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Effective—and Tolerable: Acceptance and Side Effects of Intensified Exposure for Anxiety Disorders

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Despite striking empirical support, exposure-based treatments for anxiety disorders are underutilized. This is partially due to clinicians' concerns that patients may reject exposure or experience severe side effects, particularly in intensive forms of exposure. We examined acceptance and side effects of two randomly assigned variants of prediction error-based exposure treatment differing in temporal density (1 vs. 3 sessions/week) in 681 patients with panic disorder, agoraphobia, social anxiety disorder, and multiple specific phobias. Treatment acceptance included treatment satisfaction and credibility, engagement (i.e., homework completion), and tolerability (i.e., side effects, dropout, and perceived treatment burden). Side effects were measured with the Inventory for the Balanced Assessment of Negative Effects of Psychotherapy (INEP). We found treatment satisfaction, credibility, and engagement to be equally high in both variants of exposure-based treatment, despite higher treatment burden ($\beta = 0.25$) and stronger side effects ($\beta = 0.15$) in intensified treatment. 94.1% of patients reported positive effects in the INEP. 42.2% reported side effects, with treatment stigma (16.6%), low mood (14.8%) and the experience to depend on the therapist (10.9%) being the most frequently reported. The mean intensity of side effects was low. We conclude that prediction error-based exposure treatment is well accepted by patients with different anxiety disorders and that patients also tolerate temporally intensified treatment, despite higher perceived treatment burden and stronger side effects. Clinicians should be aware of the most frequent side effects to take appropriate countermeasures. In sum, temporal intensification appears to be an acceptable strategy to achieve faster symptom reduction, given patients' well-informed consent.

Keywords: anxiety disorders; intensified exposure; treatment acceptability; side effects; negative effects of psychotherapy

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Exposure—the structured and repeated confrontation with feared stimuli or contexts—is a core feature of cognitive-behavioral therapy (CBT) for anxiety disorders (Abramowitz & Blakey, 2020; Neudeck & Wittchen, 2012). During exposure exercises individuals are instructed to abandon safety and avoidance behaviors, and to remain in the feared situation either until fear declines (habituation-based exposure) or until central concerns have been violated (prediction error-based exposure). The rationale of the latter is to create new inhibitory nonthreat associations by maximizing a prediction error, i.e., the perceived difference between a predicted negative outcome and the actual outcome of the exposure exercise (Craske et al., 2022). This approach has recently received support in clinical studies (Deacon, Kemp, et al., 2013; Guzick et al., 2020; Pittig et al., 2021; Wannemueller et al., 2019). CBT based on exposure principles is a first-line treatment for anxiety disorders according to international guidelines (e.g., Bandelow et al., 2021; NICE, 2011) and demonstrates high to moderate effects across disorders in meta-analyses, even against placebo conditions (e.g., Carpenter et al., 2018; Whiteside et al., 2020).

This evidence does not translate to routine care settings, however, where exposure is substantially underutilized. For example, cognitive-behavioral therapists in Germany administer exposure in less than half of their therapies of anxiety disorders (Külz et al., 2010; Pittig & Hoyer, 2017) and only a minority of 20–30% of patients reportedly received it (Becker et al., 2004; Böhm et al., 2008). In a large survey among North American mental health workers exposure ranked among the least frequently applied methods (Cook et al., 2010). Additionally, clinicians tend to prefer low-intensity variants of exposure. This includes treatments with few exposure exercises at all, exposure with ongoing safety behaviors, time-limited exercises, or a low temporal density of exercises (Roth et al., 2004). Pittig and Hoyer (2017), for example, found that the median session frequency in exposure-based CBT was only twice per month. Such practices can reduce the effectiveness of exposure-based CBT (Benito et al., 2021). Specifically, a lower temporal intensity of exposure sessions can result in slower symptom reduction and increased suffering (Jónsson et al., 2015; Pittig et al., 2021).

One reason for the non- and low-intensity-application of exposure-based CBT pertains to beliefs held by clinicians that it might be inacceptable or intolerable for many patients (Richard & Gloster, 2007). Concerns include that patients might be difficult to motivate for treatment, drop out of treatment, or experience detrimental side effects such as retraumatization or violation of personal boundaries (Moritz et al., 2019; Olatunji et al., 2009). Even some experts describe exposure as the psychological intervention with "the highest risk of unwanted effects" (Nestoriuc & Rief, 2013, p. 62). Moreover, transient anxiety and distress during exposure exercises are wanted phenomena that result directly from the treatment rationale (e.g., fear or threat expectancy activation). Up to one third of cognitive-behavioral therapists doubt that patients will be able to endure these feelings (Pittig et al., 2019). Clinicians who fear the wanted distress and unwanted side effects of exposure may know that the method is generally effective but will hesitate to use it—or switch to low-intensity exposure. Accordingly, therapists' negative expectations about exposure are linked to less intense application of interoceptive exposure (Deacon, Lickel, et al., 2013), and experimental induction of negative expectations can cause more cautious delivery of exposure with response prevention (Farrell et al., 2013). Concerns about potential unacceptability and side effects thus contribute to the underuse of exposure and may reduce the effectiveness of exposure-based CBT in routine care.

The doubts about exposure-based treatment among therapists contrast with relatively positive evaluations among potential patients. Students confronted with treatment vignettes for anxiety disorders consistently show a preference for exposure-based CBT over other psychological interventions or medication (Becker et al., 2007; Deacon & Abramowitz, 2005; Tarrier et al., 2006). Less intensive variants, such as exposure with safety behaviors, achieve higher acceptability in case vignette studies (Levy et al., 2014; Milosevic & Radomsky, 2013). However, clinical analogue studies found similar acceptability of exposure with and without safety behaviors (Blakey et al., 2019; Deacon et al., 2010). Temporally intensified exposure is also unassociated with dropout (Abramowitz et al., 2003; Chase et al., 2012; Jain et al., 2021; Pittig et al., 2021). These findings suggest that patients' acceptance of exposure may be better than expected, even within more intensive variants. Yet, extant studies evaluated acceptability primarily *before* treatment, have been conducted in healthy, analogue, or monosymptomatic samples, and did not cover important aspects of acceptance. Particularly, potential side effects of exposure have not been systematically analyzed, leaving much room for speculations about the intolerability of exposure-

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based treatment. Thus, there is a need to examine acceptance of exposure in larger comorbid clinical samples and to analyze potential side effects, as well as compare treatment acceptance and side effects in standard and more intensified forms of exposure.

