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RESEARCH ARTICLE

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Efficacy of temporally intensified exposure for anxiety disorders: A multicenter randomized clinical trial

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Abstract

Background: The need to optimize exposure treatments for anxiety disorders may be addressed by temporally intensified exposure sessions. Effects on symptom reduction and public health benefits should be examined across different anxiety disorders with comorbid conditions.

Trial registration: NIMH Protocol Registration System (01EE1402A), German Register of Clinical Studies (DRKS00008743).

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Methods: This multicenter randomized controlled trial compared two variants of prediction error-based exposure therapy (*PeEx*) in various anxiety disorders (both 12 sessions + 2 booster sessions, 100 min/session): temporally intensified exposure (*PeEx-I*) with exposure sessions condensed to 2 weeks ($n = 358$) and standard nonintensified exposure (*PeEx-S*) with weekly exposure sessions ($n = 368$). Primary outcomes were anxiety symptoms (pre, post, and 6-months follow-up). Secondary outcomes were global severity (across sessions), quality of life, disability days, and comorbid depression.

Results: Both treatments resulted in substantial improvements at post (PeEx-I: $d_{within} = 1.50$, PeEx-S: $d_{within} = 1.78$) and follow-up (PeEx-I: $d_{within} = 2.34$; PeEx-S: $d_{within} = 2.03$). Both groups showed formally equivalent symptom reduction at post and follow-up. However, time until response during treatment was 32% shorter in PeEx-I (median = 68 days) than PeEx-S (108 days; $TR_{PeEx-I} = 0.68$). Interestingly, drop-out rates were lower during intensified exposure. PeEx-I was also superior in reducing disability days and improving quality of life at follow-up without increasing relapse.

Conclusions: Both treatment variants focusing on the transdiagnostic exposure-based violation of threat beliefs were effective in reducing symptom severity and disability in severe anxiety disorders. Temporally intensified exposure resulted in faster treatment response with substantial public health benefits and lower drop-out during the exposure phase, without higher relapse. Clinicians can expect better or at least comparable outcomes when delivering exposure in a temporally intensified manner.

KEYWORDS
anxiety disorders, exposure therapy, intensified treatment, public health, randomized controlled trial

1 | INTRODUCTION

Exposure-based cognitive-behavioral therapy (exposure-CBT) has consistently shown large effect sizes and persistent improvement after treatment for various anxiety disorders (AD) (Carpenter et al., 2018; Gloster et al., 2011, 2013; Hofmann & Smits, 2008; Loerinc et al., 2015). Moreover, exposure-CBT typically yields higher effect sizes than CBT without exposure (Carpenter et al., 2018). Benefits of exposure-CBT extend from anxiety-specific effects to improvements on global severity, disability, and comorbid depression (Emmrich et al., 2012). Still, a substantial number of patients does not fully benefit (Carpenter et al., 2018; Loerinc et al., 2015) and treatments typically take several months or even years (Hoyer et al., 2017; Leichsenring et al., 2013). Hence, there is a need to optimize treatments towards faster and more persistent improvement (Craske et al., 2014; Richter et al., 2017).

Exposure sessions are the core ingredients of exposure-CBT. Temporally intensified exposure, that is, shorter time intervals between exposure sessions, may be a promising strategy to further increase treatment outcome and particularly, to accelerate treatment response at the same time. Increasing treatment outcomes may be achieved by optimizing core learning processes of exposure (Craske et al., 2014; Pittig et al., 2016). In contrast to traditional habituation-based models, which emphasize fear reduction within and between exposure sessions (Foa & Kozak, 1986; Mathews, 1978), extinction learning models emphasize prediction error-based inhibitory learning (Bouton, 2002, 2004; Craske et al., 2008; Pittig et al., 2016). In an extinction framework, repetitive exposure to a feared stimulus (CS) in the absence of threat (US) violates threat expectancies, thus inducing a prediction error (Rescorla & Wagner, 1972). As a result, an inhibitory association is formed in memory (CS-NoUS) and competes with the original excitatory fear memory (CS-US) for expression of the fear response. The inhibitory memory is gated by the context in which it is generated, leading to contextual specificity (Bouton, 2002, 2004; Craske et al., 2018). Accordingly, exposure can be tailored to optimize prediction error learning: while habituation-based exposure aims to establish initial fear

activation and within- and between-session fear reduction, prediction error-based exposure aims to maximally violate a patient's individual threat expectancy irrespective of the course of fear and anxiety (Boschen et al., 2009; Craske et al., 2018; Pittig et al., 2016). Efficacy of prediction error-based exposure is empirical supported (Craske & Treanor, 2015; Craske et al., 2014, 2019; Deacon et al., 2013). Yet, it is unclear whether specific strategies may boost treatment outcome. The temporal spacing of exposure sessions is one such strategy. Shorter intervals between initial exposure sessions followed by the lengthier spacing between subsequent sessions, designed to strengthen prediction error learning and reduce temporal context specificity, have shown to facilitate long-term symptom reduction in analog clinical studies (Rowe & Craske, 1998; Tsao & Craske, 2000). However, clinical evidence that shorter intervals between exposure sessions at the beginning of treatment are feasible and beneficial across different types of AD is lacking (Craske et al., 2008; Foa et al., 2018).

