PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Aversive tension of adolescents with anorexia nervosa in daily course: A case-controlled and smartphone-based ambulatory monitoring trial (SMART)
AUTHORS	Kolar, David; Bürger, Arne; Hammerle, Florian; Jenetzky, Ekkehart

VERSION 1 - REVIEW

REVIEWER	Prof. Stephan Zipfel MD Department of Psychosomatic Medicine and Psychotherapy University Medical Hospital Tuebingen, Germany
REVIEW RETURNED	25-Feb-2014

GENERAL COMMENTS	The idea of monitoring and in case of a relevant and clinical impairment of "aversive tension" in patients with anorexia nervosa, may be an interesting issue. However, there are some major methodological weaknesses of the present study protocol, which make conclusions from the collected data critical. Major Comments: Why do the authors try to do several steps in one: In a first step the authors should investigate the spectrum of eating disorders (ED) subdivided in clear subsamples of restrictive anorexia nervosa (AN), binge-purge AN, bulimia nervosa. In additional to this step1, I would advise concentrating on postpubertal ED. The rationale for this step is, that thus far there is no good evidence that “aversive tension” per se is a key psychopathological construct for the spectrum of underweight, restrictive AN patients. In this first step I would suggest to apply for a cross-sectional diagnostic approach a long with a state of the art diagnostic procedure, applying general psychiatric and eating disorder by structured interviews to validate the relevance of this construct. If the first step proved evidence for aspects of “aversive tension” in specific subgroup of ED patients, I would concentrate of this subgroup of eating disorders. So far there is no proper evidence for a relevance of this construct for prediction of outcome or as a relevant target for treatment interventions in AN. In a second step I would concentrate on clear defined situations to be monitored and measured (e.g. before and after defined meals in contrast to a defined relaxed state). I do trust in the technology part of the recording of data – however my advice for data analyzing would be to concentrate on state of the art approaches (see e.g. Wild B, et al. A graphical vector autoregressive modeling approach to the analysis of electronic diary data. BMC Med Res Methodol. 2010 Apr 1;10:28). It is a real challenge to proper deal with serial electronic diary data! A third step might be interesting in case the two initial steps proved to be relevant. Than a defined module tackling „aversive tension“

	applying DBT-E techniques might be interesting to investigate in a clear RCT-defined approach. In addition the inclusion criteria as defined are not sufficient – also due to safety aspects and potential medical confounder, somatic aspects e.g. weight, metabolic parameters, but also axis 2 diagnosis have to be assessed and a priori exclusion criteria had to be defined (BMI > 15kg/m2 – or a predefined weight percentile), being aware of the limitations of axis 2 diagnosis in prepubertal ED. I would advise to focus the study (see point 15) and to submit the study protocol after clarifying to a more eating disorder specific journal e.g. Journal of Eating Disorders (BMC open) Due to the fact that it is a diagnostic study, a study published protocol in a broad spectrum journal like the BMJopen is of limited interest and relevance.

REVIEWER	Christian Stiglmayr Arbeitsgemeinschaft fuer wissenschaftliche Psychotherapie Berlin Germany
REVIEW RETURNED	06-Mar-2014

GENERAL COMMENTS	The paper adresses aversive tension in adolescentes with anorexia nervosa, assessed via ambulatory monitoring in comparison to mentally healthy controls. It presents important findings confirming aversive tension is an important feature for clinical work with adolescents with anorexia nervosa. The methodology used in this study is very innovative especially using the subjects´ own smartphones. However, there are two features which are amenable for improvement: 1. The fist item of the electronic questionnaire question do not ask for aversive tension question but for tension only. This fact do have important implications for the interpretation of the results and should be focused in the following paper. It is even questionable, if the term “aversive tension” can be used in the title and the whole study. It could be helpful to view the paper of Stiglmayr, Bischkopf et al. (2008), where the experience of tension was examined in different patient groups and healthy controls. 2. There are only minor informations about the assessment of the diagnose AN and other diagnoses. Which standardized instruments are used from whom?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Comment 1: The idea of monitoring and in case of a relevant and clinical impairment of "aversive tension" in patients with anorexia nervosa, may be an interesting issue. However, there are some major methodological weaknesses of the present study protocol, which make conclusions from the collected data critical.

