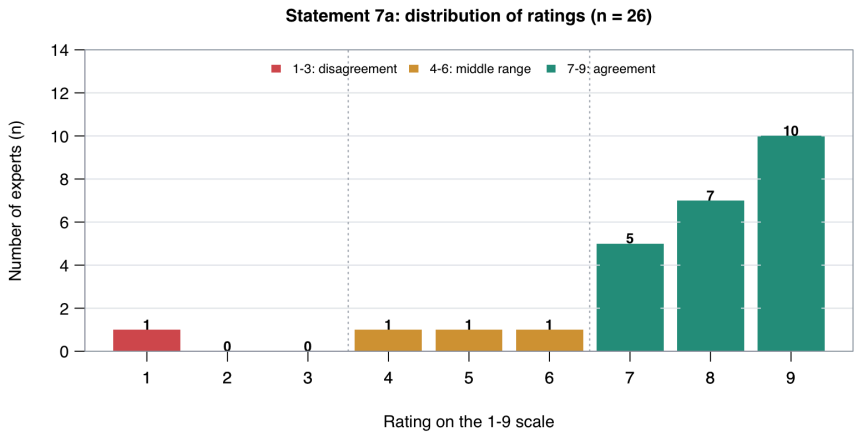
Statement 7a

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	7	9	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.8% (n=1)	11.5% (n=3)	84.6% (n=22)



Consensus status: Consensus of Agreement (84.6% agreement; median 8 [7-9]). The statement is supported by the expert panel.

Comments (see Statement 7b).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

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.

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.

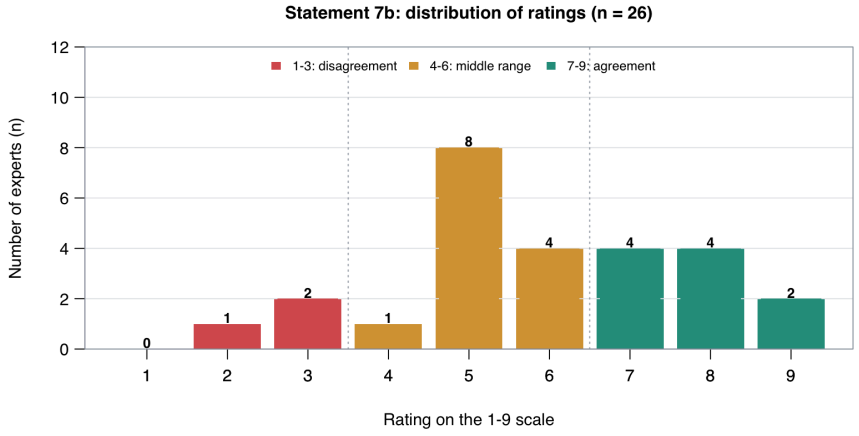
References:

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 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	6	5	7	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
11.5% (n=3)	50.0% (n=13)	38.5% (n=10)



Consensus status: No Consensus (38.5% agreement; 11.5% disagreement; median 6 [5-7]). The statement requires re-rating, revision, or is recorded as disputed.

Comments (listed in chronological order of submission):

- ➔ 518904 - TEAS can occur after longer periods of time even after months of treatment
- ➔ 351746 - Time frame should not be uniformly defined, rather intervention-specific
- ➔ 157493 - Too long
- ➔ 840362 - I'm still not sure that the term "dosage increase" is exhaustive here. I suggest replacing the phrase "dose increase" with "dose adjustment" (or "change in dose").
- ➔ 731602 - Possibly. One should also add induction of rapid cycling here
- ➔ 485621 - An 8-week window after treatment initiation or dose increase is too long. It should be equal to criteria of manic/hypomanic episode.
- ➔ 597318 - Antidepressants destabilize bipolar illness and several long term studies show that there is an increase in depression and cycling, Limiting definition to mania does not make sense, and does not capture the reality of what antidepressants do.
  El-Mallakh RS, Ghaemi SN, Sagduyu K, Thase ME, Wisniewski SR, Nierenberg AA, Zhang HW, Pardo TA, Sachs G; STEP-BD Investigators. Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients. J Affect Disord. 2008 Dec;111(2-3):372-7. doi: 10.1016/j.jad.2008.03.025. Epub 2008 Jun 20. PMID: 18565592.
  El-Mallakh RS, Vöhringer PA, Ostacher MM, Baldassano CF, Holtzman NS, Whitham EA, Thommi SB, Goodwin FK, Ghaemi SN. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. J Affect Disord. 2015 Sep 15;184:318-21. doi: 10.1016/j.jad.2015.04.054. Epub 2015 Jun 10. Erratum in: J Affect Disord. 2016 Jan 15;190:895. PMID: 26142612; PMCID: PMC4519402.
- ➔ 690284 - The problem with the above two questions is that TEAS is not necessarily linked to antidepressants which seemingly still is assumed in TEAS as conceptualized here in this survey.
- ➔ 138956 - Any temporal criteria should be based on data, not on expert consensus - i.e. evidence not eminence based medicine!

Round 3 action: Substantially revise and split. Round 2 did not establish consensus on the proposed 8-week operational time window. Expert comments indicated disagreement both about whether a single predefined time window should be used and about the appropriate duration of such a window. The item will therefore be divided in Round 3 to separately assess: (1) the need for a predefined primary operational time window; (2) 4-week and 8-week candidate windows; and (3) the need for continued clinical vigilance beyond the primary operational window. The 4-week and 8-week options will be rated independently, followed by a separate forced-choice question asking experts to indicate their preferred operational approach.

New Background: A defined temporal relationship between treatment exposure and affective switching is an important component of an operational definition of TEAS. An 8-week window following treatment initiation or dose increase has been proposed in the ISBD

nomenclature and has subsequently been used in clinical research. However, the empirical basis for a single fixed cutoff remains limited.

Round 2 did not produce consensus on the proposed 8-week window. Expert comments reflected several distinct concerns: some considered 8 weeks too long, others noted that potentially treatment-associated switches may occur later, and some argued that the relevant interval may vary according to the intervention. These comments suggest that the need for a predefined operational window, its duration, and the clinical interpretation of switches occurring beyond that window should be assessed separately.

For Round 3, the concept of a primary operational time window is therefore distinguished from the broader period of clinical vigilance. The primary window is intended to provide a standardized interval for the operational ascertainment of TEAS rather than to define an absolute biological or causal boundary. Events occurring beyond this interval may still warrant clinical consideration of a possible treatment-associated affective switch.

New Statement 7b-1: A predefined primary operational time window should be used for the ascertainment of TEAS following treatment initiation or intensification.

The following two statements represent alternative candidate durations for the primary operational time window. Please rate each statement independently according to how appropriate you consider the proposed duration.

New Statement 7b-2a: For operational purposes, a 4-week period following treatment initiation or intensification should be used as the primary time window for the emergence of TEAS.

New Statement 7b-2b: For operational purposes, an 8-week period following treatment initiation or intensification should be used as the primary time window for the emergence of TEAS.

New Statement 7b-3: Clinical vigilance for affective switching should continue throughout treatment with an intervention capable of precipitating TEAS, even beyond the primary operational time window.

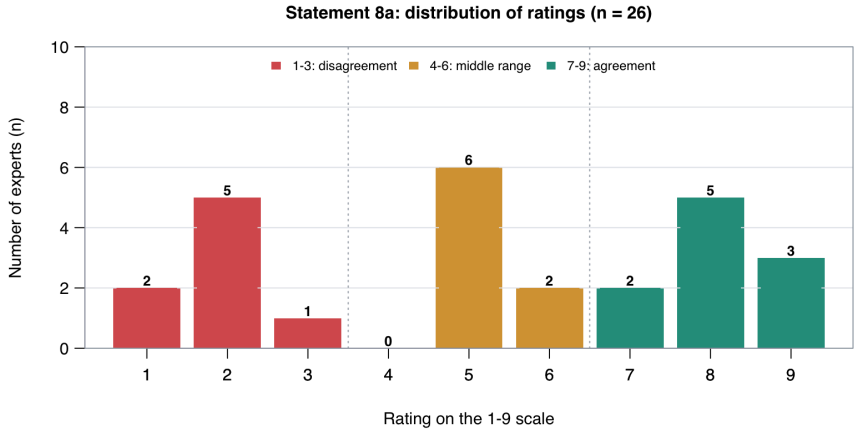
Statement 8a

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

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	5	2.25	8	5.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
30.8% (n=8)	30.8% (n=8)	38.5% (n=10)



Consensus status: No Consensus (38.5% agreement; 30.8% disagreement; median 5 [2.25-8]). The statement requires re-rating, revision, or is recorded as disputed. *No directional tendency by median.*

Comments (see Statement 8b).

