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Exploring study dropout in drug trials for adults with PTSD: insights from a conventional and individual participant data meta-analysis

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ABSTRACT

Background: Dropout rates and factors contributing to dropout in drug and placebo groups in pharmacotherapy trials for posttraumatic stress disorder (PTSD) are not well understood.
Objective: This study aimed to examine differences in all-cause study dropouts between drug and placebo groups, using conventional meta-analysis and an exploratory predictor analysis of individual participant data from three trials.
Method: We included randomized controlled trials (RCTs) of adults with PTSD, comparing drug monotherapy with placebo. Forty-three RCTs ($n = 4829$) were included in a conventional meta-analysis. Additionally, we conducted a small exploratory predictor analysis including participant-level data from three RCTs ($n = 246$).
Results: In the conventional meta-analysis, study dropout was marginally lower in the drug relative to the placebo group, but the difference was not significant, RR = 0.92, 95% CI [0.83, 1.02], $p = .099$. Drug class, dosing regimen, population, study duration, or gender were not related to dropout.
In the exploratory predictor analysis, study dropout did not differ significantly between drug and placebo groups ($p = .617$). In the drug group, gender was a significant predictor for dropout, with males having higher dropout rates ($p = .046$). When controlling for baseline PTSD symptom severity, gender was no longer a statistically significant predictor ($p = .051$). None of the other predictors in *drug, placebo, and combined* group analyses were significant in predicting drop-out.
Conclusions: This study demonstrated that study dropout rates in monotherapy pharmacotherapy RCTs for PTSD do not significantly differ between drug and placebo groups. These findings underscore the need for further research to identify the factors contributing to dropout in PTSD pharmacotherapy trials and to develop tailored treatment adherence strategies. Additionally, they highlight the importance of pooling participant-level data to facilitate more comprehensive and granular analyses in future research.

Explorando el abandono de tratamiento en estudios de ensayos farmacológicos para adultos con TEPT: hallazgos de un metaanálisis convencional y de datos individuales de participantes

Antecedentes: Las tasas de abandono de tratamiento y los factores que contribuyen a este evento en los grupos de fármaco y placebo en los ensayos de farmacoterapia para el trastorno de estrés postraumático (TEPT) no se comprenden con claridad.
Objetivo: Este estudio tuvo como objetivo examinar las diferencias en los abandonos del estudio por cualquier causa entre los grupos de fármaco y placebo, utilizando un metaanálisis convencional y un análisis exploratorio de predictores a partir de datos individuales de participantes provenientes de tres ensayos.
Método: Se incluyeron ensayos clínicos aleatorizados (ECA) en adultos con TEPT comparando la monoterapia farmacológica con placebo. Cuarenta y tres ECA ($n = 4.829$) fueron incluidos en

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PALABRAS CLAVE
Metaanálisis de datos individuales de participantes; TEPT; predictores; farmacoterapia; tratamiento

HIGHLIGHTS

- This study found no significant differences in dropout rates between drug and placebo groups in PTSD pharmacotherapy trials, with an overall high dropout rate of 28%, highlighting a major challenge in these trials.
- Initial analyses indicated that males were at a higher risk of dropping out of drug treatment compared with females, though this effect was not significant after controlling for PTSD severity. This suggests a complex interaction between gender, PTSD severity, and dropout rates.
- The study underscores the importance of standardized protocols for reporting reasons for discontinuation in clinical trials to identify precise predictors of dropout and

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el metaanálisis convencional. Además, se llevó a cabo un pequeño análisis exploratorio de predictores, que incluyó datos a nivel de participante de tres ECA ($n = 246$).
Resultados: En el metaanálisis convencional, la tasa de abandono de tratamiento durante los estudios fue marginalmente menor en el grupo de fármaco en comparación con el grupo placebo, pero la diferencia no fue estadísticamente significativa (RR = 0.92, IC del 95% [0.83, 1.02], $p = .099$). El tipo de fármaco, el régimen de dosificación, la población, la duración del estudio y la distribución por género no se asociaron con el abandono.
En el análisis exploratorio de predictores, el abandono del estudio no se diferenció significativamente entre los grupos de fármaco y placebo ($p = .617$). En el grupo de fármaco, el género fue un predictor significativo del abandono, con tasas más altas en hombres ($p = .046$). Al controlar por la gravedad basal de los síntomas de TEPT, el género dejó de ser un predictor estadísticamente significativo ($p = .051$). Ninguno de los otros predictores analizados en los grupos de fármaco, placebo y análisis combinados de grupo resultó ser significativo para predecir el abandono.
Conclusiones: Este estudio demostró que las tasas de abandono en ensayos clínicos aleatorizados de monoterapia farmacológica para el TEPT no difieren significativamente entre los grupos de fármaco y placebo. Estos hallazgos subrayan la necesidad de realizar más investigaciones que identifiquen los factores que contribuyen al abandono en los ensayos de farmacoterapia para el TEPT, y que permitan desarrollar estrategias personalizadas para mejorar la adherencia al tratamiento. Además, destacan la importancia de reunir datos a nivel del participante para facilitar análisis más completos y detallados en futuras investigaciones.

improve the reliability and comparability of research findings.

