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Enhancement of exposure therapy in participants with specific phobia: A randomized controlled trial comparing yohimbine, propranolol and placebo

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ABSTRACT

Background: Recent research indicates that pharmacological agents may enhance psychotherapeutic outcome. Yet, empirical results have not been conclusive with respect to two pharmacological agents, yohimbine hydrochloride (YOH) and propranolol. YOH is suggested to enhance emotional memory by elevating norepinephrine, whereas the β-adrenergic receptor antagonist propranolol might help better cope with feared situations by reducing accompanying bodily sensations.

Methods: In this controlled trial, fifty-six participants with specific phobia were randomly assigned to either 1) virtual reality exposure therapy (VRET) plus YOH, 2) VRET plus Propranolol, or 3) VRET plus placebo. Participants in all conditions received three sessions of VRET over a period of two weeks.

Results: We conducted 2 × 3 repeated measures MANOVA's. Results showed a significant effect for time, with partial eta squared ranging from ηp2 = 0.647 to ηp2 = 0.692, for specific phobia, yet no significant interaction effects were found.

Conclusion: No significant differences were found when VRET with YOH or a beta-blocker was compared to VRET with a non-active placebo. Implications for clinical practice and future research are discussed.

1. Introduction

A recent approach in anxiety research combines short acting medications with exposure therapy to enhance treatment outcome by augmenting extinction learning and by disrupting reconsolidation of fear memory (Holmes & Quirk, 2009; Hofmann, Fang, & Gutner, 2014; Hofmann, Mundy, & Curtiss, 2015; McGuire, Lewin, & Storch, 2014; Singewald, Schmuckemair, Whittle, Holmes, & Ressler, 2015). Yohimbine hydrochloride (YOH), an alpha-2 adrenergic receptor antagonist, is a cognitive enhancer, which can facilitate fear extinction (Holmes & Quirk, 2009) by stimulating central noradrenergic activity via blockade of the alpha-2 adrenergic autoreceptor (Charney, Woods, Goodman, & Heninger, 1987; Peskind et al., 1995). The role of the noradrenergic system in emotional memory is that of an indicator of stress and increased sympathetic nervous system activity (Van Stegeren, Rohleder, Everaerd, & Wolf, 2006). Experimental animal research has revealed that YOH can augment the process of extinction (e.g., Cain, Blouin, & Barad, 2004; Morris & Bouton, 2007). A few studies with healthy humans (e.g. O'Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999; Southwick, Davis, Horner, Cahill, Morgan, & Gold, 2002) indicate that YOH can enhance memory for emotionally arousing event processes. In a study by O'Carroll et al. (1999) the noradrenergic system was systematically stimulated or blocked to investigate the effects on memory. As expected, YOH significantly elevated and metoprolol, a selective β_1 blocker, reduced mean heart rate during exposure to emotional contents relative to placebo, thus confirming the pharmacological manipulation. One week later, participants who had taken YOH recalled significantly more slides and participants who had taken metoprolol recalled fewer slides relative to placebo. In contrast, Southwick et al. (2002) found no evidence that YOH enhanced memory for emotionally arousing slides. It is important to note, however, that O'Carroll et al. administered the drug prior to exposure while Southwick et al. administered the drug after exposure, possibly therefore the results were in contrast with the findings by O' Carrol and colleagues. Another study suggests that YOH may enhance the effects of exposure treatment (Powers, Smits, Otto, Sanders, & Emmelkamp 2009). In this placebo randomized controlled trial (RCT), exposure in vivo was combined with YOH (10.8 mg) or placebo among 24 participants with fear of enclosed spaces. Consistent with their prediction, the group that took YOH prior to exposure sessions showed significantly greater

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improvement in peak fear at the one-week follow-up behavioral assessment. However, participants in this study did not meet diagnostic criteria for specific phobia, which makes results difficult to generalize to clinical populations. In a more recent RCT with participants with a diagnosis of fear of flying, no additional benefits of YOH in combination with virtual reality exposure therapy (VRET) compared to placebo in combination with VRET could be demonstrated (Meyerbroeker, Powers, van Stegeren, & Emmelkamp, 2012). In contrast, in yet another RCT with participants with social anxiety disorder (Smits, Rosenfield, Davis, Julian, Handelsman, 2014) moderate support was found for YOH as a therapeutic augmentation strategy for exposure therapy. The augmenting benefits of YOH in combination with exposure therapy for patients with posttraumatic stress disorder (PTSD) have been demonstrated in reduced physical arousal after only one dosage of YOH (Tuerk et al., 2018), however, no positive augmentation effects were found regarding PTSD symptoms.

An alternative strategy to reduce anxiety during exposure treatment is by targeting the psychophysiological arousal with the administration of a β-adrenergic receptor antagonist (Propranolol), which makes anxiety during exposure more tolerable and might increase the chances of coping more successfully with the feared situation. In a pilot within-subjects case-series design (n = 4), propranolol was combined with one session of exposure in participants with social anxiety disorder (Morissette, Spiegel, & Barlow, 2008). A decrease of experienced anxiety was found on day two. However, results were not congruent on all measures. In an experimental study with participants with posttraumatic stress disorder (n = 19), participants received one session scripted mental imagery to their traumatic event combined with either 40 mg and 60 mg of propranolol or a non-active placebo pill (Brunet, Orr, Tremblay, Robertson, & Nader, 2008). After reactivation of the traumatic memory, propranolol reduced physiologic responding during subsequent mental imagery of the event, but there was no evidence for effects of propranolol on PTSD symptom severity. According to a recent meta-analysis further studies to support the evidence for the efficacy of propranolol in anxiety related conditions are sparse (Steenen, van Wijk, van der Heijden, Westrhenen, & de Lange, 2016).

VRET has in comparison to exposure in vivo the advantage of being able to control relevant aspects of the therapeutic virtual environment. Research has revealed strong support for the efficacy of VRET for fear of flying and acrophobia (e.g. Meyerbröker, 2014; Meyerbröker & Emmelkamp, 2010; Opris et al., 2012; Powers & Emmelkamp, 2008), with effects generalizing to daily life (Morina, Ijntema, Meyerbröker, & Emmelkamp, 2015). In the present study, we used VRET by means of conducting exposure therapy for participants with fear of flying and acrophobia. Our aim was to replicate and extend earlier findings by examining the effects of YOH and propranolol in participants with specific phobia by combining it with VRET and comparing both groups with a non-active placebo pill. To differentiate whether a lower dose in a previous study (Meyerbroeker et al., 2012) explained the difference between the study of Powers et al. (2009) and Smits et al. (2014) who did find significant differences in favor of YOH, dose used in this study was increased. While propranolol is often prescribed to reduce stress and anxiety symptoms in participants with anxiety disorders, there is hardly any research and clinical evidence to support the use of propranolol in anxiety treatment (Steenen et al., 2016). More specifically, we aimed to determine if YOH accelerates and further consolidates extinction learning during exposure and if propranolol reduces anxiety to more easily cope with the feared anxiety and thereby enhance exposure efficacy.

