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The Relationship of PTSD to Quality of Life in a Treatment-Resistant Military
Population: An Examination of Moderating and Mediating Factors

by

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Thesis submitted to the Faculty of the
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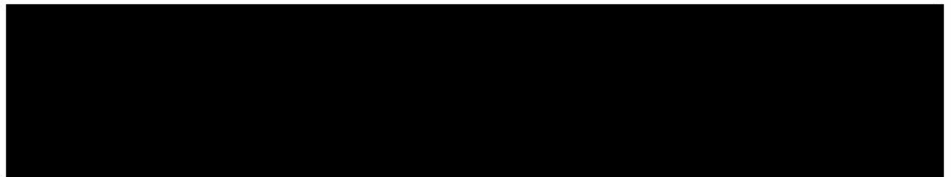
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ABSTRACT

The Relationship of PTSD to Quality of Life in a Treatment-Resistant Military

Population: An Examination of Moderating and Mediating Factors

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Thesis directed by: David S. Riggs, PhD, Department of Medical and Clinical
Psychology

Posttraumatic Stress Disorder (PTSD) is a significant problem facing service members returning from deployment to Iraq and Afghanistan. Notably, PTSD is highly comorbid with other psychological conditions and symptoms including anxiety, depression, sleep disturbances, and nightmares. These conditions are known to have debilitating consequences on a patient's quality of life (QoL); however, little is known about how they interact to impact the QoL of service members. The present study utilized data previously collected as part of a treatment study examining a novel medication (Riluzole, a glutamate modulator) for treatment-resistant PTSD (CAPS-IV ≥ 40 after eight weeks of SSRI/SNRI). To examine the complex relationship of PTSD to QoL, three interactions were examined. First, results indicated sleep quality moderated the relationship of PTSD to depression, such that lower levels of sleep disturbance were associated with a stronger association between PTSD and depression. Nightmares were not a significant moderator of the PTSD to QoL relationship. Second, an examination of anxiety and depression as mediators of the relationship of PTSD to QoL (i.e., overall, health-related, physical, psychological, social, and environmental) found depression to completely mediate each

of these relationships, while anxiety mediated all interactions except overall and environmental QoL. Finally, the moderated-mediation model was significant when sleep quality moderated the depression-mediated relationship of PTSD to physical, psychological, and environmental QoL. This study provides insight into the complex relationship of PTSD, co-occurring conditions, and QoL. These findings further emphasize the importance of considering common comorbidities of PTSD when working to improve a patient's QoL.

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CHAPTER 1: INTRODUCTION

Posttraumatic stress disorder (PTSD) is a significant problem among United States (US) military service members, with an overall incidence rate of 8.37 per 1,000-person years in the Military Healthcare System from 2007 to 2015 (Paxton et al., 2018). This chronic condition (Zatzick et al., 1997) is highly comorbid with other mental health concerns including anxiety and depression (Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). Currently, the Departments of Veterans Affairs (VA) and Defense (DoD) recognize a number of evidence-based treatments for PTSD including psychotherapy or medication (The Management of Posttraumatic Stress Disorder Work Group, 2017). Despite the research supporting these treatments, some patients will not achieve symptom remission (Hamner, Rober, & Frueh, 2004).

There is ample evidence that PTSD, anxiety and depression negatively impact quality of life (QoL; e.g., Beard, Weisberg, & Keller, 2010; Der-Martirosian, Cordasco, & Washington, 2013; IsHak et al., 2011). However, little is known about the effects of PTSD, anxiety, and depression on QoL in a military population as well as among persons whose PTSD fails to remit with treatment.

Sleep dysfunction is a common symptom of PTSD, depression, and anxiety; for example, 90% of service members with PTSD regularly experience sleep disturbances (as cited in Creamer, Brock, Matsangas, Motamedi, & Mysliwicz, 2018). Despite this, little research has examined the potential impact of sleep disturbance on the relation of PTSD to the associated disorders of depression and anxiety. This paper presents the results of a study that examined the relations among PTSD, anxiety, depression, sleep disturbance, and QoL in a sample of veterans with treatment-resistant PTSD.

POSTTRAUMATIC STRESS DISORDER

PTSD may develop following exposure to trauma from actual or possible death, injury, or sexual violence (American Psychiatric Association [APA], 2013). Symptoms of PTSD are classified into four clusters: intrusion (e.g. recurrent distressing dreams and dissociative reactions), avoidance (e.g. avoidance of upsetting memories related to the event), negative cognitions and mood (e.g. feeling detached), and arousal (e.g. hypervigilance). A PTSD diagnosis requires one or more intrusion symptoms, one or more symptoms of avoidance, two or more symptoms of negative cognitions and mood, and two or more arousal symptoms that have lasted at least one month and have resulted in clinically significant distress in the patient's life. Notably, PTSD is associated with numerous negative outcomes including suicidal ideation (Jakupcak et al., 2009), greater rates of substance use (Seal et al., 2011), and decreased quality of life (QoL; Schnurr, Lunney, Bovin, & Marx, 2009).

PTSD symptoms occur in both civilian and military populations; however, combat exposed populations exhibit higher rates of PTSD than civilian populations (Hoge et al., 2004; Hoge, Auchterlonie, & Milliken, 2006; Richardson, Frueh, & Acierno, 2010; Tanielian & Jaycox, 2008). The annual incidence of initial PTSD diagnosis within the Military Healthcare System (MHS) from 2007 to 2015 ranged from 6.74 per 1,000 person-years in 2007 to a peak incidence rate of 9.69 per 1,000 person-years in 2012 (Paxton et al., 2018). The recent conflicts in Iraq and Afghanistan have seen a high prevalence rate of approximately 11-20% of service members experiencing PTSD (National Center for PTSD, 2018). Indeed, PTSD has been termed a "signature wound" of the recent wars in Iraq and Afghanistan (Tanielian & Jaycox, 2008), with significant

implications for individual service members as well as the military mission due to its deleterious effects on readiness (Xue et al., 2015).