Treatment acceptance is the evaluation of an intervention as fair, reasonable, and appropriate (Kazdin, 1980). While *acceptability* (as assessed in vignette studies) refers to a-priori expectations, acceptance includes peri- and post-intervention evaluations (cf. Alexandre et al., 2018; Sekhon et al., 2017). Relatively little is known about the course of acceptance of exposure-based treatments over different treatment phases as most studies focused on evaluations prior to the start of treatment or at the end. Treatment acceptance for exposure-based interventions is often operationalized using: (a) treatment satisfaction, (b) treatment engagement, and (c) the tolerability of the intervention (Botella et al., 2015; Milosevic & Radomsky, 2013; Tarrier et al., 2006). *Treatment satisfaction* is the attitude towards treatment and denotes that patients perceive a treatment or a given session as helpful and effective. An important cognitive component of treatment satisfaction is credibility, i.e., how plausible and convincing a treatment appears (Devilly & Borkovec, 2000). *Engagement* describes the behavioral component of acceptance, i.e., the efforts that patients make during treatment to achieve change (Holdsworth et al., 2014). Treatment engagement includes attending sessions, participating actively during sessions and completing homework. *Tolerability* is the degree to which individuals accept a treatment despite potentially associated negative aspects (European Medicines Agency, 1998). Tolerability is thus a function of the strain and effort associated with treatment (treatment burden) and its potential side effects. Side effects are *unwanted* events or adverse reactions caused by a lege artis psychotherapy (Bystedt et al., 2014; Herzog et al., 2019). Examples are emergence of new symptoms, stigmatization, strains in the therapeutic relationship, social conflicts due to altered behavior, or hopelessness when treatment expectations are not met. Side effects need to be distinguished from therapeutic malpractice, i.e., therapeutic mistakes with a negative bearing on patients (Linden & Schermuly-Haupt, 2014). Systematic evaluations of side effects in exposure therapy are rare (Jonsson et al., 2014; Rozental et al., 2018) and most studies only examine general post-hoc tolerability of exposure, or temporary distress during exposure, which is no side effect. Two studies examined symptom deterioration during exposure therapy for PTSD, which is experienced by a minority of patients (3–15%; Cloitre et al., 2010; Foa et al., 2002). One recent survey examined therapist-reported severe side effects of exposure for obsessive-compulsive disorder (Schneider et al., 2020), which were reported in less than 0.01% of treatments. Unfortunately, this study did not include evaluations of side effects from the patients' perspective.

Main aims of this secondary analysis of an RCT (Pittig et al., 2021) were to first evaluate acceptance of prediction error-based exposure (including treatment satisfaction, engagement, and tolerability) with a focus on the type, frequency and intensity of side effects from a patient perspective. Second, we aimed to compare acceptance and side effects in intensified (3 sessions/week) vs. standard nonintensified exposure-based treatment (1 session/week), to test the hypothesis that intensified treatment would be as well accepted as standard treatment. Additionally, we explored demographic and clinical correlates of side effects.

Material and Methods

DESIGN

Data were collected in a multicenter RCT examining temporally intensified exposure-based CBT for anxiety disorders (Heinig et al., 2017; Pittig et al., 2021). Patients were randomized to one out of two variants of prediction error-based exposure therapy (PeEx) using center-specific randomization lists: either standard nonintensified treatment (PeEx-S) with weekly exposure sessions or temporally intensified treatment (PeEx-I) with 3 sessions per week during the exposure phase, resulting in a 47% shorter treatment duration (5.9 vs. 11.2 weeks; Heinig & Hummel, 2020). Treatment was content-identical in both groups and consisted of 14 100-min sessions of individual CBT. Sessions 1–4 covered cognitive preparation, including behavioral diagnostics, identification of core threat expectancies and explication of the treatment rationale. Sessions 5–10 included in-session therapist-accompanied exposures (5 sessions) and self-guided exposure after every session. Sessions 11–12 focused on relapse prevention and self-management of exposure. Two booster sessions (Session 13–14) were held 2 and 4 months after the end of treatment. From Session 4 patients were instructed to carry out self-guided exercises after every session (i.e., at minimum 7 self-guided exercises until post assessment) and further exercises during the follow-up period. The exposure rationale was explicitly based on disconfirming patients' core threat beliefs to generate a predic-

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tion error. Core threat beliefs were revealed during cognitive preparation. Specific threat beliefs for each exposure exercise were written down prior to each exercise and compared to the actual outcome of this exercise. The prediction error rationale was applied to all target diagnoses. Patients tested disorder-specific predictions, such as: "I will faint" (panic disorder or agoraphobia), "No one will answer me" (social anxiety disorder), or "I will fall off" (height phobia). Outcome measures were assessed after Session 12 (post assessment) and 6 months later (follow-up). Therapists were psychologists in clinical training or registered psychotherapists. Sessions were videotaped and constantly supervised (see Pittig et al., 2021). Study procedures were approved by local ethics committees. All patients provided written informed consent.

PATIENT SAMPLE

Six hundred eighty-one patients with primary panic disorder, agoraphobia, social anxiety disorder or multiple specific phobias were enrolled during 12/2015–09/2018 at eight outpatient clinics in Germany after referral by physicians or self-registration. Patients had to be aged 15–70 years, had to suffer from at least moderately severe anxiety (HAM-A > 18 and CGI > 3) and had to have sufficient German language skills. Patients with comorbid mental disorders and stable medication (≥3 months) were explicitly admitted to increase ecological validity of the trial. Patients with other primary disorders, suicidal ideation, substance dependencies (excluding tobacco), or concomitant psychological treatment were excluded. Patients were aged 33.3 (11.5) years, 44.6% were male. 59.5% were diagnosed with panic disorder, 55.0% with agoraphobia, 41.2% with social anxiety disorder and 36.4% with specific phobias. 46.6% suffered from comorbid major depression or dysthymia. Detailed sample characteristics and the patient flowchart are reported by Pittig et al. (2021). For the purpose of this study we included all patients who completed any of the measures of interest. Thereby, most dropouts (n = 155) also contribute data to the study. For example, credibility ratings during cognitive preparation were available from 148 (95.5%) of dropouts and side effect data were available from 103 (66.5%) of dropouts. Dropouts did not differ in baseline anxiety severity from patients who fully completed the study ($d_{\text{HAM-A}} = -0.06$, $CI_{95\%} = -0.22$ to 0.09, p = .423).

MEASURES

Treatment Satisfaction

In line with previous studies (Cox et al., 1994; Gloster et al., 2009), treatment satisfaction was assessed after every session, asking patients "How helpful and comprehensible was this session to you?" on a 11-point Likert scale (*range* 0–10). Items were averaged for each treatment phase.