Importantly, temporally intensified exposure sessions would inherently accelerate treatment response as shorter intervals between exposure sessions would imply shorter treatment duration. Shorter treatment duration, in turn, may enable faster treatment response, not in terms of number of sessions but days until treatment response. Such faster treatment response would constitute a significant public health benefit in terms of fewer sick days and days with severe impairments. However, temporally intensified treatments may also put a higher treatment burden on patients and thereby may result in higher drop-out rates. Again, comprehensive clinical evidence is missing.

Therefore, the present randomized clinical trial developed and tested an exposure-CBT manual that incorporates therapist-guided exposure accompanied by strategies to enhance extinction learning during exposure (see Heinig & Hummel, 2020; Heinig et al., 2017). We applied this exposure treatment to different ADs with and without comorbid disorders. Importantly, the temporal intensity of exposure sessions was manipulated, assuming that enhanced extinction learning is more likely to occur when exposure sessions are temporally intensified in the beginning of treatment. Patients randomized to the *temporally intensified exposure group (PeEx-I*[1]*)* received three exposure sessions per week. Patients randomized to the *standard non-intensified exposure group (PeEx-S)* received a content-identical treatment, however, the exposure sessions were scheduled only once per week.

We hypothesized that (1) patients in PeEx-I and PeEx-S would show significant symptom reduction at post and 6-month follow-up, (2) improvements in PeEx-I would be stronger and associated with more pervasive effects, and (3) improvements in PeEx-I would occur considerably faster than in PeEx-S, without increased rates of drop-out or relapse.

[1]In the trial registration and methods paper (Heinig et al., 2017), PeEx-I was called IPI and PeEx-S was called TAU, which was replaced to avoid misconception of the TAU group being a traditional treatment-as-usual condition.

2 | METHODS

The full study protocol is described elsewhere and was performed with no significant changes (Heinig et al., 2017). The RCT (12/2015 to 8/2019) involved ten psychological outpatient clinics throughout Germany. The study was registered (NIMH Protocol Registration System: 01EE1402A and German Register of Clinical Studies: DRKS00008743), approved by the TUD-Ethics Review Committee (EK 234062014, 11/14/2014), and performed according to the Declaration of Helsinki. All participants provided written informed consent. Supervision of data management according to GCP Guidelines was done by the Coordination Centre for Clinical Trials Dresden (KKS).

2.1 | Participants

Patients were eligible for inclusion if they met the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, APA., 2013) criteria for one of the following diagnoses: panic disorder, agoraphobia, social anxiety disorder, or multiple specific phobias. Inclusion criteria were (1) outpatient status, (2) age: 15–70 years, (3) current primary diagnosis of the stated anxiety disorders, (4) baseline severity of more than 18 points on the HAM-A (see below) and more than 3 points on the Clinical Global Impression scale (Guy, 1976), (5) written informed consent, (6) ability to attend sessions, and (7) language competence. Exclusion criteria were (1) any current DSM-5 psychotic or substance use disorder (except nicotine), (2) concomitant psychological or psychiatric treatment (psychopharmacological medication was allowed, if dosing was stable (for at least 3 months) and the medication was considered appropriate by the monitoring study clinician (AS)), (3) acute suicidality, (4) general medical contraindications, and (5) mono-symptomatic specific phobia. Thus, the study protocol allowed to include patients with multiple comorbid conditions typical for routine care (such as major depression) and did not require to take patients off medication before treatment if it was stable and considered appropriate. Randomization lists were generated for each study center with DatInf RandList 1.2. Patients were randomized by two members of the coordinating center (Dresden) not involved in patient care. One person kept the list of random numbers, another person kept the allocation of numbers to conditions. This ensured that no single person was able to foresee the allocation sequence.

Diagnoses, demographic variables, medication, and service use were assessed via the computer-assisted clinical version of the Composite International Diagnostic Interview (CIDI; Essau & Wittchen, 1993; Reed et al., 1998; Robins, 1988; Wittchen, 1994) followed by a standardized clinical evaluation for obtaining the primary treatment diagnosis by trained clinical personnel.

Patient flow is displayed in Figure 1. Clinical and sociodemographic characteristics are shown in Table 1. Clinically, patients can be characterized as severe: the mean disorder duration was more than 14 years, the majority reported previous treatments,