Round 3 action: Substantially revise. Round 2 revealed fundamental disagreement as to whether affective switches emerging after treatment discontinuation or dose reduction should be classified as TEAS or regarded as a distinct treatment-related phenomenon. Several experts specifically argued that post-discontinuation switches may involve a different mechanism and should be distinguished from switches emerging during active treatment. The item will therefore be reformulated in Round 3 to directly assess whether post-discontinuation affective switches should be classified separately from TEAS occurring during ongoing treatment.

New Background (see Statement 8b).

New Statement 8a: Affective switches emerging following discontinuation or substantial dose reduction of an antidepressant or another intervention with antidepressant effects should be classified separately from TEAS occurring during active treatment.

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.

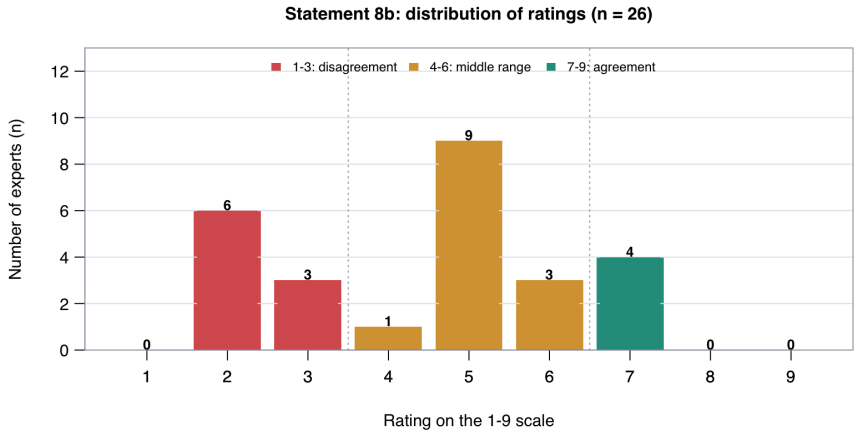
Background

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	5	3	5.75	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
34.6% (n=9)	50.0% (n=13)	15.4% (n=4)



Consensus status: No Consensus (15.4% agreement; 34.6% disagreement; median 5 [3-5.75]). The statement requires re-rating, revision, or is recorded as disputed. *No directional tendency by median.*

Comments (listed in chronological order of submission):

➔ 518904 - It is such a rare event that I would not consider it relevant

- ➔ 840362 - The basis for choosing 7 days is unclear to me, especially given the different half-lives of the drugs.
- ➔ 731602 - 7 days seems short. The interval will depend also on the half-life of the antidepressant. Clinically, most cases seem to fall withing 1-week period, but perhaps extending to two weeks might be more appropriate
- ➔ 276415 - On thinking about this further, I think treatment discontinuation-related switch might be best considered a different phenomenon than TEAS.
- ➔ 597318 - Antidepressant withdrawal is similar to antipsychotic withdrawal and is really a sign that the brain is adapting to medication. These should not be confused.
- ➔ 417960 - 7 days seems arbitrary, perhaps something like 5-half lives could be a better option
- ➔ 690284 - The above question is unclear. A 7-day period is relevant in the following situation: If a patient develops mania when initiated on antidepressants and this mania resolves within seven days after discontinuation of the antidepressant, then it most likely has been caused by the antidepressant. The question does not clearly address this situation for which reason the only answer can be uncertainty.
- ➔ 138956 - If it is after discontinuation it is no longer Treatment EAS! Plus this is likely a different mechanism. So I would not combine the two under the same term.

Round 3 action: Substantially revise. The proposed fixed 7-day window received little support in Round 2. Expert comments questioned the empirical basis of this cutoff and emphasized that the relevant interval may depend on the characteristics of the discontinued intervention, particularly drug half-life and the manner of discontinuation or dose reduction. The fixed 7-day criterion will therefore be replaced by an intervention-specific temporal approach in Round 3.

New Background: Affective switches have been reported following discontinuation or substantial dose reduction of antidepressants and other interventions with antidepressant effects. However, Round 2 demonstrated substantial disagreement as to whether these events should be included within TEAS or regarded as a distinct treatment-related phenomenon. Several experts argued that post-discontinuation switches may differ mechanistically from switches emerging during active treatment and should therefore be classified separately.

Round 2 also provided little support for a fixed 7-day post-discontinuation window. Expert comments emphasized that the relevant interval may depend on the characteristics of the discontinued intervention, including drug half-life, the persistence of biological effects, and the manner of treatment discontinuation. The classification of post-discontinuation switches and the temporal framework for their assessment are therefore addressed separately in Round 3.

New Statement 8b: For affective switches emerging after treatment discontinuation or substantial dose reduction, the relevant temporal window should be determined by the characteristics of the discontinued intervention, including its pharmacokinetic properties where applicable, rather than by a fixed time interval.

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.

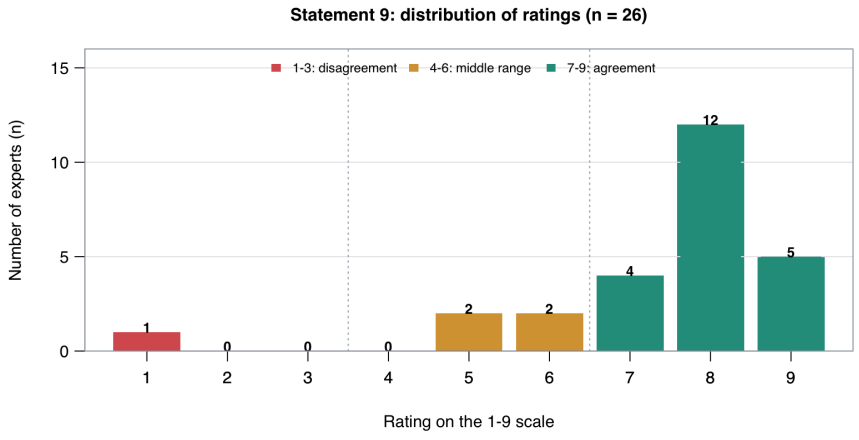
Background

A key methodological issue in 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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	7	8	1

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.8% (n=1)	15.4% (n=4)	80.8% (n=21)



Consensus status: Consensus of Agreement (80.8% agreement; median 8 [7-8]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

- ➔ 597318 - Again, antidepressant withdrawal should not be considered TEAS
- ➔ 948206 - I think it is important to distinguish between AD-related activation versus syndromal mania or hypomania in this context
- ➔ 690284 - The reason for my answer here is that it is still unclear at this point whether TEAS is used to indicate antidepressant causality.
- ➔ 138956 - Makes little sense to not call this TEAS if a patient switched to mania, but just was unable to see a psychiatrist and thus continues on their medication. These types of criteria conflate biological reactions with access to care issues. Also, we separately even considered switch following discontinuation, so insisting on discontinuation conflates this even further - are we then dealing with TEAS or discontinuation effects? Thirdly, if a patient meets criteria for mania it is not a simple activation on antidepressants, i.e. we should be able to differentiate a clinically meaningful episode from mild treatment related activation.