Treatment Credibility

Treatment credibility was measured after sessions 4, 11, 13, 14 and at post and follow-up assessment using the Credibility-Scale (Borkovec & Nau, 1972). The scale contains 4 items, answered on a 11-point Likert scale (*range* 0–10). Patients evaluate the rationale, trustworthiness, and their confidence in the treatment. Internal consistency of the scale was good ($\alpha = 0.83$).

Engagement

Subjective engagement was assessed after every session with the question, "After today's session, how motivated are you to continue the therapy with all its exercises etc.?" Objective engagement was assessed via (1) the number of completed sessions and (2) the number of completed homework exercises (i.e., returned exposure records).

Treatment Burden

Treatment burden was measured at post assessment and follow-up with 3 items: "How much of a burden did the following aspects of the treatment put on you?": (a) exposure exercises, (b) homework, and (c) time expenditure on a 11-point Likert scale (*range* 0–10). The items were highly intercorrelated ($\alpha = 0.88$) and were thus averaged.

Side Effects of Psychotherapy

Side effects were measured at post assessment and follow-up with the Inventory for the Balanced Assessment of Negative Effects of Psychotherapy (INEP; Ladwig et al., 2014). The INEP is a 21-item self-report scale assessing side effects (15 items, including the domains intrapersonal changes, partnership, stigma, low mood, workplace, friends/family) and therapeutic malpractice (6 items) in psychotherapy. Side effects are rated on a 4-point unipolar scale (0 = *not true at all*, -3 = *completely true*) or on a 7-point bipolar scale (-3 = *worse*, +3 = *better*) when positive values are also applicable to interpretation. For each item patients indicate whether the effect is due to therapy or due to other circumstances. Only such effects are registered as side effects which are (a) negative and (b) due to therapy. We used the summary score of the 15 side effects as outcome. The score was reversed so that higher values indicate stronger side effects (*range* 0–45). Additionally, we report the frequency of *positive* values in the bipolar INEP items (*range* 0–3 for each item). Malpractice items are scored on a 4-point unipolar

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scale (0 = *not true at all*, -3 = *completely true*) and are also reported separately.

Item construction for the INEP involved a literature search, expert rating, and pilot study, which speaks for good content validity compared to similar scales (Herzog et al., 2019). Psychometric properties were established among 195 individuals who had completed a psychotherapy (Ladwig et al., 2014). The INEP showed good internal consistency (α=.86) and a seven-factor structure which explained 56% of variance. The factors describe the 6 areas of side effects and malpractice. Internal consistency in the present sample was α = 0.65. Side effects as measured with the INEP have been linked to poorer therapeutic alliance (measured with the Helping Alliance Questionnaire), more interpersonal difficulties (measured with the Inventory of Interpersonal Problems; Gerke et al., 2020), higher treatment expectations (Abeling et al., 2018; Rheker et al., 2017) and lower treatment satisfaction (Ladwig et al., 2014). Treatment response, on the other hand, is not generally reduced if side effects are present (Herzog et al., 2021). Two studies using the INEP found side effects in 15–20% of mixed outpatient CBT samples in university clinics (Gerke et al., 2020; Nestoriuc & Rief, 2013).

Symptom Reduction

To assess the association of side effects with treatment efficacy we considered symptom reduction in the Hamilton Anxiety Rating Scala (HAM-A; Shear et al., 2001). The HAM-A was the primary outcome in the original RCT and was administered at baseline, post, and follow-up (Pittig et al., 2021). The HAM-A assesses a broad range of anxiety symptoms at a 5-point scale (0 = *not present*, 4 = *very severe*, *range* 0–56). The internal consistency in the present sample was α = 0.39.

STATISTICAL ANALYSIS

We compared PeEx-S and PeEx-I using hierarchical linear models with measurements nested in patients and patients nested in study centers. Models were calculated in Stata 15 using the *mixed* command. Acceptance indicators were entered as dependent variables, so we calculated one model for each outcome. The slopes of center and patient were entered as random effects; group, time and their interaction were entered as predictors. The group variable had two levels (PeEx-S vs. PeEx-I), the time variable had up to four levels, representing the four treatment phases (cognitive preparation, exposure, debriefing, follow-up). To compare PeEx-S and PeEx-I, we report standardized regression coefficients (β) and their robust 95% confidence intervals. Since we hypothesized that intensified treatment will be as well accepted as standard treatment, we tested for noninferiority of PeEx-I. We set the noninferiority margin at $\Delta = -0.2$, which is the threshold for a small effect according to Cohen (1988). Noninferiority was tested using the *tost* package in Stata 15 (Dinno, 2017). The inferiority hypothesis that PeEx-I is at least 0.2 *SD* below PeEx-S functions as the null (Schumi & Wittes, 2011). Significant results indicate that the inferiority hypothesis can be rejected, i.e., that PeEx-I can be considered noninferior. Since noninferiority hypotheses are one-sided, we used a one-tailed test (Lakens et al., 2018). Outliers were included irrespectively of their relative influence, since severe side effects and treatment rejection were expected to be rare events and yet were the main interest of the study. To compare dichotomous outcomes between groups, we calculated odds ratios (OR).

Results

SATISFACTION AND CREDIBILITY

Descriptive values and time effects across treatment phases are presented in Table 1. Between-group effects and results of noninferiority tests are presented in Table 2. The center effect did not explain a relevant proportion of variance in most outcomes, except "number of homework exercises" ($\beta = 0.05$). Figure 1 gives a graphical depiction of between-group effects. Treatment satisfaction and credibility were high both in absolute numbers (8.4–9.0 of 10) and in relation to previous studies (e.g., Arch et al., 2013; Cox et al., 1994; Twohig et al., 2018). Significant time effects indicated increasing treatment satisfaction and credibility across treatment phases. There were no between-group differences and noninferiority tests were significant, indicating noninferiority of PeEx-I.

ENGAGEMENT

Subjective engagement throughout treatment was high in both groups (Reid et al., 2017; Westra et al., 2009), with no between-group differences and noninferior values in PeEx-I. A significant time effect indicated decreased subjective engagement across treatment phases. The mean number of homework exercises was higher in PeEx-I than in PeEx-S, which implicates noninferiority of PeEx-I.

