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Worsening Anxiety, Irritability, Insomnia, or Panic Predicts Poorer Antidepressant Treatment Outcomes: Clinical Utility and Validation of the Concise Associated Symptom Tracking (CAST) Scale

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Abstract

Background: We report on the psychometric properties of the 16-item Concise Associated Symptom Tracking Scale self-report scale and its clinical utility.
Methods: The 5-domain (irritability, anxiety, mania, insomnia, and panic) structure of Concise Associated Symptom Tracking Scale was validated with confirmatory factor analysis in Combining Medications to Enhance Depression Outcomes trial participants at baseline (n = 664). Correlations with other clinical measures were used for convergent and divergent validity. In participants with at least one postbaseline visit (n = 630), worsening in each Concise Associated Symptom Tracking Scale domain was defined as ≥1.28 SD increase from baseline for each visit (weeks 1, 2, 4, and 6) only. Worsening in any domain (except mania) was defined as overall worsening. Association of domain-specific and overall worsening with remission was tested with logistic regression analyses.
Results: The 5-domain structure had adequate model fit on confirmatory factor analysis (GFI = 0.93, CFI = 0.89, and RMSEA = 0.07). Scores on anxiety, panic, insomnia, and mania significantly correlated with Hamilton Rating Scale for Depression anxiety subscale (r_s = 0.27), Psychiatric Diagnostic Screening Questionnaire-panic scale (r_s = 0.35), sum of 3 Quick Inventory of Depressive Symptomatology Self-Report insomnia items (r_s = 0.55), and Altman Self-Rating Mania scale (r_s = 0.41), respectively. From baseline to week 6, 5.2%, 7.5%, 47.6%, 15.6%, 6.2%, and 27.6% participants (n = 630) experienced irritability, anxiety, mania, insomnia, panic, and overall worsening, respectively. Participants with overall worsening were less likely to remit (31.6%) than those without any worsening (43.9%; odds ratio = 0.53, 95% CI = 0.36, 0.78).
Conclusion: The 16-item Concise Associated Symptom Tracking Scale self-report has acceptable psychometric properties. Clinically significant worsening of irritability, anxiety, insomnia, or panic with antidepressant treatment is associated with poorer outcomes.

Keywords: major depression, antidepressant, irritability, mania, anxiety, insomnia, panic

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Significance Statement

The 16-item Concise Associated Symptom Tracking (CAST) is a valid self-report scale that measures worsening of irritability, anxiety, mania, insomnia, or panic symptoms after initiation of antidepressant medications. Depressed patients who report clinically significant increase in irritability, anxiety, insomnia, or panic at any time during the first 6 weeks of antidepressant treatment are significantly less likely to remit (31.6%) with acute-phase (12-week) antidepressant treatment compared with those who experienced no worsening. Use of this easy-to-administer self-report scale in routine clinical practice can help with early treatment optimization by identifying depressed patients who may be less likely to respond to their ongoing antidepressant treatment.

Introduction

Major depressive disorder (MDD) patients may experience emergence or worsening of irritability, anxiety, panic, insomnia, and mania/hypomania with antidepressant medications (Safer and Zito, 2006; Harada et al., 2008; Sinclair et al., 2009), but there is a dearth of valid and reliable self-report assessments of these antidepressant treatment emergent symptoms. Worsening of these symptoms may contribute to early drop-out during treatment initiation or they may suggest a need for early dose adjustments (Montgomery and Kasper, 1998; Machado and Einarson, 2010; Kostev et al., 2014).

To address these concerns, Trivedi et al. (2006) developed a 16-item self-report scale, the Concise Associated Symptom Tracking (CAST), to assess irritability, anxiety, panic, insomnia, and mania/hypomania (Trivedi et al., 2011). Validation of the easy-to-administer CAST scale in a separate sample of treatment-seeking depressed outpatients is needed prior to its use in measurement-based care protocols (Trivedi et al., 2006).

This report evaluates the psychometric properties and clinical utility of CAST in a large sample of treatment-seeking depressed outpatients who participated in the Combining Medications to Enhance Depression Outcomes (CO-MED) trial (Rush et al., 2011). To evaluate the psychometric properties, we tested the (1) validity of 5-domain (anxiety, irritability, mania, panic, and insomnia) structure with confirmatory factor analyses, (2) internal consistency with Cronbach's α coefficient, and (3) construct validity with correlation of these CAST domains with other clinical assessments at baseline. To evaluate the clinical utility of CAST, we asked the following specific questions:

1. What proportion of depressed patients experience worsening in the anxiety, irritability, mania, panic, and insomnia domains of CAST over first 6 weeks of antidepressant treatment? And when?
2. Is symptomatic worsening on CAST domains associated with lower rates of remission even after adjusting for baseline depression severity?