Firstly, we predicted an overall decrease in fear of flying and acrophobia in response to VRET. Secondly, we hypothesized that relative to placebo, participants in the YOH condition will show significantly greater reduction from pre-to-post improvements on anxiety-specific measures. Thirdly, we hypothesized that relative to placebo, participants in the propranolol condition will show greater overall reduction on anxiety specific measures. Therefore, participants with fear of flying or acrophobia were randomly allocated to one of the three treatment conditions: (1) VRET plus YOH (15 mg), (2) VRET plus propranolol (40 mg) or (3) VRET plus placebo. All participants received three exposure sessions within two weeks. A follow-up assessment took place three month after terminating therapy.

2. Methods

2.1. Sample and procedure

2.1.1. Sample

Inclusion criteria were meeting the DSM-IV-TR (Diagnostic Statistical Manual; American Psychiatric Association, 2004) criteria for specific phobia and age between 18 and 75 years. Exclusion criteria were the presence of any of the following (medical) condition pregnancy, seizure disorder, respiratory disorder, cardiovascular disease, hypertension, and if resting blood pressure was greater than 140 (systolic) or 105 (diastolic) mm. Further exclusion criteria were unstable dose of psychotropic medication, other current psychological treatment, a history of psychosis, bipolar disorder or severe depression as assessed with the Structured Clinical Interview for DSM-IV (SCID-I, First, Spitzer, Gibbon, & Williams, 1996). Besides free treatment, participants received 15 euro compensation in form of a gift card after completing the three-month follow-up. The study was registered with clinicaltrials.gov (NCT02007694) and all study procedures were approved by the Institutional Ethical Review Board.

2.1.2. Screening

Potential participants were contacted via the telephone. Subjects who were willing to participate were invited to fill in online questionnaires respectively the Acrophobia Questionnaire and the Flight Anxiety Situations Questionnaire (AQ, Cohen, 1977; Van Gerwen, Spinhoven, Van Dyck & Diekstra, 1999). The cut-off score used in this study for the FAS was 70 or above as in the validity study on clinical samples (Skolnick, Schare, Wyatt, & Tillman, 2012). The cut-off score for the AQ in this study was one standard deviation below the mean of an acrophobic sample. This was 45.45 for anxiety and for avoidance it was 8.67 (Steinman & Teachman, 2011). If they passed these clinically relevant cut-off scores, they were invited for an intake during which the diagnostic interview (Structured Clinical Interview for DSM-IV, Axis I; First et al., 1996) was administered. Additionally, self-report measures (e.g. fear of flying and acrophobia) and a self-report medical screening questionnaire were administered. Given that YOH and propranolol both work on heart rate frequency a baseline rating from heart rate was taken during intake and blood pressure was measured, to ensure no health risks of participants were taken.

2.1.3. Procedure

The study was conducted at the department of Clinical Psychology at the University of Amsterdam. Individuals with fear of flying and acrophobia were contacted from an existing wait-list from earlier clinical research projects. Additionally, the study was advertised on the project's website (www.vliegangstbehandeling.nl).

After signing an informed consent, participants were randomized to either: 1) Virtual Reality Exposure Therapy (VRET) in combination with YOH (15 mg); 2) VRET in combination with propranolol (40 mg) or 3) VRET in combination with a non-active placebo pill. Participants received a total of three treatment sessions, each session twice 25 min of virtual exposure therapy, over a period of two weeks scheduled, with a maximum amount of 150 min of exposure.

2.1.4. Post-treatment- and follow-up assessment

After treatment termination, participants completed anxiety measures, identical to those during the intake. After a period of three months' participants were invited to fill in the anxiety measures identical to those during intake and post-treatment.

Protocol:

2.1.5. Dosing and safety of yohimbine hydrochloride

YOH is approved for research purposes in The Netherlands (Inspectie voor Gezondheidszorg). However, YOH is currently not used for treatment or any medical or psychiatric conditions in the Netherlands. As such, the safety data presented are from the United States and the Food and Drug Administration. Yohimbine extract is available over the counter and YOH is also FDA approved for the treatment of erectile failure (Ernst & Pittler, 1998). The half-life of YOH is only 36 min. The safety and side-effects profiles of YOH are favourable with no serious adverse effects reported (Ernst & Pittler, 1998). Side-effects are reported similar to those of placebo (Vogt et al., 1997). Based on recent data from our research group (Powers et al., 2009; Meyerbroeker et al., 2012, which were approved by the ethical committee) it was expected that YOH would be well tolerated and no serious adverse effects were observed in the current trial.

2.1.6. Dosing and safety of propranolol

Propranolol is approved for research purposes in The Netherlands (Inspectie voor Gezondheidszorg). Propranolol is currently used to control hypertension and to treat migraine and is approved for these purposes. Dosage of propranolol for medical purposes ranges from 40 mg to 160 mg daily. The half-life of propranolol is $T_{1/2}$ = oral 3–6 h. Propranolol is also used to treat Social Anxiety Disorder in dose ranging from 10 to 40 mg (van Balkom, van Vliet, Emmelkamp, Bockting, Spijker, Hermens & Meeuwissen, 2013).

Propranolol was often used in our department for research purposes in healthy participants (e.g. Bos et al., 2012) with no serious side effects reported by a dose of 40 mg. In line with these findings, no serious adverse effects were expected in the current trial.

2.1.7. Treatment protocol

At the beginning of the therapy session, participants were administered a capsule commensurate with their treatment assignment (15 mg YOH, 40 mg propranolol or a non-active placebo). After the administration of their capsule, participants took place in a waiting room and could read papers or journals for 55 min. Exposure in the virtual environment started 60 min after taking the medication.

In the first session participants filled in questionnaires and were provided with the necessary instructions about an anxiety hierarchy and the general rationale of exposure. The fear-reducing effects of confrontation of fears were emphasized. Additionally, participants were made familiar with the virtual reality equipment. For each therapy session, participants were instructed to remain in the virtual flying/fear of heights environment for as long as possible with a maximum time of 25 min. Exposure to the anxiety provoking environments was according to an extensive protocol to maintain high standardisation and consisted of two blocks per session interrupted by a break of five minutes. The exposure duration per block was 25 min to prevent participants from motion sickness. After each therapy session, participants could rest and talk about the virtual experience with the study therapist. This conversation was not exposure processing related but concerned whether participants were able to see depth and if and how severely they had been affected by nausea. No homework assignments were given and between session exposure was not actively advised.

2.1.8. Therapists

Treatment was provided by doctoral students in clinical psychology. Therapists received an extensive training in the protocol and provided treatment under weekly supervision of an experienced CBT therapist (the second author). Anxiety during exposure treatment was monitored with subjective units of discomfort (SUDs).

2.1.9. Training assessors

Assessments were done by doctoral students who were in their last year clinical psychology and who profiled themselves with extracurricular activities in social field. Assessors received an extensive training in using the SCID-I and the first and second authors supervised all assessments.

2.1.10. Randomization

Randomization was completed by an independent researcher not involved in the study. To prevent not normal distribution of kind of anxiety across drug condition, two randomizations were done for each type of anxiety. Randomization was done by using a randomization block generator (http://www.randomization.com). With randomly permuted blocks, wherein participants were assigned to treatment in blocks to ensure that equal number of subjects have been assigned to each treatment, each time the number of subjects is a multiple of the block size. Participants, research assistants, therapists and researchers were blind to the participants' group assignments.