DROPOUT

One hundred fifty-five patients (22.8%) did not complete treatment until follow-up. The majority of dropouts (51.6%) occurred in the follow-up

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Table 1
Patients' Acceptance of Exposure-Based CBT Across Treatment Phases

	N	Preparation (sessions 1–4)		Exposure (sessions 5–10)		Debriefing (sessions 11–12)		Follow-Up (sessions 13–14)		Main effect of time		Group[c] × time	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	β	*p*	*b*	*p*
Treatment satisfaction[a]	652	8.5	1.3	9.0	1.2	9.0	1.3	8.9	1.4	0.06	<0.001	−0.01	0.767
Treatment credibility[a]	674	8.4	1.2	/	/	8.8	1.3	8.8	1.3	0.10	<0.001	−0.02	0.335
Subjective engagement[a]	652	9.1	1.4	9.0	1.3	9.1	1.2	8.9	1.4	−0.07	<0.001	0.02	0.502
Treatment burden[a]	563	/	/	/	/	5.0	2.6	4.9	2.4	−0.07	>0.05	−0.14	0.023
Side Effects[b]	629	/	/	/	/	1.0	1.9	0.7	1.8	−0.09	>0.05	−0.13	0.037

Note. [a]*range:* 0–10, [b]INEP sumscore, *range:* 0–45. [c]PeEx-S = standard non-intensified exposure, PeEx-I = temporally intensified exposure.

Table 2
Patients' Acceptance of Standard Nonintensified (PeEx-S) vs. Temporally Intensified (PeEx-I) Exposure-Based CBT

	N	PeEx-I		PeEx-S		Center effect	PeEx-I vs. PeEx-S		Noninferiority test[c]	
		M	*SD*	*M*	*SD*	β	β	$CI_{95\%}$	*t*	*p*
Treatment satisfaction[a]	652	8.8	1.1	8.8	1.3	>0.01	0.01	−0.09 to 0.12	3.09	0.001
Treatment credibility[a]	674	8.7	1.2	8.7	1.3	0.01	0.01	−0.10 to 0.12	2.92	0.002
Subjective engagement[a]	652	9.0	1.1	9.0	1.2	0.01	>−0.01	−0.07 to 0.07	2.18	0.015
No. of homework exercises	623	17.4	12.7	15.4	11.3	0.05	0.18	0.08 to 0.27	4.61	>0.001
No. of completed sessions	681	13.0	2.5	12.8	2.6	>0.01	0.05	−0.03 to 0.13	5.02	>0.001
Treatment burden[a]	563	5.4	2.7	4.6	2.5	0.01	0.25	0.03 to 0.47	−0.62	0.732
Side Effects[b]	629	1.0	2.2	0.7	1.3	0.01	0.15	0.01 to 0.28	0.42	0.338

Note. [a]*range:* 0–10, [b]INEP sumscore, *range:* 0–45; [c]one-sided test, noninferiority margin = −0.2, significant results indicate rejection of the inferiority hypothesis

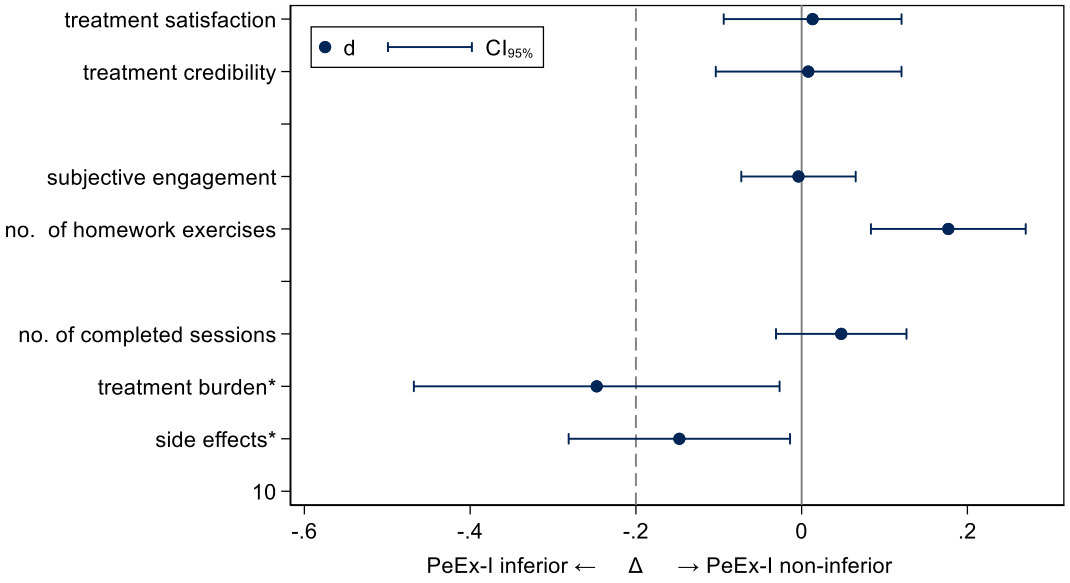

FIGURE 1 Between-group effects and confidence intervals of temporally intensified (PeEx-I) vs. standard exposure (PeEx-S). CIs below Δ indicate retention of the null hypothesis, i.e., inferiority of intensified exposure. * reversed.

phase, and patients completed on average 12.9 of 14 sessions. The primary reasons for dropout were noncompliance with trial specifications (7.0% of the sample), medical complications (1.2%), comorbid mental disorders, missing the post assessment, hospitalization, rapid response, or change of residence (each < 1%), and 13.2% dropped out without indicating a reason. Neither dropout rates (22.0 vs. 23.5, $\chi^2 = 0.21$, $p > .05$) nor the number of completed sessions differed between treatment groups, and PeEx-I was noninferior regarding the number of completed sessions (see Table 2). Interestingly, dropout rates were lower in PeEx-I during the exposure phase (2.5% vs. 9.8%, $\chi^2 = 16.49$, $p < .001$).

TREATMENT BURDEN

Individuals in PeEx-I reported a significantly higher and inferior treatment burden. The group means of 5.4 and 4.6 of 10 may reflect a moderate treatment burden. There was no main effect of time on treatment burden but an interaction of group and time, indicating reduced treatment burden in PeEx-I at follow-up (Figure 2A).