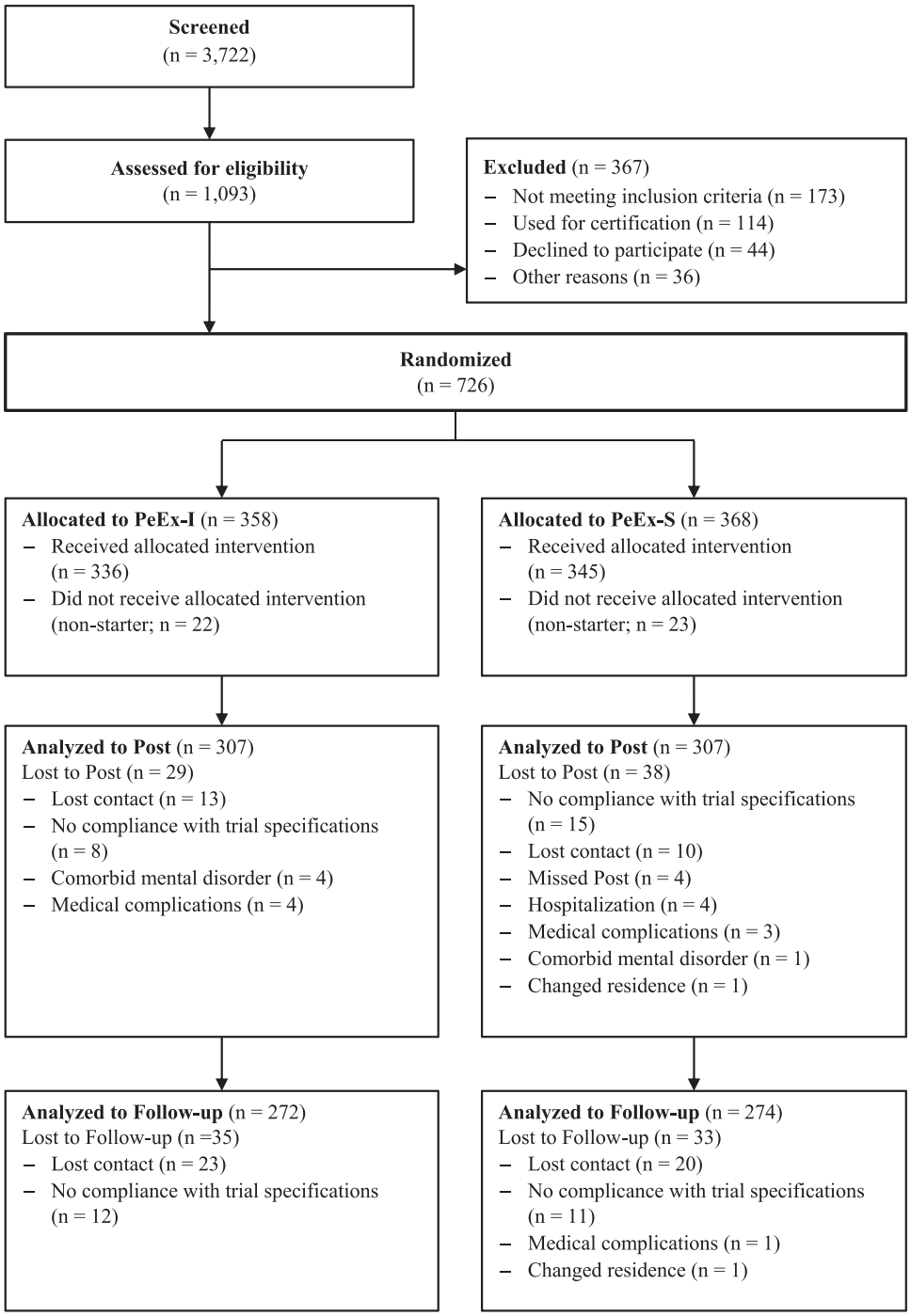

FIGURE 1 Flow chart diagram of participants

about 25% were on current stable psychotropic medication, and comorbidity was high.

2.2 | Treatment

Patients in both conditions received the same manualized treatment content of 12 treatment sessions (100 min each) plus two booster sessions 2 and 4 months after session 12 (Heinig et al., 2017). For all patients, Sessions 1–4 included psychoeducation, functional-behavioral analysis, identification of central threat beliefs and maladaptive anxiety control strategies (e.g., avoidance or safety behavior), and development of a disorder model and exposure rationale, accounting for differences in etiological pathways (Hamm, 2006; Lang et al., 2012; Stangier et al., 2003). The exposure rationale was explicitly based on the concept of prediction error learning, that is, on identifying and disconfirming patients' central threat beliefs (Craske et al., 2014; Pittig et al., 2016). In the subsequent exposure

TABLE 1 Sociodemographic and clinical characteristics

Characteristic	PeEx-I	PeEx-S	*p*
Age	32.72 (11.14)	34.1 (11.91)	.107
Men, *n* (%)	147 (41.06)	177 (48.1)	.067
Years of education (%)			.683
<8	1 (0.28)	1 (0.27)	
8–10	97 (27.09)	111 (30.16)	
11+	260 (72.63)	256 (69.57)	
Living alone, *n* (%)	156 (43.58)	161 (43.75)	.999
Employed, *n* (%)	291 (81.28)	292 (79.35)	.574
Socioeconomic status, *n* (%)			.433
Lower	95 (26.54)	109 (29.62)	
Middle	206 (57.54)	210 (57.07)	
Upper	56 (15.64)	47 (12.77)	
Primary anxiety diagnosis, *n* (%)			
Agoraphobia	18 (5.03)	24 (6.52)	.482
Agoraphobia with panic disorder	154 (43.02)	161 (43.75)	.901
Social phobias	107 (29.89)	112 (30.43)	.937
Specific phobias	37 (10.34)	37 (10.05)	.998
Panic disorder	42 (11.73)	34 (9.24)	.329
Age of onset of primary diagnosis	19.31 (10.78)	20.42 (11.76)	.228
Age of onset of first anxiety diagnosis	14.56 (10.54)	16.05 (10.83)	.073
Time between first onset and current trial	14.03 (10.86)	13.64 (12.39)	.682
Number of diagnoses[a]	3.96 (1.93)	3.92 (1.86)	.808
Comorbidities, *n* (%)			
Other anxiety disorders	263 (73.46)	256 (69.57)	.280
MDD/dysthymia	168 (46.93)	170 (46.20)	.902
PTSD	6 (1.68)	10 (2.72)	.482
OCD	39 (10.89)	49 (13.32)	.376
Others	79 (22.07)	91 (24.73)	.448
Number of previous treatments, *n* (%)			.485
0	159 (44.41)	153 (41.58)	
1	96 (26.82)	94 (25.54)	
2+	103 (28.77)	121 (32.88)	
Current stable medication, *n* (%)			
None	272 (76.84)	253 (70.28)	.057
Painkillers	17 (4.8)	19 (5.28)	.905
Sleep-inducing agents	1 (0.28)	13 (3.61)	.002**
Tranquilizers	10 (2.82)	13 (3.61)	.702
Stimulants	0 (0)	2 (0.56)	.499
Antidepressants	63 (17.8)	88 (24.44)	.037*