2.1.11. Statistical analyses

Prior to conducting the study, a power analysis was done using Cohen's Power primer (Cohen, 1992). Alpha was set at 0.05 and statistical power was set at 0.80. To generate a medium effect-size in a three groups design using an ANOVA, 52 participants were needed.

Outcome of the treatment was analyzed by using a General Linear Models repeated measures ANOVA on intent to treat sample. All further analyses were conducted using an alpha level of 0.05. Last observation carried forward was used to extrapolate missing data. Only intent-to-treat analyses are presented.

2.1.12. Computer equipment and virtual environments

The Virtual Reality Exposure equipment consisted of an Optilex 755 Intel C2D 2.66 GHz 1024 MByte computer with 128 Mb video memory. Dual monitor support generated the virtual environments. The used software and virtual environments were developed by CleVR ©. The virtual environments were projected stereographic into Sony HMD glasses (HMZ-T2′3D) further a Logitech surround sound system and a Guitammer Company 'Buttkicker' were used to provide auditive and tactile feedback. Tracking was done by the Ascension Flock of Birds.

The fear of flying environment was an aircraft wherein participants could take seat in different positions. This environment was supported by two real aircraft seats and part of an airplane fuselage, with windows. The aircraft chair vibrated during take-off, landing and during periods of turbulence via connected 'buttkicker'.

The acrophobia environment was a mall with seven floors, were participants could walk up the stairs or use an elevator to come to a certain floor. Participants could walk to the railing to look into the depth. Additionally, the floor on which participants were walking could be manipulated to be either a normal concrete floor, a screen were participants could look through to floors underneath them and a third option was a floor from glass so that participants could see every detail below them. The seventh floor was being more extra modulated so that participants did not have the other floors below them but could see directly through the glass the ground floor.

2.2. Assessment

2.2.1. Assessment and outcome measures

2.2.1.1. Clinician-Rated assessment instruments. Structured Clinical Interview for DSM-IV (SCID-I; First, Spitzer, Gibbon & Williams, 1996).

The Dutch version of the SCID-I (Groenestijn, Akkerhuis, Kupka, Schneider & Nolen, 1999) was used to investigate whether the participants met criteria for fear of flying or acrophobia and other psychiatric disorders. The SCID-I is a widely used diagnostic instrument for Axis I disorders (First, Spitzer, Gibbon & Williams, 1996) and has a good inter-rater reliability of axis I disorders (Lobbestael, Leurgans, & Arntz, 2011).

2.2.2. Primary outcome measures

2.2.2.1. The Flight Anxiety Modality Questionnaire (FAM).. The FAM (van Gerwen et al., 1999) is a commonly used 23-item self-report inventory designed to measure symptoms of fear of flying. The intensity of fear of flying is measured on a five-point-likert scale. The FAM is divided into two subscales: the Somatic Modality, which represents the physical symptoms, and the Cognitive Modality, which measures distressing cognitions. The internal consistency and concurrent validity of the FAM is good to excellent (Cronbach's alpha: 0.89).

2.2.2.2. The Flight Anxiety Situations Questionnaire (FAS). The FAS (Van Gerwen, Spinhove, Van Dyck & Diekstra, 1999) is a commonly used 32-item, self-report inventory designed to measure anxiety related to flying experienced in different situations. The FAS is divided into three subscales: the Anticipation scale, which represents situations before the actual flight, the In-flight scale, which refers to situations during a flight and the Generalized flight scale. The internal consistency and concurrent validity of the FAS is good to excellent (Cronbach's alpha ranging from 0.88 to 0.97).

2.2.2.3. The Attitude Towards Heights Questionnaire (ATHQ). The ATHQ (Abelson & Curtis, 1989) contains six questions assessing the attitude towards heights (range 0–60; Cronbach alpha 0.81).

The Acrophobia Questionnaire (AQ). The AQ (Cohen, 1977) is a 40-item self-report measure to assess anxiety in height situations. The AQ measures anxiety and avoidance behavior relative to height situations. Subject can express their fear on a scale ranging from 0 to 6, whereby 0 stands for "no fear at all" and 6 for "almost panic" (ranging from 0 to 120; Cronbach alpha ranging from 0.62 to 0.69).

2.2.3. Secondary outcome measures

The Depression Anxiety Stress Scale (DASS). The DASS (Lovibond & Lovibond, 1995) is a commonly used 42-item self-report measure that assesses level of depression, anxiety, and stress over the previous week. Each scale consists of 14 items (Cronbach's alpha ranging from 0.88 to 0.96; Brown, Chorpita, Korotitsch & Barlow, 1997).

2.2.4. Manipulation check

A questionnaire consisting of five questions concerning the medication and its possible effects was used to assess whether participants were aware of the drug condition. Participants were asked whether they had received YOH, propranolol or placebo and rated on a scale ranging from 0 (not sure at all) to 100 (definite) the extent in which they were certain to have guessed the right pill.

2.2.5. Treatment process measures

Weekly Anxiety Questionnaire (WAQ). The WAQ is a transdiagnostic anxiety questionnaire to rate severity of experienced specific anxiety. The WAQ was constructed for the purpose of this study to assess anxiety related to both fear of flying and fear of heights. It consists of 10 items that can be scored on a five-point Likert scale ranging from "not at all" to "permanently". An example of the acrophobia version is: "When I know that I have to be in a for me difficult height situation … I panic". An example of the fear of flying version is: "When I know that I have to travel with an airplane … I panic"

Cronbach's alpha during baseline assessment was good with $\alpha = 0.84$,. Bivariate correlations of the WAQ change scores from pre- to post-treatment were $r = 0.80$ for acrophobia change scores and $r = .73$ for fear of flying change scores.

3. Results

3.1. Participants

A total of 56 adult participants were included (see Fig. 1) in the study. Of all participants, n = 31 met the DSM-IV criteria (American Psychiatric Association, 2004) for fear of flying and n = 25 for acrophobia. Two participants refused treatment (n = 1 from fear of flying; n = 1 from acrophobia). Ten participants dropped out during treatment due to nausea (n = 7), adverse effects of YOH (n = 1) and expressing doubts about treatment efficacy (n = 2). All main analyses were run with the intent-to-treat data of 54 participants.

3.2. Demographic variables

The mean age of participants was 36.6 years (SD: 12.1) ranging from 19 to 65 years. No differences in age were found between drug conditions ($F(2/55) = 1.25$, $p = 0.88$). Slightly more participants were female (55%) and no differences in sex distribution between drug conditions were found ($\chi^2 = 1.373$, d.f. = 2, $p = 0.50$). The mean length of disorder was 17.08 years with a standard deviation of 11.67 years. Nine percent of participants reported previous treatment for their anxiety complaints.

