Journal of Psychiatric Research 102 (2018) 102–109

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

# Posttraumatic stress disorder and nonadherence to medications prescribed for chronic medical conditions: A meta-analysis

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A B S T R A C T

*Background:* Patients with posttraumatic stress disorder (PTSD) are at increased risk for adverse consequences from comorbid medical conditions. Nonadherence to medications prescribed to treat those comorbid conditions may help explain this increased risk. We sought to determine the association between PTSD and medication nonadherence and whether it varied according to the type of event inducing the PTSD.

*Methods:* Prospective observational cohort or cross-sectional studies relating PTSD and nonadherence among adults prescribed medications for a chronic medical illness were identified by searching MEDLINE, EMBASE, PsycINFO, the Cochrane Library, CINAHL, SCOPUS, and the PILOTS Database and by hand-searching bibliographies from selected articles. Individual estimates of odds ratios were pooled using random effects meta-analysis with inverse variance weighting. Articles were pooled separately according to whether PTSD was induced by a medical versus non-medical event.

*Outcomes:* Sixteen articles comprising 4483 patients met eligibility criteria. The pooled effect size of the risk of PTSD to medication nonadherence was OR 1.22 (95% CI, 1.06–1.41). Among the 6 studies of medical event-induced PTSD, the OR was 2.08 (95% CI, 1.03–4.18); p = 0.04. Among the 8 studies in which PTSD was not induced by a medical event, the OR was 1.10 (95% CI, 0.99–1.24); p = 0.09.

*Interpretation:* Patients with PTSD were more likely to be nonadherent to medications prescribed for chronic medical conditions – an association that may exist specifically when PTSD was induced by a medical event. Medications may serve as aversive reminders among survivors of acute medical events, magnifying avoidance behaviors characteristic of PTSD.

*Funding:* NHLBI.

With a lifetime prevalence of posttraumatic stress disorder (PTSD) in the general population of 5–14% (Yehuda, 2002; Kessler et al., 1995), and with an even higher prevalence in patients with comorbid medical conditions, PTSD is a frequently encountered psychiatric condition in primary care settings (Yehuda, 2002; Kessler et al., 1995; Liebschutz et al., 2007; Magruder et al., 2005; Spiro et al., 2006; Lecrubier, 2004; Sripada et al., 2014; Friedman, 2004). Patients with PTSD may be profoundly burdened by disabling psychological distress, elevated risk for suicide, and inability to work (Yehuda, 2002). Furthermore, a growing body of research demonstrates that PTSD, among civilians and veterans alike, increases both the risks and the consequences of comorbid medical conditions (Beckham et al., 1998; Jordan et al., 2011; Wisnivesky et al., 2011; Hoge et al., 2007; Jakupcak et al., 2008; Ahmadi et al., 2011; Pietrzak et al., 2012; Andersen et al., 2010). For example, patients with PTSD after an acute coronary syndrome have nearly twice the risk of recurrent cardiovascular events and mortality (Edmondson et al., 2011; Shemesh et al., 2004), and among patients with diabetes, those with PTSD have poorer glycemic control and worse prognosis (Miller et al., 2011; Trief et al., 2006). The mechanisms explaining the associations between PTSD and adverse outcomes from medical illness remain poorly understood (Dedert et al., 2010). Nonadherence to preventive medications may represent one such mechanism.

Some, but not all, studies have found an association between PTSD and nonadherence to medications prescribed for chronic medical conditions (we define a “chronic medical condition” as a long-lasting and typically progressive, non-psychiatric disease often treated with medications longitudinally to achieve disease control). One prior systematic review assessed the association of various mental disorders including PTSD on adherence to combination antiretroviral medications for

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https://doi.org/10.1016/j.jpsychires.2018.02.013
Received 23 October 2017; Received in revised form 31 January 2018; Accepted 15 February 2018

human immunodeficiency virus (HIV) (Springer et al., 2012). No quantitative analysis was conducted as part of this review. To our knowledge, no prior meta-analysis has examined the association between PTSD and nonadherence to medications prescribed for a variety of chronic medical conditions. Such a review may help clarify this association. It may also enable us to examine whether the association between PTSD and medication nonadherence varies between different medical conditions – HIV, for example – or by the trauma that triggered PTSD. Compared to patients with PTSD induced by non-medical events, patients with PTSD induced by acute medical events such as stroke or cancer diagnosis may be more likely to be nonadherent because medications may serve as aversive reminders of the traumatic medical event in these patients (Edmondson, 2014). Furthermore, such a review may additionally enable us to examine the method by which medication adherence is measured as a moderator.

Accordingly, we performed a systematic search and meta-analysis of observational studies examining the association between PTSD and nonadherence to medications prescribed for a range of chronic medical conditions. We hypothesized that patients with PTSD would be more likely to be nonadherent to their medications, overall, and that the association between PTSD and medication nonadherence would be stronger when PTSD was triggered by an acute medical event.