(Continues)

TABLE 1 (Continued)

Characteristic	PeEx-I	PeEx-S	*p*
Mood stabilizers	3 (0.85)	2 (0.56)	.684
Neuroleptics	2 (0.56)	5 (1.39)	.451

Note: Means (and standard deviation) or frequency (*n*, and %); *p* values determined with independent *t*-tests or Mann–Whitney-U-tests and χ^2-tests or exact Fisher-tests, as appropriate. PeEx-I temporally intensified prediction error-based exposure; PeEx-S standard non-intensified prediction error-based exposure.

[a]Including primary disorder.

$^*p < .05$; $^{**}p < .01$.

sessions (sessions 5–10), patients were introduced to the principles of exposure and the role of prediction error within an inhibitory learning framework, using first a set of standardized exercises tailored to each diagnosis (sessions 5–6; session 7 included interim evaluation and planning of further exposure) followed by individualized exercises (sessions 8–10). Using standardized records, patients and therapists monitored all exposure exercises within and between sessions by recording the targeted threat belief, exercise context, the prediction error, and strategies for enhancing inhibitory learning. For all patients, treatment included strategies to promote inhibitory learning (Craske et al., 2014; Heinig et al., 2017): therapists were trained to enhance inhibitory learning by maximizing "expectancy violations", using single and combined fear cues, preventing safety signals and behaviors, and varying the context of exercises. Sessions 11–12 focused on individual risk factors for relapse and assigning individual daily tasks for exposure in patients' everyday environment.

Importantly, PeEx-I and PeEx-S received a content-identical treatment but differed in the temporal spacing of exposure sessions: In PeEx-I, sessions 5–10 were delivered within 2 weeks, while patients received only one session per week in PeEx-S.

Therapists (and diagnosticians) were comprehensively trained and continuously supervised (see Online Supporting Information). Treatment integrity was evaluated by five independent raters blinded to treatment condition in a randomly selected sample of 350 video recordings stratified for sessions 1–14. Overall, treatment integrity was high, and therapist competence rating good (see Online Supporting Information for more details).

2.3 | Assessments

Sociodemographic and clinical characteristics were collected at baseline. Outcome variables were assessed at baseline (BL), posttreatment (POST), and 6-month follow-up (FU). Additionally, global severity was repeatedly assessed during the course of sessions (i.e., baseline, sessions 2, 4, 7, 10, 11, 12, post, booster sessions, and follow-up).

The primary outcome was the Hamilton Anxiety Rating Scale (HAM-A), assessed with the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) (Shear et al., 2001). The HAM-A measures a broad range of anxiety symptoms on a 5-point scale (*not present* to *very severe*) with high interrater and test-retest reliability (Shear et al., 2001). Treatment response was defined as more than or equal to 50% decrease in HAM-A score and remission was defined as HAMA-A score less than or equal to 7 (Matza et al., 2010). Relapse was defined as noncompliance with the response and remission criteria at follow-up in case those criteria were met at post assessment. Transdiagnostic secondary outcomes were global severity assessed with the Brief Symptom Inventory (BSI) (Derogatis & Melisaratos, 1983), quality of life assessed with the EuroQOL five-dimensional measure of health status (EQ. 5-D) (Rabin & Charro, 2001), the number of disability days in the past month assessed with the World Health Organization Disability Schedule (WHODAS 2.0) (Üstün et al., 2010), and comorbid symptoms of depression assessed with the Beck Depression Inventory (BDI-II) (Beck et al., 1996) (see Online Supporting Information detailed information).

2.4 | Statistical analyses

The sample size was estimated for a power of 80% and a one-tailed alpha level of 5% for the change on the HAM-A from baseline to posttreatment. Our study was powered to detect a difference of at least 2 points. An attrition rate of 10%–15% was assumed resulting in a targeted sample size of 720 patients (360 per group).

Main analyses focused on treatment efficacy within and between groups as well as time until treatment response. For efficacy, primary (HAM-A) and secondary outcomes (BSI, BDI, EQ-5D, and disability days) were analyzed with linear mixed models (LMM) using the lme4 package of R version 4.0.2. Effect sizes (ES) were reported as Cohen's *d* for continuous outcomes and as odds ratios (OR) for binary outcomes. To evaluate treatment effects on the continuous outcomes, we calculated 3-level linear mixed models with measurements nested in patients and patients nested in study centers (Bates, 2010). By using multilevel modeling, unbalanced data structure and missing data can be handled. Fixed effects included time and group factors, as well as their cross-level interaction. Coefficients were determined using restricted maximum likelihood estimation (REML) and used Satterthwaite approximations to calculate degrees of freedom. In addition, binary outcomes, that is, response, remission, and drop-out, were modeled using 2-level mixed logistic regression models with patients

TABLE 2 Drop-out rates in PeEx-I and PeEx-S

Treatment phase	PeEx-I	PeEx-S	χ^2	*p*
Cognitive preparation (session 1–4)	13 (3.63)	5 (1.36)	2.99	.084
Exposure (session 5–10)	9 (2.23)	36 (9.78)	15.26	<.001***
Self-management (session 11–14)	52 (14.53)	40 (10.87)	1.87	.171

Note: Frequency (and %) of drop-out; PeEx-I temporally intensified prediction error-based exposure; PeEx-S standard nonintensified prediction error-based exposure.

