PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Internet-based, therapist guided, cognitive behavioral therapy for body dysmorphic disorder with global eligibility for inclusion: An uncontrolled pilot study
AUTHORS	Gentile, Andrew; La Lima, Christopher; Flygare, Oskar; Enander, Jesper; Wilhelm, Sabine; Mataix-Cols, David; Rück, Christian

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Raquel Nogueira-Arjona Institution and Country: Dalhousie University. Department of Psychology and Neuroscience Competing interests: None declared
REVIEW RETURNED	31-Jul-2018

GENERAL COMMENTS	I would like to thank the opportunity to review this manuscript. This paper presents an innovative study that tests the feasibility and safety of an internet-based CBT intervention for BDD with a worldwide recruited sample. On the one hand, the validation of a cross-cultural online treatment like this one can help to overcome some of the barriers that prevent individuals with BDD to get access to evidence-based care (e.g. shame, scheduling limitations, and economic disadvantage). On the other hand, this paper provides valuable insight regarding the challenges inherent to this format of treatment delivery, such as the management of patients at risk. Considering this, I would like to address the following questions to the authors: 1. An exclusion criterion for participation in the study is the presence of a “personality disorder that could jeopardize treatment participation (e.g. borderline personality disorder with self-harm)”. What specific criteria did clinicians use to determine the presence or absence of a comorbid personality disorder (besides patient’s self-reported diagnosis)? In order to have a complete picture of the participant characteristics, what is the distribution of these disorders in your sample? 2. Could you provide more information about how was the decision-making process to establish that BDD was a primary diagnosis? 3. “Clinicians rated patient overall severity and symptom change on the Clinical Global Impressions Scale (CGI)”. Could you provide more information regarding who conducted this assessment? Specifically, was the patient overall symptom change assessed by independent evaluators? 4. One of the aims of this study is to evaluate the safety of a global treatment initiative.

	According to figure1, 23 participants were excluded between the Online screening phase and the Video assessment phase and 7 participants were excluded between the Video assessment phase and the Baseline phase based on excessive depression and or/suicidality. Could you provide more information about how you handled those at risk participants? Was it feasible to apply the safety measures included in your protocol for those participants excluded prior to enrollment? 5. “Throughout treatment, patients had unlimited access to their therapist from Monday through Friday via asynchronous electronic text messages”. How was the distribution of therapist contacts throughout the treatment sessions? Are there treatment sessions that require more therapist support than others do? Are there differences in response to treatment between participants that use more therapist support vs participants that use less the therapist support? 6. The authors mention the use of the Dysmorphic Concerns Questionnaire in the procedure and in the Appendix. However, there is no information regarding the outcomes on this questionnaire in results sections (paper or supplemental material). Could you provide more information about these outcomes? 7. The authors provide an ITT approach. Are results the same excluding non-completers? Are there differences in the response to treatment between participants who completed the core components vs participants who completed all sessions of the program? 8. Could you provide more information regarding the therapist level of experience and frequency of supervisions? 9. Although participants were fluent in English, their cultural background was diverse. However, the authors used assessment instruments validated within western cultures. How can the authors be sure that the constructs that you are assessing with participants with western backgrounds are the same than with individuals with non-western backgrounds or even with different native languages? 10. How the authors propose to deal with dropouts in future studies? Do you think that the treatment should be changed to deal with participants with poorer insight or higher overall severity?

REVIEWER	Reviewer name: David Gratzer Institution and Country: CAMH, Toronto, Canada Competing interests: None
REVIEW RETURNED	08-Aug-2018

GENERAL COMMENTS	In this pilot study, ICBT was offered to people with Body Dysmorphic Disorder, showing robust results. The paper is unique in that the study was unbound by geography, allowing participants evidence-based care without the usual confines of a catchment area. People were recruited using Internet ads and other strategies. A few general comments --

	* I note a small n — but it's a pilot study. * The authors put their work in context nicely, and the paper is readable and clear. * I'm not a biostatistican, but the statistical analyses look right. That said, I would make some minor suggestions — * The opening paragraphs offer background information on ICBT. The authors could push further and do a more thorough job of citing the recent literature, such as the AJP paper on ICBT for depression (Thase et al.). * The authors summarize the paper well at the end, but could push further in their conclusions. * Finally, while the decision to make the study open (and international) is reasonable, a more careful consideration of the ethical issues could have been done. These are, again, minor suggestions. Overall, this is a nice and unique contribution to the literature and should be published.