Methods

Study Overview and Participants

The analytic sample for this report includes all CO-MED trial participants who completed the CAST scale at baseline (n = 664). As described earlier by Rush et al. (Rush et al., 2011), participants were enrolled from 6 primary and 9 psychiatric care sites in the CO-MED trial after obtaining written informed consent. The trial was approved by the Institutional Review Boards at UT Southwestern Medical Center at Dallas, the University of Pittsburgh Data Coordinating Center, and each participating regional center and clinical site and was monitored by an independent data safety and monitoring board. The inclusion and exclusion criteria have been described in detail previously by Rush et al. (Rush et al., 2011).

Briefly, participants in the CO-MED trial had nonpsychotic chronic (current episode exceeded 2 years) or recurrent depression with current episode ≥2 months and a baseline 17-item Hamilton Rating Scale (HRSD17) ≥16 (Hamilton, 1960). As the primary goal of CO-MED trial was to compare outcomes of antidepressant combination vs selective serotonin reuptake inhibitor (SSRI) monotherapy, participants were assigned to one of the following treatment arms in a 1:1:1 ratio after stratification by clinical sites: (1) escitalopram plus placebo (SSRI monotherapy), (2) sustained-release (SR) bupropion plus escitalopram (bupropion-SSRI combination), and (3) extended-release (XR) venlafaxine plus mirtazapine (venlafaxine-mirtazapine combination).

Postrandomization visits were conducted at weeks 1, 2, 4, 6, 8, 10, and 12 for acute phase and weeks 16, 20, 24, and 28 for continuation phase. Study physicians used measurement-based care (Trivedi et al., 2006) to make medication dosage adjustment during the first 8 weeks based on the scores of the Quick Inventory of Depressive Symptomatology Clinician-rated version (QIDS-C) (Rush et al., 2003) scale and the Frequency, Intensity, and Burden of Side Effects Rating scale (Wisniewski et al., 2006a). Participation beyond acute phase was restricted to those who had either received an acceptable benefit (defined as QIDS-C score of ≤9 by 3 months) or had reached a score of 10 to 13 on QIDS-C and both the study physician and the participant decided to continue treatment because of substantial benefit.

Assessments

Assessments Conducted Only at Baseline

HRSD17. The 17 items of this clinician-rated scale to assess depression severity have 3 to 5 choices that are scored from either 0 to 2 or 0 to 4 (Hamilton, 1960). The individual items are summed to measure depression severity [none (<6), mild (6–13), moderate (14–18), severe (19–3), and very severe (>24)] (Hamilton, 1960). The HRSD17 has a high inter-rater reliability (kappa = 0.94) and inter-item correlations with (Cronbach's α-0.53–0.83) (Rush et al., 1996; Trajković et al., 2011). Six items of HRSD17 (psychic anxiety, somatic anxiety, gastrointestinal somatic symptom, general somatic symptoms, hypochondriasis, and insight) was used to establish anxious features in CO-MED trial (Cleary and Guy, 1977; Fava et al., 2008). Additionally, HRSD17 score of ≥16 was used as inclusion criteria for CO-MED trial.

Psychiatric Diagnostic Screening Questionnaire (PDSQ). This self-report questionnaire includes 139 questions with yes/no responses grouped in 13 subscales (mood disorders, eating disorder, panic disorders, generalized anxiety disorder, agoraphobia, posttraumatic stress disorder, obsessive compulsive

disorder, social anxiety disorder, alcohol use disorder, drug use disorder, somatoform disorder, hypochondriasis, and psychosis), which were selected on the basis of high prevalence in epidemiologic surveys (Zimmerman and Chelminski, 2006). The mood disorder and psychosis subscales of PDSQ were not included in CO-MED, as these disorders were assessed using structured clinical interview (Rush et al., 2011). In multiple reports, PDSQ subscales have demonstrated good internal consistency and strong sensitivity in detecting these disorders compared with semistructured clinician-conducted interviews (Zimmerman and Mattia, 2001; Rush et al., 2005; Zimmerman and Chelminski, 2006).