Abbreviations: PeEx-I temporally intensified prediction error-based exposure; PeEx-S standard non-intensified prediction error-based exposure.

***$p < .001$.

nested in study centers at posttreatment and follow-up. For drop-out analyses, drop-out rates were calculated for distinct treatment phases, that is, cognitive preparation (session 1–4), exposure (session 5–10), and self-management (session 11–14).

Duration of treatment was measured as days from pre to post assessment and served as manipulation check. In contrast, time until response focused on how many days (not sessions) it took until an individual response occurred during the course of treatment. The response was operationalized as more than or equal to 50% reduction from baseline on the global severity index (GSI) of the BSI, which was assessed every second session during the course of treatment. Differences between groups were evaluated in a survival analysis framework using the survival R package (Therneau & Lumley, 2015). Values were right-censored if patients withdrew from the study, were lost to follow-up, or if no response was shown until the end of the study

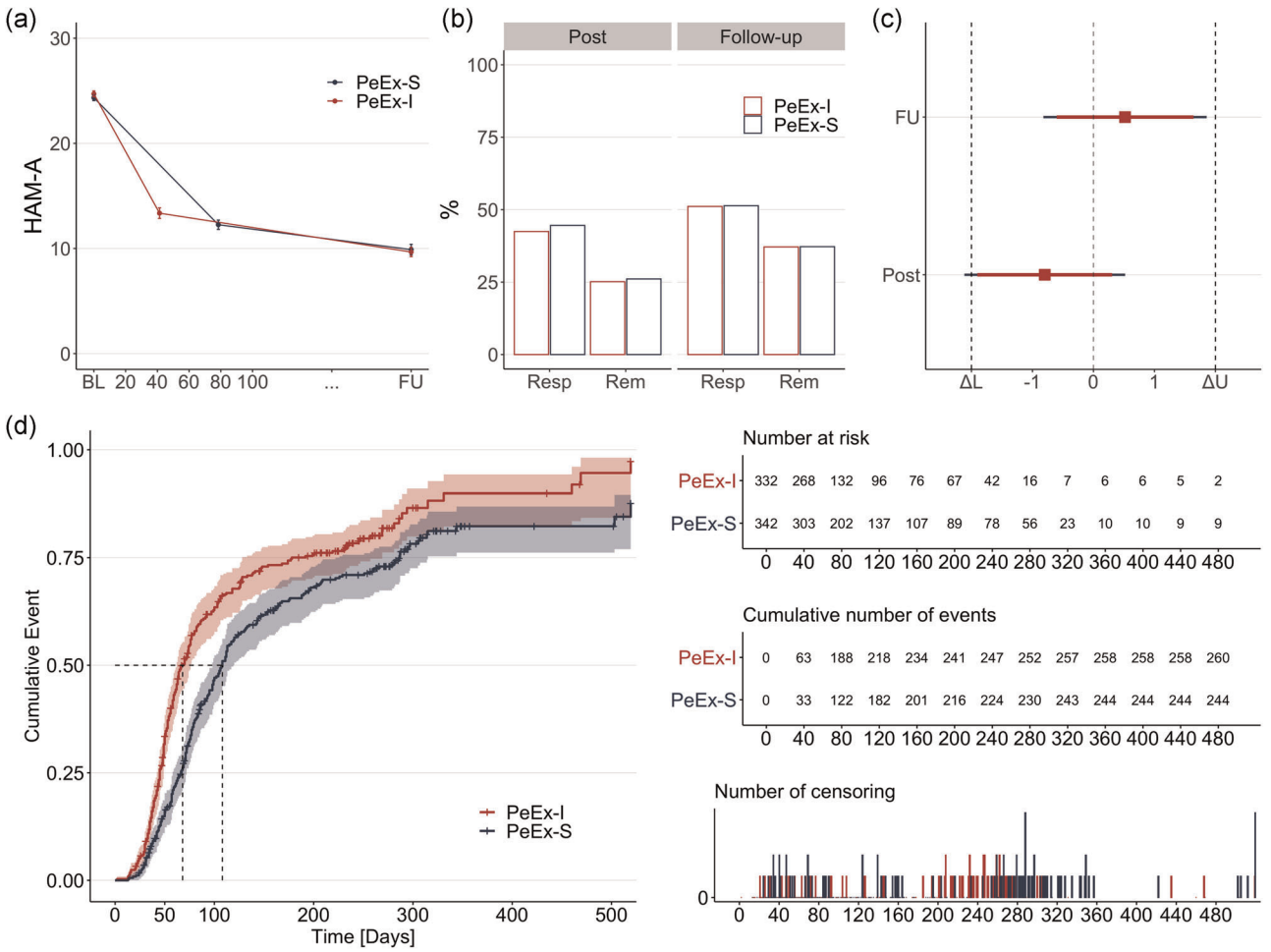

FIGURE 2 (a) Trajectories of HAM-A scores; x-axis labels present days of treatment and 6-months follow-up; error bars represent ± 1 standard error. Note that the post assessment occurred earlier in PeEx-I due to trial design. (b) HAM-A response and remission rates in percent. (c) Results of TOST-equivalence test; dotted lines represent equivalence bounds; orange error bars represent 95% confidence interval of equivalence test, blue error bars represent 95% confidence interval of null-hypothesis test for HAM-A change between groups. (d) Survival curve for time until response; black dashed lines indicate median time until response per group; cumulative number of events represents the number of responders up until the respective measurement. HAM-A Hamilton Anxiety Rating Scale; PeEx-I temporally intensified prediction error-based exposure; PeEx-S standard non-intensified prediction error-based exposure

