Shorter communication

Multiple measures of rapid response as predictors of remission in cognitive behavior therapy for bulimia nervosa

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ABSTRACT

Bulimia nervosa (BN) treatment studies consistently observe that substantial reductions in purging frequency after four weeks of treatment predict outcome. Although baseline levels of other variables have been compared to change in purging, measures of early change in other domains have not been examined. This study aimed to compare percentage change in purging, depression, and cognitive eating disorder (ED) symptoms for associations with BN remission post-treatment and at six months follow-up. Data from $N = 43$ patients with BN in a clinical trial comparing the broad and focused versions of enhanced cognitive behavior therapy (CBT-E; Fairburn, 2008) were utilized. Measures included self-reported purging frequency, Beck Depression Inventory (BDI) score, and a mean of items from the Eating Disorder Inventory Body Dissatisfaction and Drive for Thinness subscales. Results indicated that both percentage change in purging frequency and percentage change in BDI score at week four/session eight were significantly associated with remission at termination. The optimal cutoffs for purging change and BDI score change were 65% decrease and 25% decrease respectively. Only change in BDI score at week four significantly predicted remission at six-month follow-up. These data suggest that change in depressive symptoms may be as important as ED symptom change to predict outcome in some groups.

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Bulimia nervosa (BN) is a severe eating disorder (ED) characterized by recurrent, out-of control eating episodes, extreme compensatory behaviors, and distressing concerns about shape and/or weight (American Psychiatric Association, 2013). Though cognitive behavior therapy (CBT) has repeatedly shown utility to treat the symptoms of BN, substantial subsets of subjects fail to recover in treatment trials (Wilson, Grilo, & Vitousek, 2007). The identification of reliable predictors of remission may aid efforts to improve existing treatments.

Rapid response to treatment, typically defined by improvements in purging rates after four weeks of treatment, has emerged as a consistent predictor of short- and long-term outcome across BN treatment studies (Agras et al., 2000; Bulik, Sullivan, Carter, McIntosh, & Joyce, 1999; Fairburn, Agras, Walsh, Wilson, & Stice, 2004; Olmsted, Kaplan, Rockert, & Jacobson, 1996). Two key studies found that 50% and 70% reduction in purging after four weeks[1] showed the strongest relationship to BN remission among

multiple variables (Agras et al., 2000; Fairburn et al., 2004). A major limitation of the prior research concerning rapid response in CBT for BN is the singular focus on change in purging frequency as opposed to early response in other associated domains. Studies have typically compared change in purging to various baseline psychopathology variables, including baseline level of mood/ negative affect, social functioning, and personality pathology, but not measures of *early change* in other domains (Agras et al., 2000; Fairburn et al., 2004).

Depression and cognitive ED symptoms have been linked to the development and maintenance of BN and identified as mediators of CBT for BN; therefore, rapid treatment response in these domains may also be associated with BN remission. Depression and negative affect are risk factors for EDs in adolescence and young adulthood (Jacobi et al., 2011; Stice, Bohon, Marti, & Fischer, 2008); show temporal relationships to binge/purge symptoms (Selby et al., 2012); and predict short- and long-term BN persistence (Bulik, Sullivan, Joyce, Carter, & McIntosh, 1998; Keski-Rahkonen et al., 2013). Cognitive constructs related to body dissatisfaction and drive for thinness are also risk and maintenance factors for EDs (Stice, 2002); predict poor BN outcome (Keski-Rahkonen et al., 2013);

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[1] In the Agras et al. (2000) protocol sessions were conducted twice per week in the first two weeks, and once per week in the second two weeks.

and have been shown to mediate the outcome of CBT for BN (Wilson, Fairburn, Agras, Walsh, & Kraemer, 2002). The protocol for enhanced CBT (CBT-E) addresses mood intolerance and shape and weight concerns in both the focused and the broad versions, but only after the first four weeks of treatment (Fairburn, 2008). Research is necessary to examine whether early change in depression/negative affect and cognitive ED symptoms, in addition to change in purging frequency, predict outcome.

