A Possibly Mean Mean: The Importance of Considering Heterogenous Change in
Discrete Symptoms when Defining Outcomes of Cognitive Behavioral Therapy for
Patients with Anxiety and Mood Disorders

Maria Å Garke^{*1}, Nils Hentati Isacsson^{*1}, Viktor Kaldo^{1,2}

¹ Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet,
and Stockholm Health Care Services, Region Stockholm

² Department of Psychology, Faculty of Health and Life Sciences, Linnaeus University, Växjö,
Sweden

^{*}Contributed equally as first authors

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Abstract

Background: Psychiatric disorders are defined by patterns of discrete symptoms, and the variability of patients within disorders is usually large. Evaluating treatment for psychiatric disorders rely on means of total scores on disorder-specific self-report scales which are sometimes converted into categories representing purportedly successful or unsuccessful outcomes. This procedure can result in an oversimplification of clinical change, concealing heterogeneous change in separate symptoms over time. Decreases in the scale total score, could hide deterioration in important symptoms if other symptoms decreased. We sought to explore to what extent separate symptoms change (increase, decrease or maintain), if patterns of change among symptoms emerge, and to contrast these patterns with a commonly used classification of “treatment response” in a large sample of patients treated with Internet delivered Cognitive Behavioral Therapy (ICBT). **Method:** Patients included (N = 5163) had data pre- and post ICBT for social anxiety disorder, panic disorder, or major depressive disorder at the Internet Psychiatry Unit within Region Stockholm. For each patient, every item, in all scales were calculated as either maintained, increased or decreased from pre- to post-treatment. Change in separate symptoms was visualized and patterns were analyzed with k-means clustering. The overlap of these clusters and a common dichotomization of treatment response was analyzed. **Results:** It was more common that the different symptoms encompassed in the disorder-specific self-report scales had changed heterogeneously, i.e., some increasing and others decreasing, rather than having all decreased. The cluster analysis did not replicate the common treatment outcome classification. **Conclusions:** This study show that even if ICBT treatment is effective for some patients (i.e., showing a general decrease across many symptoms post-treatment), it is the rule rather than the exception that patients fluctuate (showing both increases, decreases and maintenance) among symptoms. This highlights the need to investigate treatment change on the level of discrete symptoms or behaviors, in order to investigate how we can create definitions of outcome that better capture the heterogeneity of change during psychotherapy.

Keywords: treatment outcome, measurement, cognitive behavioral therapy

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Introduction

Diagnostic categories as stated in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) are defined by patterns of a number of discrete behaviors and symptoms co-occurring over certain time spans. This definition of psychiatric disorders has a vast impact on how psychiatric care is conducted and evaluated, as well as how psychological treatments targeted towards these disorders are developed and evaluated. Cognitive Behavioral Therapy (CBT), one common type of psychological treatment, has to a large extent been influenced by diagnostic categories as stated in the DSM, where treatment manuals traditionally have been developed and tailored with a specific disorder in mind. CBT conducted in this manner (i.e., diagnosis-specific treatment) is in many cases an effective way of treating a range of different psychiatric disorders (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012) including anxiety and mood disorders (two groups of disorders that also frequently co-occur (Brown & Barlow, 2009)). Internet-delivered CBT (ICBT) has been shown to be a comparable alternative to traditional face-to-face CBT for patients willing to engage in this treatment format (Andersson, Cuijpers, Carlbring, Riper, & Hedman, 2014; Andersson, Titov, Dear, Rozental, & Carlbring, 2019). Studies evaluating CBT, including ICBT, normally use self-report scales or expert ratings assessing change in the behaviors and symptoms related to the specific disorder (Hofmann et al., 2012), where change is based on ratings of overall or average frequency and/or severity of the behaviors and symptoms.