Treatment-Resistant PTSD

A number of evidence-based treatments, both psychological and pharmacological, exist for PTSD. The recent VA/DoD clinical treatment guidelines recommend psychological treatments including Cognitive Processing Therapy (CPT) and Prolonged Exposure (PE) for PTSD (The Management of Posttraumatic Stress Disorder Work Group, 2017). Pharmaceutical treatments including *Sertraline* and *Paroxetine* are recommended as second-tier treatment.

Despite the evidence that these treatments work to reduce PTSD symptoms, no treatment works for all patients and even when they do work some patients are left with residual symptoms (Hamner et al., 2004). There is a dearth of research as to why symptoms continue for some patients. It has been hypothesized that this is may be due to complicated psychiatric comorbidities or the wide variance in PTSD presentations (Hamner et al., 2004). Some PTSD symptoms in particular have proven to be more treatment-resistant than others. Previous research on the treatment of posttraumatic nightmares suggests that standard treatments for PTSD often fail to adequately treat nightmares (Neylan et al., 1998). Neylan and colleagues (1998) noted that PTSD-related nightmares and sleep dysfunction are often refractory following treatment for PTSD.

To address treatment-resistant PTSD, alternative psychotherapeutic and pharmacological strategies have been studied. Some psychotherapy interventions have been effective in improving previously treatment-resistant PTSD, including Acceptance and Commitment Therapy (ACT; Twohig, 2009) and culturally adapted Cognitive

Behavioral Therapy (CA-CBT; Hinton et al., 2004; Hinton et al., 2005; Hinton, Hofmann, Rivera, Otto, & Pollack, 2011). Medical approaches also have been successful in treating treatment-resistant PTSD and have included medications such as Olanzapine (Jakovljević, Šagud, & Mihaljević-Peleš, 2003), synthetic cannabinoids (Fraser, 2009) and methods including vagus nerve stimulation (George et al., 2008) and stellate ganglion blocks (Mulvaney et al., 2014). Currently, little is known about these treatments and why they may address treatment-resistant symptoms.

Comorbidity of PTSD, Anxiety, and Depression

PTSD is highly comorbid with other disorders including anxiety and depression (Araújo et al., 2014; Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). In a study conducted by Araújo and colleagues (2014), depression was present in 88.9% and an anxiety disorder was present in 90.7% of patients with PTSD. An additional study found patients with PTSD had an average of 3.1 comorbid anxious or depressive diagnoses (Spinhoven et al., 2014). In a study examining civilians (Zayfert, Becker, Unger, & Shearer, 2002), nearly 50% of individuals seeking treatment for PTSD met criteria for both PTSD and at least one comorbid anxiety diagnosis. In a study of Lebanese war veterans, patients were more likely to have PTSD with comorbid diagnoses of both anxiety and depression than PTSD alone or comorbid with only one disorder (Ginzburg, Ein-Dor, & Solomon, 2010).

A meta-analysis found depression was present in 52% of patients with PTSD (Rytwinski, Scur, Feeny, & Youngstron, 2013). Notably, when Rytwinski and colleagues examined relevant moderators, they found military samples had a higher rate of comorbidity than civilians. The co-occurrence of PTSD and depression is related to

substantial problems. In a sample of VA patients, comorbid PTSD and depression were associated with increased use of outpatient services, greater suicidal ideation, and lower social support (Campbell et al., 2007). Further, patients with comorbid PTSD and depression were given a worse prognosis by clinicians and often responded slower to treatment for depression. Comorbid PTSD and depression are associated with worse PTSD impairment, satisfaction with life, and worse health as well as a greater rate of not receiving desired mental health care compared to patients with only one disorder (Caramanica, Brackbill, Liao, & Stellman, 2014).

SLEEP DYSFUNCTION AND PTSD

Sleep difficulties, including poor sleep quality, insomnia, and nightmares, are common in patients with PTSD (Maher, Rego, & Asnis, 2006). Nightmares and sleep disturbances are included in the intrusion and arousal criteria of the PTSD diagnosis, respectively (APA, 2013). Sleep complaints, such as insomnia and nightmares, are common in patients with PTSD and sub-threshold PTSD (Spoormaker & van den Bout, 2005). Recent reports indicate sleep problems are present in 30 to 70% of PTSD cases (Lettieri, 2013; Belleville, Guay, & Marchand, 2009); however, other studies suggest 70 to 91% of patients with PTSD struggle to fall asleep or stay asleep (Maher et al., 2006; as cited in Creamer et al., 2018). PTSD has a number of disruptive nocturnal behaviors (DNBs) that are common in the disorder (Germain, Hall, Krakow, Shear, & Buysse, 2005). These include hot flashes, traumatic nightmares, and nervousness.

Nightmares, specifically, are highly prevalent in patients with PTSD, and in one study of veterans, 61% indicated they experienced significant nightmares (Pigeon, Campbell, Possemato, & Ouimette, 2013). Nightmares are positively correlated with

PTSD severity and depression (Pigeon et al., 2013). Ecological momentary assessment (EMA) studies have further elucidated this complex relationship: baseline and daily PTSD significantly increased nightmares (Short, Allan, Stentz, Portero, & Schmidt, 2018). Furthermore, patients with nightmares had more severe PTSD, and these nightmares influenced the trajectory of PTSD symptom development.