Response 1: We thank reviewer 1 for his time and the evaluation of our study manuscript and we hope that we can clarify and improve the further mentioned concerns regarding the methodology. We hope that you find our responses mentioned below satisfactory.

Comment 2: Why do the authors try to do several steps in one:
In a first step the authors should investigate the spectrum of eating disorders (ED) subdivided in clear subsamples of restrictive anorexia nervosa (AN), binge-purge AN, bulimia nervosa. In additional to this step1, I would advise concentrating on postpubertal ED.

Response 2: We agree with the reviewer that an investigation regarding the occurrence of aversive tension in different subsamples of eating disorders is an interesting topic. However, regarding ED besides restrictive Anorexia nervosa, theoretical framework on the occurrence of aversive tension is lacking. As Haynos and Fruzetti [12] proposed a model of emotion dysregulation in patients with AN only and not for other ED, we focused this study on patients with AN only. Nevertheless, investigating aversive tension in other ED seems an interesting research topic for further studies and we address this in the discussion section of the manuscript:
“After this trial has been successfully conducted and if a difference in the experience of aversive tension of patients with AN compared to control participants has been observed, the relevance of aversive tension in other eating disorders could be examined […]”

Comment 3: The rationale for this step is, that thus far there is no good evidence that “aversive tension” per se is a key psychopathological construct for the spectrum of underweight, restrictive AN patients.

Response 3: We agree with the reviewer that there is yet no good evidence that aversive tension is important in patients with AN, as this was exactly the reason for conducting this study. Currently, DBT, which focuses on emotion regulation and aversive tension in treatment, is being adopted for the treatment of AN (e.g. [21]). Hence, with this study we want to clarify the validity of aversive tension in patients with AN as a core-construct for this disorder and DBT treatment.

Comment 4: In this first step I would suggest to apply for a cross-sectional diagnostic approach a long with a state of the art diagnostic procedure, applying general psychiatric and eating disorder by structured interviews to validate the relevance of this construct.
Response 4: In this comment, reviewer 1 addresses two issues. First, he mentions a cross-sectional diagnostic approach to validate aversive tension between all eating disorders. We addressed this comment already in response 2 and further investigate the existing evidence for AN and indirect evidence of therapeutic successful cases with DBT techniques in juvenile AN patients.

Second, he mentions the importance to use state of the art diagnostical procedures. Generally, in the medical centre the standard diagnostic procedure for the assessment of patients with eating disorders contains two semi-structured interviews. Based on these, the diagnoses are given. The chEDE (Hilbert, A. et al. Psychometric Evaluation of the Eating Disorder Examination Adapted for Children. Eur Eat Disorders Rev 2013;4,330-339) for ED diagnosis and the K-SADS-PL (Delmo, C et al. Kiddie-SADS - Present and Lifetime Version (K-SADS-PL): Deutsche Forschungsversion. University of Frankfurt, 2001) for the assessment of co-morbid disorders are often used tools both in research and

clinical treatment. We did not mention this before as this is our standard procedure. We clarified this in the manuscript and the table of inclusion criteria as followed:
“The diagnosis must be made by the outpatient clinic of the medical centre Rheinhessen-Fachklinik Mainz with the German version of the Eating Disorder Examination adapted for children (chEDE) [29], a structured interview for the assessment of eating disorders. Co-morbidity will be assessed with the German Kiddie-Sads-Present and Lifetime Version (K-SADS-PL), a reliable and valid semi-structured interview for the assessment of mental disorders.[30]”

Comment 5: If the first step proved evidence for aspects of “aversive tension” in specific subgroup of ED patients, I would concentrate of this subgroup of eating disorders. So far there is no proper evidence for a relevance of this construct for prediction of outcome or as a relevant target for treatment interventions in AN.

Response 5: It is true that there is yet evidence missing for the relevance of aversive tension in patients with AN. Nevertheless, DBT, focusing on emotion regulation and aversive tension has good effects in the therapy of patients with AN with and without additional BPD [21-23]. That is why we believe a naturalistic approach for the measurement of aversive tension is of particular interest especially for the treatment of AN with DBT techniques.