However, there are some caveats with using these definitions of psychiatric disorders and their associated measurements, as well as typical definitions of treatment outcome. Clinical trials evaluating psychological treatments often use disorder-specific self-report scales to measure each patient before and after treatment, where each self-report scale results in an average or sum of the overall burden of a range of different

symptoms and behaviors encompassed in the diagnostic definition (Carlbring, Andersson, Cuijpers, Riper, & Hedman-Lagerlöf, 2018). This summary of each patient's symptoms is then used to create averages with which one can e.g., compare outcomes across different treatment groups. It is also common to use these self-report total scores to define and classify which patients had a successful treatment response (or nonresponse), usually by assessing if a self-report scale total score has decreased by a certain amount (e.g., percentage change from pre-treatment) and/or fallen below a certain level (e.g., a predefined clinical cut-off score) (Bandelow, Baldwin, Dolberg, Andersen, & Stein, 2006; Langkaas, Wampold, & Hoffart, 2018).

Since treatment evaluation in the context of randomized controlled trials usually is performed on a group-level (Kaptchuk, 2001) and make use of averaged scores which lump together a number of different symptoms or behaviors, it is often unknown how patients' discrete symptoms and behaviors change over time or differ between groups. This way of measuring treatment outcome conceals if some symptoms decrease more than others or, even more vitally from a clinical perspective, if some specific symptoms increase even if the average symptom burden decreases or remains unchanged. As an illustrative example, in an eating disorder patient sample receiving treatment in specialized care approximately a fifth of the sample had simultaneous increases and decreases in their ratings of different eating disorder-related symptoms over the course of one year (Garke, Sörman, Jayaram-Lindström, Hellner, & Birgegård, 2019). Thus, the average or sum of symptoms for a patient could remain the same indicating no change, while in reality a few crucial symptoms for the patient could increase as several other minor symptoms decrease. This relative importance of discrete symptoms might not be sufficiently reflected or weighted in commonly used diagnosis-specific self-report scales that often focus on covering all criteria that make up the diagnosis. This aspect is especially important since negative effects of psychological treatments historically has been ignored, which limits the overall understanding of how many patients actually may deteriorate during treatment (Mohr, 1995; Rozental et al., 2018).

Adding further to the complexity of evaluating psychological treatment, different

psychiatric symptoms can respond differently, and at different times, to different treatments (Kopta, Kenneth, Jenny, & Larry, 1995). Due to the heterogeneity of between-patient treatment responses to CBT and ICBT that has been demonstrated in previous research (Forsell et al., 2019), it would be useful to gain more detailed knowledge of how patients respond to treatment with regards to discrete symptoms and their change over time. Due to the focus on disorder-level total or average symptom burden and the classification of treatment responders based on this, it is unclear to what extent specific symptoms decrease, increase or are maintained over time in CBT and ICBT treatment. The purpose of the current study was to explore how discrete symptoms, rather than the average symptom burden, change during ICBT across three types of common psychiatric disorders (major depressive disorder, social anxiety disorder, and panic disorder). Further, we wanted to explore how these symptom changes correspond to a traditional definition of being a treatment responder which is based on change in the overall symptom burden. We investigated (i) to what degree discrete items in disorder specific self-report scales either decreased, increased or maintained the same value from pre- to post-treatment, (ii) if we could cluster patients according to their patterns of change in discrete symptoms (decrease, increase or maintained) using cluster analysis, and (iii) how these data-driven patterns compare to a commonly applied classification of treatment "response" based on the total score of the symptom scales.

Method

Participants

Data used in the current study was from the Internet Psychiatry Clinic within Region Stockholm, a clinic established in 2007 which delivers internet-based treatment to patients in Stockholm and the rest of Sweden within regular public health care (Titov et al., 2018). All participants were patients who had received ICBT for either major depressive disorder, social anxiety disorder or panic disorder in routine psychiatric care at the clinic between the years 2007 and 2019. In order to receive treatment, patients

had to be over the age of 18, fulfill diagnostic criteria for either panic disorder, social anxiety disorder, or major depressive disorder (as assessed by an MD on site), and having adequate knowledge in the Swedish language. Additional inclusion criteria applied to the current study was the patient having complete data with regards to the pre- and post-treatment self-report scale measuring their primary symptom area (regardless of treatment being terminated at an earlier date). A total of $n = 5163$ patients could be included, where 2447 (47.4%) were in treatment for major depressive disorder, 1350 (26.1%) in treatment for social anxiety disorder, and 1366 (26.5%) in treatment for panic disorder. For a more detailed description of the Internet Psychiatry Unit as well as procedures and treatments for patients see; (El Alaoui et al., 2015) for social anxiety disorder, (Hedman et al., 2013) for panic disorder, (Hedman et al., 2014) for major depressive disorder, and (Titov et al., 2018) for a more recent update. The use of the data in the current study was approved by the Regional Ethical Review Board in Stockholm (2011/2091-31/3, 2016/21-32, 2017/2320-32 and 2018/2550-32).