In a study examining sleep disturbances and the DSM-IV TR (APA, 2000) defined PTSD symptom categories (intrusion, avoidance, arousal), Spoomaker and van den Bout (2005) found intrusion symptoms were associated with sleep apnea, insomnia, sleepwalking, and narcolepsy. Additionally, nightmares were correlated with intrusion symptoms before controlling for disturbing dreams on a self-report measure of PTSD but did not remain after. Avoidance symptoms were related to sleep apnea, insomnia, narcolepsy, circadian rhythm problems, and sleep walking. Finally, hyperarousal was correlated with sleep apnea, insomnia, narcolepsy, and circadian rhythm problems.

Notably, the relationship between sleep and PTSD is likely bidirectional, a finding which has been supported by EMA findings. Increases in PTSD have been linked to lower sleep quality and sleep efficiency (Short, Allan, & Schmidt, 2017), and in a study of posttraumatic stress symptoms (PTSS), an additional hour of sleep led to a decrease in PTSS the following day in Service members with PTSD (Wang et al., 2018). In an EMA study examining the daily effects of PTSD on nightmares and sleep, findings show a clear relationship between PTSD and sleep, such that PTSD fluctuations affected sleep quality, and nightmares affected sleep efficiency (Short et al., 2018).

SLEEP DISTURBANCES, ANXIETY, AND DEPRESSION

Sleep disturbances often co-occur with anxiety and depression (Taylor, Lichstein, Durrence, Reidel, & Bush, 2005). It has been proposed that sleep disturbances may serve as the best indicator of the development of an anxious or depressive disorder (Gillin, 1998). Insomnia, in particular, is associated with a nearly 10 times increased risk of comorbid depression, and patients with insomnia are approximately 17 times more likely to have anxiety than patients without insomnia (Taylor et al., 2005). Comorbid insomnia increases depression and anxiety symptom levels, and patients with a greater number of sleep arousals also have greater levels of depression (Taylor et al., 2005). Of note for the present study, patients with PTSD and comorbid depression or anxiety reported significantly worse sleep quality than those with PTSD alone (Belleville et al., 2009).

People with anxiety often experience significant sleep disturbances. Ohayon and colleagues (1998) found GAD and insomnia are the most commonly comorbid disorders. Anxiety is also associated with a number of sleep disorders including OSA, insomnia, narcolepsy, circadian rhythm, and sleepwalking (Spoormaker & van den Bout, 2005) and precipitates daytime sleepiness (Alvaro et al., 2013). Objective measures of sleep, such as polygraphic recordings, indicate patients with anxiety experience significant sleep related issues including increased arousals, alertness, increased time to fall asleep as well as decreased time asleep and slow-wave sleep (Bourdet & Goldenberg, 1994). However, nightmares were found to be independent of and not related to anxiety (Wood & Bootzin, 1990).

Some patients with anxiety do not report sleep disturbances. However, findings suggest patients with anxiety whose sleep cycles are otherwise unaffected show sleep disturbances in the first sleep cycle of the night, thus differentiating them from healthy

controls (Fuller, Waters, Binks, & Anderson, 1997). Anxiety and worry increase sleep latency, transition into Stage 1 sleep, time in light sleep, and number of arousals as well as decrease slow-wave sleep and REM in patients without clinical levels of anxiety (Fuller et al., 1997). These findings were similar to patients with clinical levels of anxiety, thus indicating anxiety and worry may cause clinically significant sleep disruptions in patients without an anxiety disorder.

Symptoms of depression also are associated with a number of sleep disturbances including insomnia, narcolepsy, and circadian rhythm dysfunction (Spoormaker & van den Bout, 2005). Indeed, this relationship is so strong that Luca and colleagues (2013) caution against diagnosing depression without concurrent sleep complaints due to the high comorbidity rates, such as the 60% to 80% comorbidity with insomnia.

A longitudinal study examining the relationship between insomnia and depression demonstrated a bidirectional effect in which insomnia and depression are both predictors for the other (Sivertsen et al, 2012). Much of the current literature supports sleep disturbances predicting depressive symptoms at later time points. As in PTSD, sleep disturbances often precipitate onset and resurgence of depression (Luca et al., 2013; Gillin, 1998) as well as predict disorder onset (Cukrowicz et al., 2006). Moreover, insomnia doubles the risk of developing depression when compared to healthy controls (Baglioni et al., 2011).

Insomnia symptoms have been shown to affect depression trajectory, inhibit treatment effects, and increase risk of decline (Perlis, Giles, Buysse, Tu, & Kpuffer, 1997; Manber et al., 2008). Comorbid insomnia and OSA also significantly increased service members' odds of having depression (Mysliwiec et al., 2013). Furthermore, nightmares

and insomnia independently increase depression symptoms, and this effect is strengthened when these two co-occur (Nakajima et al., 2014).

QUALITY OF LIFE

Felce and Perry (1995) reviewed the existing literature on QoL and concluded that there was no agreed upon definition and no appropriate scale existed to measure subjective QoL. Thus, in 1998, the World Health Organization Quality of Life Group (WHOQOL Group) began work to create an assessment to measure QoL. The group aimed to create a measure that covered key physical, psychological, social, and spiritual domains of life (WHOQOL Group, 1998). Through the course of this effort, they defined QoL as:

Individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment (as cited in Saxena, Orley, & WHOQOL Group, 1997, p. 263s).