REVIEWER	Reviewer name: Michael Barkham Institution and Country: University of Sheffield, UK Competing interests: None declared
REVIEW RETURNED	29-Aug-2018

GENERAL COMMENTS	I have been asked to focus on the statistical components of this manuscript, plus any other general comments. In terms of the statistical analyses, these are generally in line with what might be expected from such a trial. Effect sizes are reported as are 95% confidence intervals. The ESs for the d statistic appear large as they are within group ESs rather than between group comparisons. The reporting of statistically significant effects tends to lack clinical meaning or relevance and calculating the percentage of participants reaching criterion for reliable and clinically significant improvement might be helpful to clinicians in the field. However, the authors argue that the main focus of the report is about showing potential global uptake across national borders. My view is that the authors overstate their claim about the global nature of the take up. Of the 32 participants, 7 are from the homeland and therefore should, it could be argued, be excluded from the analyses, making the study N = 25. Of these, 12 and 4 participants were drawn from the US and England respectively. I would not be convinced that take-up in these two countries made the point about global reach. This leaves just 9 participants, one each from each of 9 countries. I do not see this as convincing evidence that the programs are applicable across national boundaries as there can be no generalisation beyond each single person drawn from these 9 countries. If this argument is accepted, then it would be logical to compare the outcomes between these major groupings of countries. Are the outcomes from the 9 single participant countries the same as from Sweden? In effect, an analysis could use the Swedish subsample as the benchmark and compare the US/English and the group of 9 countries to the benchmark.

	However, I would still remain sceptical that the study as reported shows reliable take-up at a potentially global level. I do not think single participant take-up in a country is a reliable index of anything. I hope these comments are helpful.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Raquel Nogueira-Arjona

Institution and Country: Dalhousie University. Department of Psychology and Neuroscience

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I would like to thank the opportunity to review this manuscript.

This paper presents an innovative study that tests the feasibility and safety of an internet-based CBT intervention for BDD with a worldwide recruited sample. On the one hand, the validation of a cross-cultural online treatment like this one can help to overcome some of the barriers that prevent individuals with BDD to get access to evidence-based care (e.g. shame, scheduling limitations, and economic disadvantage). On the other hand, this paper provides valuable insight regarding the challenges inherent to this format of treatment delivery, such as the management of patients at risk. Considering this, I would like to address the following questions to the authors:

1. An exclusion criterion for participation in the study is the presence of a "personality disorder that could jeopardize treatment participation (e.g. borderline personality disorder with self-harm)". What specific criteria did clinicians use to determine the presence or absence of a comorbid personality disorder (besides patient's self-reported diagnosis)? In order to have a complete picture of the participant characteristics, what is the distribution of these disorders in your sample?

We thank the reviewer for pointing this out, as comorbid personality disorders are an important consideration in clinical settings. Participants were initially screened for personality disorders based on self-report, and after the assessment no one was excluded based on this criterion. The Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) was not utilized in this process. Associated features of borderline personality disorder (i.e., non-suicidal self-injury and suicidal ideation/behavior) were assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) prior to enrollment.

2. Could you provide more information about how was the decision-making process to establish that BDD was a primary diagnosis?

BDD symptoms were screened using the Dysmorphic Concerns Questionnaire (DCQ) and Body Dysmorphic Disorder Questionnaire (BDDQ). A diagnosis of BDD was established through the Structured Clinical Interview for DSM 5 - Research Version (SCID-5-RV), module G. The BDD-YBOCS was used to help supplement assessment for BDD diagnosis, and to indicate BDD symptom severity. Establishment of BDD as the primary diagnosis was determined through clinical judgment by the evaluator and the licensed supervising clinician taking into account the report of the participant.