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

Additional Clinical Manifestations

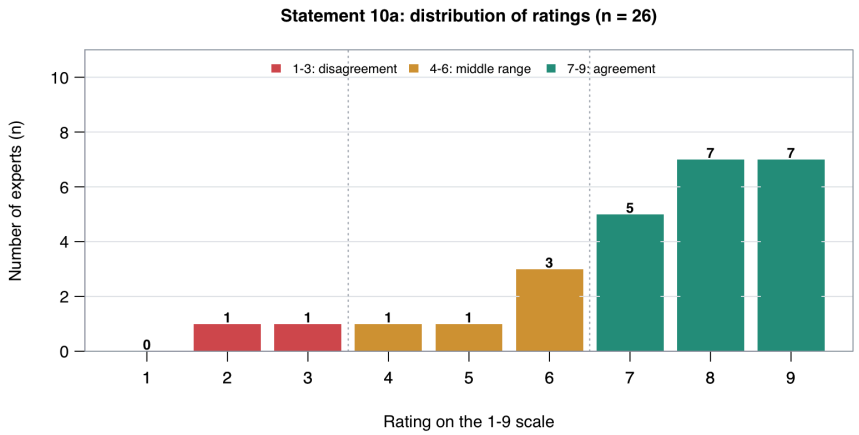
Statement 10a

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	6.25	8.75	2.5

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
7.7% (n=2)	19.2% (n=5)	73.1% (n=19)



Consensus status: Consensus of Agreement (73.1% agreement; median 8 [6.25-8.75]). The statement is supported by the expert panel.

Comments (see Statement 11).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

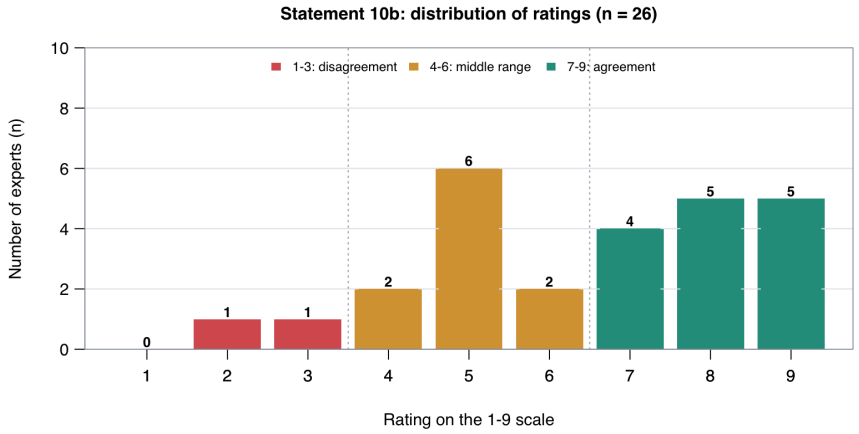
Statement 10b

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	7	5	8	3

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
7.7% (n=2)	38.5% (n=10)	53.8% (n=14)



Consensus status: No Consensus (53.8% agreement; 7.7% disagreement; median 7 [5-8]). The statement requires re-rating, revision, or is recorded as disputed. *Directional tendency toward agreement (without consensus).*

Comments (see Statement 11).

Round 3 action: Revise and re-rate. Round 2 showed a directional tendency toward agreement, but expert comments indicated that suicidal behavior should not be considered a manifestation of TEAS in isolation. The item will therefore be revised to clarify that suicidal behavior may accompany TEAS when it occurs in association with emerging hypomanic, manic, or mixed symptoms, rather than as a consequence of worsening depression alone.

New Statement 10b: Suicidal behavior emerging during treatment may accompany TEAS when it occurs in association with treatment-emergent hypomanic, manic, or mixed symptoms.

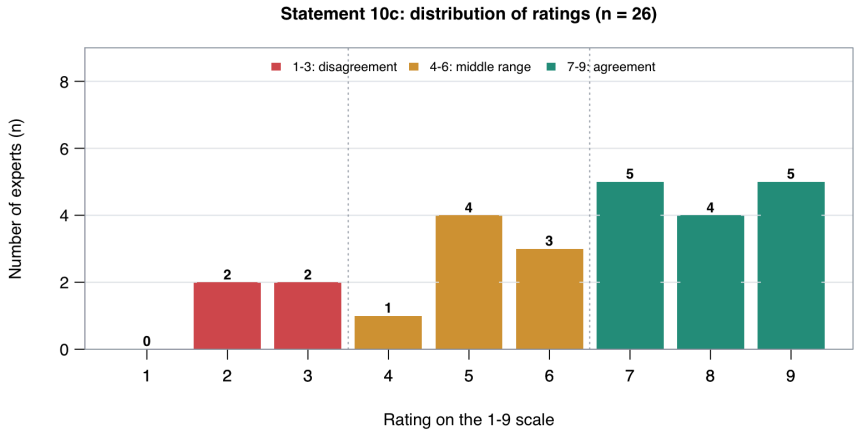
Statement 10c

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	7	5	8	3

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
15.4% (n=4)	30.8% (n=8)	53.8% (n=14)



Consensus status: No Consensus (53.8% agreement; 15.4% disagreement; median 7 [5-8]). The statement requires re-rating, revision, or is recorded as disputed. *Directional tendency toward agreement (without consensus).*

Comments (see Statement 11).

Round 3 action: Substantially revise. Round 2 did not establish consensus that paradoxical worsening of depression should be considered a manifestation of TEAS. Expert feedback highlighted that worsening of depressive symptoms without emerging hypomanic, manic, or mixed features does not represent an affective switch and may constitute a distinct treatment-emergent adverse outcome. The item will therefore be reformulated to assess whether such worsening should be classified separately from TEAS.

New Statement 10c: Paradoxical worsening of depression occurring during treatment, in the absence of emerging hypomanic, manic, or mixed symptoms, should be considered separately from TEAS.

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

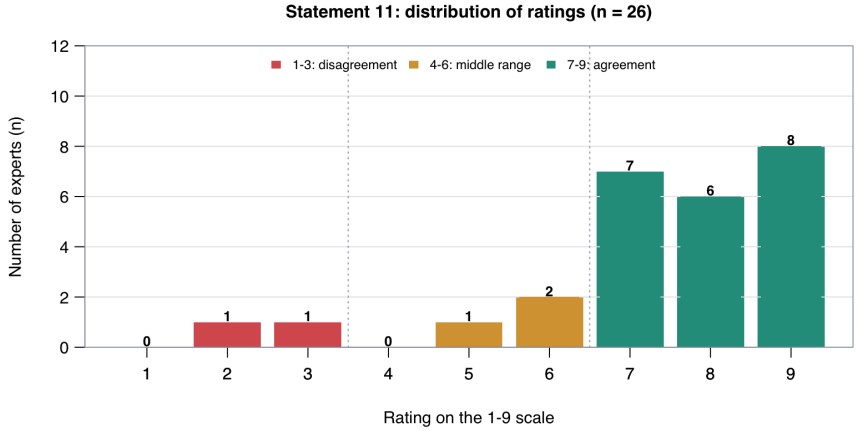
Existing definitions of TEAS have focused predominantly on polarity switch, particularly hypomania, mania, and mixed states. However, other clinically significant phenomena have been described in temporal association with antidepressant treatment, including psychotic symptoms, suicidal behavior, paradoxical 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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	7	9	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
7.7% (n=2)	11.5% (n=3)	80.8% (n=21)



Consensus status: Consensus of Agreement (80.8% agreement; median 8 [7-9]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

- ➔ 518904 - I agree with all these possible occurrences
- ➔ 276415 - I personally believe that antidepressants can cause worsening SI or depression in vulnerable individuals. But since the term TEAS refers to affective SWITCH, worsening depression wouldn't seem to apply. Likewise for worsening SI, if it's felt to be due to the emergence or worsening of mixed symptoms it makes sense to include it, but not if it's due to worsening of depression.
- ➔ 690284 - Again, I chose uncertainty of three of the above questions since TEAS has still not been defined as a phenomenon occurring during treatment but not necessarily caused by the treatment. If this more correct and broad definition had been used, obviously I would have answered higher on the scale.