This study of rapid treatment response utilized data from a randomized control trial assessing the effect of CBT-E for patients with BN and co-occurring psychopathology, specifically co-occurring Axis I mood or anxiety disorders and borderline personality disorder (BPD; Thompson-Brenner et al., 2013). CBT-E was developed to enhance ED outcomes for patients with persistent co-occurring psychopathology (Fairburn, 2008). The primary aim of the clinical trial was to compare CBT-E focused and broad versions for complex patients. Primary outcome analyses suggested that co-occurring mood and interpersonal problems (measured dimensionally by interview at baseline) moderated response to broad vs. focused CBT-E, i.e., meaning that patients with more severe pathology in these areas showed better BN outcomes in CBT-E broad (Thompson-Brenner et al., 2013). Important to the current study, however, the focused and broad forms have identical interventions in the first four weeks, including self-monitoring, regular eating, weekly weighing, and reduction of binge/purge behaviors (Fairburn, 2008).

The specific aim of this study was to compare rapid response in purging rate to rapid response in depression and cognitive ED symptoms for significant associations with remission at termination (20 weeks) and at six-months follow-up, in a clinical trial of CBT-E for patients with BN and co-occurring Axis I and personality pathology.

Method

The study received Human Subjects approval from the Boston University Institutional Review Board and was conducted at the Center for Anxiety and Related Disorders (CARD) (see Thompson-Brenner et al., 2013; for more detail). Consecutively assessed patients who met inclusion criteria and signed informed consent were assigned to receive four weeks (eight sessions) of initial CBT-E according to the treatment manual (Fairburn, 2008) followed by sixteen weeks (twelve sessions) of either the broad or focused version of CBT-E. Research staff with established reliability on the interview instruments, blind to treatment condition, conducted all assessments. Participants were assessed by interview at baseline, termination, and six month follow-up. Participants completed self-report measures at baseline and once per week throughout treatment. The trial was registered in a national clinical trial registry database (NCT00494858).

The primary inclusion criteria were bulimia nervosa (BN) as assessed by the Eating Disorder Examination (Fairburn & Cooper, 1993) with criteria consistent with DSM-IV and −5 diagnostic criteria; diagnosis of a mood or anxiety disorder episode within in the past two years per the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 2002); and BPD pathology, defined as a score of >5 on the Diagnostic Interview for Borderlines-Revised (DIB-R; Zanarini, Gunderson, Frankenburg, & Chauncey, 1989).[2] Females ages 18–65 were included. Exclusion criteria were present suicide risk, current substance dependence,

history of psychosis, cognitive dysfunction precluding CBT, concurrent ED treatment, and recent psychopharmacological changes, i.e., changes to psychopharmacological prescriptions within the past 6 weeks. The full trial included $N = 50$, of which $n = 7$ had dropped out or been withdrawn by week four. The current analyses include the $N = 43$ participants with week four data. This study adhered to the CBT-E instructions (Fairburn, 2008) that therapist and patient explicitly agree at the outset of therapy to twice per week sessions in the first four weeks without any breaks. Strong efforts were made to insure that all sessions were conducted or rescheduled (e.g., night sessions, double sessions, use of substitute therapists). As a result, the large majority of patients who had not dropped out by week four had completed eight sessions.

Measures

Baseline and outcome interviews

ED diagnosis and frequency of OBEs/compensatory behaviors were assessed by the Eating Disorders Examination (EDE; Fairburn & Cooper, 1993) at baseline, termination, and six-month follow-up. EDE assessment of OBEs and purging were used to establish whether participants achieved remission (OBEs/purging = 0 over the most recent 28 days) at termination and at six-month follow-up. The EDE has well-established reliability and validity to assess the symptoms of BN. Study assessors had established excellent inter-rater reliability on the EDE interview ($\kappa > .90$ over three interviews). As noted, all participants met criteria for at least one mood or anxiety disorder within the past two years assessed via the SCID-IV (First et al., 2002). The severity of co-occurring BPD was assessed using the Diagnostic Interview for Borderlines-Revised (Zanarini et al., 1989). The DIB-R assesses the presence of enduring and chronic BPD psychopathology in the areas of affect, interpersonal functioning, cognition, and impulsivity.

Weekly self-report measures

Research staff collected the weekly self-report battery at the baseline assessment and once per week prior to a treatment session. The questionnaires were kept confidential from the treating therapist. The measures included in the weekly assessment battery were chosen for their utility to briefly assess multiple domains of symptoms and psychosocial functioning in this complex sample.