TABLE 3 Trajectories of primary and secondary outcomes for the intent-to-treat analyses

Outcome	PeEx-I					PeEx-S					PeEx-I versus PeEx-S						
	M (*SD*) or *N* (%)			Within ES		*M* (*SD*) or *N* (%)			Within ES		Between ES		Time		Time × Group		R^2
	BL	Post	FU	BL to Post	BL to FU	BL	Post	FU	BL to Post	BL to FU	Post	FU	*F*	*p*	*F*	*p*	
HAM-A	24.7 (5.33)	13.36 (8.77)	9.67 (7.25)	1.50 (1.32–1.69)	2.34 (2.07–2.61)	24.34 (5.31)	12.26 (7.75)	9.89 (8.26)	1.78 (1.56–2.00)	2.03 (1.79–2.27)	0.05 (−0.03 to 0.13)	−0.04 (−0.12 to 0.05)	1223.-53	<.001***	1.84	.16	0.67
CGI	5.04 (0.7)	3.26 (1.33)	2.87 (1.29)	1.65 (1.44–1.86)	2.03 (1.76–2.31)	5.00 (0.66)	3.16 (1.25)	2.73 (1.44)	1.77 (1.55–1.99)	1.95 (1.70–2.21)	0.03 (−0.07 to 0.13)	0.05 (−0.06 to 0.16)	959.78	<.001***	0.45	.64	0.59
BSI	0.98 (0.54)	0.53 (0.45)	0.39 (0.39)	0.92 (0.79–1.06)	1.24 (1.07–1.40)	0.94 (0.55)	0.52 (0.46)	0.42 (0.46)	0.81 (0.68–0.93)	0.98 (0.83–1.12)	−0.05 (−0.13 to 0.04)	−0.08 (−0.17 to 0.01)	509.45	<.001***	1.64	.19	0.67
EQ-5D	0.65 (0.14)	0.77 (0.16)	0.83 (0.17)	0.81 (0.66–0.97)	1.11 (0.94–1.28)	0.66 (0.15)	0.79 (0.16)	0.8 (0.17)	0.84 (0.69–0.98)	0.89 (0.73–1.05)	−0.03 (−0.13 to 0.07)	0.11 (0 to 0.22)	301.33	<.001***	3.51	.03*	0.51
BDI	17.07 (9.79)	9.26 (9.09)	6.92 (7.96)	0.84 (0.72–0.97)	1.09 (0.94–1.24)	16 (9.78)	8.68 (8.97)	7.54 (8.37)	0.78 (0.66–0.90)	0.91 (0.77–1.05)	−0.04 (−0.12 to 0.05)	−0.09 (−0.18 to 0)	416.42	<.001***	1.95	.14	0.66
Disability Days	8.91 (11.79)	4.11 (7.31)	2.48 (5.81)	0.50 (0.37–0.62)	0.61 (0.46–0.75)	7.15 (10.39)	2.81 (5.54)	2.8 (5.84)	0.47 (0.34–0.60)	0.44 (0.31–0.57)	−0.05 (−0.15 to 0.06)	−0.15 (−0.26 to −0.04)	117.27	<.001***	3.46	.03*	0.46
Response		152 (42.46)	183 (51.12)				164 (44.57)	189 (51.36)			0.92 (0.64 to 1.32)	0.84 (0.61 to 1.16)					0.03, 0.06
Remission		90 (25.14)	133 (37.15)				96 (26.09)	137 (37.23)			0.95 (0.68 to 1.34)	0.91 (0.64 to 1.28)					0.02, 0.03

Note: Numbers rounded to 2 decimal positions; effect sizes are reported as Cohen's *d* with 95% confidence interval and computed as the standardized difference between model slopes for continuous outcomes and as odds ratio with 95% confidence interval for binary outcomes; R^2 conditional to fixed and random effects.

Abbreviations: BL, baseline; BSI, Brief Symptom Inventory; BDI, Beck Depression Inventory; CGI, Clinical Global Impression scale; EQ-5D, EuroQOL five-dimensional measure of health status; ES, effect size; FU, follow-up; HAM-A, Hamilton Anxiety Rating Scale; *M*, mean; PeEx-I, temporally intensified prediction error-based exposure; PeEx-S, standard non-intensified prediction error-based exposure; *SD*, standard deviation.

*$p < .05$; ***$p < .001$.

period. The acceleration effect associated with PeEx-I was estimated using a lognormal accelerated failure time model (AFT) controlling for the study center (Collett, 2015; Kalbfleisch & Prentice, 2011). This model can be employed to analyze time-to-event data, when proportional hazards cannot be assumed. By exponentiation of the AFT regression coefficient, a time ratio (TR) can be derived which indicates that treatment either prolongs (TR > 1) or reduces the time until response (TR < 1). The significance of the treatment effect was determined using the likelihood-ratio test (LR-test). One patient was excluded from this analysis due to a GSI score of zero on the baseline measurement. The highest 1% of survival times were winsorized (Signorell et al., 2016) to avoid outlier effects due to extreme treatment durations in both groups ($n = 2$ cases in PeEx-I and $n = 5$ cases in PeEx-S with durations of >519 days).