Assessment Conducted at Baseline and Each Postrandomization Visit

Inventory of Depressive Symptomatology Clinician Rated (IDS-C). Of the 30 items of this clinician-rated assessment of depression (each item scored from 0 to 3), 28 items are summed to generate total score (range 0–84) to indicate depression severity as follows: none (<13), mild (14–25), moderate (26–38), severe (39–48), and very severe (>49) (Rush et al., 1996). The IDS-C correlates very highly (r = 0.95) with HRSD17 (Rush et al., 1996). The Cronbach's α of IDS-C range from 0.67 to 0.94 (Rush et al., 1996; Trivedi et al., 2004). Using principal component analysis, Rush et al. (Rush et al., 1996; Trivedi et al., 2004) have previously reported a 3-factor structure for IDS-C, namely cognitive/mood, anxiety/arousal, and sleep/appetite regulation.

QIDS-C and Self-Report (QIDS-SR). The 16 items (each scored from 0 to 3) of QIDS-C and QIDS-SR are based on the 9 criterion symptom domains of the 16 items and total score ranged from 0 to 27 (Rush et al., 2003). Both scales correlate highly with HRSD17 (0.86–0.93) and have high inter-item correlations (Cronbach's $\alpha = 0.86–0.87$) (Rush et al., 2003). In the CO-MED trial, the QIDS-SR served as the measure of depressive symptoms for primary outcome, while the QIDS-C was used to monitor symptom changes and guide treatment decisions.

CAST Self-Report. The 16 items of this self-report scale assess symptoms across the 5 following domains where each individual item is rated on a 5-point Likert scale with responses of "strongly disagree," "disagree," "neither agree nor disagree," "agree," and "strongly agree" corresponding to scores of 1, 2, 3, 4, and 5, respectively: anxiety (3 items, range 3–15), irritability (5 items, range 5–25), mania (4 items, range 4–20), insomnia (2 items, range 2–10), and panic (2 items, range 2–10) (Trivedi et al., 2011). The Cronbach's α of CAST-SR was 0.78 (Trivedi et al., 2011) and high agreement between clinician rated and self-report versions of CAST with weighted Kappa ranging from 0.59 to 0.78 (Trivedi et al., 2011). The scores in each domain correlated highly with separately administered assessments. For example, anxiety and panic domains of CAST-SR correlated significantly with the scores on Beck Anxiety Inventory (r = 0.51–0.59) and HRSD17 anxiety subscale (r = 0.30–0.31). Similarly, the insomnia domain on CAST-SR had high correlation with the 3 insomnia items of QIDS (r = 0.51). The irritability domain had significant correlations with impulsivity rating scale (r = 0.39), Beck Anxiety Inventory (r = 0.42), and irritability item of Clinician-Administered Rating Scale of Mania (r = 0.30) (Trivedi et al., 2011).

Altman Self Rating Mania Scale (ASRM). The ASRM is a 5item self-reported scale designed to evaluate for the presence and/or severity of manic and hypomanic symptoms over the past 7 days. Each item consists of 5 possible responses, with scores ranging from 0 to 4. Item scores are added to give a scale total score, 0 being the lowest possible score and a maximum possible of 20. The ASRM is significantly correlated to the CARS-M and the Young Mania Rating Scale (Altman et al., 1997).

Statistical Analyses

We included all CO-MED trial participants with CAST at baseline (n = 664) as the analytic sample for testing the psychometric properties of CAST. For analyses of worsening of preexisting or treatment emergent symptoms (described subsequently and heretofore referred to as "worsening") to evaluate the clinical utility, we restricted only to participants who had at least one postbaseline visit, at weeks 1, 2, 4, or 6 (n = 630). As the purpose of CAST is to identify worsening, we took a conservative approach and classified missing scores as "not worsened." We used descriptive statistics to summarize the 5 domains of CAST as well as other clinical assessments at baseline in CO-MED trial.

To validate the 5-domain structure of CAST, we used confirmatory factor analysis as implemented in SAS. We a priori defined acceptable model fit as Goodness of Fit index (GFI) ≥0.90, comparative fit index (CFI) ≥0.90, and root mean square error of approximation ≤0.08 (Hooper et al., 2008). To evaluate the internal consistency, we calculated the Cronbach's α coefficient for each CAST domain (Cronbach, 1951). We also calculated spearman's correlation coefficient (r_s) between the 5 domains of CAST and the baseline clinical assessments in CO-MED trial.