Measures

A primary and complementary symptom measure was used to calculate symptom change during the course of treatment for each patient group. The Montgomery-Åsberg Depression Rating Scale Self-report version (MADRS-S)(Montgomery & Asberg, 1979) is a self-report scale measuring depressive symptoms corresponding to the diagnostic criteria for major depressive disorder, and was used as a primary symptom measure for patients receiving ICBT for major depressive disorder. The Liebowitz Social Anxiety Scale-Self report version (LSAS-SR)(Fresco et al., 2001) is a self-report scale measuring fear and avoidance pertaining to social situations, and was used as a primary symptom measure for patients receiving ICBT for social anxiety disorder. The Panic Disorder Symptom Scale-Self Report (PDSS-SR)(Houck, Spiegel, Shear, & Rucci, 2002) is a self-report scale measuring the severity of panic disorder symptoms, and was used as a primary symptom measure for patients receiving ICBT for panic disorder. In addition to this, the MADRS-S was used as a complementary symptom measure for patients

undergoing ICBT for social anxiety disorder and panic disorder, and the Patient Health Questionnaire (PHQ-9) (Kroenke, Spitzer, & Williams, 2001) was used as an complementary scale for calculating symptom change in patients undergoing ICBT for depression. In all of these measures, a higher score is related to a higher symptom burden.

Procedure

Definition of symptom change. Two self-report scales were included for each patient group to calculate the change of symptoms pre- to post-treatment, a primary symptom measure (specific to treatment) and a complementary symptom measure (to get a larger number of symptoms). See table 1 for an overview of the number of measures and discrete items for each ICBT treatment. For every item i for each patient p , the change-status, $S = \{decreased, same, increased\}$, of that item between pre- to post was calculated, and classified as c such that $c \in S$ defined by; decreased ($item_{ip}^{pre} > item_{ip}^{post}$), maintained ($item_{ip}^{pre} = item_{ip}^{post}$), increased ($item_{ip}^{pre} < item_{ip}^{post}$). For each patient the fraction of items in each category c was calculated, dependent on the number of items N for treatment t (see table 1) ergo, $fraction_{cp} = \frac{\sum_{c \in S} item_{cp}}{N_t}$. In summary, we calculated how many percent of discrete symptoms that had decreased, stayed the same, and increased pre- to post-treatment for each patient.

Definition of responder. The status of overall symptom change over the course of treatment denoted, r , was categorized by $r \in \{R_{yes}, R_{some}, R_{no}\}$. These categories were defined by the percentage of decline pre- to post-treatment of the summed total score ($\sum_{i=1}^n item_{ip}$)_{primary} of the primary symptom measure. Based on Karin, Dear, Heller, Gandy, and Titov (2018) the cutoffs were defined as follows: if there was a decrease in total score by; 50% or more this was classified as the patient being a "responder", if there was a decrease in symptoms by 25-50% this was classified as the patient having "some response", and patients not falling into the two first categories were classified as "nonresponder". This categorization was made keeping in mind that it is not possible to draw any causal conclusions about if the patient had actually

"responded" to treatment or not. Thus, the purpose of the categories was to illustrate how the patient had changed over time in the symptoms over the course of treatment.