1. Introduction

Pharmacotherapy is widely used in the management of posttraumatic stress disorder (PTSD), either as a standalone (monotherapy) treatment or in combination with psychotherapy (Hoskins et al., 2021). First-line pharmacological treatments include antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and the serotonin–norepinephrine reuptake inhibitors (SNRIs; Forbes et al., 2020; World Health Organization, 2013). There have been relatively fewer trials investigating other drug classes (e.g. anticonvulsants, antipsychotics and mood stabilizers).

Study dropout rates in psychotherapy interventions for PTSD have received considerable attention. Earlier findings reported an average dropout rate of 18% ($k = 42$) among randomly assigned active psychotherapy treatments, with a range of 15% to 22% (Imel et al., 2013). Further, treatment modality appears to influence dropout rates. CBT with exposure components has been associated with greater attrition (33%) compared to treatments without exposure elements (17%; Bradley et al., 2005). Recent comprehensive meta-analyses ($k = 114$) support these findings, with dropout rates ranging from 14% in non-trauma-focused treatments to 18% in trauma-focused approaches, yielding an average rate of 16% across randomized controlled psychotherapy trials (Lewis et al., 2020).

Similar concerns have been raised in relation to study dropout from pharmacotherapy for PTSD (Gu et al., 2016). However, the literature is scarce. A meta-analysis of RCTs investigating the efficacy and dropout in pharmacotherapy trials for PTSD found an average dropout rate ranging from 3.5% to 54% ($k = 30$), with no significant difference between drug and placebo groups (Gu et al., 2016). Similarly, a recent network meta-analysis found no difference in dropout rates between different drugs and placebo, except for phenelzine which had lower dropout rates (Cipriani et al., 2018).

High dropout in clinical trials introduces attrition bias and confounds the evaluation of efficacy (Gu et al., 2016). All-cause study dropout, which refers to the premature termination of participation in the study by patients for any reason during the intervention before completing the post-intervention assessment. This can significantly influence outcomes as dropout may result from various factors such as adverse effects, lack of efficacy, or personal reasons (Berke et al., 2019). Additionally, the dropout ratio (drug to placebo) differs across pharmaceutical agents in PTSD treatment (Williams et al., 2022). For the SNRI, venlafaxine, the dropout rate was 4% compared to 3% in the placebo groups. Antipsychotics were associated with a higher dropout rate compared to placebo, with 16% in the experimental group compared to 7% in the placebo group (Williams et al., 2022). The lack of a clear definition of dropout in these studies may have also accounted for the heterogeneity in reported rates (Schottenbauer et al., 2008). Some studies examine treatment dropout, which can vary across studies, while others focus on study dropout, which is typically more straightforward.

Dropout can have serious consequences for both patients and mental health care providers. One study found that patients who did not drop out were more likely to experience clinically significant gains compared to those who dropped out (Berke et al., 2019). Similarly, another study reported no significant treatment effects for those who dropped out and large

effects for those who did not (Tuerk et al., 2013). Furthermore, when not taking prescribed medications, patients are more likely to exhibit a reduced quality of life that can extend to family members, friends, coworkers, and communities (Swift & Greenberg, 2012). Non-adherence might be associated with feelings of frustration on the part of providers (Piselli et al., 2011). Gaining a deeper insight into patients who are prone to dropping out of treatment can help alleviate provider frustration and mitigate the severity of patients' symptoms.

Factors contributing to dropout from pharmacotherapy for PTSD patients are manifold and include adverse effects, experimental conditions, and dose-related effects (Gu et al., 2016). Additionally, patient characteristics such as gender, age, and trauma type can also contribute to dropout (Bremer-Hoeve et al., 2023). Other factors that have been found to predict dropout are lower baseline PTSD severity, not receiving the preferred treatment, and greater differences in the perceived credibility of one treatment over another (Kline et al., 2020). An RCT examining predictors and moderators of dropout among 165 adults randomized to one of four treatment arms (naltrexone (NAL), NAL plus prolonged exposure (PE), placebo, or placebo plus PE) found that the type of trauma and the degree of improvement in PTSD significantly predicted dropout and together accounted for 76% of the variance in dropout (Zandberg et al., 2016). Patients with PTSD stemming from accidents and 'other trauma' were associated with the highest dropout, while physical assault was associated with the lowest dropout. However, it is important to note that a sample size of 165 is heavily underpowered to detect significant predictors or moderators of dropout. This underscores the need for conducting research with larger sample sizes to validate these findings. Trials have included a variety of patient groups, such as veterans and patients with different illness duration (Duek et al., 2021; Lee et al., 2016), and have predominantly focused on dropout from psychotherapy, leaving a gap in our understanding of dropout from pharmacotherapy (Duek et al., 2021; Kline et al., 2020). Bremer-Hoeve et al. (2023) highlighted the need to investigate patient characteristics as predictors of dropout.