To evaluate the clinical utility, we restricted the analyses to the first 6 weeks to capture early change with treatment initiation and optimization, as CO-MED trial design included addition of a second drug (placebo, escitalopram, or mirtazapine) at week 2 with dosage adjustments recommended using MBC approach (Rush et al., 2011). We created a clinically significant change threshold of 1.28 times the SD at baseline for each domain of CAST. Next, we categorized participants who experienced increase, compared with baseline, at weeks 1, 2, 4, and 6 above this clinically significant change threshold as significantly worsening in that domain. We used 1.28 times SD threshold as it reflects large change consistent with FDA's warning (Wisniewski et al., 2006b; Iscan et al., 2015) and our previous use of 1.28 times SD to define normal threshold (Greer et al., 2016; Jha et al., 2017). We used descriptive statistics to summarize the proportion of participants who (1) experienced worsening in each CAST domain at any time during the first 6 weeks and (2) first experienced worsening in each CAST domain at weeks 1, 2, 4, and 6. In posthoc analyses after finding that increase above the a priori defined threshold was substantially higher in mania domain compared with other domains, we also calculated the proportion of participants who experienced any worsening in domains of irritability, anxiety, insomnia, or panic (all CAST domains except mania) at any postbaseline visits during the first 6 weeks (includes visits at weeks 1, 2, 4, or 6, hereafter referred to as "overall worsening").

We then tested the association of worsening of symptoms in each domain as well as overall worsening with remission during the acute phase of CO-MED in separate logistic regression analyses after controlling for baseline depression severity. We included baseline depression severity as a covariate, as it was associated with remission in previous reports (Friedman et al., 2012; Jha et al., 2016). Remission in CO-MED trial, the primary study outcome, was ascribed if, of the last 2 consecutive QIDS-SR scores, at least 1 was <6 while the other was <8 (Rush et al., 2011).

Table 1. Response to Individual Items of CAST at Baseline in CO-MED Trial Participants (n = 664)

No.#	Individual Items	Domain of CAST	Strongly Disagree		Disagree		Neither Agree nor Disagree		Agree		Strongly Agree		Mean	SD
			N	%	N	%	N	%	N	%	N	%		
1	I feel anxious all the time	Anxiety	55	8.3	148	22.3	121	18.2	221	33.3	119	17.9	3.30	1.23
2	I have been feeling really good lately	Mania	308	46.4	270	40.7	48	7.2	27	4.1	11	1.7	1.74	0.88
3	I feel as if I am going to have a heart attack	Panic	304	45.8	171	25.8	90	13.6	74	11.1	25	3.8	2.01	1.17
4	I wish people would just leave me alone	Irritability	54	8.1	91	13.7	153	23.0	239	36.0	127	19.1	3.44	1.18
5	I have been having more trouble sleeping than usual	Insomnia	50	7.5	108	16.3	77	11.6	226	34.0	203	30.6	3.64	1.27
6	I am feeling restless, as if I have to move constantly	Anxiety	84	12.6	150	22.6	124	18.7	233	35.1	73	11.0	3.09	1.23
7	I suddenly feel very confident	Mania	308	46.4	250	37.6	66	9.9	32	4.8	8	1.2	1.77	0.90
8	I am more talkative than normal	Mania	247	37.2	271	40.8	88	13.2	51	7.7	7	1.1	1.95	0.95
9	I feel very uptight	Irritability	56	8.4	102	15.4	110	16.6	285	42.9	111	16.7	3.44	1.18
10	I find myself saying or doing things without thinking	Irritability	86	13.0	202	30.4	120	18.1	205	30.9	51	7.7	2.90	1.20
12	I can feel my heart racing	Panic	159	24.0	193	29.1	95	14.3	170	25.6	47	7.1	2.63	1.29
13	Lately everything seems to be annoying me	Irritability	17	2.6	87	13.1	111	16.7	295	44.4	154	23.2	3.73	1.04
14	I slept very little last night	Insomnia	65	9.8	147	22.1	65	9.8	216	32.5	171	25.8	3.42	1.34
15	I cannot sit still	Anxiety	104	15.7	185	27.9	129	19.4	199	30.0	47	7.1	2.85	1.21
16	I find people get on my nerves easily	Irritability	21	3.2	65	9.8	91	13.7	317	47.7	170	25.6	3.83	1.02
17	I have been having lots of great ideas	Mania	218	32.8	249	37.5	99	14.9	69	10.4	29	4.4	2.16	1.12

CO-MED, Combining Medications to Enhance Depression Outcomes.
No. refers to the item numbers originally reported in the 17-item CAST as reported in Figure 1 of Trivedi et al. primary CAST paper (Trivedi et al., 2011). Note that 16-item CAST SR excluded item 11 as it loaded on 2 different factors.