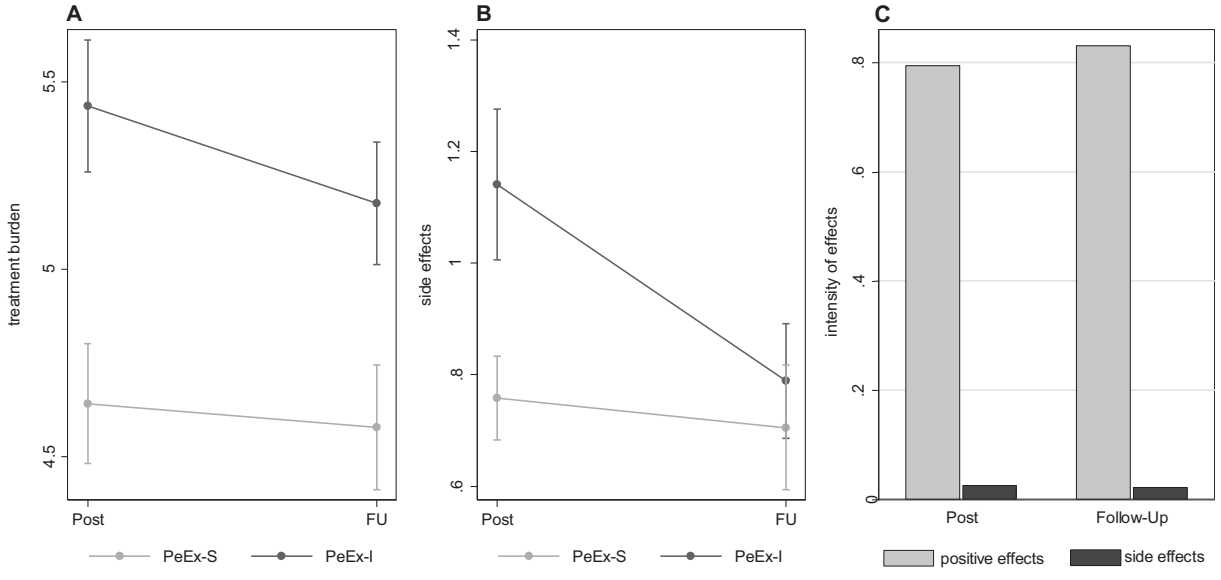

FIGURE 2 A and B: interaction of time and group with the outcomes treatment burden and side effects. C. Mean intensity of positive effects and side effects in bipolar INEP items (*range* 0 to 3).

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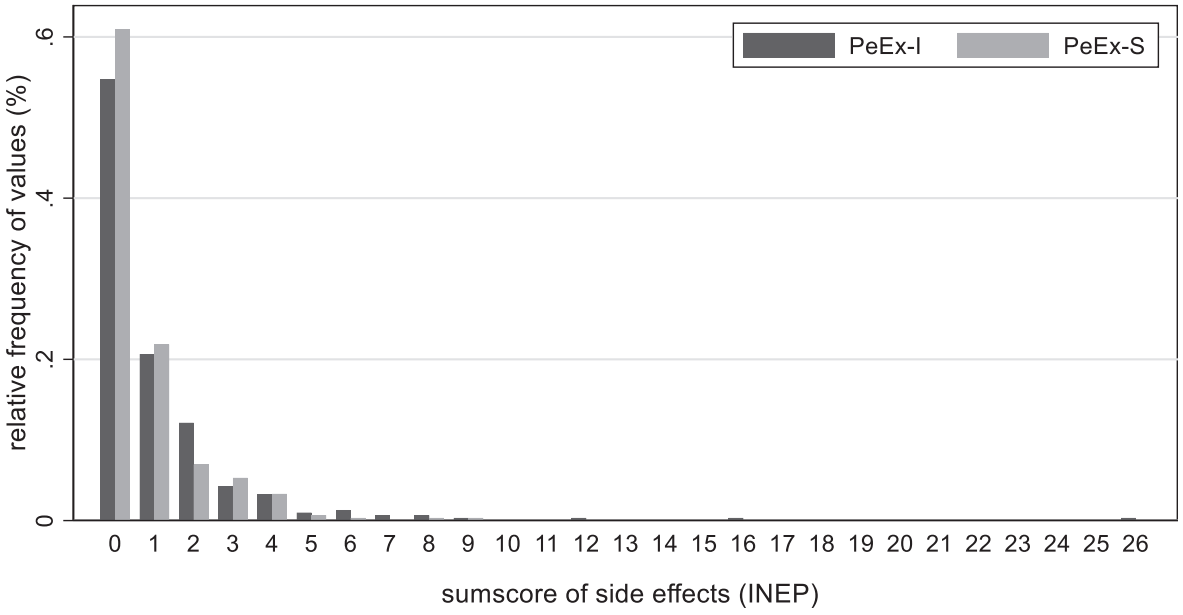

FIGURE 3 Frequency distribution of side effects in the Inventory for the Balanced Assessment of Negative Effects of Psychotherapy (INEP, *range* 0-45).

SIDE EFFECTS

Side effects were reported by 42.2% of patients. The mean intensity of side effects was low ($M = 0.95$, $SD = 1.92$ on the 45-point scale; see Table 1). Experiencing at least one strong side effect (any rating of +3) was reported by 4.3% of all patients. Three patients in PeEx-I (1%) reported exceedingly high side effects (>5 SD above the mean, see Figure 3). Frequency of side effects did not differ between groups, but intensity did, in the sense that PeEx-I was inferior. Reporting of side effects was less frequent at follow-up (31.2%). For example, experiences of "low mood" dropped from 14.8% at post to 6.7% at follow-up. There was no main effect of time on the intensity of side effects, but an interaction of group and time indicating reduced side effects in PeEx-I at follow-up (Figure 2B). Positive effects in the INEP were indicated by 94.1% of all patients with no group differences ($OR = 1.01$, $CI_{95\%}$ 0.52 to 1.98, $p = .976$), and 29.8% experienced any strong positive side effect. Additionally, we descriptively compared the mean intensity of reported positive vs. negative values (i.e., side effects) in bipolar items (both ranged 0 to 3). Intensity of positive effects was $M = 0.79$ ($SD = 0.58$), the intensity of side effects was $M = 0.03$ ($SD = 0.15$; see Figure 2C).

Frequencies of different types of side effects are shown in Figure 4. The most frequent side effects were fear of treatment stigma, low mood and an experience to depend on the therapist. Patients in PeEx-I more frequently reported that their partners were jealous of the therapist (6.5% vs. 1.6%, $OR = 4.30$, $CI_{95\%}$ 1.19 to 15.49, $p = .026$). Regarding therapeutic malpractice, 1.3% of patients ($n = 8$) felt hurt by the therapist, 1.3% ($n = 8$) felt forced to do things that they did not want to do, and 1.0% ($n = 6$) felt mocked, resulting in 3.3% who reported therapeutic malpractice with no between-group differences (2.0% in PeEx-S and 4.6% in PeEx-I, $OR = 2.37$, $CI_{95\%}$ 0.90 to 6.26, $p = .081$).