Behavioral symptoms of BN
To assess weekly objective binge and purging episodes (including vomiting, laxative and diuretic use), a self-report questionnaire was constructed. Explicit definitions for each symptom were provided in the measure, and education regarding the correct definition of each symptom was provided to the patient during the baseline assessment. This education is associated with more valid and reliable self-report (Goldfein, Devlin, & Kamenetz, 2005; Loeb, Pike, Walsh, & Wilson, 1994). Frequency of purging was calculated using the participant's primary form of purging, which was typically purging by vomiting ($n = 2$ purging by laxative abuse).

Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996)
The BDI is a 21-item self-report questionnaire assessing depressive symptoms. The BDI was selected for use in the weekly battery and in the current statistical analyses for two primary reasons. First, it is a brief, reliable measure of current depressive symptoms including suicidality (Pulos, 1996). Second, recent research has demonstrated that the broader construct of *negative*

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[2] Details regarding the reliability and validity of the assessments and assessors relevant to the inclusion and exclusion criteria in the current study as well as other details are reported in Thompson-Brenner et al., 2013.

affect (as measured in ED studies by the BDI but also by the Positive and Negative Affect Scale, e.g., Selby et al., 2012; Negative Temperament Scale, e.g., Presnell, Bearman, & Stice, 2004; and Neuroticism, e.g. Ferguson, Munoz, Winegard & Winegard, 2012) is a core risk and maintaining factor for BN; the construct of negative affect has shown stronger associations to depressed mood than to certain specific aspects of anxiety (Crawford & Henry, 2004; Watson, Gamez, & Simms, 2005). The internal consistency of the BDI at baseline in this sample was good ($\kappa = .86$).

Eating Disorder Inventory—Body dissatisfaction and drive for thinness subscales (EDI; Garner, Olmsted, & Polivy, 1983)

The Body Dissatisfaction subscale (7 items) and the Drive for Thinness subscale (6 items) of the EDI were included in the weekly measure to briefly assess two key domains of cognitive ED symptoms. These subscales include some measures of behavior that function as indicators of the cognitive constructs. Because only these subscales were included in the weekly measure, and because internal consistency for the 13 total items was good in this sample ($\kappa = .85$), a mean score of these items was used as a weekly measure of ED cognitions.

Interventions

CBT-E is a transdiagnostic protocol designed to flexibly apply to multiple EDs including BN (Fairburn, 2008). Treatment for BN includes an initial 90-min session and 20 50-min sessions, scheduled twice per week during the first four weeks. The first four weeks of CBT-E for BN are focused on the establishment of self-monitoring, weekly weighing, regular eating, and strategies to reduce binge eating and purging. Therapy was conducted by six experienced therapists who received training and supervision from Dr. Zafra Cooper (Oxford University). Therapy practices were modeled closely the Oxford CBT-E program (see Fairburn, 2008; Thompson-Brenner et al., 2013). Therapy sessions were audio recorded and audited to ensure therapist competency and adherence.

Statistical analyses

To assess whether multiple measures of rapid response were associated with BN remission at termination and follow-up, we first calculated three variables reflecting symptom response in different domains after four weeks/eight sessions of treatment. We chose to use percentage change in purging frequency as the main behavioral symptom variable to be consistent with the findings of the best prior research on early symptom change in BN (Agras et al., 2000; Fairburn et al., 2004). In addition to percentage change in purging at week four ([purging w0 − purging w4]/purging w0), we also calculated percentage change in BDI total score and EDI subscales mean score at week four. We used two steps to assess whether each of the dimensional change variables (percentage change in purging frequency, percentage change in BDI score, and percentage change in EDI subscales mean) accurately classified participants into remitters/non-remitters at termination at different cutoff points. First, we conducted independent samples *t*-tests to determine whether there were any significant associations between each of the percentage-change variables and remission at termination. Next, we calculated receiver operating characteristics (ROC) curves for each of the variables that showed mean differences between remitter/non-remitter groups in *t*-test analyses to see how well the variable predicted remission. We examined the areas under the ROC curves (AUC) as well as sensitivities and specificities at each cutoff point for each variable to determine the optimal cutoffs of each variable to distinguish remitters/non-remitters. ROC curves were calculated for all predictor variables significant in *t*-tests at

Table 1
Comparison of means for participants who did/did not achieve binge/purge remission at termination.