3.3. Baseline equivalence of groups

One-way ANOVA's were used to compare pre-treatment measures between drug conditions. Results showed no significant differences between groups at baseline on different flight measures (FAM: $F(2/26) = 0.813$, $p = .45$; FAS: $F(2/30) = 0.1.121$, $p = .34$), nor on a scale for avoidance and anxiety in acrophobia (AQ-avoidance: $F(2/24) = 0.252$, $p = .78$; AQ-anxiety: $F(2/24) = 1.426$, $p = .26$. There were no significant differences between drug condition on the generic anxiety measure (WAQ: $F(2/50) = 0.813$, $p = .45$).

3.4. Mean and standard deviations

For means (M) and standard deviations (SD) of al main outcome measures and general anxiety and depression measures see Table 1.

3.5. Primary outcome

To compare the overall effect across drug conditions a 3 (drug condition) × 3 (time: pre- and post- and follow-up) general linear model mixed repeated-measures ANOVA was conducted on the main outcome measures (WAQ, AQ, ATHQ and FAS, FAM).

3.6. WAQ

According to Mauchly's test the assumption of sphericity was not met ($\chi^2(2) = 6.728$, $p = 0.035$) and therefore the degrees of freedom were adapted by Greenhouse- Geisser correction ($\varepsilon = 0.88$). Intent to treat analyses showed a significant main effect for time: [$F(2, 90.5) = 59.64$, $p < .001$, $\eta p^2 = 0.539$]. A significant groups effect was found: ($F(2/51) = 3.438$, $p = .04$, $\eta p^2 = 0.119$. Post-hoc analysis showed significant differences between YOH and Propranolol: $p = .03$ at posttreatment. No significant differences were found between placebo and YOH. No significant time-by-condition interaction was found: $F(4, 90.5) = 0.960$, $p = .426$, $\eta p^2 = 0.036$]. See Fig. 2 for changes over the whole group, repeated contrast analysis showed that within effects were found from pre- to posttreatment ($p < .01$) and from pretreatment to follow-up ($p < .01$), but not from posttreatment to follow-up for each condition. Within-group effect-sizes from pre to post and pre to follow up were calculated with Cohen's d for each drug condition separately (Placebo, pre-post: $d = 2.09$; pre-follow-up $d = 2.35$; YOH, pre-post: $d = 2.06$; pre-follow-up $d = 2.14$; Propranolol, pre-post: $d = 1.66$; pre-follow-up $d = 1.01$) and were all found to exceed Cohen's (1988) convention for a large effect ($d = .80$).

3.7. Fear of flying measures

Analyses with the fear of flying instruments showed a significant

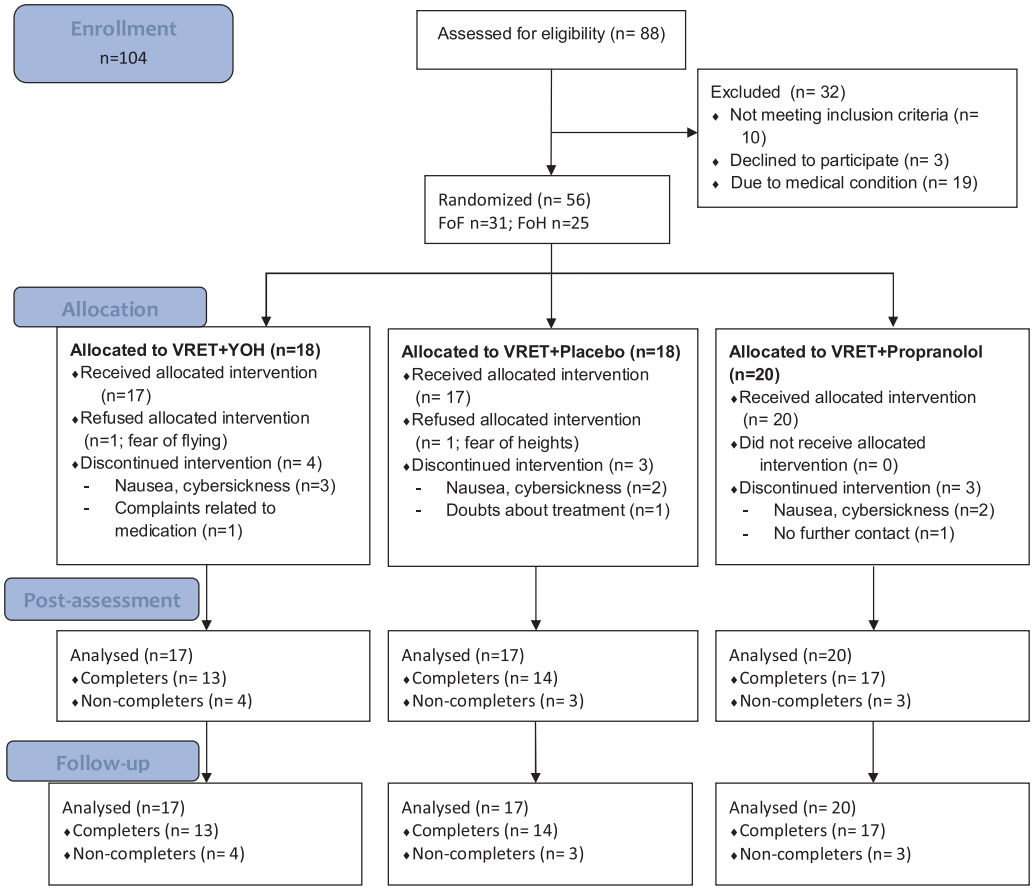

Fig. 1. Study design.

main effect for time on the FAM [$F(2, 54) = 18.915$, $p < .001$, $\eta p^2 = 0.412$]. No significant groups effect or time-by-condition interaction was found [Groups effect: $F(2, 27) = 1.127$, $p = .339$, $\eta p^2 = 0.077$; Interaction: $F(4, 54) = 0.478$, $p = .752$, $\eta p^2 = 0.034$]. Similarly, also on the FAS a significant main effect for time was found [$F(2, 42.51) = 15.676$, $p < .001$, $\eta p^2 = 0.367$]. According to Mauchly's test the assumption of sphericity was not met ($\chi^2(2) = 8.188$, $p = .017$) and therefore the degrees of freedom were adapted by Greenhouse- Geisser correction ($\varepsilon = 0.787$). No significant groups effect or time-by-condition interaction was found [Groups effect: $F(2, 27) = 2.702$, $p = .085$, $\eta p^2 = 0.167$; Interaction: $F(4, 42.51) = 0.211$, $p = .896$, $\eta p^2 = 0.015$]. See Fig. 3 for changes in fear of flying.

3.8. Acrophobia measures

Further analyses among participants with acrophobia showed a significant main effect for time on the AQ-Anxiety [$F(2, 42) = 33.99$, $p < .001$, $\eta p^2 = 0.618$]. No significant groups effect or time-by-condition interaction was found [Groups effect: $F(2, 21) = 0.938$, $p = .407$, $\eta p^2 = 0.082$; Interaction: $F(4, 42) = 2.011$, $p = .110$, $\eta p^2 = 0.161$]. Similarly, also on the AQ-Avoidance a significant main effect for time was found [$F(2, 29.74) = 34.436$, $p < .001$, $\eta p^2 = 0.621$]. According to Mauchly's test the assumption of sphericity was not met ($\chi^2(2) = 10.622$, $p = .005$) and therefore the degrees of freedom were adapted by Greenhouse- Geisser correction ($\varepsilon = 0.708$). No significant groups effect or time-by-condition interaction was found [Groups effect: $F(2, 21) = 0.874$, $p = .432$, $\eta p^2 = 0.077$; Interaction: $F(4, 29.74) = 1.286$, $p = .297$, $\eta p^2 = 0.109$]. Comparably, a significant main effect for time was also found on the ATHQ [$F(2, 42) = 36.592$, $p < .001$, $\eta p^2 = 0.635$]. No significant groups effect or time-by-condition interaction was found [Groups effect: $F(2, 21) = 0.124$, $p = .884$, $\eta p^2 = 0.012$; Interaction: $F(4, 42) = 1.179$, $p = .334$, $\eta p^2 = 0.101$]. See Fig. 4 for changes in acrophobia.