Despite the importance of understanding factors that contribute to dropout, research on pharmacotherapy dropout in PTSD treatment remains limited. Previous studies have identified a variety of potential predictors, including adverse effects, experimental conditions, patient demographics, trauma type, baseline symptom severity, and treatment preference. However, most research has focused on psychotherapies rather than pharmacotherapies, creating a significant knowledge gap. Therefore, there is a pressing need to investigate patient characteristics as predictors of dropout specifically in pharmacotherapy trials (Bremer-Hoeve et al., 2023).

To address this gap, we conducted an individual participant data meta-analysis exploring all-cause study dropout and its potential predictors in PTSD pharmacotherapy. To our knowledge, this is the first study to focus specifically on predictors of dropout in RCTs of pharmacotherapy for PTSD. Our approach was twofold: first, we compared differences in all-cause study dropout between drug and placebo groups using conventional meta-analysis; second, we conducted an exploratory investigation of putative predictors of dropout in the pooled drug group, placebo group, and the combined sample (drug + placebo) using individual participant data meta-analysis. For the purpose of this meta-analysis, a participant was considered a dropout if they did not complete the post-intervention assessment. This allowed us to retain data for the greatest number of available participants in the analyses, while maintaining a uniform definition of dropout across the included trials.

2. Methods

Further details can be found in the protocol paper (Wright et al., 2022).

2.1. Eligibility criteria

Study inclusion was restricted to monotherapy RCTs comparing *drug* to inactive *placebo* for adults, 18 years or older, with a clinical diagnosis of PTSD as determined by an established diagnostic interview. Trials where a diagnosis was based on any version of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) or the International Classification of Diseases (World Health organization, 2018) were included.

2.2. Search strategy and study identification

The initial systematic literature search was completed by the Cardiff University Traumatic Stress Research Group (till 1st May 2018). We updated the search twice, the initial update included trials from the 1st of May 2018 till 13th of May 2019, and the second included trials from 1 January 2019 till the 11 January 2021. Academic databases included PubMed, EMBASE, PsycINFO, PTSDpubs, and CENTRAL. An example of the search strategy used is presented in Appendix 1. Two reviewers (SLW and DP for the first and SLW and ABW for the second update) independently assessed the titles and abstracts of all hits discovered in the academic search. Each reviewer independently reviewed the eligible full texts, while a third reviewer addressed any uncertainties regarding study inclusion.

2.3. Data collection

For the participant-level datasets, we contacted the principal authors of the trials that met the eligibility criteria through email with a request to share their anonymized, participant-level data. We utilized the email addresses provided in the study's publication, as well as email addresses on more recently published articles. Six emails were sent to the corresponding authors before reaching out to at least two other co-authors (when possible). Data sharing and storage adhered to European General Data Protection Regulation (Regulation [EU] 2016/679) requirements. Prior to sharing, participant-level datasets were anonymized and then securely uploaded to an encrypted folder at Vrije Universiteit Amsterdam. To maintain data security, we sent the encrypted folder link to different email addresses from the ones used for the passwords.

2.4. Data extraction

The outcome of interest was all-cause study dropout only as reasons for treatment discontinuation were not available. Study-level data collected included available sociodemographic information, the specific drug, drug class, trial and dosing details, number of patients randomized to the drug and placebo arms, and the total number of dropouts in each arm.

2.4.1. Conventional meta-analysis

To examine potential sources of heterogeneity, we extracted data on drug class, flexible versus fixed-dose, dose frequency (daily versus twice daily), population (military versus community versus mixed), study duration (weeks), and percentage of male participants.

2.4.2. Individual participant data predictor analysis

Potential predictors included age in years, gender (male or female), marital status (married or other), clinician-rated PTSD symptom severity, clinician-rated baseline PTSD intrusion severity, clinician-rated baseline PTSD avoidance severity, clinician-rated baseline PTSD hyperarousal severity, self-report PTSD symptom severity, self-report baseline PTSD intrusion severity, self-report baseline PTSD avoidance severity, diagnosis of a current mood disorder (yes or no) based Structured Clinical Interview for DSM-IV (First et al., 1994), and diagnosis of a current anxiety disorder (yes or no) based Structured Clinical Interview for DSM-IV (First et al., 1994). As a self-report measure of hyperarousal severity was not available for all studies included in this IPD, we did not include it as a predictor – only clinician-rated baseline PTSD hyperarousal severity.