This definition offers a comprehensive view of QoL previously missing from the literature and addresses QoL through several categories (World Health Organization, 1996). Physical QoL includes impact on normal activities of daily living, stamina and tiredness, mobility, perceived pain, sleep quality and quantity, and ability to work. Positive and negative feelings, self-respect, religiosity, bodily image, and cognitive abilities are incorporated into psychological QoL. The social domain evaluates relationships with family and friends, perceived social support, and sexual health. Finally,

financial situation, sense of security, access to health services, home situation, opportunities for advancement, engagement in hobbies, transportation, and natural setting are assessed in the environmental QoL domain.

Quality of Life and Military

The QoL of active duty and retired service members is affected in many ways, as military service has unique impacts on one's QoL. The research comparing QoL in veteran and non-veteran populations is unclear. An early study found small or no differences in health-related QoL (HRQoL; Boehmer, Boothe, Flanders, & Barrett, 2003); however, more recent studies have found significant differences. For example, in a study examining HRQoL in rural and urban veterans, Luncheon & Zack (2012) found that veterans reported lower mental health scores than civilians on the Veterans 12-Item Short Form Survey (SF-12; Ware, Kosinski, & Keller, 1996), a modified version of the Medical Outcomes Study Short Form-36 (Ware, Kosinski, & Keller, 1996; Wallace et al., 2010). Further, HRQoL was significantly lower for veterans compared to civilians within their own race/ethnicity groups (Luncheon & Zack, 2012). This suggests veterans may have worse mental HRQoL than civilians in the general population.

Demographic factors appear to influence the QoL in active duty service members and veterans. In a large study of military service members, risk factors for lower QoL included being female, unmarried, lower education level, and lower military rank (Smith et al., 2007). Service members who were married and had no significant medical history reported higher HRQoL (Saffari, Koenig, Pakpour, & Sehlo, 2014). Similar results were found in a study of female veterans: married and employed senior female veterans with

higher income and education levels had higher physical QoL than other female veterans (Der-Martirosian et al., 2013).

Certain military characteristics may influence service members' QoL. For example, QoL differs among the branches: Air Force personnel reported better QoL compared to other branches (i.e., Army, Navy, Coast Guard, Air Force, and Marine Corps; Smith et al., 2007). Deployment history also may influence QoL. A study of Gulf War Era service members found that service members without a history of deployment were more likely to report their health as "excellent," while veterans who had deployed were more likely to rate their health as "good," "fair," or "poor" (Voelker et al., 2002). Further, the study found that general wellness and energy were the most affected by deployment whereas physical and emotional functioning were similar in deployed and non-deployed service members. Currently, research is limited on the influence of military service on QoL in United States service members; however, research in other countries suggests aspects such as rank may be related to perceived QoL. In a study of Taiwanese service members, higher ranking service members reported higher levels of QoL (Chou et al., 2014). Officers had significantly greater QoL scores than enlisted personnel and greater environmental and physical QoL than non-commissioned officers (NCOs).

QoL and Mental Health

It is well known mental health diagnoses are associated with poorer QoL. In a civilian study of PTSD and QoL, researchers found PTSD, depression, anxiety, lower PTSD avoidance symptoms, advanced age, and ethnicity were correlated with lower QoL (d'Ardenne, Capuzzo, Fakjoury, Jankovic-Gavrilovic, & Priebe, 2005). Giaco, Matanov, and Priebe (2013) further found hyperarousal symptoms were significantly associated

with lower QoL in a bidirectional manner, such that improvements in hyperarousal symptoms increased QoL and improvements in QoL decreased hyperarousal symptoms.

Many service members experience a mental health disorder, with a one-year prevalence of approximately 15% (Sareen et al., 2007). It is widely known that mental health disorders greatly affect QoL, yet the specific implications on military and veteran populations are not yet well understood. PTSD was negatively correlated with psychosocial and HRQoL and symptom improvement was associated with improved QoL in a sample of veterans with PTSD (Schnurr, Hayes, Lunney, McFall, & Uddo, 2006). Zatzick and colleagues (1997) also found that PTSD was associated with diminished physical and emotional health and social functioning in combat veterans. This is consistent with findings from Iraq and Afghanistan war veterans, with PTSD associated with lower mental HRQoL in both males and females as well as lower physical HRQoL in women (Fang et al., 2015). Further, a study of Vietnam war veterans also showed PTSD was negatively associated with QoL though without significant gender differences (Schnurr & Lunney, 2008).

QoL has been proposed as the definitive measure of treatment outcome for MDD (IsHak et al., 2011), as depression has extensive impacts on QoL (IsHak et al., 2011; Strine et al., 2009). Depression increases dissatisfaction with life, perceived lack of social support, and disability (Strine et al., 2009). Treating MDD increases QoL; however, at a lesser level than healthy controls (IsHak et al., 2011).

As previously noted, PTSD often co-occurs with depression. Research suggests this comorbidity may play a role in the relationship of PTSD to QoL. Comorbid depression and PTSD are associated with worse mental and physical HRQoL (e.g., Der-

Martirosian et al., 2013; Richardson, Long, Pedlar, Elhai, 2008; Beard et al., 2010; Pittman, Goldsmith, Lemmer, Kilmer, & Baker, 2012) relations that have been found to remain when controlling for age (Richardson et al., 2008). These results are similar to those found in a sample of Primary Care patients where PTSD and comorbid depression predicted worse HRQoL (Beard et al., 2010). In female veterans, this comorbidity is associated with lower mental HRQoL (Der-Martirosian et al., 2013). A study of male veterans found comorbid PTSD and depression was associated with lower satisfaction-related QoL, primarily due to the numbing symptoms of PTSD (Raab, Mackintosh, Gros, & Morland, 2015). Notably for the present study, depression severity has been identified as a critical influence on the QoL of patients with PTSD (Araújo et al., 2014).