We compared baseline clinical features between those who experienced overall worsening during the first 6 weeks vs those who did not. We repeated the above-mentioned logistic regression analysis for overall worsening after adjusting for the baseline variables that significantly differed between those with and without overall worsening during the first 6 weeks. We set the level of significance at 0.05 and used SAS 9.3 (SAS Inc) for all analyses.

Results

Of the 664 CO-MED trial participants who completed CAST at baseline, most were females (68.1%), white (64.0%), and earned <$2000 (62.9%) per month (also see supplementary Table 1). We found that mean (SD) scores of irritability (5 items), anxiety (3 items), mania (4 items), insomnia (2 items), and panic (2 items) domains were 17.34 (3.80), 9.24 (2.95), 7.61 (2.79), 7.06 (2.33), and 4.64 (2.19), respectively. At weeks 1, 2, 4, or 6, compared with baseline, an increase ≥4.86, 3.78, 3.57, 2.98, and 2.80 was defined as worsening in irritability, anxiety, mania, insomnia, and panic domains, respectively. We have provided detailed frequency of responses to individual items of CAST-SR in Table 2 along with the mean (SD) for these items.

Psychometric Properties of the CAST Scale

Validity of 5-Domain Structure of CAST

We found GFI = 0.93, CFI = 0.89, and RMSEA = 0.07 for the 5-domain structure of CAST using confirmatory factor analysis. As 2 of the 3 a priori-defined criteria were met, we found the model fit to be acceptable. The standardized factor loadings for the anxiety, irritability, mania, insomnia, and panic ranged from 0.42 to 0.85, 0.41 to 0.80, 0.50 to 0.71, 0.7 to 0.79, and 0.68 to 0.86, respectively (Table 2). The domains of irritability, anxiety, insomnia, and panic were significantly correlated with each other (correlation coefficient = 0.33–0.51) (Table 2). Mania domain had poor correlation with other domains of CAST (correlation coefficient = -0.09–0.15) (Table 2).

Internal Consistency

The Cronbach's α of irritability, anxiety, mania, insomnia, and panic domains were 0.83, 0.87, 0.84, 0.92, and 0.92, respectively.

Construct Validity

Irritability, anxiety, insomnia, and panic domains were positively correlated with measures of overall depression severity included at baseline, namely QIDS-SR (r_s = 0.31–0.45), HRSD17 (r_s = 0.26–0.40), and IDS-C (r_s = 0.29–0.41) (Table 3). Conversely, mania domain was negatively correlated with QIDS-SR (r_s = -0.30), HRSD17 (r_s = -0.15), and IDS-C (r_s = -0.22). Anxiety domain was positive correlated with anxious features on HRSD17(r_s = 0.28), anxiety/arousal factor of IDS-C (r_s = 0.37), and PDSQ generalized anxiety disorder subscale (r_s = 0.29). While there were no measures specifically of

Table 2. Factor Loading of Individual Items and Correlation among Individual Domains of CAST Obtained from Confirmatory Factor Analysis

	Anxiety	Irritability	Mania	Insomnia	Panic
Standardized factor loadings					
I feel anxious all the time	0.42				
I have been feeling really good lately			0.50		
I feel as if I am going to have a heart attack					0.68
I wish people would just leave me alone		0.49			
I have been having more trouble sleeping than usual				0.79	
I am feeling restless, as if I have to move constantly	0.84				
I suddenly feel very confident			0.71		
I am more talkative than normal			0.60		
I feel very uptight		0.48			
I find myself saying or doing things without thinking		0.41			
I can feel my heart racing					0.86
Lately everything seems to be annoying me		0.80			
I slept very little last night				0.75	
I cannot sit still	0.85				
I find people get on my nerves easily		0.76			
I have been having lots of great ideas			0.61		
Correlation coefficient					
Anxiety	1				
Irritability	0.51	1			
Mania	0.15	-0.09	1		
Insomnia	0.37	0.37	0.01	1	
Panic	0.44	0.36	0.17	0.33	1

CAST, Concise Associated Symptom Tracking Scale.