2.5. Risk of bias

To evaluate the risk of bias across the available trials included in our analyses, we used the Cochrane Risk of Bias 2 (Higgins et al., 2022). The risk of bias related to the domain 1 (bias due to the randomization process), domain 2 (bias due to deviations from intended intervention), domain 3 (bias due to missing outcome data), domain 4 (bias due to measurement of the outcome), and domain 5 (bias due to the selection of the reported result) were independently evaluated by two reviewers (SW and AK). Each domain's risk of bias was evaluated as *low*, *high*, or having *some concerns*.

In the risk of bias for the individual participant data predictor analyses, domain 3 (bias due to missing outcome data) and domain 5 (bias due to the selection of the reported result) were not applicable.

2.6. Data analysis

2.6.1. Conventional meta-analysis

The data analysis was conducted in R statistical software (version 4.3) using the *meta* and *metafor* packages. Pooled dropout rates for the drug, placebo, and combined groups were calculated using the *metaprop* function. We conducted pairwise meta-analyses of the drug versus placebo groups, using random-effects meta-analysis. The effect size was the risk ratio (RR). Heterogeneity was quantified using I^2 and is presented with the 95% prediction intervals. Potential factors (effect modifiers) contributing to heterogeneity were explored through subgroup analysis and meta-regression when data were available across all included studies. A sensitivity analysis was performed to assess the impact of excluding trials with a high risk of bias in the main analyses comparing drug and placebo groups. We inspected the contour-enhanced funnel plot and used Peters test (Peters et al., 2008) to assess for small-study effects.

2.6.2. Individual participant data predictor analysis

For research question II, we examined all-cause dropout in *drug* and *placebo* groups independently, as well as combined. After receiving participant-level datasets, we extracted the available baseline sociodemographic and clinical data for both groups. For each trial, baseline PTSD measures were transformed into z scores before combining the individual datasets into one large, master dataset. This process of standardizing the variables allowed us to compare trials using different tools to measure PTSD symptoms. We investigated the influence of the potential predictors (see the Data extraction section) on dropouts while considering clustering by study. We conducted a series of bivariate analyses to assess the risk ratio (RR) of each factor independently (the 'bivariate model')

before running the multivariate model. Participants who discontinued the study before reaching the halfway point were categorized as early dropouts, whereas those who withdrew after the halfway point were classified as late dropouts. We ran additional sensitivity analyses to explore our findings. First, we ran a series of chi-squared tests to determine whether the proportion of dropouts was equal between *drug* and *placebo* groups, whether the proportion of early and late dropouts was equal between *drug* and *placebo* groups, and whether the proportion of males to females was equal between *drug* and *placebo* groups. Lastly, we ran t-tests to examine whether there was a significant difference in baseline PTSD total score by gender for the *drug*, *placebo,* and *combined* groups separately.

3. Results

The systematic literature search identified 48 eligible trials (see Appendix 2). The PRISMA flowchart is presented in Appendix 3. Of the 48 eligible trials, 35 (73%) were published before 2012. Dropout data from 43 trials were available and used in the conventional meta-analysis.

3.1. Risk of bias

3.1.1. Conventional meta-analysis

The results of the risk of bias assessment for study dropout per domain and study, are presented in the Appendix 4. Seven of the 43 trials had a low overall risk of bias. The other 36 trials were rated as having some concerns, and none being rated as a high risk of bias. Some concerns were mostly related to domain 1, because of a lack of information regarding the specific method used for randomization, and domain 5, insufficient information regarding a pre-specified analysis plan. All trials were rated as a low risk of bias for domain 2, except for two which were conducted per protocol analyses. All studies were rated as low for domain 3 and 4.

3.1.2. Individual participant data predictor analyses

Exploratory participant-level predictor analyses for dropout could be analyzed in three trials (Brady et al., 2005; Dowd et al., 2020; Dunlop et al., 2017). We received five eligible trial datasets, however, two trials only had completer trial data available (Carey et al., 2012; Yeh et al., 2011). All three RCTs with available participant-level data were rated as having a low risk of bias on domain 1, 2 and 4. Refer to Appendix 5 for the risk of bias ratings for each trial.

3.2. Research question i: conventional dropout meta-analysis

3.2.1. Participant and study characteristics

For the 43 trials ($n = 4829$) included in the meta-analysis, the earliest trial was published in 1988, and the most recent in 2021. The median sample size was 66 participants per trial. The median of the mean participant age was 41 years (range32 to 55). All trials ranged from 5 to 12 weeks, excluding two which were 24 weeks (Davidson et al., 2006A) and 26 weeks (Raskind et al., 2018). A summary of the trial and intervention characteristics for the 43 trials are presented in Appendix 6 and Appendix 7, respectively. Appendix 8 presents the details of the pharmacological interventions.