Data preparation and statistical analysis

All data preparation and analysis was done in R version 3.6.0 (R Core Team, 2018). All scripts and packages used can be found in the supplementary material <https://osf.io/dwjtc/> together with a synthetic data set, results, and a docker container which enable replication of analysis procedure. For creating clusters in order to explore patterns of discrete symptom (item) change we used k-means clustering (Hartigan & Wong, 1979), generating 100 initial centroids for stability. To decide optimal number of clusters we inspected total within cluster sum of squares, "prediction strength" (Tibshirani & Walther, 2005) and silhouette score (Rousseeuw, 1987), for 1 to 10 clusters. The averaged silhouette score (between 0-1) was used to indicate how well the overall clustering captured the spread of the data, a higher number indicating more coherent clusters. The "prediction strength" is succinctly summarised as an iterative reliability check of the chosen clustering by splitting the data set in half and conducting the clustering in each half to see how many percent of pairs of observations in each cluster agree across the two halves. This was repeated 100 times and the average "prediction strength" and its standard deviation was calculated. After the optimal number of clusters was chosen, the distribution of number of each responder class over the clusters was tested using pearsons χ^2 -test. All patients were subsequently plotted in a three dimensional graph using the plotly package (Sievert, 2020), where each axis represents the percentage of items for each patient that fell into one of the categories; decreased, maintained, or increased. This creates a plane of $x + y + z = 1$ and including both designated responder status (shape) as well as cluster membership (color and number).

Results

For an overview of the distribution of symptom change across the different treatments as well as the differences in responder status across treatments, see Figure 2.

For patients in the major depressive and panic disorder treatments, the majority of symptoms decreased over time. However, for patients in the social anxiety disorder treatment, the majority of symptoms were maintained over time (see Figure 2). With the exception of symptoms that increased for patients (roughly 9% of the items), the distribution across patients for both the items that decreased and stayed the same was uniform over the whole patient group regardless of diagnosis. In regards to the distribution of responder status, 60.5% of patients in treatment for panic disorder decreased at least 50% of their total score on their primary symptom measure, while the corresponding proportion for major depressive disorder and social anxiety disorder was 42.9% and 19.9%.

For the k-means clustering, the results with regards to "prediction strength", silhouette score, and the within sum of squares differences is shown in Figure 1. After plot inspection, a clear decrease in reduction of variance was decided to occur after 4 clusters as well as an increase in silhouette score between 3-4 clusters. However, likely due to the three-dimensional nature of the data, a three cluster solution was superior to four with regards to "prediction strength". Taking all parameters into account, a four cluster solution was decided by the authors to be an optimal fit for this data. The location of the centroids is reported in Table 2, showing one cluster dominating one of each axis predominantly, with one cluster being in the "center" of the hyperplane. By inspecting and interpreting the relative numbers of symptoms that had decreased, increased or maintained in each cluster, the following could be described. Cluster 1, termed "Broad response", was dominated by a large percentage of symptoms decreasing, thus indicating a group of patients homogeneously "responding" to treatment. Cluster 2, termed "Half response" showed an approximate split distribution of percentage of symptoms that had decreased and maintained, indicating a cluster of patients that had for the most part decreased in symptoms over the course of treatment. Cluster 4, termed "Part non-response", was interpreted as consisting of a patient group characterized by treatment nonresponse, with about 40% of symptoms increased and maintained respectively. Cluster 3, termed "Mixed unchanged" was

characterized by a patient group showing some decline in symptoms over treatment but with a majority of symptoms maintained on the same level.

This clustering together with each patient's treatment and responder status is shown in the snapshot in Figure 3 with the interactive three dimensional plot accessible for inspection here: <https://osf.io/3jc4q/>. This plot shows that "responder" status is spread out across the three dimensions and clusters, and as a consequence the clusters do not directly replicate the three responder statuses. There is however a clear tendency for the different statuses of responder to fall into each category $\chi^2(6, N = 5163) = 3260, p < 0.0001$. This is tabulated in Table 3. Overall the results thus indicate that, despite the norm of interpreting a decrease in the overall sum of symptoms as a positive treatment outcome, the absolute majority of patients show fluctuations (both increases and decreases) in discrete symptoms over time.