All DSM-IV anxiety diagnoses correlated with decreased physical and mental functioning (Beard et al., 2010), particularly mental health and social QoL (Olatunji, Cisler, & Tolin, 2007). Although no anxiety disorder worsened QoL more than another (Olatunji et al., 2007), they have been shown to impact different areas of HRQoL (Beard et al., 2010). GAD is associated with worsened mental, social, emotional functioning as measured by the SF-12 (Comer et al., 2011). Other anxiety disorders such as social phobia and panic disorder have been shown to decrease QoL as well, with greater symptom severity being associated with poorer QoL (Barrera & Norton, 2009). Notably, social phobia, panic disorder, and OCD have a similar level of QoL, which is further decreased by comorbid depression. Comorbid PTSD and Obsessive-Compulsive Disorder (OCD) were associated with poor physical functioning when a medical condition was also present (Beard et al., 2010). Treatment of anxiety can improve QoL: patients treated with Cognitive Behavioral Therapy (CBT) reported greater increases in psychological

and physical domains than environmental and social when compared to those in the control condition (Hofmann, Wu, & Boettcher, 2014).

QoL and Sleep Disturbances

Sleep problems are shown to negatively impact patients' QoL and functioning (Maher et al., 2006). Sleep disturbances such as OSA insomnia, and excessive daytime sleepiness worsen physical HRQoL below the general population of the US (Baldwin et al., 2010). Patients with sleep disturbances scored worse on all SF-36 subscales (Ware & Sherbourne, 1992), and those with both sleep disturbances and daytime impairment had increased odds of scoring lower on the SF-36 than healthy controls (Lee et al., 2009).

Specific sleep symptoms are shown to lower QoL. Insomnia has vast effects on many areas of HRQoL, including mental, social, and physical (Kyle, Morgan, & Espie, 2010; Ishak et al., 2012) and leads to activity impairment and increased interference with job performance (Bolge, Doan, Kanna, & Baran, 2009). A study examining sleep disturbances in fire evacuees found no evidence of reduced mental health due to snoring; however, insomnia symptoms correlated significantly with reduced physical QoL (Krakow, et al., 2004). Treating insomnia can improve a patient's physical, social, and emotional functioning (Kyle et al., 2010). Nightmares also negatively affect quality of life (Kung, Espinel, & Lapid, 2012), and treating them improves reported QoL (Davis et al., 2011).

STUDY RATIONALE

The relations of PTSD, anxiety, depression, sleep, and nightmares to QoL is not well understood in military populations. Given the prevalence of these and other mental health disorders in the military, it is important to understand the effects of these disorders

on QoL. It is well known that PTSD, anxiety, depression, and sleep affect QoL in civilian populations; however, the interplay of these symptoms, to our knowledge, has not been studied in a military population.

We aimed to provide further insight into the effects of deployment-related PTSD on QoL in the US military by examining the primary areas of QoL: perceived overall, health-related, physical, social, psychological, and environmental. Based on the research suggesting sleep disturbances worsen both depression and anxiety in patients with PTSD, we hypothesized nightmares and sleep dysfunction would moderate the relationships of PTSD to anxiety and depression, such that higher levels of sleep disturbances (e.g. nightmares and poor sleep quality) would strengthen the relationship of PTSD to anxiety and depression. Due to the significant overlap in symptoms between PTSD and anxiety and depression, we hypothesized anxiety and depression symptoms would partially mediate the relationship between PTSD and QoL. Finally, because PTSD is rarely in isolation of these symptoms and disorders (i.e., sleep disturbances, nightmares, anxiety, and depression), we explored whether these individual models could be combined to form a more complete view of the effects of PTSD on QoL in a moderated-mediation model.

To our knowledge, this is the first study to examine the effect of PTSD, anxiety, depression, and sleep disturbances on the many subtypes of QoL (e.g. overall, health, physical, psychological, social, and environmental) in a military population using a moderated-mediation model. One previous study has shown depression and anxiety mediate the relationship of PTSD symptoms to QoL; however, this study was conducted in civilians who had been in a motor vehicle accident and only examined QoL as one

large construct (Gudmundsdottir et al., 2004). Thus, this model should be tested and expanded with the current sample, as a better understanding of the effect of these symptoms will provide a critical understanding to inform treatment strategies and methods to improve patient QoL.

SPECIFIC AIMS

Specific Aim 1

Examine the effect of sleep quality and nightmares on the relationship of PTSD to anxiety and depression.

Hypothesis 1a

Sleep quality and nightmares will individually moderate the relationship between PTSD and anxiety.

Hypothesis 1b

Sleep quality and nightmares will individually moderate the relationship between PTSD and depression.

Specific Aim 2

Examine the effect of anxiety and depression on the relationship of PTSD to quality of life.

Hypothesis 2

Anxiety and depression will individually mediate the relationship of PTSD to the domains of quality of life (perceived overall, health, physical, psychological, social, and environmental).