ADDITIONAL ANALYSES

Figure 5 additionally shows the frequency of positive effects in the bipolar INEP items. The most frequent positive effects were feeling better, suffering less from the past, and finding it easier to trust others. Additional analyses revealed that intensity of side effects was not predicted by age ($\beta < -0.01$, $CI_{95\%}$ −0.01 to 0.01, $p = .925$), employment ($\beta < -0.04$, $CI_{95\%}$ −0.24 to 0.15, $p = .646$), baseline severity ($\beta = 0.02$, $CI_{95\%}$ −0.04 to 0.09, $p = .455$), and number of comorbidities ($\beta = 0.03$, $CI_{95\%}$ −0.01 to 0.06, $p = .119$). Patients with different primary diagnoses did not differ in reporting side effects either ($R^2 = 0.01$, $p = 0.288$). However, women ($\beta = 0.14$, $CI_{95\%}$ 0.03 to 0.25, $p = .013$) and individuals with prior psychological treatment ($\beta = 0.21$, $CI_{95\%}$ 0.09 to 0.33, $p < .001$) reported more side effects. Intensity of side effects at post predicted subsequent dropout ($OR = 1.28$,

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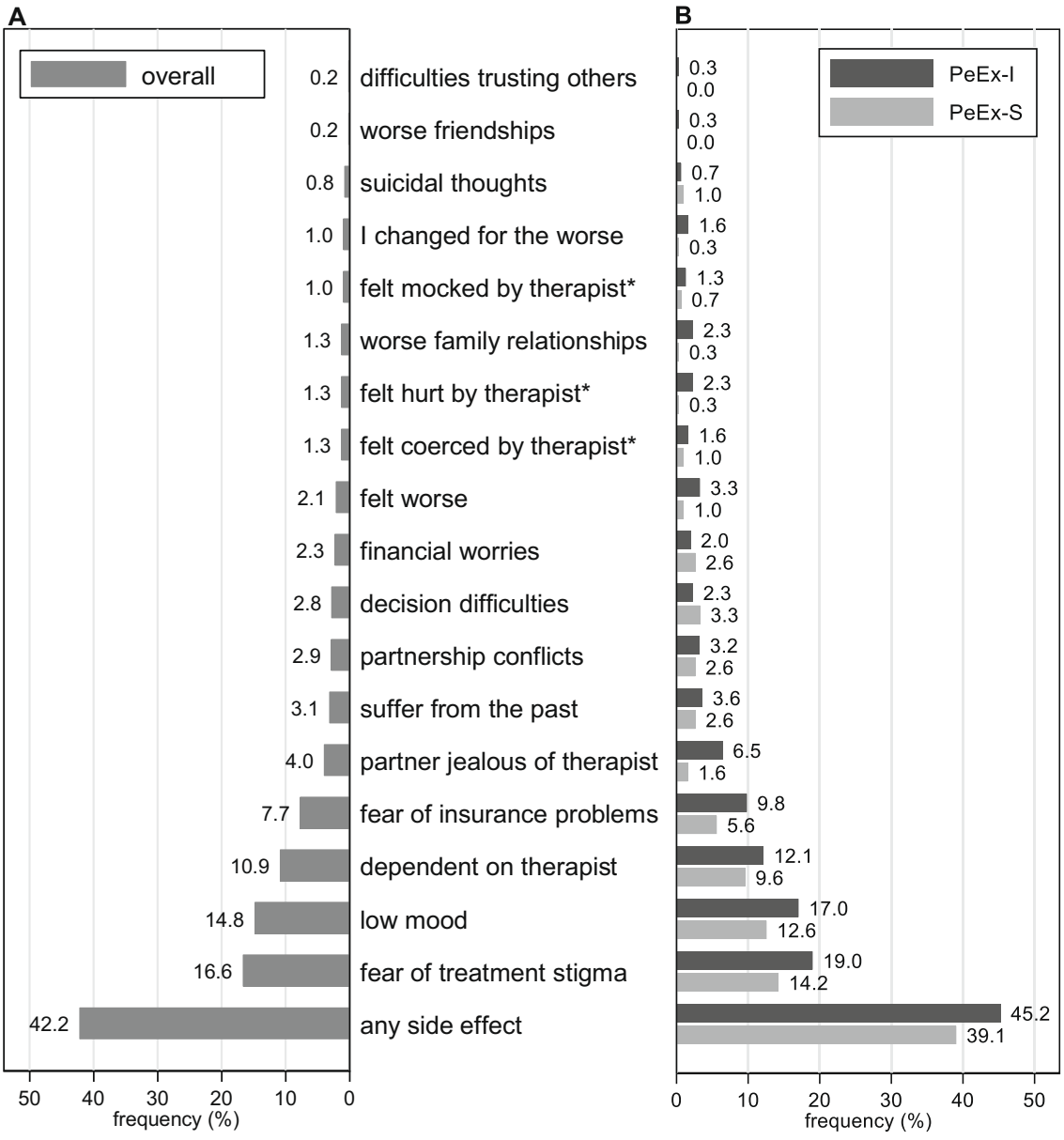

FIGURE 4 Frequency of side effects and reported malpractice (*). A. over both groups; B. in temporally intensified (PeEx-I) vs. standard exposure (PeEx-S).

$CI_{95\%}$ = 1.05 to 1.55, p = .014) as well as attenuated treatment outcome at post (β = −0.39, $CI_{95\%}$ −0.25 to −0.48, p < .001) and follow-up (β = −0.29, $CI_{95\%}$ −0.11 to −0.47, p = .002).

Discussion

We aimed at evaluating treatment acceptance of standard and temporally intensified prediction error-based exposure therapy in a multicenter clinical trial with a focus on patient-reported side effects. The added scientific value of our data lies in the large and diagnostically heterogeneous sample, experimental manipulation of temporal intensity, first-time application of an established instrument for side effects in exposure-based treatment, and in the analysis of trajectories of acceptance measures across treatment, including a follow-up assessment (as suggested by Rozental et al., 2018).