Discussion

The aim of the current study was to explore how patients undergoing ICBT fluctuate with regards to discrete symptoms of either major depressive disorder, social anxiety disorder or panic disorder. Furthermore, we aimed to explore patterns of symptom change - decreases, increases, and maintained levels - and how this corresponds to a commonly used traditional classification of treatment response based on summed scores of disorder-specific scales. Our investigation of these symptom-level changes during ICBT treatment indicated that even if there is some correspondence between symptom-level changes and treatment responder status, a considerable amount of information is lost using these conventions.

By classifying each symptom in a primary and complementary symptom measure as either having decreased, increased or maintained from pre- to post treatment, it was apparent that there was a large heterogeneity in how the different symptoms had either changed or maintained during treatment for the patients undergoing ICBT. This was true for the majority of patients, irrespective of how their change during the course of treatment was classified according to a more traditional way of classifying treatment

response based on scale total scores (i.e., responder, some response, nonresponder). This type of heterogeneity would typically be hidden when studying average total scores as well as effect sizes. Based on previous research indicating that psychiatric symptoms can respond differently to psychological treatment (Kopta et al., 1995), this finding was to be expected. With regards to the different diagnoses, there were some differences in the distributions of percentage of discrete symptoms which had either decreased, increased or maintained. The relative frequencies of discrete symptoms that had increased during treatment was similar across major depressive disorder, social anxiety disorder, and panic disorder. In the relative frequencies of discrete symptoms that had decreased or maintained, patients undergoing treatment for social anxiety disorder had a higher relative number of symptoms that had maintained as well as a lower relative number of discrete symptoms that had decreased, as compared to the other disorders. This corresponded somewhat to the fact that the number of patients classified as nonresponders was largest in the social anxiety disorder treatment. This observed difference in the patterns of symptom change across the three disorders could be due to a number of different reasons. Possible explanations include differences with regards to the effectiveness of the specific treatment protocols, the selection of patients (both when entering treatment as well as the specific selection included in the current study), as well as the primary symptom scale for social anxiety disorder itself being constructed somewhat differently than the other scales (with two subscales measuring fear and avoidance).

To discern possible patterns of change or maintenance in discrete symptoms over the course of ICBT, we performed an exploratory cluster analysis across discrete items of all primary and complementary measures. The resulting number of clusters deemed to fit the data best was four, dividing the patterns of discrete symptom change into four categories. Our interpretation of the four clusters indicated one group of patients that showed an overall "response" to treatment (broad response), two groups that showed some "response" to treatment (half response and mixed unchanged), and one group that showed a lack of treatment "response" (part nonresponse). One of the caveats of cluster

analysis is the interpretation of the results, due to the fact that groupings are generated on a data-driven basis. This makes it difficult to say anything about the validity or generalizability of the results. Thus, we are cautious about making any theoretical extrapolations or suggesting that either way of classifying treatment outcomes is superior to the other.

However, the resulting clusters are useful as a point of comparison to the previously commonly used traditional classification of treatment response. The categorization resulting from the cluster analysis corresponded to some degree to the common treatment responder classification, as well as emphasized some important differences. One important point of divergence was that the classification of treatment response only takes into account the total sum of the scale score, and if this sum had decreased by a certain percentage from pre- to post-treatment. Inspection of cluster 1 and 2, indicating a group of patients having some "response" to treatment, showed that although a majority of discrete symptoms had indeed decreased (50-80%), a significant number of symptoms also had maintained (20-40%) as well as increased (2-8%). We cannot from these results see what specific symptoms actually had decreased and what symptoms had increased, and if they belong to the primary or complementary measure. Nonetheless, theoretically a depressed patient could have increased in their suicidal ideation whilst decreasing in a number of less acute depressive symptoms, begging the question if these patients would actually perceive themselves as having "responded well" to treatment. In a study where patients undergoing psychotherapy for depression were interviewed, there were cases where patients classified as having improved (as measured by self-report scale total scores) did not state feeling any better as a result of treatment (De Smet et al., 2019). In the previously mentioned study of patients receiving treatment for eating disorders, approximately a tenth of the sample had decreased in an eating disorder-related behavior whilst simultaneously increased in deliberate self-harm behavior, which would from a clinical perspective be considered a more adverse symptom (Garke et al., 2019). This also begs the question if these patients, as well as clinicians, would have considered their treatment outcome as positive although the sum