3. “Clinicians rated patient overall severity and symptom change on the Clinical Global Impressions Scale (CGI)”. Could you provide more information regarding who conducted this assessment? Specifically, was the patient overall symptom change assessed by independent evaluators?

Thank you for letting us clarify this. Treating therapists conducted CGI-I ratings. Independent evaluators were not utilized.

4. One of the aims of this study is to evaluate the safety of a global treatment initiative. According to figure1, 23 participants were excluded between the Online screening phase and the Video assessment phase and 7 participants were excluded between the Video assessment phase and the Baseline phase based on excessive depression and or/suicidality. Could you provide more information about how you handled those at risk participants? Was it feasible to apply the safety measures included in your protocol for those participants excluded prior to enrollment?

Yes, patients excluded before enrollment in the study were subjected to the same safety procedures. Patients presenting with levels of depression or suicidality that were too high to be included in the study identified a 24 hour psychiatric emergency center in their local area and verbally agreed to go there if they were at imminent risk of taking their own life. Furthermore, therapists provided at least one referral for mental health services in their area. We thank the reviewer for pointing this out and have clarified the procedures on page 7 of the manuscript in response to the reviewer’s comment.

5. “Throughout treatment, patients had unlimited access to their therapist from Monday through Friday via asynchronous electronic text messages”. How was the distribution of therapist contacts throughout the treatment sessions? Are there treatment sessions that require more therapist support than others do? Are there differences in response to treatment between participants that use more therapist support vs participants that use less the therapist support?

The reviewer raises interesting questions about treatment participation and we have added additional analyses. Unlike traditional face to face therapy, treatment was not delivered in discreet “sessions”, but rather, patients moved through self-help treatment modules, at their own pace, with therapist support provided through electronic messages. Data was not collected on how the messages were distributed across different time points in treatment. For each additional message sent, participants had on average a reduction of BDD-YBOCS score of 0.11 points (95% CI = -0.23 to 0.01), but the number of messages sent were not a statistically significant predictor of BDD-YBOCS score when controlling for time ($F[1, 28.80] = 3.01$, $p = .09$). We have added these results to page 13 in the manuscript.

6. The authors mention the use of the Dysmorphic Concerns Questionnaire in the procedure and in the Appendix. However, there is no information regarding the outcomes on this questionnaire in results sections (paper or supplemental material). Could you provide more information about these outcomes?

The DCQ was only used as a screening measure administered during the initial online screening. Therefore, there are no DCQ outcome data to report.

7. The authors provide an ITT approach. Are results the same excluding non-completers? Are there differences in the response to treatment between participants who completed the core components vs participants who completed all sessions of the program?

We thank the reviewer for raising this issue. In response to this, we have done additional analyses to investigate the effect of treatment completion on the main outcome (BDD-YBOCS) and added the results to page 13. Patients who completed the core treatment modules (modules 1-5) were considered completers. Individuals who completed at least 5 modules had, on average, a lower score on the BDD-YBOCS (Estimate = -6.35, 95% CI = -11.72 to -0.99).

The effect of number of modules completed was statistically significant when including time as a co-variate (F[1, 37.62] = 5.39, p = .03).

8. Could you provide more information regarding the therapist level of experience and frequency of supervisions?

Therapists in the study were doctoral level clinical psychology PhD students with no previous experience treating BDD, supervised by licenced psychologists and psychiatrists at Karolinska institutet. A previous RCT of BDD-NET showed good outcomes despite the absence of prior specialized BDD experience among therapists and adds to the scalability of the treatment (Enander et al., 2016). Similar to the the delivery of the treatment itself, supervision was primarily delivered on a continuous basis any time that decisions were made related to patient inclusion/exclusion or withdrawal from treatment, any time a patient reported elevated risk, and as needed to address other questions related to the delivery of the treatment itself. In addition, several additional supervisions were scheduled throughout the course of the treatment in order to provide additional oversight for maintenance of the study. All in all, supervision was provided at least once a week throughout the course of the study.