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

New Background: Round 2 demonstrated different levels of support for additional clinical phenomena occurring in temporal association with treatment. Psychotic symptoms reached consensus as a possible accompanying feature of TEAS, whereas suicidal behavior and paradoxical worsening of depression did not.

Expert comments suggested that suicidal behavior may be clinically relevant to TEAS when it emerges in association with treatment-emergent hypomanic, manic, or mixed symptoms, but should not be attributed to TEAS when it reflects worsening depression alone. Similarly, paradoxical worsening of depressive symptoms in the absence of counterpolar or mixed features may represent a distinct treatment-emergent adverse outcome rather than an affective switch. These distinctions will therefore be assessed explicitly in Round 3.

Temporal Criteria for Clinical Manifestations

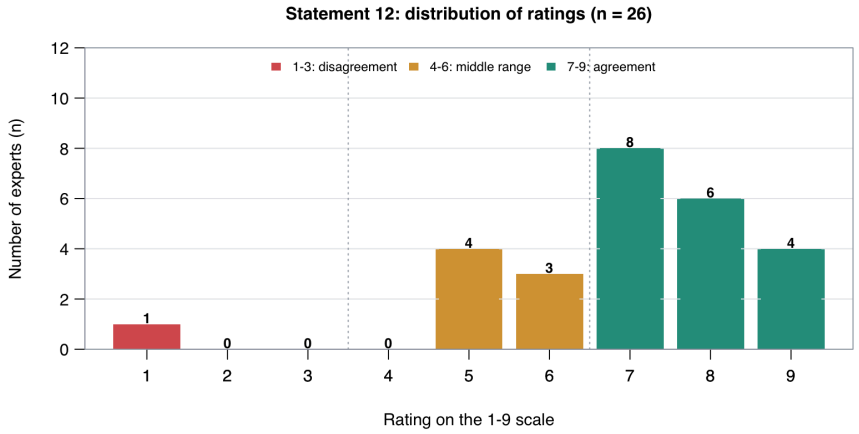
Statement 12

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	7	6	8	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.8% (n=1)	26.9% (n=7)	69.2% (n=18)



Consensus status: No Consensus (69.2% agreement; 3.8% disagreement; median 7 [6-8]). The statement requires re-rating, revision, or is recorded as disputed. *Directional tendency toward agreement (without consensus).*

Comments (see Statement 13).

Round 3 action: Retain unchanged and re-rate. Round 2 showed a strong directional tendency toward agreement and narrowly missed the predefined consensus threshold (69.2% agreement; median 7 [6–8]), with only one expert rating the statement in the disagreement range. No specific Round 2 comments identified a substantive problem with the wording or underlying concept. The statement will therefore be retained unchanged for re-rating in Round 3.

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

Background

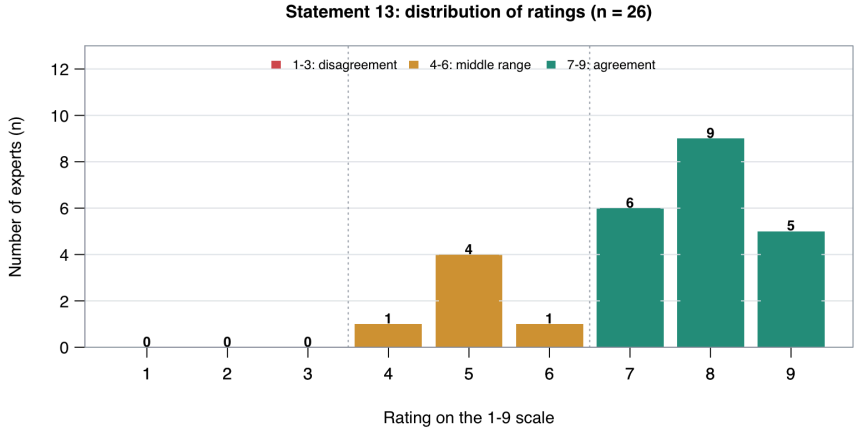
Statements 12 and 13 address whether the temporal requirements for TEAS should differ according to the baseline diagnostic context. In patients with an established diagnosis of bipolar disorder, clinically significant treatment-emergent hypomanic, manic, or mixed symptoms may be relevant even when their 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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	7	8	1

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
0.0% (n=0)	23.1% (n=6)	76.9% (n=20)



Consensus status: Consensus of Agreement (76.9% agreement; median 8 [7-8]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

- ➔ 597318 - I do not think we need to switch the diagnostic criteria.
- ➔ 690284 - The question is unclear.

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

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 2 established consensus that, in major depressive disorder, ascertainment of TEAS should require fulfillment of the temporal criteria for the corresponding presentation according to the applicable diagnostic classification and should prompt diagnostic reassessment for bipolar disorder. In patients with established bipolar disorder, however, the panel showed a strong but formally insufficient tendency toward accepting clinically significant treatment-emergent hypomanic, manic, or mixed symptoms of shorter duration. Statement 12 is therefore retained unchanged for final re-rating in Round 3.

Method of Assessment

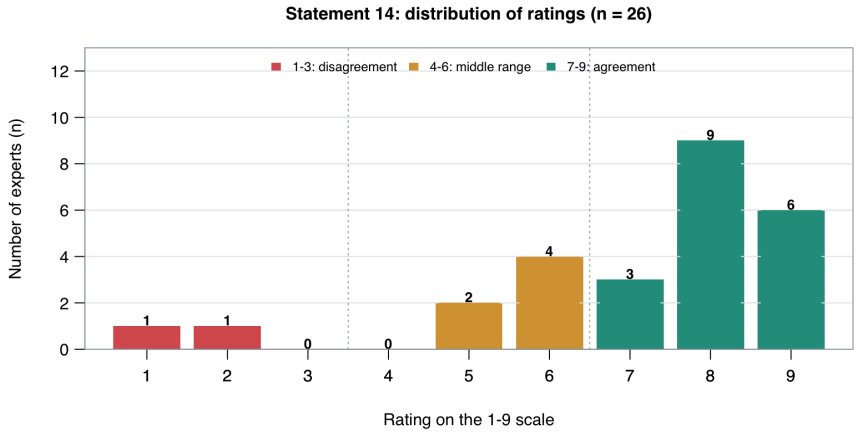
Statement 14

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	6	8	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
7.7% (n=2)	23.1% (n=6)	69.2% (n=18)



Consensus status: No Consensus (69.2% agreement; 7.7% disagreement; median 8 [6-8]). The statement requires re-rating, revision, or is recorded as disputed. *Directional tendency toward agreement (without consensus).*

Comments (see Statement 16).

Round 3 action: Revise and re-rate. Round 2 showed a strong directional tendency toward agreement and narrowly missed the predefined consensus threshold. Expert comments generally supported the use of rating scales as adjunctive tools but indicated that the adequacy of a specific threshold depends on the operational definition of TEAS and the broader clinical assessment. The statement will therefore be simplified to assess directly whether a rating-scale threshold alone is sufficient for TEAS ascertainment.

New Statement 14: For the ascertainment of TEAS, reaching a threshold score on a symptom rating scale alone is insufficient to establish the presence of hypomanic, manic, or mixed symptoms.

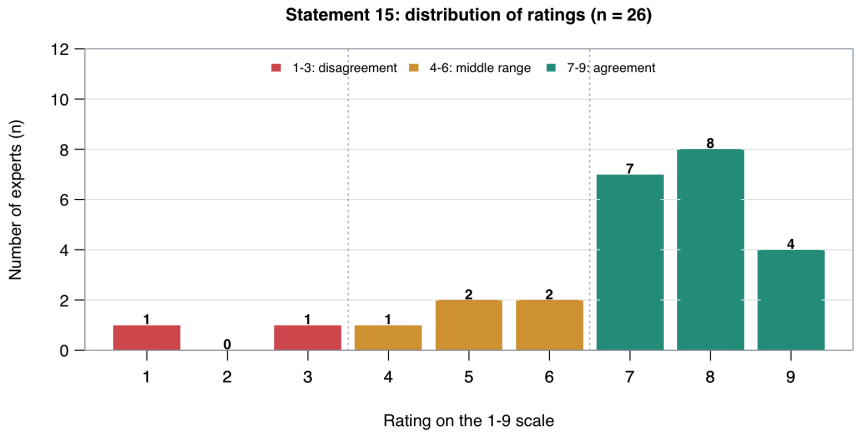
Statement 15

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

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	7	6.25	8	1.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
7.7% (n=2)	19.2% (n=5)	73.1% (n=19)



Consensus status: Consensus of Agreement (73.1% agreement; median 7 [6.25-8]). The statement is supported by the expert panel.