	M Remitted ($n = 19$)	(SD)	*M* Not remitted ($n = 24$)	(SD)	*t*	*p*
Percentage decrease in purging at week four	82.1%	(28.4)	25.0%	(89.4)	−2.67	.011
Percentage decrease in BDI at week four	51.2%	(25.7)	1.0%	(60.5)	−3.38	.002
Percentage decrease in EDI at week four	12.4%	(14.3)	5.8%	(8.7)	−1.85	.071
Baseline purging frequency	8.89	(7.07)	6.25	(4.32)	−1.51	.138
Baseline BDI score	21.00	(5.93)	17.25	(8.49)	−1.63	.110
Baseline EDI score	56.72	(8.85)	56.92	(7.00)	.08	.937

Note. BDI = Beck Depression Inventory; EDI = Eating Disorders Inventory (body dissatisfaction and drive for thinness subscales).

the .10 level and below. We chose $p < .10$ as the criterion for further analysis in order to be optimally inclusive; it is theoretically possible that variables with only weak associations with remission when treated dimensionally might still have highly significant categorical break points. Based on the ROC curve coordinate values that maximized both sensitivity and specificity, new variables were created reflecting each participant's achievement of the established cutoff (coded no = 0, yes = 1). Chi-square and crosstab analyses were conducted to establish the number of participants accurately classified as remitters/non-remitters according to each predictor variable cutoff, and the significance level of the classification scheme. Less than 5% of the data were missing for the participants included in analyses, and data were not replaced or imputed. The sample size for each analysis is reported separately.

Results

Participant characteristics

$N = 43$ patients completed treatment and weekly assessments through week four, and are included in these analyses. Mean age was 25.7 ($SD = 8.4$). Self-reported ethnicity/race was 86.0% ($n = 37$) White/Caucasian; 9.3% ($n = 4$) Asian, 2.3% ($n = 1$); African-American, and 2.3% ($n = 1$) American Indian. One participant indicated being Hispanic (2.3%). Mean BMI was 23.5 ($SD = 3.5$). The most frequent co-occurring disorders were full criteria BPD ($n = 27$; 62.8%)[3]; major depressive disorder ($n = 17$; 39.5%); generalized anxiety disorder ($n = 18$; 41.9%); social phobia ($n = 7$; 16.3%); and posttraumatic stress disorder ($n = 6$; 14.0%). The mean BDI score was 18.9 ($SD = 7.6$), indicating moderate depression on average.

Predictors of remission

Of the $N = 43$ with week four data, 44.2% ($n = 19$) reported remission from OBEs and purging at termination. Table 1 shows the comparison of means between those who achieved remission from OBE/purging at termination and those who did not. As Table 1 shows, percentage reduction in purging and percentage reduction in BDI at week four were both significantly associated with remission at termination at the $p < .05$ level, and percentage reduction in EDI subscales mean was associated with remission at termination at the $p < .10$ level. None of the baseline variable mean raw scores were associated with remission at termination at the $p < .10$ level.

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[3] The remainder had subthreshold but significant BPD traits (see Inclusion criteria).

Next, we conducted ROC curve analyses to further examine variables that significantly discriminated remitters from non-remitters at termination in mean comparisons at the $p < .10$ level (see Statistical analyses section). The results from the ROC curve analyses are presented in Fig. 1.

As Fig. 1 shows, percentage change in BDI score was the most highly predictive, followed by percentage change in purging, followed by percentage change in EDI score, which was not significant at the $p < .05$ level. Percentage change in BDI had AUC of .821 (s.e. = .064), with 95% CI .695−.946, $p < .001$, reflecting a moderate degree of predictive validity (Greiner, Pfeifer & Smith, 2000). Percentage change in purging was also moderately predictive, with an AUC of .760 (s.e. = .076), with 95% CI .611−.910, $p = .004$.