of all symptoms at one time point could have equaled zero. Contrasting the cluster analysis performed in the current study to the commonly used traditional responder classification paints a picture where these categories are not transparent and sensitive to adverse treatment outcomes, and highlights potential scenarios where the use of summed scale total scores could hide important information. These potentially disguised scenarios could be of different natures. For example, a patient's perceived improvement could also be hidden by total scale scores that instead indicate nonresponse to treatment. Interestingly, a meta-analysis comparing patient outcomes as measured by disorder-specific scales to personalized treatment goals found that effect sizes for psychotherapy were significantly larger when evaluating personalized treatment goals (Lindhiem, Bennett, Orimoto, & Kolko, 2016).

This study adds to previous research on the topic of psychological treatment outcomes by further illustrating the heterogeneity of treatment change in a large sample of regular care patients undergoing ICBT. Results show that alternative methods of treatment outcome evaluation may be warranted. Although this study has some strengths, including the large naturalistic sample of patients in a public healthcare setting, some important limitations are worth mentioning. The sample included in the current study excluded 1219 patients who did not complete the post treatment measurement. Missing data is to be expected in a setting like this, where patients enter into care voluntarily. However, we cannot know if and how our results would have been effected by this missing data. Furthermore, this study cannot say anything about how the patients themselves experience the relative change in symptoms. For example, a patient increasing by one scale point in 50% of the discrete symptoms might not be perceived as a significant deterioration for one patient, just as a decrease in 100% of the symptoms might not be perceived as a significant improvement for another patient (De Smet et al., 2019, Magnusson, 2019). We also chose to include both the primary (social anxiety disorder, panic disorder, major depressive disorder) as well as a complementary self-report measure to include a wider array of often co-occurring symptoms. However, we unfortunately did not have a corresponding measure of anxiety in the group receiving

ICBT for major depressive disorder and as such the results should be interpreted in light of this. In addition, the specific scales used have all been psychometrically evaluated based on the sum of the items. As such we do not know as much regarding the measurement error of the discrete items themselves and to what extent this influences our results. We believe this is a worthy and important consideration in future research investigating possible alternatives to analyzing total scale scores.

Initiatives to deepen our understanding of who responds to psychological treatment or not have been put forward from researchers within the field of clinical psychology and psychiatry (e.g., The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science (Holmes et al., 2018)). The initiatives usually highlight the importance of knowing more about for whom the treatment is effective, as well as providing more precise treatments tailored to specific problem areas or deficits of the patient rather than only focusing on diagnostic categories. We additionally would, for future research, consider it of importance to continue investigating how we define and measure patient outcomes. While self-reported disorder-specific scales can be useful, it is important to also investigate methods of measurement that allow us to understand treatment change on the symptom level, as well as developing methods of taking into account the relative weighting of different symptoms. For example, a promising avenue of research on the symptom level is using network analysis (sometimes referred to as the network perspective on psychopathology) where focus lies on understanding the relations and centrality of discrete symptoms (Fried et al., 2017). Another potential approach is to investigate how to weight symptoms according to which are considered most subjectively important to patients and clinicians. These lines of research could be useful to improve our understanding of how symptoms co-occur, effect one another, and which symptoms are most theoretically and subjectively central (rather than weighting them all equally). Another avenue worth exploring in defining more clinically relevant treatment outcomes is to measure and evaluate specific target behaviors of patients, as is commonly done in a functional analysis (Haynes & O'Brien, 1990). Regardless of focusing on questionnaires or behavioral measures, future research

could also further investigate the benefits of complementing traditional treatment outcomes with individualized treatment goals (Lindhiem et al., 2016). Measuring individualized treatment goals would be a relatively easy way of gaining more insight on patient-centered improvements that could be directly implemented in the current treatment model based on diagnosis-specific treatment. Additionally, improvement with regards to function and quality of life could be studied to a larger extent as a way of assessing change over the course of treatment as a complement to the current way of measuring treatment outcome. There are a number of self-report scales assessing function (Ustun, Kostanješek, Chatterji, Rehm, & Organization, 2010) and quality of life in use e.g., (Lindner et al., 2016), and complementing current measures with these outcomes to a larger degree than currently done today could have the potential benefit of increasing our understanding of treatment response. Both individualized treatment goals and function/quality of life have in common that they focus on the increase of positive outcomes related to treatment, contrasting diagnosis-specific measures which focus on the decrease of aversive outcomes. Lastly, we also consider it an important addition to investigate patterns of treatment outcomes which also takes into account the occurrence of negative effects resulting from treatment (Rozental, Boettcher, Andersson, Schmidt, & Carlbring, 2015).