Comments (see Statement 16).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

Statement 16

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

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.

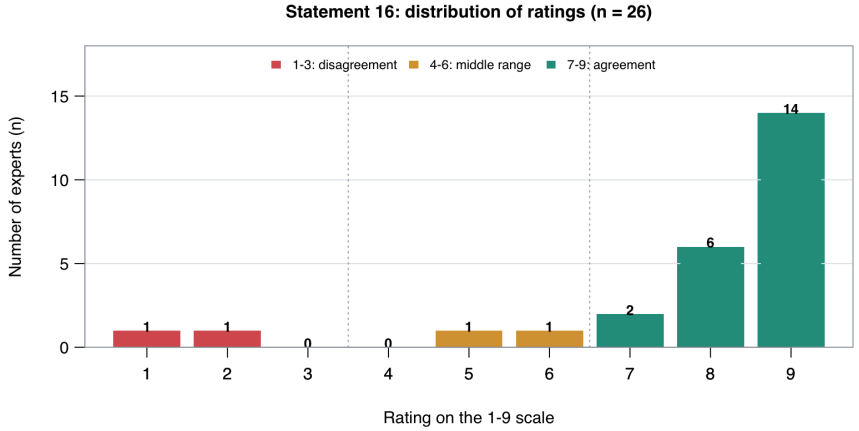
Structured and semi-structured clinical diagnostic interviews allow a more comprehensive assessment of symptom pattern, duration, severity, functional consequences, and clinical context, while preserving a standardized approach to ascertainment. However, such interviews require trained personnel and 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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	9	8	9	1

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
7.7% (n=2)	7.7% (n=2)	84.6% (n=22)



Consensus status: Consensus of Agreement (84.6% agreement; median 9 [8-9]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

- ➔ 518904 - YMRS can help the diagnosis but after a clinical evaluation
- ➔ 597318 - Making a diagnosis should not be based on a scale or diagnostic interview, but such instruments can be used to augment the diagnosis.
- ➔ 690284 - The two first questions are answered with uncertainty since still no clear definition of switch has been presented. In context of drug trials, the term can refer to an episode fulfilling diagnostic criteria or to a threshold on a rating scale appearing e.g. twice with one week interval. So, the answer depends on the definition of switch.

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

Causality Assessment

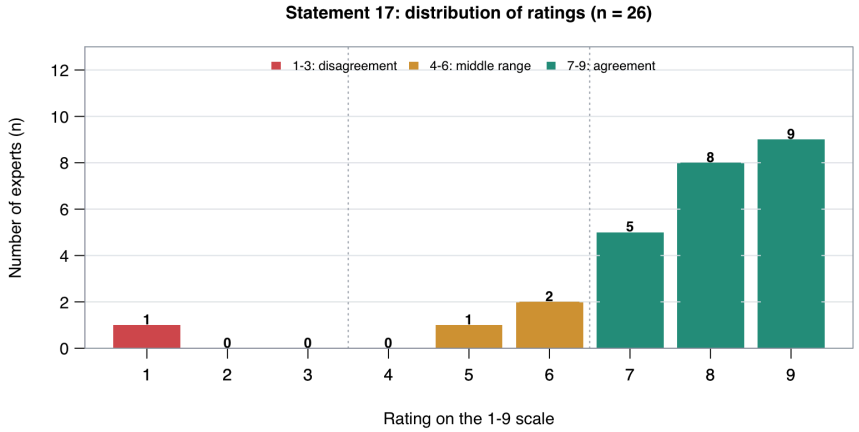
Statement 17

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).

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	7	9	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.8% (n=1)	11.5% (n=3)	84.6% (n=22)



Consensus status: Consensus of Agreement (84.6% agreement; median 8 [7-9]). The statement is supported by the expert panel.

Comments (see Statement 21).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

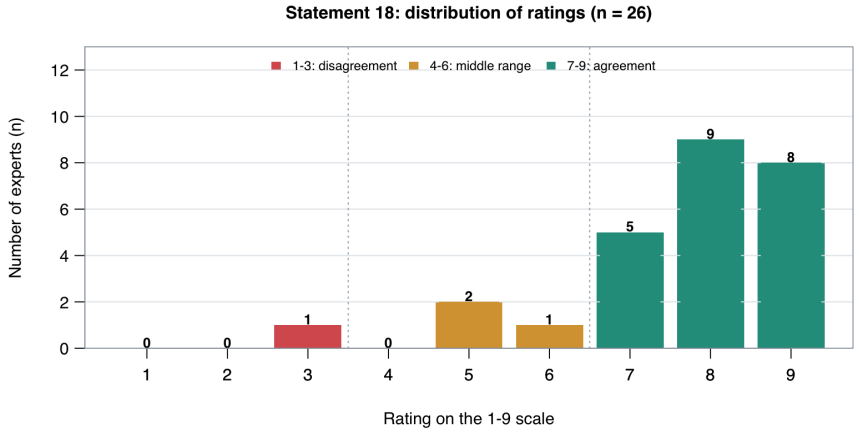
Statement 18

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	7	9	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.8% (n=1)	11.5% (n=3)	84.6% (n=22)



Consensus status: Consensus of Agreement (84.6% agreement; median 8 [7-9]). The statement is supported by the expert panel.

Comments (see Statement 21).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

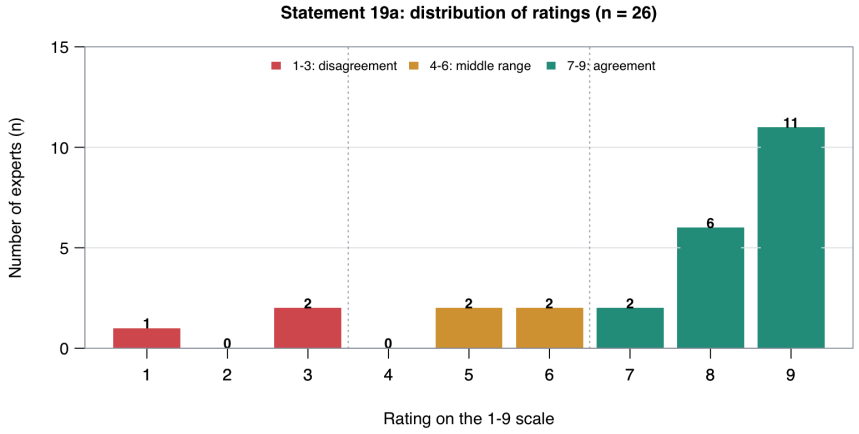
Statement 19a

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	6.25	9	2.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
11.5% (n=3)	15.4% (n=4)	73.1% (n=19)



Consensus status: Consensus of Agreement (73.1% agreement; median 8 [6.25-9]). The statement is supported by the expert panel.