The optimal cutoffs to maximize sensitivity and specificity were established from the coordinates of the curves. For purging frequency, a 65% reduction by the fourth week maximized sensitivity (.83) and specificity (.67) for predicting remission at termination. For BDI score, a 25% reduction by the fourth week maximized sensitivity (.83) and specificity (.71) for predicting remission at termination.

Next, to illustrate and further examine the utility of the identified cutoff scores to correctly classify remitters/non-remitters at termination, we conducted cross-tabulations and Chi-square (χ^2) analyses. Among those who did achieve 65% reduction in purging, 68% recovered ($n = 15$) and 32% did not recover ($n = 7$); among those who did not achieve 65% reduction in purging, 19% recovered ($n = 4$) and 81% did not recover ($n = 17$; $\chi^2 = 10.52$; $p = .001$). Therefore, the total percentage correctly classified using the cutoff of 65% reduction in purging at week four was 74.4% ($n = 32$). Among those who did achieve a 25% reduction in BDI score, 70% recovered ($n = 16$) and 30% did not recover ($n = 7$); among those who did not achieve a 25% reduction in BDI score, 15% did recover ($n = 3$) and 85% did not recover ($n = 17$; $\chi^2 = 12.92$; $p < .001$). Therefore, the total percentage correctly classified using BDI reduction of 25% as a cutoff was 76.7% ($n = 33$).

To assess whether the two cutoffs were correctly identifying the same remitters/nonremitters, we conducted bivariate correlations (Pearson's correlations) of percentage change in BDI and

percentage change in purging rate as well as crosstab analyses comparing those participants who achieved purging reduction of 65% and those who achieved BDI reduction of 25%. Bivariate correlations of the two percentage change rates at week four were nonsignificant ($N = 43$; $r = .22$; $p = .151$). $N = 34$ of the participants were matched on both variables (either achieved both cutoff scores or did not achieve both cutoff scores), but $n = 9$ participants achieved one but not the other of the two cutoff scores.

To assess whether 65% reduction in purging and 25% reduction in BDI score were significantly associated with enduring remission, Chi-square (χ^2) analyses were conducted with the $n = 35$ participants with week four data who completed the follow-up EDE assessment six months after termination. Purging reduction of 65% was associated with remission at the six-month time point only at the trend level of significance ($\chi^2 = 3.54$; $p = .060$); 65.7% of remitters ($n = 25$) at six months were correctly classified according to the 65% reduction in purging cutoff. BDI reduction of 25% was still significantly associated with remission at six months ($\chi^2 = 6.99$; $p = .008$); 71.4% of remitters at six months were correctly classified according to the 65% reduction in BDI score cutoff.

Discussion

The results of this study add substantially to the existing data concerning the importance of rapid response as a predictor of outcome in CBT for BN. The study sample was carefully selected to include patients with complex co-occurring psychopathology, including current or recent Axis I mood or anxiety disorders and clinical or subclinical BPD. Within this complex population, which might be expected to have difficulty achieving rapid and enduring improvement, rapid response at week four strongly predicted remission from OBEs and purging at termination.

Unique results from this sample indicated that rapid response in BDI score, defined as 25% reduction in BDI score or more, was a better predictor of enduring remission at six-months follow-up than 65% reduction in purging. The relevant reduction in BDI score was as good or slightly better at predicting remission at termination than was 65% reduction in purging rate.

One clinical application of this data is the recommendation that patients in treatment for BN—particularly those patients with substantial negative affect—receive an assessment at week four and are reassigned to a different treatment if they show inadequate response (Bulik et al., 1999; Grilo, White, Wilson, Gueorguieva, & Masheb, 2012). This approach has showed some success (Treasure et al., 1996), however, a substantial number of patients who do not respond by week four drop out when reassigned to a different treatment (Mitchell et al., 2002), representing a significant risk for this approach. Furthermore, while failure to reduce depression score was an extremely good predictor of eventual non-remission in this sample, almost half of the patients who *did* remit by termination did *not* demonstrate the 25% reduction in depression score at week four. Given the lack of empirically supported treatments for BN, and the lack of availability of those empirically supported treatments that do exist, there is a risk in this approach of reducing rather than increasing the remission rate.