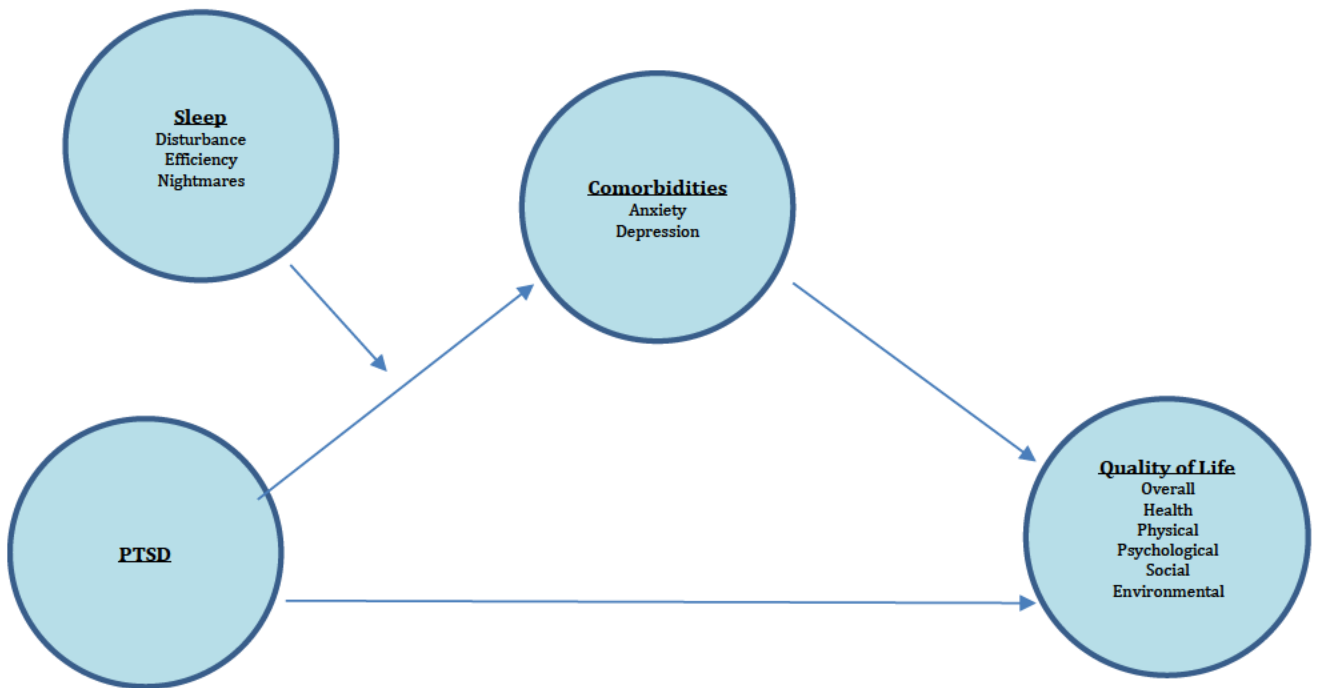
Specific Aim 3

Evaluate a comprehensive model of PTSD to quality of life by examining the roles of anxiety, depression, sleep disturbance, and nightmares.

Hypothesis 3

Sleep quality and nightmares will moderate the relationship of PTSD to anxiety and depression, which mediates the relationship of PTSD to QoL.

Hypothesized Model



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CHAPTER 2: GENERAL METHODS

PARTICIPANTS

Data were obtained from participants in a randomized controlled trial studying the efficacy of Riluzole, a glutamate modulator, as augmentation to selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitor (SNRI) for the treatment of PTSD (West et al., 2018). The parent sample consisted of 76 active duty and returning Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND) veterans between the ages of 18 and 65 with treatment-resistant PTSD. Treatment resistance was defined as a Clinician Administered PTSD Scale-IV (CAPS-IV; Blake et al., 1995) score of 40 or above, though not requiring a full PTSD diagnosis, despite at least eight weeks of medication treatment. Treatment-resistant participants were recruited from Walter Reed National Military Medical Center (WRNMMC) and the larger National Capital Region as well as the Syracuse Veterans Health Administration from January 2012 to November 2017. Data for the present study were collected prior to initializing Riluzole (or placebo) at the screening visit (e.g., demographic information) or at the first baseline visit (e.g., symptom measures, QoL). All participants deemed eligible for the parent study and who completed baseline measures were included in the present analyses (one participant in the parent study did not complete baseline measures.)

Due to the interest in nightmares in the present study, 24 participants were excluded from the current analyses for use of Prazosin, which is frequently used as treatment for posttraumatic nightmares. Thus, there were 51 participants available for the present analyses. The participants who were excluded for use of Prazosin had a mean age

of 37.3 and 83.3% were male, 66.7% were White, 83.3% were NCOs, 66.7% were Army, 58.3% were active duty, and 95.8% had previously deployed (Table 1). Excluded participants had significantly greater nightmares (excluded Mdn. = 9.00, included Mdn. = 6.00, $U = 418.00$, $p = .027$) and PTSD (excluded $M = 74.83$; included $M = 62.31$; $t = -2.43$, $p = .02$). Excluded participants did not significantly differ from included participants in regards to demographics or other baseline symptoms (i.e., anxiety and depression). Participants in the present study had a mean age of 37.6 and 86.3% were male, 70.6% were White, 82.4% were NCOs, 45.1% were Army, 47.1% were active duty, and 94.1% had previously deployed (Table 1). Approximately 80% of participants met full criteria for PTSD (see Table 2 for baseline characteristics).

PROCEDURES

Recruitment efforts for the parent study included tabling events; trifold brochures; and referrals from providers, collaborators, and other research studies. Participants were pre-screened via telephone for initial qualification in the study, and if criteria were met, they were asked to come for an in-person screening appointment with a study psychologist. Participants who met all inclusion criteria were invited to participate in the treatment study. Inclusion criteria included age 18 to 65; active-duty service member or retired DEERS eligible veteran of OIF, OEF, OND; CAPS-IV score of 40 or higher; and eight weeks of treatment with a SSRI or SNRI. Participants were excluded for psychotic features; serious, unstable medical illness; alcohol or substance abuse or dependence within the last 90 days; current or past diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or dementia; elevated risk for suicide or homicide; or current engagement in evidence-based psychotherapy.