TREATMENT ACCEPTANCE

We found high rates of overall treatment satisfaction and credibility both in absolute terms and compared to other CBTs with exposure (Arch et al., 2013; Cox et al., 1994; Westra et al., 2009), indicating that patients experience prediction error-based exposure generally as reasonable and helpful. Interestingly, satisfaction and credibil-

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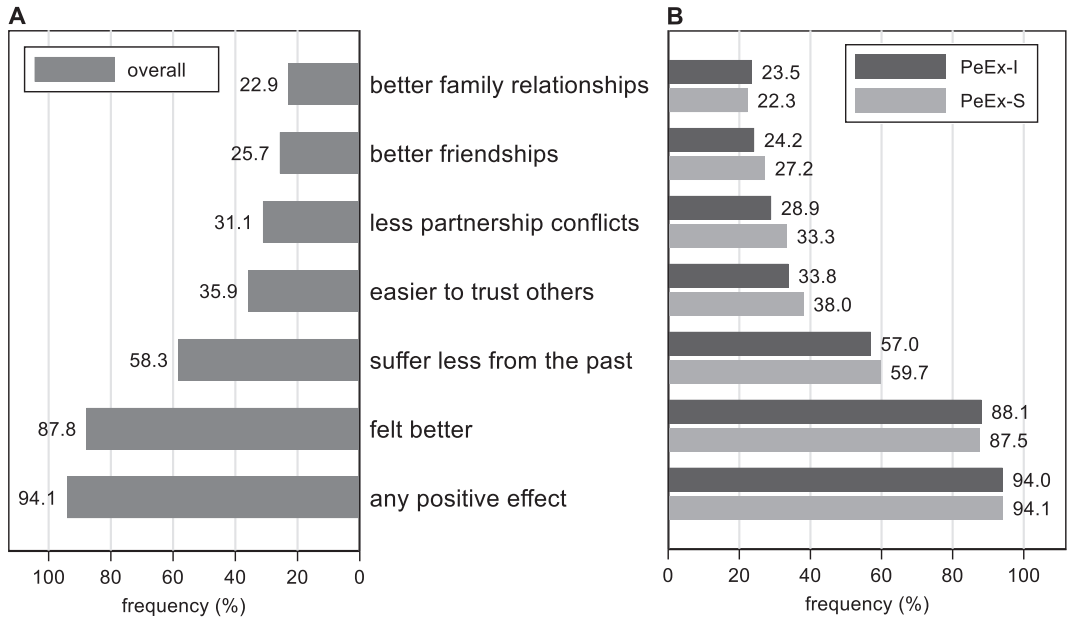

FIGURE 5 Frequency of positive effects in the INEP. A. over both groups; B. in temporally intensified (PeEx-I) vs. standard exposure (PeEx-S)

ity ratings were *increasing* when exposure exercises were introduced. Patients seem to become more confident about treatment when they start to engage in individual exercises. It is possible that the application of exposure exercises actually increases aspects of treatment acceptance, which would directly contradict typical negative beliefs about exposure. Patients also perceived their own treatment engagement as high and showed good objective engagement, since they completed on average 13 out of 14 sessions and conducted the designated number of exposure exercises during the main treatment phase. Subjective engagement slightly diminished during treatment. This probably reflects that treatment intensity in this study decreased over time or that gradual alleviation of clinical symptoms and impairment reduced the urge to engage in treatment activities. With 22.8%, dropout in the present study was in line with meta-analyses of dropout in anxiety-CBT (Fernandez et al., 2015; van Ingen et al., 2009). Negligible center effects and independence of baseline severity and acceptance furthermore indicated that the results are relatively stable.

Side effects in the present sample can be characterized as frequent (>40%) but weak (≤1.0 on a 45-point scale). Other studies that used the same measure in mixed outpatient settings (Gerke et al., 2020; Nestoriuc & Rief, 2013) report a lower frequency of side effects, around 20–25%. However, these studies used retrospective surveys with delays of up to 10 years. The frequency of reported side effects is considerably higher when surveyed during treatment (Grünberger et al., 2017). It is probable that weak and punctual side effects are forgotten or devaluated over time. This is supported by the reduced side effect rates in our 6-month follow-up. Our results thus encourage the assumption that exposure-based therapy is not the intervention with "the highest risk" but with a typical risk of side effects compared to other psychological interventions. Women and patients with prior psychological treatment were more susceptible to side effects. This may reflect a higher willingness to disclose negative effects or an increased vulnerability, for example, after unsuccessful prior treatment. We also found reduced treatment effectiveness in individuals with side effects. It is plausible that negative experiences during treatment reduce its effectiveness. Alternatively, lack of success could draw attention to perceived side effects, or individual variables like aversive childhood experiences simultaneously reduce treatment effectiveness and increase the vulnerability for side effects. Almost all patients experienced "positive side effects" after exposure-based treatment, the intensity of which was far higher than that of the corresponding negative effects. This suggests that, on average, positive effects outweigh negative effects. Reports of malpractice were rare in our sample. Notably, only 1.3% of patients felt pushed towards exposure at some point. This underscores that patients generally do not perceive exposure exercises as intrusive. In Strauß' et al. (2021) mixed representative sample, 6.5% indicated having felt forced

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during psychological treatment. Incidences of coercion may be rarer in correctly performed exposure therapy than in other treatments.

STANDARD VS. TEMPORALLY INTENSIFIED EXPOSURE

The interest in brief or condensed versions of exposure-based treatment has been increasing in recent years (Öst & Ollendick, 2017; Zoellner et al., 2022). In our analysis of temporally intensified treatment it was equivalent to weekly treatment regarding satisfaction, credibility, and engagement. Intensively treated patients even conducted *more* homework exercises, although they had fewer time between sessions. In line with lower dropout rates during the exposure phase, this documents that temporally confined treatment can be beneficial for patient engagement (Swift & Greenberg, 2012). Expectations that temporally intensified exposure exercises are rejected by patients are not supported. Given that temporal intensification also leads to faster symptom reduction (e.g., Pittig et al., 2021), this variant should be considered as an alternative to standard weekly treatment.

At the same time, intensified treatment was associated with higher perceived treatment burden. During the intensive phase, patients spent more than 10 hours per week with treatment, which obviously required more effort than weekly sessions. Temporal intensification also increased the intensity (but not frequency) of reported side effects. Yet, the overall difference between treatment groups was small and was attenuated at follow-up. This suggests that side effects induced by temporal intensification were typically not severe or enduring. Taken together, temporal intensification of exposure has both benefits and costs. A central question is thus whether the faster success in intensified treatment is worth the higher effort and potential side effects. We argue that patients in the present sample were obviously willing to take on the costs since they did not withdraw their engagement or satisfaction. This indicates that, despite higher strain, they perceived intensified treatment as tolerable.