3.9. Anxiety during exposure

Anxiety during exposure was monitored with subjective units of discomfort (sud's). In Fig. 5 changes across sessions in peak sud's are presented.

3.10. Discriminant validity of the WAQ

As expected, none of the specific anxiety change scores of the self-constructed anxiety instrument (i.e., WAQ) correlated with more general anxiety and depression change scores (DASS; Lovibond & Lovibond, 1995;) bivariate correlations ranging from $r = 0.008$ to $r = -0.171$).

3.11. Reliable change index

Reliable Change index (RCI; Jacobson & Truax, 1991) was computed to register whether participants' symptoms changed sufficiently, so that change is unlikely to be due to simple measurement unreliability. To determine whether participants had changed reliably, the difference between the follow-up and initial scores on the WAQ was calculated The RCI for the WAQ was calculated according to the following formula:

$$RCI = \frac{x_1 - x_2}{2\,(s_1 1 - R_{xx})^2}$$

For each group, standard error of measurement, standard difference,

Table 1
Mean ($\bar{x}$) and standard deviation (SD) for placebo, YOH, and propranolol.

		Placebo	YOH	Propranolol	
		$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	
WAQ		n = 17	n = 17	n = 20	n = 54
	Pre	32.66 (6.56)	33.69 (4.85)	30.94 (9.56)	
	Post	19.16 (6.33)	23.30 (5.21)	18.11 (5.27)	
	3 month fu	18.08 (5.83)	23.69 (4.51)	20.82 (10.36)	
FAM					n = 30
	Pre	43.73 (12.76)	45.22 (6.63)	49.00 (15.62)	
	Post	29.18 (16.45)	37.89 (14.45)	35.70 (16.49)	
	3 month fu	22.09 (16.25)	28.67 (11.03)	33.40 (22.21)	
FAS					n = 30
	Pre	108.6 (12.59)	122.89 (11.45)	113.30 (23.40)	
	Post	88.55 (19.24)	105.44 (20.79)	85.90 (19.75)	
	3 month fu	85.45 (28.51)	98.44 (24.40)	84.10 (30.75)	
AQ-ANX					n = 24
	Pre	67.17 (15.62)	72.25 (8.63)	64.00 (8.65)	
	Post	46.67 (26.23)	46.12 (17.73)	31.20 (16.78)	
	3 month fu	31.00 (25.79)	45.50 (17.68)	42.30 (17.81)	
AQ-AVO					n = 24
	Pre	18.17 (5.11)	17.50 (4.87)	16.10 (3.66)	
	Post	7.17 (6.67)	9.13 (6.05)	5.40 (6.64)	
	3 month fu	3.67 (4.88)	9.00 (4.5)	8.10 (5.30)	
ATHQ					n = 24
	Pre	47.17 (8.66)	44.62 (5.97)	48.10 (5.04)	
	Post	30.17 (15.22)	31.50 (11.20)	28.30 (10.33)	
	3 month fu	24.83 (18.25)	32.00 (10.28)	32.10 (10.98)	

Note: WAQ: Weekly Anxiety Questionnaire; FAM: Flight Anxiety Modulations Questionnaire; FAS: Flight Anxiety Situations Questionnaire; AQ-ANX: Acrophobia Questionnaire, subscale anxiety; AQ-AVO: Acrophobia Questionnaire, subscale avoidance; ATHQ: Attitude towards heights questionnaire.

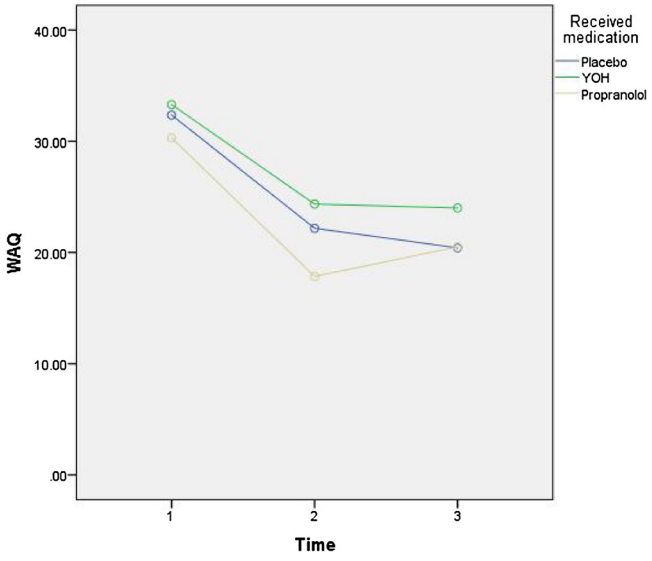

Fig. 2. WAQ changes over the whole group.

RCI and effect-sizes were calculated. RCI is a standardized measure with values bigger than 1.645 (Cronbach's $\alpha = 0.05$) indicating significant change in symptom reduction. For the placebo group the RCI was 14.58 with an effect-size of 2.22. For the YOH and propranolol group the RCI was respectively 10.0 and 10.12 and effect-sizes were 2.06 and 1.06 respectively.

3.12. Manipulation check

All participants were asked to guess which pill they thought they were taking throughout the study. From the participants who had taken placebo, 42.9% thought that they had received placebo, 50% thought that they had received propranolol and 7.1% thought that they had received YOH. Among the participants who had taken YOH, 37.5% thought that they received YOH, 43.8% thought that they had received propranolol and 18.8% thought that they had received placebo. From the participants who had taken propranolol, 45% thought that they had received propranolol, 40% thought that they had received placebo and 15% thought that they had received YOH.

4. Discussion

The aim of this study was to investigate the relationship between YOH and propranolol and their effects on increasing the effect of exposure therapy in reducing symptoms of specific phobia. To this end, both conditions were contrasted with a third condition who received non-active placebo in combination with exposure therapy. Consistent with the first hypothesis, participants with fear of flying and acrophobia improved significantly on anxiety specific measures independent of drug condition, which is in line with previous research (e.g. Powers & Emmelkamp, 2008; Opris et al., 2012). Contrary to our hypothesis, participants in the YOH condition did not report greater improvement after treatment relative to the placebo condition, which is in contrast to the findings of previous research (e.g. Powers et al., 2009; Smits et al., 2014, Tuerk et al., 2018). Contrary to our last hypothesis, it was found that participants in the propranolol condition did not show significantly greater overall reduction of anxiety symptoms than participants in the YOH condition or the non-active placebo condition.