After a two to four-week stabilization period prior to beginning medication, participants were randomly assigned to placebo or Riluzole in a double-blind manner. Throughout the study period, participants had weekly appointments for assessment by a study psychologist, have a blood-draw to test for liver functioning, have their vitals checked, and to receive the week's medication. A PTSD Checklist (PCL-S) for DSM-IV score at week three was used to determine if a participant would benefit from a higher medication dose. Participants at WRNMMC could enroll in an optional imaging portion of the study that occurred at baseline and post-treatment to assess for changes in N-acetyl aspartate (NAA) levels in the hippocampus and anterior cingulate. At the conclusion of the study, participants were offered the opportunity to continue receiving Riluzole as an open-label medication to augment their current treatment. Participants received compensation up to \$590 for completing study activities.

MEASURES

As part of the larger study, participants completed a number of clinician-administered and self-report measures. For the purposes of the current aims and hypotheses, a limited number of measures were used and only the relevant assessments will be described below.

Clinician Administered PTSD Scale-IV (CAPS-IV)

The CAPS-IV is a clinician administered structured interview that measures frequency and intensity of PTSD symptoms (Blake et al., 1995) and is considered the gold standard for assessing and diagnosing PTSD. This measure has been found to have excellent reliability and validity (Weathers, Ruscio, & Keane, 1999). PTSD severity was calculated using the sum of the severity and intensity scores for each item. Modified

CAPS-IV scores were used for nightmare and sleep analyses by removing the nightmare or sleep item for the respective analyses, as suggested in LaMotte, Taft, Weatherill, Scott, and Eckhardt (2016). Item B-2 (“recurrent distressing dreams of the event”) was removed for analyses involving the nightmare variable, and both items B-2 and D-1 (“difficulty falling or staying asleep;” Blake et al., 1995) were removed for analyses related to sleep disturbances to prevent artificially inflated results due to overlap. Both modified measures were tested for internal consistency and were found to have acceptable levels comparable to that of the complete measure (Sleep-modified: Cronbach’s alpha = .72; Nightmare-modified: Cronbach’s alpha = .72; CAPS-IV: Cronbach’s alpha = .72). Further, the adapted measures were highly correlated with the complete measure (Sleep-modified: $r = .98, p < .001$; Nightmare-modified: $r = .99, p < .001$).

PTSD Checklist – Stressor Specific Version (PCL-S)

This 17-item self-report assessment is a common measure of PTSD symptoms and has demonstrated adequate psychometric properties (Weathers, Litz, Huska, & Keane, 1994). Item two (“Repeated, disturbing dreams of a stressful experience from the past?”) of the PCL-S was used as part of the nightmare measure.

Montgomery-Åsberg Depression Rating Scale (MADRS)

Depression was measured using the MADRS (Montgomery & Åsberg, 1979). This clinician-administered 10-item scale has strong psychometric properties (Cusin, Yang, Yeung, & Fava, 2009). The items were summed to create a total depression severity score.

Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a 14-item clinician-administered measure of anxiety severity (Riskind, Beck, Berchick, Brown, & Steer, 1987). The scale was found to have adequate psychometric properties (Maier, Buller, Philipp, & Heuser, 1988). An overall score was obtained by summing the 14-items.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI comprehensively examines sleep over a one-month period (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This 19-item self-report measure evaluates sleep efficiency and sleep quality from the patient and bed partner. The PSQI is made up of seven components that are combined into a global score, with higher scores indicating lower sleep quality. This measure demonstrates good psychometric properties (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002). Sleep quality was measured using the PSQI Global Score.

World Health Organization Quality of Life (WHOQOL)-BREF

The WHOQOL-BREF is a 26-item self-report measure assessing QoL across many domains, including overall perception, health-related, physical, psychological, social, and environmental (WHOQOL Group, 1998). Physical, psychological, social, and environmental QoL are measured using domain composite scores. Additionally, the WHOQOL-BREF assesses perceived physical and overall QoL through single items. Individual domain scores were used to assess impact on QoL. The WHOQOL-BREF has strong reliability and validity (Skevington, Lotfy, & O'Connell, 2004) and has been found to be a reliable measure of QoL in the US military (Lindsay, Ferrer, Davis, & Nichols, 2017). Domain scores were used to evaluate symptom effects on quality of life.

The majority of the QoL research in the military has focused on HRQoL and used the SF-36 (Ware & Sherbourne, 1992). Studies have demonstrated conflicting results regarding the convergent validity of the SF-36 to the WHOQOL-BREF (Skevington et al., 2004). In studies of older adults (Castro, Driusso, & Oishi, 2014), coronary artery disease (Najafi, Sheikhatan, Montazeri, Abbasi, & Sheikhatollahi, 2008), and a nationally representative Taiwanese sample (Huang, Wu, & Frangakis, 2006), convergent validity has been poor. However, a study of patients with HIV infection found adequate correlations between the two measures (Hsiung, Fang, Chang, Chen, & Wang, 2005). Therefore, it is unknown if QoL as measured by the WHOQOL will align with previous studies using the SF-36 and its variants.