Table 3. Spearman Correlation Coefficients of CAST Domains with Baseline Clinical Characteristics in CO-MED Trial

	Anxiety	Irritability	Mania	Insomnia	Panic
QIDS-SR	0.35	0.45	-0.30	0.31	0.31
HRSD17	0.26	0.31	-0.15	0.40	0.29
IDS-C	0.29	0.41	-0.22	0.37	0.33
IDS-C factor 1	0.18	0.38	-0.28	0.24	0.22
IDS-C factor 2	0.38	0.32	-0.05	0.49	0.39
IDS-C factor 3	0.09	0.22	-0.14	0.37	0.18
HRSD anxiety	0.27	0.26	-0.05	0.19	0.33
ASRM	0.12	0.08	0.41	0.04	0.10
QIDS-SR insomnia total	0.11	0.20	-0.07	0.55	0.14
PDSQ generalized anxiety disorder	0.29	0.27	-0.02	0.24	0.28
PDSQ panic	0.22	0.17	-0.03	0.21	0.35
PDSQ agoraphobia	0.22	0.22	0.02	0.19	0.20
PDSQ alcohol use disorder	0.07	0.07	0.09	0.04	0.05
PDSQ bulimia	0.06	0.09	-0.01	0.02	0.04
PDSQ hypochondriasis	0.13	0.08	0.02	0.11	0.16
PDSQ drug use disorder	0.07	0.08	0.08	0.01	0.05
PDSQ obsessive compulsive disorder	0.20	0.20	0.12	0.12	0.18
PDSQ posttraumatic stress disorder	0.26	0.20	0.04	0.14	0.23
PDSQ social anxiety	0.21	0.29	0.03	0.17	0.25
PDSQ somatic	0.01	0.11	-0.01	0.05	0.07

irritability in CO-MED trial, scores on irritability were significantly correlated with the mood/cognitive subscale of IDS-C ($r_s = 0.38$) and poorly correlated with scales of mania ($r_s = 0.08$) and nonanxiety subscales of PDSQ ($r_s = 0.0.07–0.11$) (Table 3). Mania, insomnia, and panic domains were positive correlated with ASRM ($r_s = 0.41$), sum of insomnia items of QIDS-SR ($r_s = 0.55$), and PDSQ panic subscales ($r_s = 0.35$), respectively.

Clinical Utility of CAST Scale

What Proportion of Depressed Patients Experience Worsening in the Anxiety, Irritability, Mania, Panic, and Insomnia Domains of CAST during First 6 Weeks of Antidepressant Treatment? And When?

Of the 630 participants, 33 (5.2%), 47 (7.5%), 300 (47.6%), 98 (15.6%), and 39 (6.2%) met our predefined threshold for

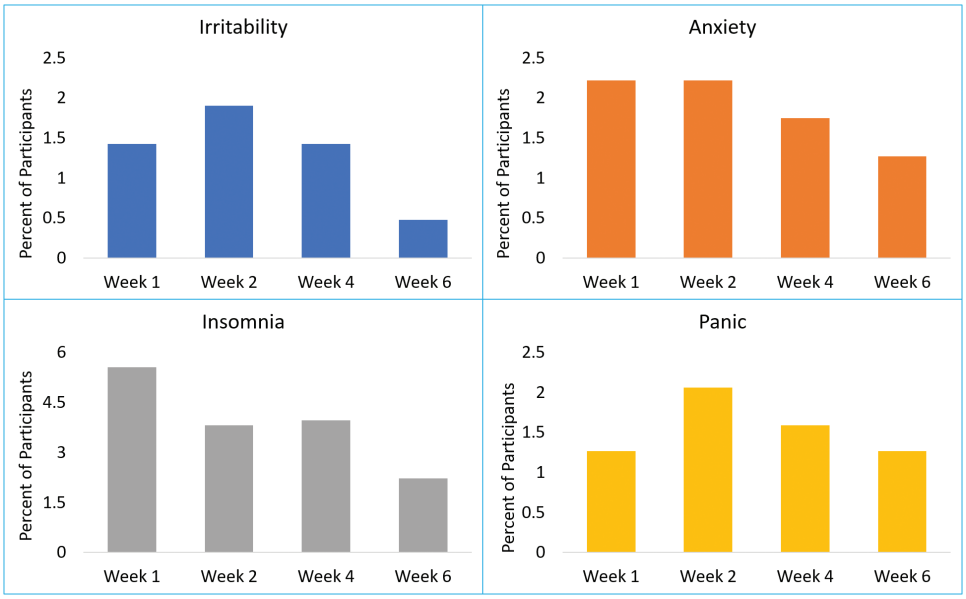

Figure 1. Proportion of participants who first experiences worsening in Concise Associated Symptom Tracking (CAST) domains during the first 6 weeks of the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. Worsening is defined as an increase of ≥1.28 baseline SD at week 1, 2, 4, or 6 in the CAST domains of irritability, anxiety, insomnia, and panic.