3.2.2. Dropout rates

The study dropout rate for *drug*, *placebo*, and *combined* groups was 27% (95% CI [0.23, 0.31], $I^2 = 72.8\%$), 30% (95% CI [0.24, 0.35], $I^2 = 80.2\%$), and 28% (95% CI [0.24, 0.32], $I^2 = 86.6\%$), respectively.

3.2.3. Conventional meta-analysis of dropout

Forty-three trials provided data for 2555 participants who received *drug* and 2274 who received placebo. The forest plot for the risk of dropout is shown in Appendix 9. Dropout rates were marginally lower in the drug group relative to the placebo group, but the difference was not significant, RR = 0.92, 95% CI [0.83, 1.02], $p = .099$. Confidence intervals of nearly all individual trials crossed the line of no effect. Low heterogeneity was found as suggested by the narrow prediction (0.72–1.18) and confidence (0.83–1.02) intervals.

3.2.3.1. Subgroup analyses and meta-regressions. No significant difference was found in the risk of dropping out between *drug* and *placebo* groups by drug class ($p = .364$).

No significant difference was found in the risk of dropping out between *drug* and *placebo* groups in trials with flexible versus fixed dosing ($p = .432$).

No significant difference was found in the risk of dropping out between *drug* and *placebo* groups by the frequency of dosing ($p = .809$).

No significant difference was found in the risk of dropping out between *drug* and *placebo* groups by population (military versus community versus mixed; $p = .824$).

Overall, there is no strong evidence that study duration influenced dropout. Meta-regression analysis yielded a coefficient of −0.01 (95% CI [−0.03, 0.02], $p = .557$).

The percent of males in a trial did not affect dropout with meta-regression analysis yielding a coefficient of −0.16 (95% CI [−0.49, 0.18], $p = .363$).

Appendix 10 present the results of the subgroup analyses and meta-regressions.

3.2.4. Sensitivity analysis

When we only included the seven trials with a low risk of bias rating, there was no significant difference in the risk of dropping out between drug and placebo groups, RR = 1.15, 95% CI: 0.88, 1.50, $p = .316$ (see Appendix 11).

3.2.5. Publication bias

Visual inspection of the contour-enhanced funnel plot suggested some publication bias (see Appendix 12). Furthermore, Peters test for small study effects was non-significant ($p = .684$).

3.3. Research question ii: predictors of dropout using individual participant data

3.3.1. Participant and study characteristics

Participant-level data from 3 available placebo-controlled drug trials for PTSD ($n = 246$) comprised Sertraline (Brady et al., 2005), GSK561679 (Dunlop et al., 2017), and Eszopiclone (Dowd et al., 2020). All three trials were conducted in the USA. The mean (SD) age of participants receiving drug ($n = 124$) was 38.78 years (range = 19–64) with 88 (70.97%) females. While the mean age of participants receiving placebo ($n = 122$) was 39.62 years (range = 19–63) with 92 (75.41%) females. A summary of participant characteristics for *drug* ($n = 124$) and *placebo* ($n = 122$) groups are presented in Appendix 13.

3.3.2. Dropout rates

In the *drug* group, 36 participants (29.03%) of 124 dropped out. Of the 36 dropouts, 23 did so before the midpoint and 13 dropped out after. In the *placebo* groups, 39 participants (31.97%) of 122 dropped out. Of the 39 dropouts, 21 dropped out before the trial midpoint and 18 dropped out after the midpoint. The proportion of dropouts did not differ significantly between *drug* and *placebo* groups ($p = .480$).

3.3.3. Predictors of dropout

3.3.3.1. Drug group. The results of bivariate and multilevel analyses of participant-level predictors of dropout are presented in Table 1.

In bivariate analysis, the chance of dropping out was significantly higher for male participants, RR = 1.96, 95% CI [1.01, 3.77], $p = .046$.

In bivariate analysis, the other putative predictors (age, marital status, clinician-rated PTSD symptom severity, clinician-rated baseline PTSD intrusion severity, clinician-rated baseline PTSD avoidance severity, clinician-rated baseline PTSD hyperarousal severity, self-reported PTSD symptom severity, self-reported baseline PTSD intrusion severity, self-reported baseline PTSD avoidance severity, diagnosis of a mood disorder, diagnosis of an anxiety disorder) did not achieve statistical significance, $p < .05$. When controlling for baseline PTSD severity, gender was no longer a significant predictor of dropout, RR = 1.97, 95% CI [1.00, 3.89], $p = .051$.

3.3.3.2. Placebo group. The results of bivariate and multilevel analysis of participant-level predictors and dropout are presented in Table 2. In bivariate analysis, none of the putative predictors achieved statistical significance, $p < .05$.

3.3.3.3. Combined groups. The results of bivariate and multilevel analysis of participant-level predictors and dropout are presented in Table 3. In bivariate analysis, none of the putative predictors achieved statistical significance, $p < .05$.