Results were significant at p values below .05. All analyses were performed in the intent-to-treat (ITT) sample and repeated in a completer sample (606 patients, PeEx-I = 309, and PeEx-S = 297). As completer analyses yielded an identical pattern of results, they are provided in the supplement.

3 | RESULTS

3.1 | Drop-out

There were significantly higher dropouts in PeEx-S compared with PeEx-I during the exposure phase (Table 2). No differences in drop-out rates were found during cognitive preparation and self-management.

3.2 | Primary outcome

Both groups showed significant and substantial improvements in anxiety symptoms ($F_{(2,1263)} = 1223.53$, $p = <.001$; Figure 2a, Table 3). For PeEx-I, baseline to posttreatment slope was −11.31 points on the HAM-A ($t_{(1256)} = 25.82$, $p < .001$; $d_{within} = 1.50$, $CI_{95\%}$ 1.32–1.69). For PeEx-S, baseline to posttreatment slope was −12.05 points ($t_{(1271)} = 27.60$, $p < .001$; $d_{within} = 1.78$, $CI_{95\%}$ 1.56–2.00). Improvement increased during follow-up (PeEx-I: $\beta = -14.92$, $t_{(1280)} = 32.68$, $p < .001$; $d_{within} = 2.34$, $CI_{95\%}$ 2.07–2.61; PeEx-S: $\beta = -14.40$, $t_{(1293)} = 31.73$, $p < .001$; $d_{within} = 2.03$, $CI_{95\%}$ 1.79–2.27).

There was no statistically significant difference in treatment effect between groups ($F_{(2,1263)} = 1.84$, $p = .16$). This was true for HAM-A change from baseline to posttreatment ($\beta = -0.74$, $t_{(1262)} = -1.20$, $p = .23$, $d = 0.05$, $CI_{95\%}$ −0.03 to 0.13), as well as to follow-up ($\beta = .51$, $t_{(1287)} = 0.80$, $p = .42$, $d = -0.04$, $CI_{95\%}$ −0.12 to 0.05).

Formal tests for statistical equivalence of symptom reduction (Lakens et al., 2018), using the TOST-procedure (Schuirmann, 1987) with bounds (Δ_{Lower} and Δ_{Upper}) set at the score differences the samples were adequately powered to detect (2 points on the HAM-A) revealed statistical equivalence at post assessment ($t_{(612)} = 1.79$, $p = .04$, $CI_{95\%}$ −1.90 to 0.31) and follow-up ($t_{(544)} = -2.18$, $p = .01$, $CI_{95\%}$ −0.60 to 1.64) (Figure 2c). This formally indicates that both treatments resulted in equivalent improvement.

Response rates and remission rates did not differ significantly between groups at posttreatment (Figure 2b and Table 3). Furthermore, PeEx-I did not show increased relapse rates following response (PeEx-S: 14%, PeEx-I: 16%, OR = 1.21, $CI_{95\%}$ 0.62–2.38) or remission (PeEx-S 21%, PeEx-I 19%, OR = 0.90, $CI_{95\%}$ 0.41–1.94).

3.3 | Secondary outcomes

Significant improvements over time were found for all secondary outcomes (Table 3, Figure S1 in supplement). Group differences were found for quality of life (EQ-5D, $F_{(2,1234)} = 3.51$, $p = .03$) and disability days ($F_{(2,1178)} = 3.46$, $p = .03$). Both outcomes showed superior improvement from baseline to follow-up in PeEx-I (EQ-5D: $\beta = .03$, $t_{(1257)} = 2.03$, $p = .04$, $d = 0.11$, $CI_{95\%}$ 0.01–0.22; disability days: $\beta = -1.99$, $t_{(1204)} = -2.61$, $p = .01$, $d = -0.15$, $CI_{95\%}$ −0.26 to −0.04).

3.4 | Treatment duration and time until response

Average treatment duration for PeEx-I ($M = 41.38$ days, $SD = 12.80$) was 47% shorter compared with PeEx-S ($M = 78.47$ days, $SD = 19.13$, $t_{(516)} = 28.00$, $p < .001$, d = 2.29, $CI_{95\%}$ 2.08–2.49). Still, both groups showed equivalent symptom improvement.

For time until response, group-specific global severity trajectories (BSI) and distributions of event times (T_i) and censoring times (C_i) are displayed in the supplement (Figure S2; $n_{PeEx\text{-}I} = 332$, $n_{PeEx\text{-}S} = 342$). Response was reached after a median of 68 days in PeEx-I ($CI_{95\%}$ 62–76) and 108 days in PeEx-S ($CI_{95\%}$ 98–120) (Figure 2d). The time ratio (TR) associated with PeEx-I was 0.68 (LR-Test: $\chi^2_1 = 24.93$, $p < .001$, $CI_{95\%}$ 0.59–0.79), resulting in an acceleration effect of 32% compared with PeEx-S.

4 | DISCUSSION

In this large-scale multi-center RCT, the feasibility and efficacy of two variants of exposure therapy was examined. Both treatments emphasized prediction error-based inhibitory learning in a heterogeneous group of patients with various anxiety disorders and typical comorbid conditions. As expected, both groups showed substantial improvements in all symptom, disability, and quality of life outcome measures at post and further improvements over the 6-month follow-up period. Effect sizes of our transdiagnostic approach at post (PeEx-I: 1.5; PeEx-S: 1.78) and follow-up (PeEx-I: 2.34; PeEx-S: 2.03) were substantial and in the range or above previously reported effects of exposure-based treatments tailored to specific anxiety disorders (Bandelow et al., 2015; Loerinc et al., 2015; Norton & Price, 2007). Identical findings were found in the completer analysis.