Anxiety specific measures (AQ, ATHQ and FAS, FAM) were consistent with the findings of results on the WAQ. Effect-sizes across measures varied for pre-treatment to post-assessment between $\eta p^2 = 0.539$ and $\eta p^2 = 0.635$, indicating robust findings consistent with effect-sizes found in efficacy research about VRET in specific phobias (Meyerbröker, 2014). Although the fear of flying scores were higher than mean scores of non-phobic populations (Skolnick et al., 2012) at follow-up, reliable change was found to be significant. In line with our expectation, we found that participants in the propranolol condition improved significantly from pre- to post- assessment. Although, in comparison with the other drug conditions (placebo and YOH) we found a slight return of symptoms at three-month follow-up. This might indicate that beta-blockers may support participants by getting through or engaging in exposure, but that arousal level might be insufficient to make it successful exposure. We found a significant difference between conditions (YOH) and propranolol at post-assessment, however, this was not found in a time × drug interaction effect. A further decrease of anxiety from post-treatment to follow-up assessment was found in the placebo condition while a contrary development was found in the propranolol condition. This relevant finding should be investigated in future research because – if replicated – it might indicate a contra-indication for combining exposure therapy and propranolol in long term. In participants with acrophobia, it was observed that anxiety increased from posttreatment to follow-up, yet not avoidance. We are not aware of existing publications on long-term follow-up data on the use of propranolol in participants during exposure therapy. The only existing data of propranolol used during exposure generated inconsistent results in participants with social anxiety disorder (Morissette, Spiegel & Barlow, 2008). A possible explanation for the increased anxiety scores from post-treatment to follow-up in the propranolol group

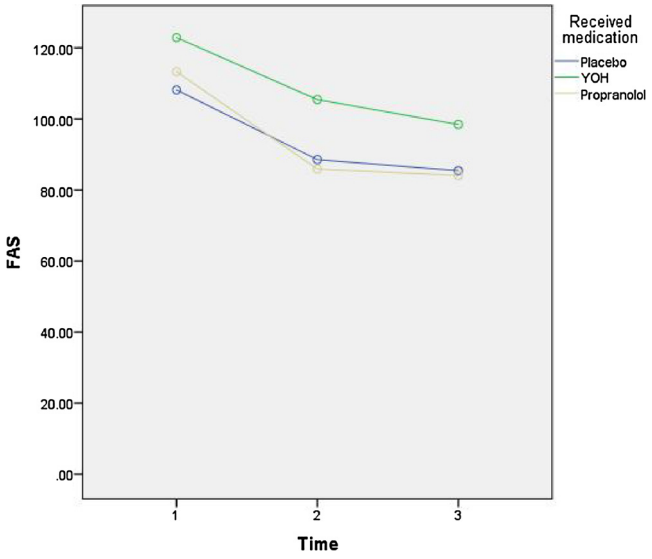

Fig. 3. changes in fear of flying across conditions.

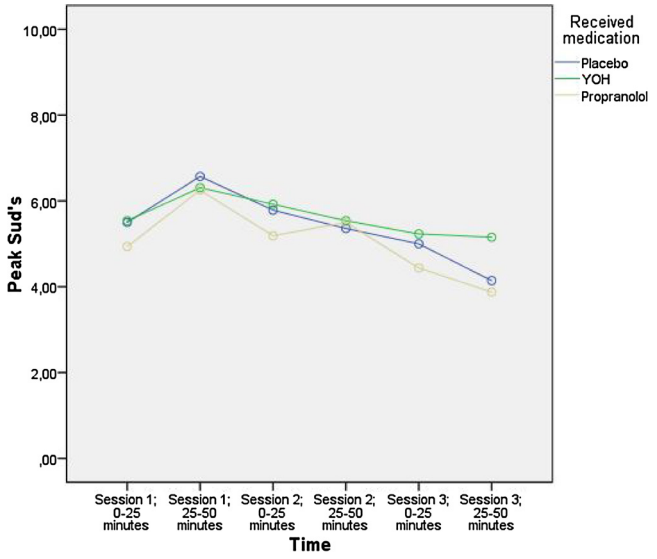

Fig. 5. Peak SUD's across conditions and sessions.

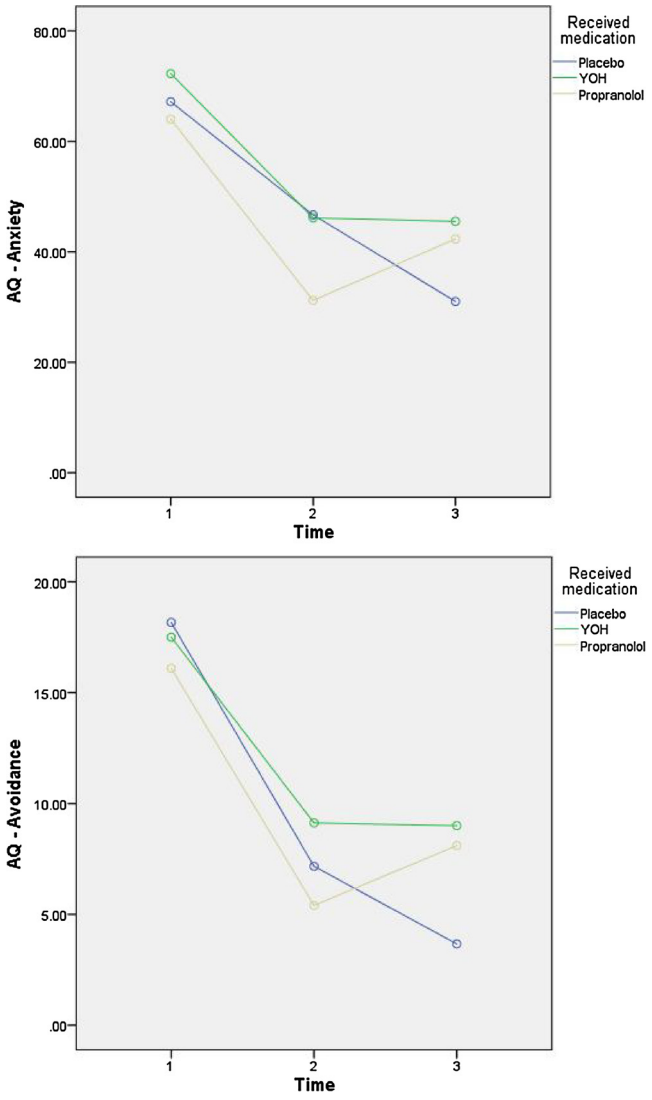

Fig. 4. changes in acrophobia across the conditions.

is that propranolol might be perceived as a form of safety behavior, which is known to interfere with cognitive behavioral therapy outcome as it is protecting them from feared catastrophe (e.g. Powers, Smits & Telch, 2004; Salkovskis, Clark, & Gelder, 1996). Another explanation is that anxiety had been suppressed during exposure by propranolol and therefore the learning experience has not been profound enough to generalize to future situations (follow-up).