3.3.4. Sensitivity analysis

The chi-square goodness of fit tests revealed no significant differences between *drug* and *placebo* groups in the proportions of dropouts, X^2 (1, 246) = 0.25, $p = .617$; early and late dropouts, X^2 (2, 246) = 1.03, $p = .598$; and males to females, X^2 (1, 246) = 0.62, $p = .432$.

We ran t-tests to examine whether there was a significant difference in baseline PTSD total score by

Table 1. Predictors of dropout for the drug group using participant-level data.

			Multilevel Bivariate Model				Multilevel Multivariate Model *N* (*k*) = 121 (3)			
Predictor	*k*	*n*	RR	95% CI	z	*p*	RR	95% CI	z	*p*
Age (years)	3	124	1.00	0.97–1.03	−0.25	.803	1.00	0.97–1.03	−0.17	.866
Male gender	3	124	1.96	1.01–3.77	2.00	.046*	1.97	1.00–3.89	1..95	.051
Marital status (married)	2	61	0.96	0.37–2.46	−0.09	.925	.	.	.	.
Baseline PTSD total severity: clinician-rated	3	121	1.06	0.75–1.52	0.34	.734	1.10	0.77–1.57	0.52	.601
Baseline PTSD total severity: self-report	3	120	0.97	0.68–1.39	−0.15	.877	.	.	.	.
Baseline PTSD intrusion severity: clinician-rated	3	121	1.12	0.80–1.57	0.67	.502	.	.	.	.
Baseline PTSD intrusion severity: self-report	2	108	0.93	0.63–1.38	−0.35	.728	.	.	.	.
Baseline PTSD avoidance severity: clinician-rated	3	121	1.01	0.70–1.47	0.06	.949	.	.	.	.
Baseline PTSD avoidance severity: self-report	2	108	0.92	0.60–1.39	−0.42	.678	.	.	.	.
Baseline PTSD hyperarousal severity: clinician-rated	3	121	0.99	0.70–1.41	−0.04	.966	.	.	.	.
Baseline diagnosis of a mood disorder	2	112	1.17	0.45–3.05	0.33	.742	.	.	.	.
Baseline diagnosis of anxiety disorder	2	112	0.76	0.18–3.19	−0.37	.712	.	.	.	.

Note. *n* = number of participants; RR = risk ratio; *z* = *z*-score; *p* = *p*-value; *k* = number of studies.

Table 2. Predictors of dropout for the placebo group using participant-level data.

			Multilevel Bivariate Model				Multilevel Multivariate Model *N* (*k*) = 122 (3)			
Predictor	No. of studies	*n*	RR	95% CI	z	*p*	RR	95% CI	z	*p*
Age (years)	3	122	1.00	0.97–1.02	−0.30	.766	0.99	0.97–1.02	−0.45	.652
Male gender	3	122	1.20	0.60–2.42	0.52	.601	1.26	0.62–2.53	0.64	.552
Marital status (married)	2	57	1.23	0.50–3.04	0.46	.647	.	.	.	.
Baseline PTSD total severity: clinician-rated	3	122	1.23	0.92–1.65	1.39	.166	1.25	0.93–1.67	1.46	.145
Baseline PTSD total severity: self-report	3	119	1.32	0.94–1.85	1.61	.106	.	.	.	.
Baseline PTSD intrusion severity: clinician-rated	3	122	1.21	0.89–1.66	1.22	.222	.	.	.	.
Baseline PTSD intrusion severity: self-report	2	108	1.21	0.88–1.67	1.19	.236	.	.	.	.
Baseline PTSD avoidance severity: clinician-rated	3	122	1.17	0.87–1.57	1.03	.301	.	.	.	.
Baseline PTSD avoidance severity: self-report	2	107	1.30	0.94–1.80	1.58	.114	.	.	.	.
Baseline PTSD hyperarousal severity: clinician-rated	3	122	1.14	0.83–1.56	0.81	.417	.	.	.	.
Baseline diagnosis of a mood disorder	2	110	0.81	0.36–1.85	−0.50	.618	.	.	.	.
Baseline diagnosis of anxiety disorder	2	110	1.45	0.56–3.73	0.77	.439	.	.	.	.

Note. *n* = number of participants; RR = risk ratio; *z* = *z*-score; *p* = *p*-value; *k* = number of studies.

Table 3. Predictors of dropout for the drug and placebo groups combined using participant-level data.