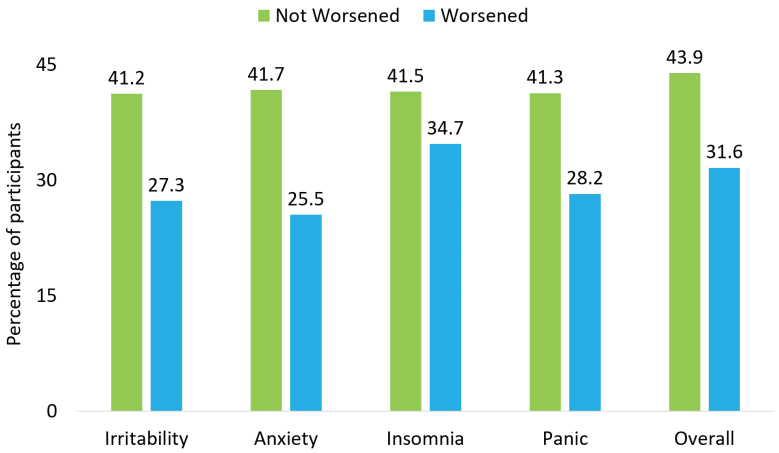

Figure 2. Observed rates of remission during the Combining Medications to Enhance Depression Outcomes (CO-MED) trial based on overall and individual Concise Associated Symptom Tracking (CAST) domain-specific worsening. Remission was ascribed if, of the last 2 consecutive quick inventory of depressive symptomatology self-report scores during 12-week-long acute-phase, one was <6 and the other was <8. Worsening is defined as an increase of ≥1.28 baseline SD at week 1, 2, 4, or 6 in the CAST domains of irritability, anxiety, insomnia, and panic.

worsening in irritability, anxiety, mania, insomnia, and panic, respectively, at week 1, 2, 4, or 6. The rate of overall worsening was 27.6% (174/630). Most participants experienced worsening early in the course of treatment by week 4, as shown in Figure 1. Of the 630 participants, those receiving bupropion-SSRI experienced significantly higher rates (21/208, 10.1%) of worsening at weeks 1, 2, 4, or 6 in panic domain ($\chi^2 = 8.33$, df = 2, $P = .015$) than those on SSRI monotherapy (8/212, 3.8%) or on venlafaxine-mirtazapine combination (10/210, 4.8%). We found no significant difference in rates of worsening based on treatment arm either in overall worsening ($\chi^2 = 3.13$, df = 2, $P = .21$) or in irritability ($\chi^2 = 0.002$, df = 2, $P = .999$), anxiety ($\chi^2 = 1.52$, df = 2, $P = .47$), mania ($\chi^2 = 1.41$, df = 2, $P = .49$), and insomnia ($\chi^2 = 1.21$, df = 2, $P = .55$) domains (see supplementary Table 2 for proportion of participants experiencing worsening by each treatment arm).

Is Symptomatic Worsening on CAST Domains Associated with Lower Rates of Remission Even After Adjusting for Baseline Depression Severity?

Yes. As shown in figure 2, participants with worsening of irritability, anxiety, insomnia, and panic during the first 6 weeks of CO-MED trial had numerically lower rates of remission compared with those who reported no worsening in these domains. Using separate logistic regression analyses that controlled for baseline severity for each CAST domain and overall worsening, we found lower likelihood of remission with worsening in anxiety (OR = 0.43, 95% CI = 0.21, 0.86), insomnia (OR = 0.62, 95% CI = 0.39, 0.99), and panic (OR = 0.47, 95% CI = 0.22, 0.99) domains. Conversely, we found that participants with a 1.28 SD increase in the mania domain were more likely to remit (49.3%) compared with those without this increase (32.4, number needed to treat [NNT] = 5.9); this difference was statistically significant even

after controlling for baseline severity (OR = 2.22, 95% CI = 1.59, 3.11). The lower likelihood of remission with worsening in irritability domain was not statistically significant (OR = 0.47, 95% CI = 0.21, 1.05). Participants with overall worsening were less likely to remit (31.6%) than those without any worsening (43.9%, NNT = 8.1) even after controlling for baseline depression severity (OR = 0.53, 95% CI = 0.36, 0.78).