Comment 6: In a second step I would concentrate on clear defined situations to be monitored and measured (e.g. before and after defined meals in contrast to a defined relaxed state).

Response 6: Thank you for your recommendation. Indeed, we thought about using a more laboratory design for this study, additionally we discussed the assessment of the last meal before entering data as well. However, mainly due to two reasons we decided to use a more naturalistic setting:

First, there is yet no study conducted regarding the experience of aversive tension in patients with AN. Concentrating only on meal situations might result in clear effects but might miss out other situations in which patients with AN experience aversive tension. As we ask explicitly for events immediately before data entry, we hope that we can identify specific situations (and emotions) in which aversive tension is high. In a subsequent study, the recommended design might be used to test aversive tension (and maybe even the appliance of DBT techniques!) in defined situations compared to relaxed situations.

Second, we discussed asking explicitly for the last meal before data entry, as we indeed believe that meal situations go along with high aversive tension. However, because of the assumed participation burden and methodological reactivity (provoking patients with AN to think about their last food intake might increase tension itself) we go along with the naturalistic setting. We address this concern in the discussion section as followed:
“A possible trigger for aversive tension in patients with AN might be meal situations. We decided to not assess the last food intake, as this might cause aversive tension itself and therefore confound the data. Additionally, there is no literature on which situations or emotions could trigger aversive tension in patients with AN. Therefore, we decided to conduct a naturalistic trial.”

Furthermore we could assess this issue through specific analysis of answers with mentioned “meals” on the fourth question. As this is the first study investigating aversive tension in AN, we designed the study with a time-contingent rather than an event-based approach to assess a broad spectrum of evens and emotions which could possibly trigger aversive tension and not using a-priori assumptions.

Comment 7: I do trust in the technology part of the recording of data – however my advice for data analysing would be to concentrate on state of the art approaches (see e.g. Wild B, et al. A graphical vector autoregressive modeling approach to the analysis of electronic diary data. BMC Med Res

Methodol. 2010 Apr 1;10:28). It is a real challenge to proper deal with serial electronic diary data!

Response 7: It is true that there are analysis strategies which account for intraclass-correlations or lag-correlations of time series data, e.g. the proposed graphical vector method and mixed model approaches. There are mainly two reasons why we decided to analyse the data primarily regarding aggregated measures:

1. No general group differences between controls and patients with AN have yet been identified. This is the main concern of this study and aggregated measures are reliable and the most economic method to assess group differences.
2. There are yet no possible influencing factors identified. As aversive tension in patients with AN has never been assessed prior to this study, there is no literature on influencing factors which could be reliable included in the analysis. A subsequent analysis, if group differences were detected, should be conducted using mixed models or graphical vector analysis.

However, we mention the recommended method and other multi-level approaches in the discussion for further analysis:
“Regarding the statistical analysis, group comparisons of aggregated measures only permit analysis on one data level.[38] As in this study, we are primarily interested in a general group difference and not on interactions with other variables, standard group comparisons are the most economic statistical analysis regarding sample size and data structure requirements. However, if group differences appear to be significant, subsequent analyses using more advanced techniques, e.g. graphical vector analysis [39] or mixed model approaches [38] are recommended.”

Comment 8: A third step might be interesting in case the two initial steps proved to be relevant. Than a defined module tackling „aversive tension“ applying DBT-E techniques might be interesting to investigate in a clear RCT-defined approach.

Response 8: A RCT-approach regarding effects on DBT techniques seems very interesting. We mention this as a possible subsequent study in the discussion section:
“After this trial has been successfully conducted and if a difference in the experience of aversive tension of patients with AN compared to control participants has been observed, the relevance of aversive tension in other eating disorders could be examined and effects of DBT for patients with AN or adolescents patients in general on aversive tension could be investigated more thoroughly.”

Comment 9: In addition the inclusion criteria as defined are not sufficient – also due to safety aspects and potential medical confounder, somatic aspects e.g. weight, metabolic parameters, but also axis 2 diagnosis have to be assessed and a priori exclusion criteria had to be defined (BMI > 15kg/m2 – or a predefined weight percentile), being aware of the limitations of axis 2 diagnosis in prepubertal ED.