Comments (see Statement 21).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

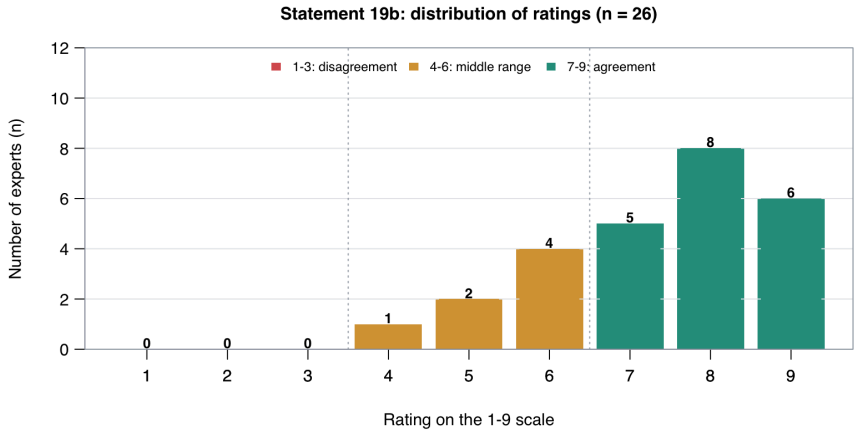
Statement 19b

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	6.25	8	1.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
0.0% (n=0)	26.9% (n=7)	73.1% (n=19)



Consensus status: Consensus of Agreement (73.1% agreement; median 8 [6.25-8]). The statement is supported by the expert panel.

Comments (see Statement 21).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

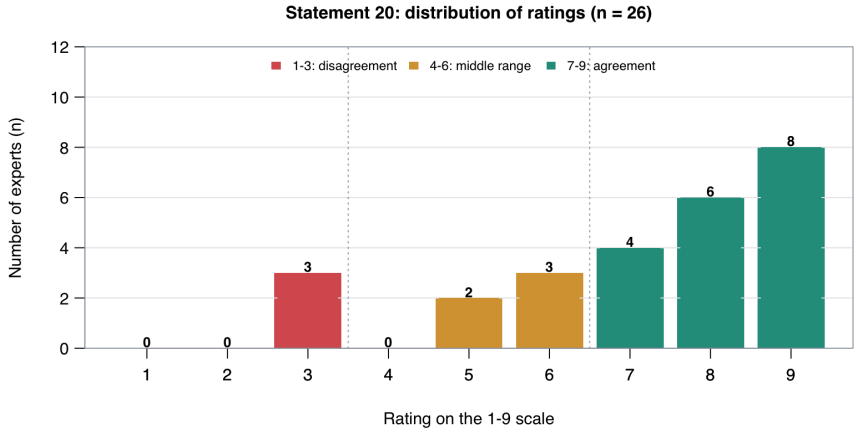
Statement 20

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	6	9	3

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
11.5% (n=3)	19.2% (n=5)	69.2% (n=18)



Consensus status: No Consensus (69.2% agreement; 11.5% disagreement; median 8 [6-9]). The statement requires re-rating, revision, or is recorded as disputed. *Directional tendency toward agreement (without consensus).*

Comments (see Statement 21).

Round 3 action: Revise and re-rate. Round 2 showed a strong directional tendency toward agreement but narrowly missed the predefined consensus threshold. Expert feedback indicated that automatic discontinuation may be overly categorical because management should take into account both the likelihood that the intervention contributed to the switch and the potential risks of treatment withdrawal. The statement will therefore be revised to emphasize prompt reassessment and individualized consideration of discontinuation or dose reduction.

New Background: Round 2 showed strong support for modifying treatment when hypomania, mania, or a mixed state emerges, but did not reach formal consensus on mandatory discontinuation of the potentially contributing intervention. Expert feedback emphasized that clinical management should distinguish causal attribution from treatment decisions and should consider both the likelihood that the intervention is contributing to the switch and the potential consequences of stopping treatment.

For Round 3, the statement is therefore revised to emphasize prompt reassessment of the potentially contributing intervention and individualized consideration of discontinuation or dose reduction rather than automatic withdrawal in all cases.

New Statement 20: When hypomania, mania, or a mixed state emerges during treatment, any antidepressant or other intervention with antidepressant effects that may have contributed to the switch should be promptly reassessed, and discontinuation or dose reduction should be considered on the basis of clinical judgment.

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.

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.

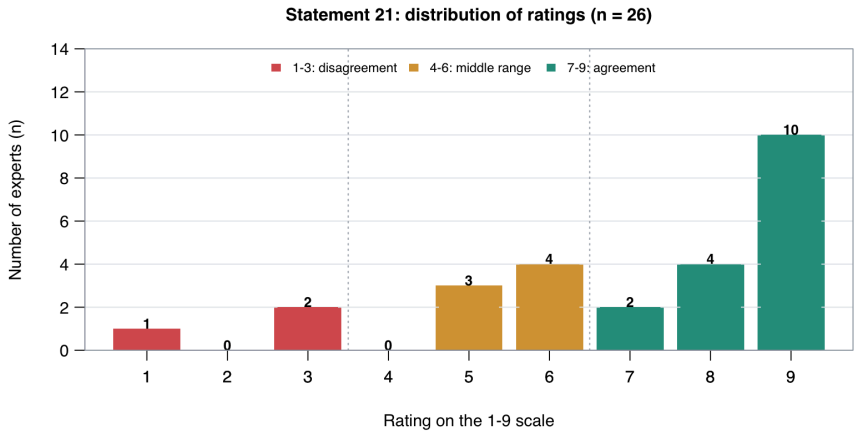
At the group level, research aimed at determining whether an intervention causally increases the risk of TEAS requires comparative evidence. Randomized, double-blind, placebo-controlled trials provide the strongest protection against confounding and bias and therefore offer the strongest evidence for 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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	6	9	3

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
11.5% (n=3)	26.9% (n=7)	61.5% (n=16)



Consensus status: No Consensus (61.5% agreement; 11.5% disagreement; median 8 [6-9]). The statement requires re-rating, revision, or is recorded as disputed. *Directional tendency toward agreement (without consensus).*

Comments (listed in chronological order of submission):

- ➔ 731602 - "Structured approach" sounds good but needs to be better defined and operationalized. I am not sure how the last question (randomized trial) is meant. RCT with TEAS as an outcome? Using data from RCTs that report TEAS?
- ➔ 854317 - I agree that randomized, double-blind, placebo-controlled trials provide the strongest evidence for causal inference. However, it should be acknowledged that such trials are often not feasible or ethically appropriate, and evidence from other well-designed study designs may therefore also be important for assessing TEAS risk.
- ➔ 276415 - In deciding whether to discontinue an antidepressant, clinical judgement should be used to take into account 1) the likelihood that the antidepressant is prolonging the switch and 2) potential harms of stopping the antidepressant - e.g. return of a severe depression, SI, etc (especially if this has happened in the past).
- ➔ 597318 - The problem with focusing on switch from depression to mania is that it does not match reality where depression is the most common increase in affective switches. Doing a RCT would be undesirable because of the harm it would do to the participants.

- ➔ 690284 - Regarding the second question in this section my answer is uncertainty since even a temporal relationship may not indicate causality, then obviously depending on the degree of the relationship. My answer 6 on the above question reflects that such a trial can be helpful but dependent on how it is designed. An agent that has antidepressant potential over placebo may be associated with switch since the switch may simply be a spontaneous switch arising when depression is terminated. Here, the ratio of switch to the number of responders should be the major outcome.
- ➔ 138956 - Dose-response relationship, disappearance and re-emergence of symptoms following treatment modification are tricky - this is not going to follow exactly the changes in medications, but rather the kinetics of receptors, transporters impacted, as well as any adaptive processes.

Round 3 action: Substantially revise and re-rate. Round 2 showed a directional tendency toward agreement, but expert comments indicated ambiguity regarding the intended trial design and raised concerns about feasibility and ethics. The item will therefore be revised to clarify that it concerns group-level causal inference and that randomized controlled trials with a prespecified TEAS outcome and an appropriate comparator provide the strongest evidence when such trials are feasible and ethically appropriate.

New Background: Establishing whether an intervention increases the risk of TEAS at the population level requires comparative evidence and should be distinguished from causal attribution in an individual patient. Round 2 comments generally supported the methodological advantages of randomized controlled trials but highlighted that placebo-controlled or double-blind designs may not always be feasible or ethically appropriate and that the interpretation of TEAS risk depends on how the outcome and comparator are defined.