Discussion

We found confirmatory evidence for the 5-domain structure and psychometric properties of the 16-item CAST scale in a large sample of depressed outpatients. One in 4 (27.6%) participants reported worsening in at least one of the CAST domains (except mania) during the first 6 weeks. Participants with any worsening were significantly less likely to attain remission (NNT = 8.1) compared with those with no overall worsening. A clinically significant increase in mania domain was associated with higher rate of remission (NNT = 5.9) compared with those with no increase. The association of overall worsening with lower likelihood of remission continued to be significant even after controlling for baseline depression severity.

An unexpected finding of our report is the high rate of change in mania domain. This may be related to the wording of our questions where improved depression with treatment was reflected in clinically significant increase in mania symptoms. As valid self-report measures for manic/hypomanic symptoms such as ASRM are already used frequently, a shortened 12-item version of CAST, which excludes mania items, may be clinically useful. Alternatively, a different threshold of clinically significant change, other than the 1.28 times baseline SD, may be able to detect worsening manic/hypomanic symptoms in mania domain.

Among all CAST domains excluding mania, rates of worsening were highest for insomnia (15.6%) and lowest for irritability (5.2%). The rate of insomnia worsening with SSRI monotherapy (14.2%) was comparable with previously reported rates of treatment emergent insomnia (14%) with escitalopram 20 mg/d (Iscan et al., 2015). The rate of worsening insomnia (17.8%) and anxiety (8.2%) with bupropion-SSRI is similar to the treatment-emergent insomnia (16%) and anxiety (6%) reported previously with bupropion 400-mg/d dose (Wisniewski et al., 2006b). Interestingly, we found that worsening on CAST domains did not differ among treatment arms, except the bupropion-SSRI arm had significantly higher rates of worsened panic compared with SSRI monotherapy and venlafaxine-mirtazapine.

There are several limitations of our report. Validation of psychometric properties of CAST was not a primary goal of CO-MED trial. Hence, study design did not include any measures of irritability, anxiety, or panic beyond the baseline visit. Additionally, our use of threshold of 1.28 times baseline SD may have captured only severe worsening of symptoms and missed our participants with mild-moderate worsening. As the primary purpose of this report was to evaluate worsening, we did not test for improvement in these symptom domains with treatment and the potential clinical implications.

In conclusion, we find that 16-item CAST has good psychometric properties and can detect clinically significant worsening across domains of irritability, anxiety, insomnia, and panic with significant treatment implications. Use of CAST in clinical practice can help identify depressed patients who may be less likely to respond to their ongoing antidepressant treatment.

Supplementary Material

Supplementary data are available at *International Journal of Neuropsychopharmacology* online.

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Statement of Interest

Drs. Jha, Minhajuddin, and South do not report any personal, financial, or professional relationships or conflicting interests. Dr. Trivedi has in the past 24 months consulted or served on the advisory boards of Alkermes Inc., Akili Interactive Inc., Allergan, Arcadia Pharmaceuticals Inc., AstraZeneca, Brintellix, BMS, Cerecor, Global Medical Education Inc., Health Research Associates, Lundbeck, Medscape, MSI Methylation Sciences Inc., Merck, Naurex Inc., Navitor, Nestle Health Science – Pamlab Inc., One Carbon Therapeutics, Otsuka America Pharmaceuticals Inc., PamLab, Pfizer Inc., Roche, SHIRE Development, and Takeda Pharmaceuticals Inc; has conducted research activities with NIMH, NIDA, J&J, Janssen Research, and Development LLC; and has claimed royalties from Janssen Research and Development LLC. Dr. Rush has received consulting fees from Akili Inc., the American Psychiatric Association, Brain Resource Ltd., Compass Inc., Curbstone Consultant LLC., Eli Lilly, Emmes Corp., Holmusk, Liva-Nova, Lundbeck A/S, National Institute of Drug Abuse, Santium Inc., Sunovion, Taj Medical, and Takeda USA; speaking fees from Live Nova; and royalties from Guilford Publications and the University of Texas Southwestern Medical Center.

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