Response 9: Participants in the study are outpatients at the beginning of treatment. The treatment underlies the guidelines of AWMF (the German institution in the counsel for international organizations of medical sciences, CIOMS). Therefore, only patients above the third BMI-percentile receive treatment at the medical outpatient centre. This is clarified in the method section now.

The diagnosis of axis 2 disorders in adolescents is controversial, mainly because of the instability of personality traits in young adolescents and the lack of reliable and valid diagnostic tools for the assessment of axis 2 disorders in adolescence (cf. Westen et al. Personality Diagnoses in Adolescence: DSM-IV Axis II Diagnoses and an Empirically Derived Alternative. Am J Psychiatry 2003; 160:952–966), with the exception of the SKID-II, which on the other hand regarding its language and content is not recommended for under 18-year-olds. Therefore, we apply a rather strict exclusion criterion, namely excluding all participants with a (presumed) axis 2 disorder. We modified

this in the manuscript:
“Participants of the patient group will be excluded in case of or presumed diagnosis of a personality disorder. In case of a BMI under the third percentile, patients will be referred to inpatient treatment and will not be included in the study.”

Comment 10: I would advise to focus the study (see point 15) and to submit the study protocol after clarifying to a more eating disorder specific journal e.g. Journal of Eating Disorders (BMC open)
Due to the fact that it is a diagnostic study, a study published protocol in a broad spectrum journal like the BMJopen is of limited interest and relevance.

Response 10: We are aware that the topic of the study is of primary interest to researchers in the field of eating disorders. Nevertheless the presented approach may be generalizable for other medical problems. As the methodology, namely using the participants private smartphones, is a very innovative approach, we think this might be interesting to researchers in other medical fields, which we mentioned also in the discussion section:
“The principle of using the smartphone as a tool in therapy for promptly self-reflection has to be developed in further investigations. A transfer of the concept to further conditions and disorders is welcomed.”

Reviewer: 2

The paper addresses aversive tension in adolescents with anorexia nervosa, assessed via ambulatory monitoring in comparison to mentally healthy controls. It presents important findings confirming aversive tension is an important feature for clinical work with adolescents with anorexia nervosa. The methodology used in this study is very innovative especially using the subjects´ own smartphones. However, there are two features which are amenable for improvement:

Response: We sincerely appreciate the time spent in reviewing this manuscript and your advice to improve it. Please, see below our answers to your queries and comments. We hope that you find them satisfactory.

Comment 1: 1. The first item of the electronic questionnaire question does not ask for aversive tension question but for tension only. This fact does have important implications for the interpretation of the results and should be focused in the following paper. It is even questionable, if the term “aversive tension” can be used in the title and the whole study. It could be helpful to view the paper of Stiglmayr, Bischkopf et al. (2008), where the experience of tension was examined in different patient groups and healthy controls.

Response 1: Thank you for this important comment. We are aware that we indeed do not mention aversive tension explicitly in the questionnaire. In line with both available DBT manuals (Bohus and Wolf-Arehult, 2013, Interaktives Skillstraining für Borderline-Patienten and Fleischhaker, C., Sixt, B. & Schulz, E. 2011. DBT-A: Dialektisch-behaviorale Therapie für Jugendliche.), we wanted to keep a dialectical stance and not value the experienced tension. On the other hand, in the preparation of the participants the definition of aversive tension by the DBT-Manual is explained and examples as an anchor point of aversive tension are given. This is now clarified in the method section:

“Additionally, the participants will receive a short briefing regarding aversive tension. The participants will be advised that aversive tension is a state of unpleasant and high arousal which is only randomly accompanied by a specific emotion in line with the DBT manuals.[7, 25] They will be told that on a scale from 0 to 100, the range of 70 to 100 stands for high tension normally only experienced in traumatic situations. Furthermore, participants will be told to imagine two exemplary events and their respective range of aversive tension that could possibly be provoked by such events.”

Comment 2: 2. There are only minor informations about the assessment of the diagnose AN and other diagnoses. Which standardized instruments are used from whom?

Response 2: We clarified this lack of information and mentioned our standard diagnosic procedures in adolescent AN patients in the method section (cf. response 2 for reviewer 1).