Combined with low drop-out rates, these findings highlight that a transdiagnostic prediction error-based exposure treatment is feasible for various severe anxiety disorders.

Main comparisons between the two treatment groups focused on improved symptom reduction and accelerated treatment response. For symptom reduction, the hypothesis of stronger and more pervasive effects in patients treated with temporally intensified exposure was not confirmed in primary (HAM-A anxiety symptoms) and secondary outcomes of global severity (BSI) and comorbid depression (BDI). Indeed, a formal test of equivalence highlighted that both treatments resulted in equivalent symptom reduction at post and follow-up. Using a large sample, which was sensitive enough to detect even small effects, our findings suggest that the beneficial effects of temporally intensified exposure reported in animal and analog clinical research do not translate to moderate to severe anxiety disorders with multiple comorbidities. One explanation may be that intensified exposure in analog studies was typically designed with fewer exposure sessions occurring on the same day (Rowe & Craske, 1998; Tsao & Craske, 2000), whereas more exposure sessions were condensed to two weeks in the present study. Moreover, the present trial included patients with more severe anxiety disorders and complex comorbidities compared with previous studies focusing mostly on specific phobias and subclinical samples. Follow-up analyses may therefore examine whether patients with specific anxiety disorders or less severe symptoms may better respond to intensified treatment.

Nevertheless, temporally intensified exposure was equivalent in reduction of primary symptoms and superior in reducing the number of disability days as well as improving quality of life at follow-up. These findings suggest that although intensified exposure did not result in stronger symptom reduction, it was beneficial for decreasing the disease burden and improving the general functioning of patients with severe anxiety disorders. These differences occurred six months after treatment (follow-up), that is, during a time period that had no overlap with the intensified exposure phase. The differences in disability and quality of life may thus relate to processes that are operating after intensified treatment. For example, more persuasive prediction-error-based learning may have selective effects on these measures in the long-run. Alternatively, higher self-efficacy or distress tolerance after completing intensified exposure may have boosted long-term quality of life. Future research may directly analyze which processes are boosted by intensified exposure (e.g., prediction error, self-efficacy, distress tolerance, etc.) and whether these processes are differentially associated with symptom reduction and quality of life.

Moreover, intensified exposure resulted in faster treatment effects. Inherent to the study design, overall treatment duration of intensified exposure was significantly shorter. Shorter treatment duration at post-assessment was thus essentially driven by an earlier completion of the treatment due to the trial design. Importantly, analyses of symptom reduction over the course of sessions (i.e., survival analysis framework) revealed that treatment response on average occurred about 32% faster during intensified exposure. This finding highlights that treatment responses were already faster during the course of treatment, not only after treatment completion. A higher risk of drop-out or relapse for intensified exposure could not be verified. Relapse rates did not differ between treatments. Drop-out rates were actually lower during the intensified exposure phase as compared with temporally spaced exposure and did not differ for the other treatment phases. These findings may carry important implications for public health regulations. They suggest that intensified exposure-CBT provides a faster treatment option, which is linked to fewer days until response and even fewer drop-outs during the exposure phase. While treatments in routine care oftentimes take several months or years (Hoyer et al., 2017; Leichsenring et al., 2013), these findings highlight that severe anxiety disorders can be treated in a limited time period at least for a substantial proportion of patients. In sum, intensified exposure-based CBT represents a valuable approach to restore well-being in patients with anxiety disorders, lowering the individual and societal burden of disease. The results also imply that clinicians can expect better or at least comparable outcomes when delivering exposure therapy in a temporally intensified manner. In this regard, the choice for or against temporally intensified exposure could be adapted to the needs or characteristics of the individual patient. Moving towards individualized psychotherapy, future research may examine which patients may benefit more from intensified or non-intensified exposure.

In this study, we specifically focused on the major group differences associated with the temporal spacing of exposure sessions. Although this was the main goal of the study, many potential processes, moderators, and mediators were not addressed such as the specific effect of temporal spacing on process-based variables (e.g., prediction error, and behavioral activation) or what type of patients' most likely profit from intensified treatment. In addition, more detailed analyses on treatment acceptance, burden, and commitment may shed light on differential drop-out rates in specific treatment phases. Future research incorporating individual patient characteristics and exposure records collected in the trial may further help to better understand the mechanisms and individual responses to exposure-based CBT.

5 | CONCLUSION

Both temporally intensified and temporally spaced exposure substantially reduced symptom severity and disability of severe anxiety disorders with multiple comorbid conditions. Effects were stable and significantly enlarged at follow-up. Importantly temporally intensified exposure did not result in stronger symptom reduction, but treatment response was reached considerably faster. In addition, temporally intensified exposure was linked to lower disability and higher quality of life at follow-up, without increasing dropout or relapse. Jointly, these findings underline the efficacy of prediction error-based exposure and public health benefits of intensified exposure sessions across major types of anxiety disorders with and without comorbidity.

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CONFLICT OF INTERESTS

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ETHICS STATEMENT

The study program is performed according to the Declaration of Helsinki and was approved by the Ethics Committee of Technische Universität Dresden (EK 234062014, November 14, 2014). The clinical trial has been registered with NIMH Protocol Registration System (01EE1402A) and with the German Register of Clinical Studies (DRKS00008743).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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