			Multilevel Bivariate Model				Multilevel Multivariate Model *N* (*k*) = 243 (3)			
Predictor	No. of studies	*n*	RR	95% CI	z	*p*	RR	95% CI	z	*p*
Age (years)	3	246	1.00	0.98–1.02	−0.37	.710	0.99	0.97–1.02	−0.47	.636
Male gender	3	246	1.53	0.96–2.46	1.78	.075	1.56	0.96–2.52	1.80	.071
Marital status (married)	2	118	1.08	0.57–2.04	0.24	.808	.	.	.	.
Baseline PTSD total severity: clinician-rated	3	243	1.15	0.92–1.45	1.24	.215	1.18	0.94–1.48	1.41	.159
Baseline PTSD total severity: self-report	3	239	1.15	0.90–1.47	1.13	.259	.	.	.	.
Baseline PTSD intrusion severity: clinician-rated	3	243	1.17	0.93–1.47	1.35	.177	.	.	.	.
Baseline PTSD intrusion severity: self-report	2	216	1.10	0.85–1.41	0.73	.466	.	.	.	.
Baseline PTSD avoidance severity: clinician-rated	3	243	1.10	0.87–1.39	0.83	.408	.	.	.	.
Baseline PTSD avoidance severity: self-report	2	215	1.14	0.88–1.48	1.03	.304	.	.	.	.
Baseline PTSD hyperarousal severity: clinician-rated	3	243	1.06	0.84–1.34	0.52	.604	.	.	.	.
Baseline diagnosis of a mood disorder	2	222	0.96	0.52–1.80	−0.12	.908	.	.	.	.
Baseline diagnosis of anxiety disorder	2	222	1.16	0.53–22.53	0.37	.712	.	.	.	.

Note. *n* = number of participants; RR = risk ratio; *z* = *z*-score; *p* = *p*-value; *k* = number of studies.

gender. No significant difference was found for baseline PTSD total score by gender for *drug* t(119) = 0.92, $n = 121$, $p = .358$, *placebo*, t(120) = 0.70, $n = 122$, $p = .483$, and for the *combined* group, t(241) = 1.09, $n = 243$, $p = .276$.

4. Discussion

This study employed both conventional meta-analysis and individual participant data meta-analysis, providing a robust and comprehensive evaluation of dropout rates and predictors across different pharmacotherapy trials for PTSD. The use of individual participant data allowed for more precise and nuanced analyses of dropout predictors, enabling the investigation of specific sociodemographic and clinical factors at a granular level.

Findings from the conventional meta-analysis revealed no significant differences in dropout rates between drug (27%) and placebo (30%) groups, with an overall dropout rate of 28%. These dropout rates are notably high, with more than one in four participants dropping out. When compared to dropout rates in psychotherapy, which range from 14% to 18% ($k = 114$; Lewis et al., 2020), pharmacotherapy appears to be associated with higher dropout rates. However, the literature on this topic remains scarce.

Previous research has documented dropout rates in pharmacotherapy ranging from 3.5% to 54% ($k = 30$), with no significant difference between drug and placebo groups (Gu et al., 2016). These variations may be attributed to differences in definitions of dropout, resulting in studies conceptualizing dropout differently. Hatchett and Park (2003) demonstrated a range of 17.6% to 53.1% in dropout rates depending on the definition used, such as failure to attend the last scheduled appointment or failure to return to therapy after the intake appointment.

Results of our individual participant data meta-analysis are consistent with our conventional meta-analysis, showing no significant difference in dropout rates between drug and placebo groups. This finding aligns with an earlier RCT analysis ($k = 30$) by Gu et al. (2016). The robustness of these results is supported by sensitivity analyses for both analytical approaches. Previous conventional meta-analyses on pharmacotherapy efficacy for adult PTSD have reported similar patterns (Hoskins et al., 2021; Stein et al., 2006).

Further analysis indicated that this finding was consistent across various subgroups, dosing strategies, drug classes, frequency of administration, population, and study duration. Similarly, Williams et al. (2022) found no significant differences in dropout rates across drug classes in PTSD treatment trials. The absence of significant differences between drug and placebo groups suggests that the decision to continue or discontinue participation is not primarily

influenced by treatment arm assignment. Although we could not examine specific reasons for study dropout, this pattern suggests that factors other than drug efficacy and potential side effects might play more critical roles in participant retention.

In our predictor analysis, gender emerged as a significant factor in the drug group, with males having nearly twice the risk of dropping out compared to females. Importantly, this effect disappeared when controlling for PTSD severity in sensitivity analyses. In the placebo group, gender differences in dropout were not significant. This finding highlights a potentially complex interaction between gender, PTSD severity, and dropout that warrants further investigation.

Regarding other predictors, neither self-reported nor clinician-rated PTSD symptom severity predicted dropout in any group analysis. Age, marital status, and comorbid mood or anxiety disorders also did not reach statistical significance as predictors. These findings align with earlier research reporting no predictive value of age or relationship status on study dropout among guideline-recommended treatments for PTSD (Varker et al., 2021).

4.1. Limitations

Several limitations should be considered when interpreting these findings. The exploratory predictor analysis using individual participant data was limited by the small sample, as it included data from only three pharmacotherapy trials. Despite numerous attempts to contact authors, lack of response and unavailability of earlier datasets presented significant impediments. This highlights a broader issue regarding data sharing in the field.