IMPLICATIONS

This work has implications for the dissemination of exposure-based treatments, the prevention and handling of side effects, and the implementation of temporal enhancement strategies. This large trial with different anxiety disorders and comorbid disorders comes close to a phase IV study and possesses relatively good external validity. The results illustrate that exposure-based treatment is not only safe, acceptable, and engaging for the "standard" patient with, for example, panic disorder, but for most patients with anxiety disorders. This is relevant since therapists often exclude patients from exposure that have special characteristics (Meyer et al., 2014). Side effects of exposure-based therapy appeared mostly minor or transient. The symptoms of anxiety disorders by contrast are persistent and significantly impairing. The opportunity to remedy these symptoms justifies the to-be-expected side effects of exposure-based treatment. As for severe side effects, they are rare and there is currently no model available to reliably predict them. The ethically correct decision is thus to routinely offer exposure-based treatment and to adapt it if relevant side effects occur. Nonetheless, at least half of all recipients of exposure-based treatment experience some type of side effect. Clinicians should therefore have strategies at hand to mitigate and deal with these effects. The most frequent side effects in this study were (fear of) treatment stigma, insurance problems, low mood, the experience to depend on the therapist and conflicts with patients' partners, which is largely in line with previous research (Gerke et al., 2020; Rheker et al., 2017; Schermuly-Haupt et al., 2018). Since there is a tendency in clinicians to neglect negative effects (Hatfield et al., 2010; Sarkozy, 2010), they should actively encourage patients to report them in treatment. For example, regarding potential insurance problems, patients should be informed from the beginning whether being in treatment complicates contracting future health policies. Regarding potential "low mood," patients should know that they may at times feel troubled about treatment and that it is essential to discuss this with the therapist.

The "fear of treatment stigma" is inherent to psychotherapy. In exposure-based treatment, it can be specifically triggered when exercises take place in public spaces (Olatunji et al., 2009). Clinicians should be sensitive to potential violations of therapeutic boundaries during exposure and consider measures like preparing patients how to react in a helpful manner when they meet a familiar person during an exposure exercise. Core strategies to reduce feelings of "dependency on the therapist" are offering options, letting patients decide on forthcoming steps, and handing the responsibility for exposure exercises over to patients as soon as possible (cf. Hardy et al., 2019). This can even be beneficial for symptom reduction (Levy & Radomsky, 2016). Since partnership conflicts can be a relevant side effect, clinicians should take the patients' social environment into account. A couple session could be considered early in treat-

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ment to discuss the partner's role during exposure-based therapy and to recommend sources of information for relatives. Last, but not least, appropriate supervision and peer support are relevant measures to manage side effects (Becker-Haimes et al., 2020).

Regarding temporal intensification, clinicians need to gauge the potential benefits and costs for a specific patient. Benefits include faster symptom reduction and less impairment (Pittig et al., 2021); potential costs include higher treatment burden and risk for side effects. If a patient aims for rapid symptom reduction (e.g., in order to master a planned exam or a flight), he or she will be more ready to accept the efforts of temporal intensification. On the other hand, patients who experience the treatment already as very burdening or have a history of negative treatment effects are probably at higher risk for costly intensification and should be offered a standard schedule. Determining the optimal treatment intensity for a given patient is an important challenge for the field of personalized psychotherapy (Huibers et al., 2021).

LIMITATIONS

Limitations of this study include, first, potential selection bias, since individuals who did not consent to intensified treatment were not included. Second, we did not apply a comprehensive treatment acceptance scale (e.g., Tarrier et al., 2006), which reduces the comparability of acceptance scores. We rather operationalized acceptance using different facets drawn from the literature. A strength of this approach is that it includes behavioral measures. Yet, we did not include all potentially relevant aspects of acceptance. For example, we did not explicitly assess willingness to exposure, although this has also been linked to faster symptom reduction (Reid et al., 2017). We however assessed the general willingness to continue the treatment on a session-by-session level—which was high—and used it as a measure of engagement. Third, we used a relatively broad measure of side effects that did not specifically aim on exposure. This allows to compare negative event rates of different therapies but prevents disentangling the side effects of exposure from that of other treatment components (e.g., cognitive preparation) and does not reveal specific side effects of exposure, which would require a more qualitative approach (as in Schneider et al., 2020). Future studies might also ask more specifically whether side effects are "due to exposure" instead of "due to therapy." Fourth, we did not include the clinicians' perspective on side effects. Their evaluation may considerably differ from the patients' perspectives. Including therapists' perspectives may help to further discern transient negative experiences from true side effects and would allow for a further test of therapists' negative beliefs about exposure. Fifth, some individuals who quit treatment during exposure did not complete the post assessment. It is possible that dropouts were more critical towards treatment or experienced more side effects, which would bias our evaluation of exposure to the positive. To close that gap, future studies should specifically focus on side effects in dropouts from exposure therapy. Finally, the malpractice scale of the INEP was not fully included: we did not assess physical and sexual transgressions and breaches of confidentiality. However, these severe forms of malpractice are very rare (Nestoriuc & Rief, 2013) and are unlikely in a highly controlled trial with videotaped sessions and therapists under constant supervision.

The scope of our results is also limited by the specific design of the trial: First, our patients used exposure to test their central concerns, which may have detracted the focus away from fear as a negative side effect. Second, although the overall number of exposure exercises in this study (21 exercises per patient including the self-management phase) was comparable to other RCTs (Deacon, Kemp, et al., 2013; Lang et al., 2012; Lindner et al., 2019), the condensed treatment format applies fewer exposure exercises than other types of exposure-based CBT (e.g., Clark et al., 2006). Third, we manipulated the time frame but no other aspects of intensity, like the difficulty of exercises. Our results thus cannot be generalized to other forms of intensive exposure, such as flooding. High acceptance of exposure with prolonged and difficult exercises has been demonstrated elsewhere (Sciarrino et al., 2020).

Conclusions

Prediction error-based exposure is highly accepted by patients regarding satisfaction, engagement, and credibility, in a standard as well as temporally intensified variant. Just as with other psychological treatments, side effects are relatively frequent in exposure-based treatment. The most common side effects, such as treatment stigma, low mood, or consequences for insurance policies, are present in any form of psychotherapy and can be appropriately addressed during treatment (Linden & Strauss, 2013). For the large majority of patients, side effects are tolerable and are outweighed by positive effects in terms of frequency and intensity. Intense negative effects of exposure are not an entire myth but are very rare. Accordingly, the

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strong reservations that some clinicians hold against exposure cannot be upheld. Exposure-based therapy altogether appears to be a powerful treatment for ameliorating the burden of anxiety disorders and the present results encourage its use, even in temporally dense variants.

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