For Round 3, the statement therefore focuses on the principle of randomized comparative evidence with a prespecified assessment of TEAS and an appropriate comparator, while explicitly acknowledging feasibility and ethical constraints.

New Statement 21: At the group level, when feasible and ethically appropriate, a randomized controlled trial with a prespecified assessment of TEAS and an appropriate comparator provides the strongest evidence for determining whether an intervention increases the risk of TEAS.

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.

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.

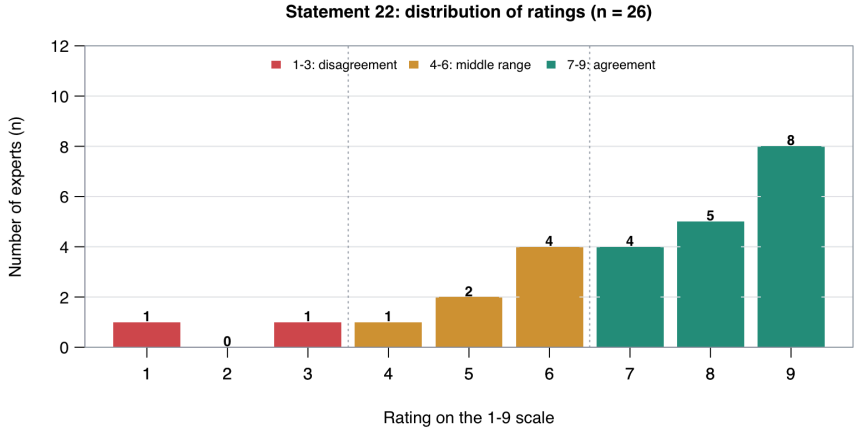
However, Round 1 comments indicated that a fixed washout period is unlikely to be appropriate across different treatments. The duration required to minimize residual effects may depend on pharmacokinetic characteristics such as elimination half-life and active metabolites, and may differ substantially 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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	7.5	6	9	3

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
7.7% (n=2)	26.9% (n=7)	65.4% (n=17)



Consensus status: No Consensus (65.4% agreement; 7.7% disagreement; median 7.5 [6-9]). The statement requires re-rating, revision, or is recorded as disputed. *Directional tendency toward agreement (without consensus).*

Comments (listed in chronological order of submission):

- ➔ 518904 - Washour period would be certainly of importance
- ➔ 840362 - This statement is not entirely consistent with the statement limiting the period to 7 days. It appears that the recommendations for research and clinical practice differ.
- ➔ 690284 - A relevant trial would be to add an antidepressant versus placebo on top of a mood stabilizer, at least in bipolar 1 disorder and in that case there should be no drug discontinuation up till randomization even the mood stabilizer may have antidepressant efficacy.
- ➔ 138956 - This is perhaps too simplistic, as absence of medications in serum does not mean absence of ongoing neurobiological changes related to the medication.

Round 3 action: Substantially revise and re-rate. Round 2 showed a directional tendency toward agreement, but expert feedback indicated that mandatory washout is not appropriate for all trial designs and that pharmacokinetic elimination alone may not capture persistent biological effects of prior treatment. The statement will therefore be revised to require that potentially confounding prior treatments be accounted for in the study design, with an intervention-appropriate washout applied when treatment discontinuation is required.

New Background: Prior exposure to antidepressants or other interventions with antidepressant effects may complicate attribution of an affective switch to an investigational treatment. However, Round 2 feedback indicated that a mandatory washout is not appropriate for every trial design. Some studies may appropriately retain background treatment, whereas in others discontinuation of prior treatment is necessary to reduce carry-over effects.

In addition, the relevant carry-over period may not be determined by serum elimination alone, because biological effects may persist beyond pharmacokinetic clearance. For Round 3, the statement therefore focuses on the broader methodological principle that potentially confounding prior treatments should be accounted for in trial design and that, when washout is required, its duration should reflect both pharmacokinetic properties and persistent biological effects.

New Statement 22: In clinical trials assessing TEAS risk, prior treatments that could confound attribution of an affective switch to the investigational intervention should be appropriately accounted for in the study design. When a prior treatment is discontinued, the washout period should take into account its pharmacokinetic properties and, where relevant, the persistence of its biological effects.

Retrospective Assessment

Statement 23

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

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.

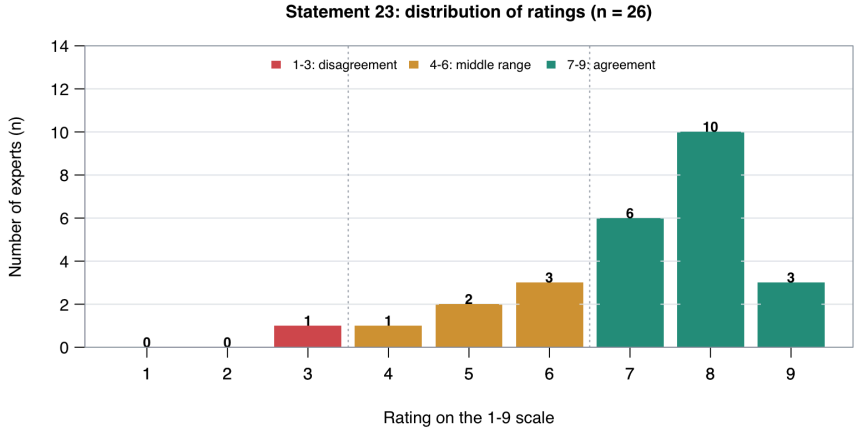
Retrospective assessment has important limitations. Recall of the onset, duration, and severity of symptoms may be inaccurate, particularly for brief hypomanic or mixed presentations, and subsequent experiences may influence how earlier episodes are interpreted. Information relevant to causal assessment, 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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	7.5	6.25	8	1.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.8% (n=1)	23.1% (n=6)	73.1% (n=19)



Consensus status: Consensus of Agreement (73.1% agreement; median 7.5 [6.25-8]). The statement is supported by the expert panel.

Comments (listed in chronological order of submission):

➔ 518904 - An interview about past TEAS is mandatory

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

High-Risk Groups

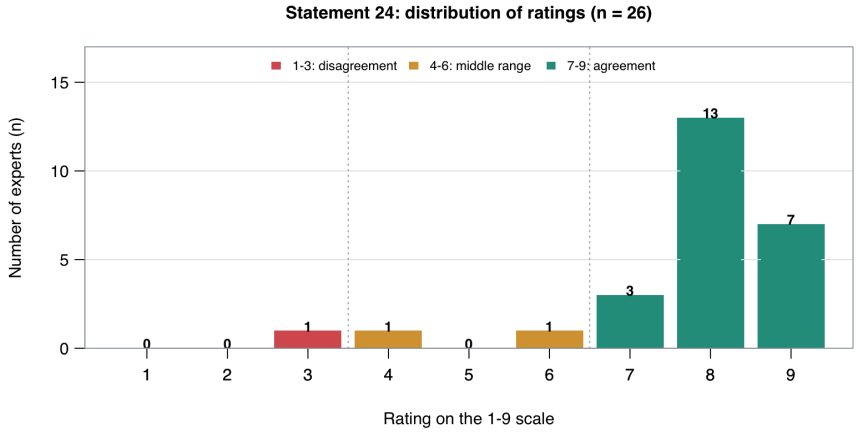
Statement 24

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	8	8.75	0.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
3.8% (n=1)	7.7% (n=2)	88.5% (n=23)



Consensus status: Consensus of Agreement (88.5% agreement; median 8 [8-8.75]). The statement is supported by the expert panel.