Another limitation worth noting is the narrow definition of dropout, which was guided by the availability of data across the included studies, ensuring a consistent and comparable approach. Specifically, we defined dropout as failure to complete the post-intervention assessment, as this was consistently reported across the included trials. To provide further context, previous meta-analyses on PTSD pharmacotherapy trials have employed similar approaches when defining dropout. For instance, Williams et al. (2022) categorized dropout based on study discontinuation as reported in the trial publications, often relying on post-treatment assessment completion as a key indicator. However, we acknowledge that this definition does not fully distinguish between participants who discontinued treatment early and those who completed other in-trial assessments but did not complete the post-intervention assessment.

Further, our analysis focused solely on all-cause study dropout, as consistent reporting of specific dropout reasons was unavailable across trials. Patients might discontinue pharmacotherapy for various reasons, including perceived lack of progress, treatment credibility concerns, or side effects – distinctions that could provide valuable clinical insights.

The ability to examine certain predictors (e.g. trauma type which may influence dropout rates in PTSD treatment trials; Zandberg et al., 2016) was constrained by inconsistent data collection methods and reporting practices across studies. Variables were sometimes operationalized differently or not reported at all, limiting data comparability for meta-analytic synthesis.

4.2. Strengths

This study offers several methodological strengths that enhance the validity of our findings. First, the combination of both conventional meta-analysis and individual participant data meta-analysis provides a multi-level approach that strengthens confidence in our results. While the conventional meta-analysis offered breadth by synthesizing findings across multiple studies, the individual participant data analysis provided depth by examining predictors at the participant level.

Second, our sensitivity analyses across various subgroups (drug classes, dosing strategies, administration frequencies, and study durations) confirmed the robustness of our findings.

Third, by examining not just treatment effects but specifically focusing on dropout patterns, this study addresses an under-researched but critical aspect of PTSD pharmacotherapy trials that directly impacts treatment efficacy interpretation.

Fourth, our study was prospectively registered before data extraction and analysis, ensuring transparency and methodological rigour. Additionally, we used the Cochrane Risk of Bias 2 tool to systematically evaluate bias risk across included studies, enhancing the reliability of our findings.

4.3. Implications

This meta-analysis emphasizes the necessity of standardized protocols for defining and reporting dropout in RCTs. The current lack of consistent reporting presents a major barrier to identifying reliable dropout predictors. Future studies should prioritize standardized reporting to enhance the reliability and applicability of findings in PTSD treatment trials.

Our findings underscore the need for implementing FAIR (Findable, Accessible, Interoperable, and Reusable) data principles in pharmacotherapy trials for PTSD (Wilkinson et al., 2016). Better adherence to these principles would enhance transparency, reproducibility, and research quality by making datasets more readily available for secondary analyses.

From a clinical perspective, awareness of potentially at-risk patient characteristics, such as sex and gender, can inform targeted interventions to reduce dropout rates. Clinicians should consider addressing factors that may contribute to dropout, including treatment efficacy communication, safety concerns, logistical issues, and psychosocial factors to enhance treatment adherence.

Future research should aim to distinguish between dropout due to adverse effects or lack of efficacy versus dropout resulting from perceived improvement, as this differentiation could provide a more nuanced understanding of treatment adherence and effectiveness.

In conclusion, this study provides valuable insights into dropout patterns and predictors in PTSD pharmacotherapy trials while highlighting the critical need for standardized reporting practices and improved data sharing. These findings have important implications for the design and interpretation of future clinical trials, ultimately contributing to more effective and patient-centered treatment strategies for PTSD.

Disclosures

Dr. Dunlop has received research support from Boehringer Ingelheim, Compass Pathways, NIMH, and the Usona Institute, and has served as a consultant for Biohaven, Cerebral Therapeutics, Myriad Neuroscience, and Otsuka.

Dr. Rothbaum has received Research/Grants from Wounded Warrior Project, NIH, Department of Defense, NSF, Bob Woodruff Foundation, MAPS; is a stockholder in Virtually Better; has been paid as a consultant by Otsuka, Psychwire, Senseye, MAPS, Jazz Pharmaceuticals, GoodCap, Transcend, Penumbra; serves on the Scientific Advisory Boards for Anxiety and Depression Association of America (ADAA), National Center for PTSD; serves on the Board of Directors for Gratitude America; receives Royalties from Oxford University Press, APPI, Emory University. The terms of these arrangements have been reviewed and approved by Emory University in accordance with its conflict-of-interest policies.

Dr Pollack has received Research/Grants from Wounded Warrior Project and NIH. He is currently an employee of Reunion Neuroscience, and prior to this was an employee of Sage Therapeutics and Myriad Genetics. He serves on the Scientific Advisory Board of the Anxiety and Depression Association of America (ADAA and receives Royalties from Oxford University Press).

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No potential conflict of interest was reported by the author(s).

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Data availability statement

The study made use of secondary data.

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