The findings that YOH does not facilitate fear reduction in participants with pathological anxiety is in line with our earlier findings (Meyerbroeker et al., 2012). The pre- vs. follow up effect-sizes in the YOH and placebo group on all measures indicated improvements of over two standard deviations, which are considered large effects (Cohen, 1988). This might be an indication that a possible ceiling effect of exposure (Kazdin, 2008) might explain the lack of any positive augmentation effect in this study. On the other hand, the symptom scores at post-treatment still left sufficient room for improvement. Additionally, it cannot be ruled out that the dosage of YOH was too low to find even stronger effects. However, that is in contrast to recent findings in patients with PTSD, where reduced physical arousal was found after only one session of YOH augmented imaginal exposure (Tuerk et al., 2018). Our results contradict findings with subclinical samples (Powers et al., 2009; Smits et al., 2014) and suggests that given that findings of recent research wherein traumatized patients only after one-time dose improved on heart-rate variability (Tuerk et al., 2018), the multiple administration of YOH in the current study could have diminished effects. A plausible alternative explanation that our results are not in line with experimental research with YOH is that pathological fear has a different working mechanism than conditioned fear (Southwick et al., 2002) or fear in subclinical populations (Powers et al., 2009). Pathological anxiety might be more complex in its development and maintenance than fear conditioned in a classical learning paradigm and might therefore respond differently than expected according to experimental research. However, compared to animal research (e.g. Cain, Blouin & Barad, 2004) the dosage used in our study was still low to make possible nausea during virtual reality treatment manageable for the participant. Findings were stable at three months' follow-up, but varied across conditions with the placebo condition revealing strongest effects. Another plausible alternative explanation for not finding the expected effects could be due to different peak plasma levels of YOH (around 45–60 min after administration) and propranolol (around 60–120 min after administration). Therefore, in the YOH condition the optimal time window was earlier and shorter than for the propranolol condition.

In an earlier study, it was found that attribution of improvements achieved with combined exposure-based and pharmacological treatments for anxiety disorders could be influenced by instructions and as a consequence attribution of participants (Powers, Smits, Whitley, Bystritsky, & Telch, 2008). Given that in our study only a minority of participants in each condition were able to correctly guess which medication they had received, this attributional effect should be minimalized, but cannot be completely excluded. Although, it was thought that the extent to that the placebo pill causes an underestimation of standard treatment gains and that the observed effect of pharmacological enhancers brings an overestimation of their actual clinical value (Vervliet, 2009), this seems not to be true for our study.

The study has some formal limitations. Due to the combination of two different forms of specific phobias, we constructed an instrument (the WAQ) that can be applied among both groups of participants to increase statistical power. Although internal consistency of the WAQ was good and correlated highly with anxiety specific main outcome measures, other psychometric features of the instrument have not been assessed yet. Another limitation of our current study is the relatively high percentage of drop-out (18.5%). In comparison with earlier studies (e.g., Meyerbroeker et al., 2012), a higher than usual number of participants complained about nausea. A possible explanation could be that one of the side-effects of YOH is nausea, which in combination with anxiety and possibly simulator sickness can be more than participants could tolerate. Another explanation is that we used highly developed virtual reality environments with high resolution, which might increase the chances of simulator sickness/nausea.

In summary, our analyses showed that VRET was effective in treating fear of flying and fear of heights. However, participants receiving YOH and propranolol did not report higher treatment gains than participants in the placebo conditions at follow-up. In fact, participants in the placebo group profited most at three months' follow-up. Participants in the propranolol group presented more anxiety symptoms at follow-up than at post-assessment. Participants in the YOH group experienced less symptom reduction across post-test and follow-up and post-hoc tests showed that there was a significant difference between the propranolol group and the YOH on generic anxiety measures. Overall, our findings do not support the use of YOH or propranolol in enhancing exposure therapy with the present doses, present dose timing and present exposure lengths.

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References

Abelson, J. L., & Curtis, G. C. (1989). Cardiac and neuroendocrine responses to exposure therapy in height phobics: Desynchrony within the 'physiological response system'. *Behaviour Research and Therapy, 27*(5), 561–567.

American Psychiatric Association (2004). *Diagnostic and statistical manual of mental disorders* (4 ed.). Washington: American Psychiatric Association [text rev (DSM-IV-TR)].

Bos, M. G. N., Beckers, T., & Kindt, M. (2012). The effects of noradrenergic blockade on extinction in humans. *Biological Psychology, 89*, 598–605.

Brown, T. A., Chorpita, B. F., Korotitsch, W., & Barlow, D. H. (1997). Psychometric properties of the depression anxiety stress scale (DASS) in clinical samples. *Behavior Research Therapy, 35*, 79–89.

Brunet, A., Orr, S. P., Tremblay, J., Robertson, K., Nader, K., & Pitman, R. K. (2008). Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *Journal of Psychiatric Research, 42*, 503–506.

Cain, C. K., Blouin, A. M., & Barad, M. (2004). Adrenergic transmission facilitates extinction of conditional fear in mice. *Learning Memory, 11*, 179–187.

Charney, D. S., Woods, S. W., Goodman, W. K., & Heninger, G. R. (1987). Neurobiological mechanisms of panic anxiety: Biochemical and behavioral correlates of yohimbine-induced panic attacks. *American Journal of Psychiatry, 144*, 1030–1036.

Cohen, D. C. (1977). Comparison of self-report and overt-behavioral procedures for assessing acrophobia. *Behaviour Therapy, 8*, 17–23.

Cohen, J. W. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*, 155–159.

Ernst, E., & Pittler, E. E. (1998). Yohimbine for erectile dysfunction: A systematic review and meta-analysis of randomized controlled trials. *Journal of Urulogy, 159*, 433–436.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1996). *Structured clinical interview for DSM-IV axis I disorders.* Washington D.C: American Psychiatric Association.

Groenestijn, M. A. C., Akkerhuis, G. W., Kupka, R. W., Schneider, N., & Nolen, W. A. (1999). *Structured clinical interview for DSM-IV axis I disorders dutch translation by van lisse.* The Netherlands: Swets and Zeitlinger B.V.

Hofmann, S. G., Fang, A., & Gutner, C. A. (2014). Cognitive enhancers for the treatment of anxiety disorders. *Restorative Neurology and Neuroscience, 32*, 183–195.

Hofmann, S. G., Mundy, E. A., & Curtiss, J. (2015). Neuroenhancement of exposure therapy in anxiety disorders. *AIMS Neuroscience, 2*, 123–138.

Holmes, A., & Quirk, G. J. (2009). Pharmacological facilitation of fear extinction and the search for adjunct treatments for anxiety disorders – the case of yohimbine. *Trends in Pharmacological Science, 31*, 2–7.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to denning meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology, 59*, 12–19.

Kazdin, A. E. (2008). Understanding how and why psychotherapy leads to change. *Psychotherapy Research, 19*, 418–428.

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the structured clinical interview for DSM-IV axis I disorders (SCID I) and axis II disorders (SCID II). *Clinical Psychology and Psychotherapy, 18*, 75–79.

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the depression anxiety stress scales (DASS) with the beck depression and anxiety inventories. *Behaviour Research and Therapy: An International Multi-disciplinary Journal, 33*, 335–344.