In response to this comment a revision was added to page 10 of the manuscript to clarify the level of therapist's previous experience with BDD.

9. Although participants were fluent in English, their cultural background was diverse. However, the authors used assessment instruments validated within western cultures. How can the authors be sure that the constructs that you are assessing with participants with western backgrounds are the same than with individuals with non-western backgrounds or even with different native languages?

Thank you for raising this important question. We agree, and have revised the limitations section on page 17 to comment on this issue.

10. How the authors propose to deal with dropouts in future studies? Do you think that the treatment should be changed to deal with participants with poorer insight or higher overall severity?

We agree with the reviewer that droupout from treatment and insight are two important considerations in the psychological treatment of BDD. While research has shown insight and severity to be related to outcome in the treatment of OCD and other disorders, the meta-analysis by Harrison et al., (2016) was unable to show that insight or symptom severity predicts outcomes in the treatment of BDD. Therefore, we don't currently have evidence to suggest that the main structure or content of treatment should be adjusted for patients with lower insight or higher severity. On the other hand the sample was self-referred, making it plausible to assume that those with no insight would probably not register to the study and therefore we cannot assume that our results generalize to the entire BDD population.

Reviewer: 2

Reviewer Name: David Gratzer

Institution and Country: CAMH, Toronto, Canada

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

In this pilot study, ICBT was offered to people with Body Dysmorphic Disorder, showing robust results.

The paper is unique in that the study was unbound by geography, allowing participants evidence-based care without the usual confines of a catchment area. People were recruited using Internet ads and other strategies.

A few general comments --

* I note a small n — but it's a pilot study.

* The authors put their work in context nicely, and the paper is readable and clear.

* I'm not a biostatistican, but the statistical analyses look right.

Reply: We thank the reviewer for the appreciation.

That said, I would make some minor suggestions —

* The opening paragraphs offer background information on ICBT. The authors could push further and do a more thorough job of citing the recent literature, such as the AJP paper on ICBT for depression (Thase et al.).

Response: Thank you for pointing this out. We agree, and have made a revision on page 4 of the manuscript in order to reference some of the literature on ICBT and related technology based adjuncts to face to face therapy like the Thase paper you mention.

* The authors summarize the paper well at the end, but could push further in their conclusions.

We thank the reviewer for the encouraging comment. While we are indeed positive about the results, this is still the first study of its kind and we are therefore careful not to overstate the conclusions as there are still unanswered questions.

* Finally, while the decision to make the study open (and international) is reasonable, a more careful consideration of the ethical issues could have been done.

We agree that the ethical issues are central and we hope that the parts of the discussion on legal consideration and risk would constitute a careful consideration of the ethical issues. If the reviewer or editor indeed wants us to elaborate on the this we would happily do so if we are provided with more specifically what is lacking.

These are, again, minor suggestions. Overall, this is a nice and unique contribution to the literature and should be published.

Reviewer: 3

Reviewer Name: Michael Barkham

Institution and Country: University of Sheffield, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

bmjopen-2018-024693 entitled "Internet-based, therapist guided, CBT for Body Dysmorphic Disorder with Global Inclusion: A Pilot Study"

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In terms of the statistical analyses, these are generally in line with what might be expected from such a trial. Effect sizes are reported as are 95% confidence intervals. The ESs for the d statistic appear large as they are within group ESs rather than between group comparisons. The reporting of statistically significant effects tends to lack clinical meaning or relevance and calculating the percentage of participants reaching criterion for reliable and clinically significant improvement might be helpful to clinicians in the field.