## 1. Methods

This meta-analysis aimed to include all evidence from observational studies that have investigated PTSD and nonadherence to medications prescribed for comorbid chronic medical conditions. The protocol for this systematic review was registered in PROSPERO prior to conducting the review (Kronish et al., 2013).

### 1.1. Search strategy

The research methodology was done in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). With the assistance of an information specialist (L.F.), potentially relevant articles were identified by searching publicly available computerized databases. The search included all articles and abstracts including unpublished doctoral theses referenced from database inception to June 15, 2015 in MEDLINE, EMBASE, PsycINFO, the Cochrane Library, CINAHL, SCOPUS, and the PILOTS Database. All relevant subject headings and free text terms for PTSD and medication adherence were identified and combined with AND. No language restrictions were applied (Appendix 1). Additional studies were sought by searching the reference lists of studies already identified for inclusion following the screening of the electronic database search results.

### 1.2. Study selection

Articles were eligible for inclusion if they satisfied the following criteria: the authors reported data from an original, peer-reviewed study; the study design was a prospective observational cohort or cross-sectional survey; the study population included adults prescribed medications for a chronic medical illness; there was no study intervention to improve adherence (because in these studies all baseline subjects were by definition nonadherent, precluding the extraction of an odds-ratio showing the odds of those subjects being nonadherent); PTSD was measured using a validated self-report instrument or psychiatric interview; adherence was measured using a validated self-report instrument or an objective measure; and the authors reported on the association between PTSD and nonadherence.

Two investigators (R.B., L.W.) independently reviewed all citations identified through the literature search using a predefined protocol that included the eligibility criteria. Articles that clearly did not meet inclusion criteria were excluded at the title and abstract level. The remaining articles were selected for full, English-language text review. When limited information was available from the abstract, full text was always obtained. The two investigators (R.B., L.W.) then independently reviewed all full text articles to identify eligible articles.

All eligible articles were assigned a quality rating (poor, fair, good, excellent) by two investigators (E.B., L.W.) using the Methodologic Evaluation of Observational Research (MEVORECH) checklist developed by the Agency for Healthcare Research and Quality (Shamliyan et al., 2011). Key features that determined quality included study design (i.e., prospective observational studies were rated higher than cross-sectional ones), response rate, follow-up rate, duration of follow-up, consideration of confounders in models of the association of PTSD with adherence, statistical analysis, and generalizability to other study populations. Each of these elements was assigned a grade, and then an overall rating was assigned based on the combination of these elements' scores.

Disagreements regarding the selection of articles and quality ratings were resolved through discussion with a third reviewer (I.K.) and full consensus was achieved at each stage of review. A study was included in this meta-analysis if there was consensus that it met eligibility criteria and had risk assessments in the format of hazard ratios (HRs) or odds ratios (ORs) or a summary statistic that could be converted into HRs or ORs.

### 1.3. Data extraction

Two investigators (R.B., L.W.) independently extracted data from selected studies using a standardized form. Information was collected regarding study characteristics (study name, authors, publication year, journal, study site, follow-up years, and number of participants), participant characteristics (age, gender, race, ethnicity, education), PTSD assessment (timing of assessment, self-report questionnaire or clinical interview), medication adherence assessment (type of self-report instrument or objective instrument), and analysis strategy (statistical models, lists of covariates in models).

### 1.4. Data synthesis and analysis

Eligible studies that included quantitative risk estimates for the association between PTSD and medication nonadherence were pooled. We sought to contact authors to obtain risk estimates when these were unavailable from eligible articles. We pooled articles according to prespecified analyses including type of medical condition and type of traumatic event (medical versus non-medical). We also pooled articles according to their overall quality rating and inclusion of possible confounders in their adjusted analyses. In particular, we pooled studies that included depression as a covariate because depression frequently accompanies PTSD and has been associated with medication nonadherence in prior studies (DiMatteo et al., 2000). Finally, we pooled studies according to method of adherence measurement. Risk estimates were standardized to express odds ratios of nonadherence. Individual estimates of odds ratios were pooled using random effects meta-analysis with inverse variance weighting in Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ). The I-squared statistic was calculated to estimate the percentage of variability across studies that is attributable to heterogeneity, and was tested for deviation from zero. To test for sources of heterogeneity for our primary outcome, we performed mixed-effects subgroup analyses, in which random-effects models were used to combine studies within subgroups, that compared pooled ORs separately for articles by quality assessment (poor, fair, good, or excellent quality); types of patients (e.g., HIV or cardiovascular disease); and PTSD trigger (secondary to an acute medical event versus other). We used chi-square to test for significance in these analyses and log transformed ORs to approximate normality. We assessed for publication bias using visual methods and the fail-safe N.