Comments (see Statement 27).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

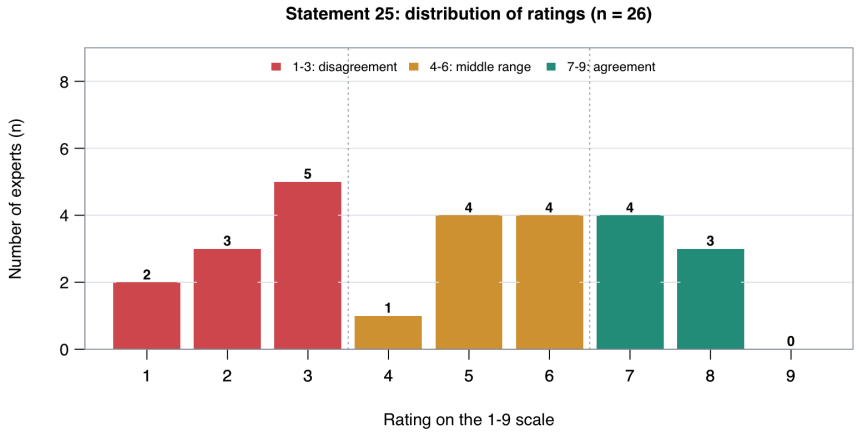
Statement 25

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	5	3	6.75	3.75

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
38.5% (n=10)	34.6% (n=9)	26.9% (n=7)



Consensus status: No Consensus (26.9% agreement; 38.5% disagreement; median 5 [3-6.75]). The statement requires re-rating, revision, or is recorded as disputed. *No directional tendency by median.*

Comments (see Statement 27).

Round 3 action: Substantially revise and re-rate. Round 2 did not support classifying rapid improvement of depressive symptoms as a stand-alone marker of high TEAS risk. Expert feedback emphasized that some patients may respond rapidly to treatment without subsequently developing an affective switch. The item will therefore be reformulated to focus on the clinical implication of such a response: rapid improvement will be considered a reason for heightened vigilance for emerging hypomanic, manic, or mixed symptoms rather than, by itself, a criterion for classification as a high-risk state.

New Background: Rapid improvement of depressive symptoms shortly after initiation of an antidepressant or another intervention with antidepressant effects may represent a favorable therapeutic response and does not necessarily indicate an impending affective switch. In Round 2, the panel did not reach consensus that such improvement alone should identify a patient as belonging to a high-risk group for TEAS.

At the same time, an unusually rapid transition from depression to euthymia may be clinically relevant in the context of treatment-emergent affective instability. Because the specificity and predictive value of this phenomenon remain uncertain, the revised statement does not classify rapid improvement itself as TEAS or as a definitive marker of high risk. Instead, it addresses whether this pattern should prompt heightened clinical vigilance for the subsequent emergence of hypomanic, manic, or mixed symptoms.

New Statement 25: Rapid improvement of depressive symptoms to euthymia within 1-2 weeks after initiation of an antidepressant or other intervention with antidepressant effects should warrant heightened clinical vigilance for the subsequent emergence of hypomanic, manic, or mixed symptoms.

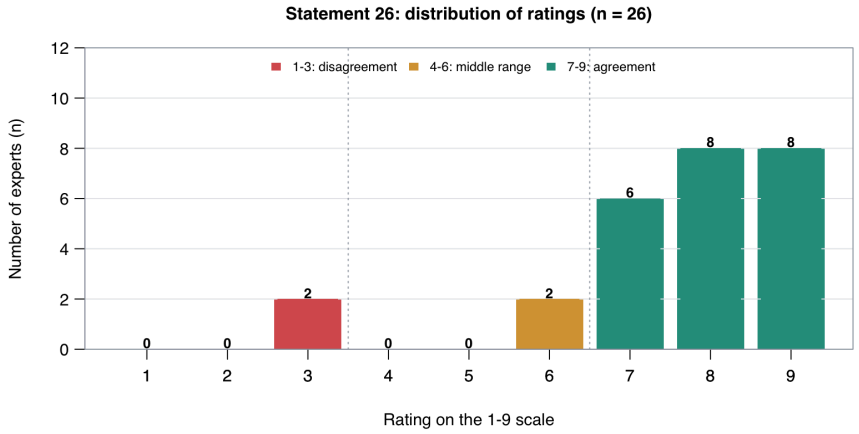
Statement 26

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.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	8	7	9	2

Ratings 1-3 | disagreement	Ratings 4-6 | middle range	Ratings 7-9 | agreement
7.7% (n=2)	7.7% (n=2)	84.6% (n=22)



Consensus status: Consensus of Agreement (84.6% agreement; median 8 [7-9]). The statement is supported by the expert panel.

Comments (see Statement 27).

Round 3 action: Consensus reached; statement accepted as final and not carried forward to Round 3.

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

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.

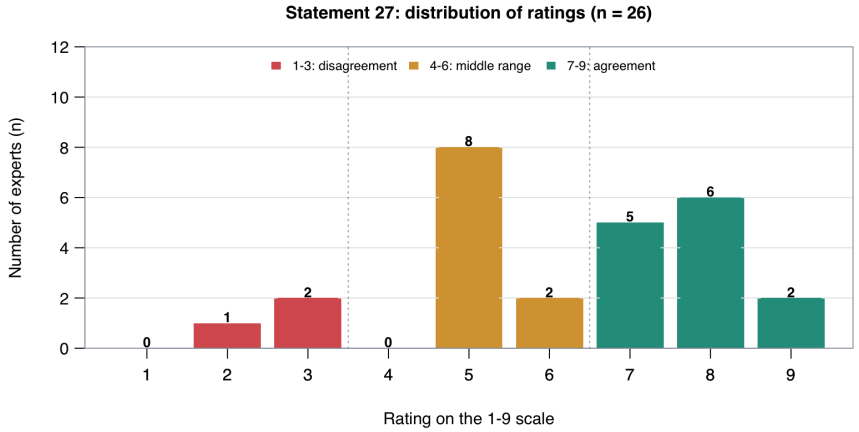
Accordingly, the statements in this section distinguish between clinical features that may identify patients requiring closer monitoring and the criteria used to ascertain TEAS itself.

Round 2 results

Valid n	Median	Q1	Q3	IQR (Q3-Q1)
26	6.5	5	8	3

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

11.5% (n=3)	38.5% (n=10)	50.0% (n=13)



Consensus status: No Consensus (50.0% agreement; 11.5% disagreement; median 6.5 [5-8]). The statement requires re-rating, revision, or is recorded as disputed. *No directional tendency by median.*

Comments (listed in chronological order of submission):

- ➔ 731602 - First question - mood regulation in BD is highly variable and some pateints may respond rapidly without a switch. Children adolescent question - the effect of treatment can be destabilizing in different ways, so yes.
- ➔ 597318 - Anxiety and panic should not be included in "affective switch."
- ➔ 948206 - But these individuals should be followed closely as they may be at increased risk for BD and TEAS

Round 3 action: Revise, split, and re-rate. Round 2 did not establish consensus on whether antidepressant-related activation in children and adolescents should be excluded from TEAS in the absence of a distinct hypomanic, manic, or mixed presentation. Expert feedback suggested that such activation may represent a clinically important form of treatment-related destabilization and may warrant closer follow-up even when it does not itself constitute TEAS. The item will therefore be divided to separately assess its classification and its implications for clinical monitoring.

New Background: Antidepressant-related activation in children and adolescents may include restlessness, insomnia, impulsivity, irritability, and behavioral disinhibition. These symptoms may be clinically significant but are not necessarily equivalent to a hypomanic, manic, or mixed presentation. Round 2 did not establish consensus on excluding such activation from TEAS altogether. Expert feedback indicated that treatment-related activation may represent clinically relevant destabilization and that affected patients may warrant closer follow-up because hypomanic, manic, or mixed symptoms could subsequently emerge. For Round 3, classification and clinical monitoring are therefore addressed separately: activation symptoms alone are distinguished from TEAS, while their potential significance as a reason for heightened vigilance is assessed independently.

Statement 27a: In children and adolescents, antidepressant-related activation symptoms such as restlessness, insomnia, impulsivity, irritability, or behavioral disinhibition, in the absence

of a clinically significant hypomanic, manic, or mixed presentation, should not by themselves be sufficient for classification as TEAS.

Statement 27b: Antidepressant-related activation symptoms in children and adolescents should warrant closer clinical monitoring for the subsequent emergence of hypomanic, manic, or mixed symptoms.