The alternative approach described in the protocol for CBT-E, in which assessment by the treating psychologist and adjustments to treatment are conducted at week four, is supported by these data. The data also strongly suggest that the assessment of change in BDI score at week four may help the clinical application of the algorithms suggested in the enhanced, transdiagnostic version of CBT (Fairburn, 2008), particularly because the single variable that best predicts both remission at termination and remission at six-months follow-up in this study is change in BDI score of 25% or more. The wisdom of making treatment decisions based on week
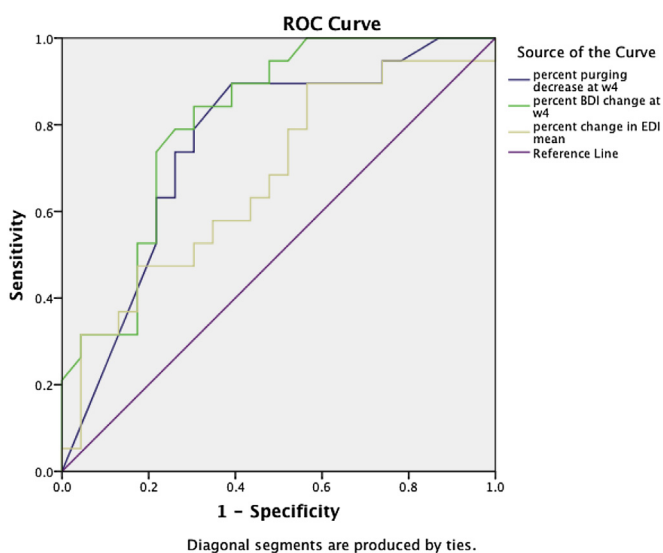

Fig. 1. Receiver operating characteristics (ROC) curves predicting binge/purge remission at termination based on percentage reduction in purging, percentage reduction in Beck Depression Inventory score, and percentage reduction in Eating Disorder Inventory (Body Dissatisfaction and Drive for Thinness subscales) at week four (determined by prospective weekly self-monitoring).

four data—within the same treatment protocol, administered by a single therapist—is supported by observations that rapid response is an important predictor of the trajectory of therapy overall. More data is needed, however, to identify the optimal approach for patients who fail to show rapid response in negative affect.

Additional research is necessary to identify possible explanatory factors accounting for the relationship between rapid response and likelihood of remission in CBT for BN. Additional research is also necessary to explain why the cutoffs of 25% reduction in depression and 50−70% reduction in purging appear to have particular significance. In addition to the simple trajectory of improvement over time, it seems likely that additional psychological factors pertain. A decrease in depression may be associated with an increase in optimism or energy. Decreases in depression and in purging may have differing reward values, or they may be associated with improved self-efficacy, increased quality of life, or improved therapeutic alliance (e.g., Brown, Mountford, & Waller, 2013). There may be important associated differences in psychopathology that is malleable versus that which is more resistant—for example, symptoms that are less responsive to early change may be associated with more secondary rewards. Improvements in one domain (e.g., purging) without improvement in the other domain (e.g., depression) may indicate a patient with "primary depression" or more severe personality pathology, differences that are not apparent at baseline using our existing measures. It is likely that there is a complex and synergistic effect between aspects of early treatment response that likely shows individual differences. However, in order to improve CBT early in treatment—already a busy period of treatment—it is important to isolate important explanatory factors.

Limitations

Because other BN outcome studies have not examined early change in BDI score, it is not clear whether this finding is particular to the population with co-occurring diagnoses, or whether similar results would apply for the general population with BN. However, co-occurring depression and BPD traits are common in BN (Herzog, Keller, Sacks, Yeh, & Lavori, 1992; Stice et al., 2008). These results also cannot be generalized to treatments other than CBT-E at this time. The sample size for this study is also a significant limitation. Additional research using larger sample sizes is needed to establish more stable estimates, replicate these results using adequately powered multivariate statistical analyses, and increase generalizability. Furthermore, there was significant attrition at the six month follow-up period. Rapid response variables were based on self-report data, which may overestimate frequency of some of the behavioral symptoms of BN (Fairburn & Beglin, 1994). The study was also limited by the measures selected for the weekly battery, other measures of negative affect or ED pathology that may have been more valid, reliable, or useful.

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Conflict of interest statement

The authors report no conflicts of interest.

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