We thank the reviewer for this comment and elaborate on our decision to use “treatment responder” as a clinically meaningful outcome below. Previous trials on BDD (pharmacological and psychological) have all used change in symptoms, as measured with the BDD-YBOCS, as the primary outcome measure. The “treatment responder”, i.e. 30% reduction of symptoms, is widely used and based on an empirically derived cut-off point (Phillips et al 2014). This cut-off corresponds to a clinician-rated clinical global impression (CGI) score of 1 (“Very much improved”) or 2 (“Much improved”). Therefore it represents a simple way to express how many patients achieved clinically significant improvement in each group. This criterion is defined on page 9 in the methods, and the results using this criterion is reported in the “secondary outcomes” section on page 12.

Reference: Phillips, K. A., Hart, A. S., & Menard, W. (2014). Psychometric evaluation of the Yale–Brown Obsessive-Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS). Journal of Obsessive-Compulsive and Related Disorders, 3(3), 205–208. http://doi.org/10.1016/j.jocrd.2014.04.004

However, the authors argue that the main focus of the report is about showing potential global uptake across national borders. My view is that the authors overstate their claim about the global nature of the take up. Of the 32 participants, 7 are from the homeland and therefore should, it could be argued, be excluded from the analyses, making the study N = 25. Of these, 12 and 4 participants were drawn from the US and England respectively. I would not be convinced that take-up in these two countries made the point about global reach. This leaves just 9 participants, one each from each of 9 countries. I do not see this as convincing evidence that the programs are applicable across national boundaries as there can be no generalisation beyond each single person drawn from these 9 countries.

If this argument is accepted, then it would be logical to compare the outcomes between these major groupings of countries. Are the outcomes from the 9 single participant countries the same as from Sweden? In effect, an analysis could use the Swedish subsample as the benchmark and compare the US/English and the group of 9 countries to the benchmark.

However, I would still remain sceptical that the study as reported shows reliable take-up at a potentially global level. I do not think single participant take-up in a country is a reliable index of anything.

I hope these comments are helpful.

We appreciate your concerns about overstating the global nature of this study. We used the word “global” to highlight the most unique aspects of the current study and distinguish it from other multi-centre international trials which have delivered treatment across international borders, but were unlike the current study in which there were no restrictions on inclusion based on geographic location, and that all aspects of recruitment, assessment, and treatment delivery were done remotely.

While recruitment efforts were made on a global level, naturally, the demographics of the participants that were ultimately eligible for this english language based treatment, to some degree, reflect the global distribution of fluent english speakers.

Indeed, it is outside the scope of an uncontrolled pilot study of this size to recruit a sufficient number of participants from every country such that would claim to generalize treatment on a global level, and we want to be clear that we do not intend to make any claims that the subject enrollment and/or effects of the BDD-NET treatment are generalizable to populations in every country in the world, and it's hard to realistically imagine any one study that could make such a claim. Instead we hope to show that recruitment efforts could be deployed on a global level, that all aspects of the study could be could be conducted remotely, and that this could be done safely, with results that are comparable to previous BDD-NET trials.

However, we have carefully reviewed the manuscript and made a number of revisions in an effort to be more clear and precise with the language used and not make any claims which the current study cannot support. Specifically, as you highlight that global recruitment is an overstatement, we attempt clarify that we mean global eligibility and recruitment efforts which can be distinguished from global enrollment. Furthermore, we have made several revisions and were careful to not make any claims of global generalizability. In doing so, we have attempted to state as clearly as possible, claims which we believe can be supported by our data. You can find the aforementioned claims and revisions on pages: 1, 2, 3, 5, 14, 16, and 17

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Raquel Nogueira-Arjona Institution and Country: Dalhousie University, DEPARTMENT OF PSYCHOLOGY AND NEUROSCIENCE Competing interests: None declared
REVIEW RETURNED	29-Oct-2018

GENERAL COMMENTS	The authors addressed all my concerns satisfactorily.

REVIEWER	Reviewer name: David Gratzer Institution and Country: CAMH Competing interests: None declared.
REVIEW RETURNED	29-Oct-2018

GENERAL COMMENTS	I reviewed the original submission and submitted several comments. At this point, I believe that this manuscript is now publishable - the authors have done a solid job of incorporating the feedback. As I have stated before, I think that this study adds nicely to the literature.