McGuire, J. F., Lewin, A. B., & Storch, E. A. (2014). Enhancing exposure therapy for anxiety disorders, obsessive compulsive disorder, and posttraumatic stress disorder. *Expert Review of Neurotherapeutics, 14*, 893–910.

Meyerbröker, K., & Emmelkamp, P. M. G. (2010). Virtual reality exposure therapy in anxiety disorders: A systematic review of process- and outcome studies. *Depression and Anxiety, 0*, 1–12.

Meyerbröker, K. (2014). Virtual reality exposure. In P. M. G. Emmelkamp, & T. Ehring (Vol. Eds.), *The wiley handbook of anxiety disorders: Vol. II*, (pp. 1310–1324). Oxford: Blackwell-Wiley.

Meyerbroeker, K., Powers, M. B., Van Stegeren, A., & Emmelkamp, P. M. G. (2012). Does Yohimbine hydrochloride facilitate fear extinction in virtual reality treatment of fear of flying? A randomized placebo-controlled trial. *Psychotherapy & Psychosomatics, 81*, 29–37.

Morina, N., Ijntema, H., Meyerbröker, K., & Emmelkamp, P. M. G. (2015). Can virtual reality exposure therapy gains be generalized to real life? A meta-analysis of studies applying behavioral assessments. *Behaviour Research and Therapy, 74*, 18–24.

Morissette, S. B., Spiegel, D. A., & Barlow, D. H. (2008). Combining exposure and pharmacotherapy in the treatment of social anxiety disorder: A preliminary study of state dependent learning. *Journal of Psychopathological Behavior Assessment, 30*, 211–219.

Morris, R. W., & Bouton, M. E. (2007). The effect of yohimbine on the extinction of conditioned fear: A role for context. *Behavioral Neuroscience, 121*, 501–514.

O'Carroll, R. E., Drysdale, E., Cahill, L., Shajahan, P., & Ebmeier, K. P. (1999). Stimulation of the noradrenergic system enhances and blockade reduces memory for emotional material in man. *Psychological Medicine, 29*, 1083–1088.

Opris, D., Pintea, S., García-Palacios, A., Botella, A., Szamosközi, S., & David, D. (2012). Virtual reality exposure therapy in anxiety disorders: A quantitative meta-analysis. *Depression and Anxiety, 29*, 85–93.

Peskind, E. R., Wingerson, D., Murray, S., Pascually, M., Dobie, D. J., Le Corre, P., et al. (1995). Effects of Alzheimer's disease and normal aging on cerebrospinal fluid norepinephrine responses to yohimbine and clonidine. *Archives of General Psychiatry, 52*, 774–782.

Powers, M., & Emmelkamp, P. M. G. (2008). Virtual reality exposure therapy for anxiety disorders: A meta-analysis. *Journal of Anxiety Disorders, 22*, 561–569.

Powers, M. B., Smits, J. A., & Telch, M. J. (2004). Disentangling the effects of safety-behavior utilization and safety-behavior availability during exposure-based treatment: A placebo- controlled trial. *Journal of Consulting and Clinical Psychology, 72*, 448–454.

Powers, M. B., Smits, J. A. J., Whitley, D., Bystritsky, A., & Telch, M. J. (2008). The effect of attributional processes concerning medication taking on return of fear. *Journal of Consulting and Clinical Psychology, 76*, 478–490.

Powers, M. B., Smits, J. A. J., Otto, M. W., Sanders, C., & Emmelkamp, P. M. G. (2009). Facilitation of fear extinction in phobic participants with a novel cognitive enhancer: A randomized placebo controlled trial of yohimbine augmentation. *Journal of Anxiety Disorders, 23*, 350–356.

Salkovskis, P. M., Clark, D. M., & Gelder, M. G. (1996). Cognitive behaviour links in the persistence of panic. *Behaviour Research and Therapy, 34*, 453–458.

Singewald, N., Schmuckemair, C., Whittle, N., Holmes, A., & Ressler, K. J. (2015). Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacological Therapy, 149*, 159–190.

Skolnick, R. B., Schare, M. L., Wyatt, K. P., & Tillman, M. A. (2012). Aviophobia

assessment: Validating the Flight Anxiety Situations Questionnaire as a clinical identification measure. *Journal of Anxiety Disorders, 26*, 779–784.
Smits, J. A., Rosenfield, D., Davis, M. L., et al. (2014). Yohimbine enhancement of exposure therapy for social anxiety disorder: A randomized controlled trial. *Biological Psychiatry, 75*, 840–846.
Southwick, S. M., Davis, M., Horner, B., Cahill, L., Morgan, C. A., Gold, P. E., et al. (2002). Relationship of enhanced norepinephrine activity during memory consolidation to enhanced long-term memory in humans. *American Journal of Psychiatry, 159*, 1420–1422.
Steenen, S. A., van Wijk, A. J., van der Heijden, G. J., Westrhenen, R., de Lange, J., & de Jongh, A. (2016). Propranolol for the treatment of anxiety disorders: Systematic review and meta-analysis. *Journal of Psychopharmacology, 30*, 128–139.
Steinman, S. A., & Teachman, B. A. (2011). Cognitive processing and acrophobia: Validating the heights interpretation questionnaire. *Journal of Anxiety Disorders, 25*, 896–902.
Tuerk, P. W., Wangelin, B. C., Powers, M. B., Smits, J. A., Acierno, R., Myers, U. S., et al. (2018). Augmenting treatment efficiency in exposure therapy for PTSD: A randomized double-blind placebo-controlled trial of yohimbine HCl. *Cognitive Behavior Therapy*, 1–21. http://dx.doi.org/10.1080/16506073.2018.1432679.
van Balkom, A. L. J. M., van Vliet, I. M., Emmelkamp, P. M. G., Bockting, C. L. H., Spijker, J., Hermens, M. L. M., et al. (2013). *Multidisciplinaire richtlijn Angststoornissen (Derde revisie). Richtlijn voor de diagnostiek, behandeling en begeleiding van volwassen patiënten met een angststoornis.* Utrecht: Trimbos-instituut namens de Werkgroep Multidisciplinaire richtlijnontwikkeling Angststoornissen/Depressie.
van Gerwen, L. J., Spinhoven, P., Van Dyck, R., & Diekstra, R. F. W. (1999). Construction and Psychometric Characteristics of two self-report questionnaires fort he assessment of fear of flying. *Psychological Assessment, 11*, 146–158.
van Stegeren, A. H., Rohleder, N., Everaerd, W., & Wolf, O. T. (2006). Salivary alpha amylase as maerker for adrenergic activity during stress: Effect of betablockade. *Psychoneuroendocrinology, 31*, 137–141.
Vervliet, B. (2009). Pharmacological enhancers of psychotherapeutical processes: The placebo problem. *Journal of Psychopharmacology, 23*, 602.
Vogt, H. J., Brandl, P., Kockott, G., Schmitz, J. R., Wiegang, M. H., Schadrack, J., et al. (1997). Double-blind, placebo-controlled safety and efficacy trial with yohimbine hydrochloride in the treatment of nonorganic erectile dysfunction. *International Journal of Impotency Research, 9*, 155–161.