In conclusion, by further highlighting the complexity of symptom-level change, including measures spanning broad problem domains in a large sample of regular care patients undergoing psychological treatment, we hope that this study contributes to an increased understanding of the possible caveats of analyzing total or average scores of disorder-specific measures. We believe that a more concerted effort is needed in defining treatment outcomes. Although a larger and likely long-spanning effort is required to increase our basic understanding of measurement in the realm of psychopathology and treatment outcomes, many suggestions for improvement outlined above are already and can be further implemented today. This would be essential to reaching the final goal of understanding who responds to treatment and why.

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Table 1

Overview of measurement characteristics of self-report scales included in the study

	Treatment		
	Major Depressive Disorder	Panic Disorder	Social Anxiety Disorder
Disorder Specific measure	MADRS-S	PDSS-SR	LSAS-SR
Range	0 – 54	0 – 28	0 – 144
Test-retest reliability	0.83*	0.81**	0.83***
Complementary disorder specific measure	PHQ-9	MADRS-S	MADRS-S
Range	0 – 31	0 – 54	0 – 54
Test-retest reliability	0.84****	0.83*	0.83*
Total number of items across measures	19	16	57

* (Svanborg & Åsberg, 2001), ** (Houck et al., 2002), *** (Baker, Heinrichs, Kim, & Hofmann, 2002),

**** (Kroenke et al., 2001). MADRS-SR = Montgomery-[U+FFFD]berg Depression Rating Scale

Self-report, PDSS-SR = Panic Disorder Symptom Scale-Self Report, LSAS-SR = Liebowitz Social

Anxiety Scale-Self report, PHQ-9 = Patient Health Questionnaire.)

Table 2

Percentage of items in each change category by cluster

Cluster	% symptoms increased	% symptoms maintained	% symptoms decreased
1 "Broad response"	1.8	17.8	80.5
2 "Half response"	6.6	41.9	51.6
3 "Mixed unchanged"	10.9	65	24.1
4 "Part nonresponse"	40.7	43.5	15.8

Cluster centroid locations on the separate axes corresponding to the 3 categories of symptom change

Table 3

Number (%) of patients in each cluster belonging to each treatment responder status classification

Cluster	Nonresponder	Some response	Responder
1 "Broad response"	16 (0.31%)	277 (5.37%)	1397 (27.06%)
2 "Half response"	383 (7.42%)	764 (14.80%)	628 (12.16%)
3 "Mixed unchanged"	941 (18.23%)	223 (4.32%)	104 (2.01%)
4 "Part nonresponse"	398 (7.71%)	20 (0.39%)	12 (0.23%)

Figure 1. Parameters of cluster analysis evaluation including silhouette score, "prediction strength", and difference in sum of squares

a) Average silhouette score as a function of number of clusters. A higher score indicates on average a more coherent clustering b) Mean prediction strength" as a function of numbers of clusters with 100 iterations, a higher prediction strength indicates a better reliability of the clustering. Bars indicate 2 times the standard deviation c) Difference in total within cluster variance for k-means clustering as a function of number of clusters. Difference was between the current number of clusters total within cluster variance compared to the previous one.

Figure 2. Distribution of (a) type of change of specific symptoms and (b) frequency of responder status across treatments

Figure 3

Clusters delimited by color: 1 = "Broad response"; 2 = "Half response", 3 = "Mixed unchanged", 4 = "Part nonresponse". Responder status is delimited by shapes.

Responder = 50% symptom improvement; Some response = 25-50% symptom improvement; Not responder = 0-25% symptom improvement