Nightmares

The nightmare score was created using the total frequency and severity score of Item B-2 (“recurrent distressing dreams of the event”) on the CAPS-IV (Blake et al., 1995) and question two (“repeated, disturbing dreams of a stressful experience from the past?”) on the PCL-S (Weathers, Litz, Huska, & Keane, 1994). A reliability analysis was conducted and indicated the scale had acceptable internal consistency (Cronbach’s alpha = 0.744).

Demographics

Participants completed a Demographics & Background Questionnaire, which assessed age, gender, race/ethnicity, employment status, education, marital status, pain rating, and military characteristics, such as branch, rank, and deployment history.

DATA ANALYSIS

SPSS 25.0 was used to conduct statistical analyses. Prior to analyzing the specific aims of the study, analytics were run to examine the impact of removing overlapping items (e.g. nightmares, sleep disturbances) on the reliability of the measures. A correlation matrix was run with the adjusted measures. A confirmatory factor analysis with all measures assessed if nightmare measures were cohesive. Moderation and mediation analyses were conducted using the PROCESS MACRO (Hayes, 2017) plug-in for SPSS. This plug-in was used to center the variables and bootstrap with 10,000 samples. Centering was performed so that the X and W coefficients were more interpretable and so that the hypotheses testing was more meaningful, per Hayes, 2017. Bootstrapping is recommended when testing indirect effects and was used to ensure the assumption of normality (per Preacher, Rucker, & Hayes, 2007). Finally, analyses assessed for demographic differences such as gender, duty status, and research site. Due to missing data, some analyses had fewer than the total 51 participants. Analyses that included the PSQI had 23 usable participants.

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CHAPTER 3: RESULTS

CORRELATIONS

Correlation analyses were conducted among PTSD, anxiety, depression, and the subscales of QoL (Table 3). PTSD was highly correlated with both anxiety ($r = .62, p < .01$) and depression ($r = .51, p < .01$). Additionally, anxiety and depression were strongly related ($r = .62, p < .01$). PTSD was correlated to most forms of QoL; however, it was not correlated with overall QoL ($r = -.11, p = .44$). PTSD was related to health ($r = -.34, p = .02$), physical ($r = -.46, p < .01$), psychological ($r = -.30, p = .03$), and social ($r = -.42, p < .01$). It had a nearly significant association with environmental QoL ($r = -.28, p = .05$). Anxiety was related to health, physical, psychological, social, and environmental QoL. Depression was related to all forms of QoL. These correlations are reported in Table 3.

SLEEP AS A MODERATOR

To examine the effect of sleep disturbances on the association between PTSD and anxiety, a moderation analysis was conducted (Table 4). Sleep quality (PSQI Global Score) did not moderate the relationship between PTSD and anxiety ($b = -0.05$; 95% confidence interval = $-0.10, 0.00, p = .07$; Figure 1). Nightmares also did not moderate this relationship ($b = -0.02$; 95% confidence interval = $-0.06, 0.01, p = .16$; Figure 2).

Sleep quality and nightmares were examined as potential moderators of the relationship of PTSD to depression. Sleep quality significantly moderated this relationship ($b = -0.07$; 95% confidence interval = $-0.12, -0.02, p = .01$), with lower levels of sleep quality being associated with a stronger association between PTSD and

depression (Figure 3). Nightmares were a nearly significant moderator of this relationship ($b = -0.03$; 95% confidence interval = $-0.06, 0.00$, $p = .05$; Figure 4).

ANXIETY AND DEPRESSION AS MEDIATORS OF PTSD IMPACT ON QUALITY OF LIFE

To examine if the relationship between PTSD and QoL was mediated by anxiety, mediation analyses were conducted using PROCESS Macro (Hayes, 2017; Table 5). Anxiety did not mediate the relationship to overall QoL. PTSD was related to anxiety ($b = 0.32$, $SE = 0.06$, $t = 5.49$, $p < .001$); however, anxiety was not related to overall QoL ($b = -0.0256$, $SE = 0.018$, $t = -1.4034$, $p = .17$). Anxiety completely mediated the relationship between PTSD and health-related QoL (a path: $b = 0.32$, $SE = 0.06$, $t = 5.49$, $p < .001$; b path: $b = -0.06$, $SE = 0.02$, $t = -2.89$, $p < .01$; c' path $b = -0.00$, $SE = 0.01$, $t = -0.33$, $p = .74$). The relationship between PTSD and physical QoL was also completely mediated by anxiety (a path: $b = 0.32$, $SE = 0.06$, $t = 5.49$, $p < .001$; b path: $b = -1.01$, $SE = 0.37$, $t = -2.75$, $p < 0.01$; c' path $b = -0.25$, $SE = 0.19$, $t = -1.31$, $p = .20$). Additionally, the relationship of PTSD to psychological QoL was completely mediated (a path: $b = 0.32$, $SE = 0.06$, $t = 5.49$, $p < .001$; b path: $b = -1.02$, $SE = 0.34$, $t = -2.98$, $p < .01$; c' path $b = 0.00$, $SE = 0.18$, $t = -0.02$, $p = .98$). PTSD's effect on social QoL was completely mediated as well (a path: $b = 0.32$, $SE = 0.06$, $t = 5.49$, $p < .001$; b path: $b = -1.27$, $SE = 0.45$, $t = -2.86$, $p < .01$; c' path $b = -0.21$, $SE = 0.23$, $t = -0.93$, $p = .36$) [NOTE: One participant had incomplete data and a social QoL subscale could not be computed so that participant was omitted from this analysis]. Finally, anxiety did not mediate the relationship to environmental QoL. PTSD was related to anxiety ($b = 0.32$, $SE = 0.06$, $t = 5.49$, $p < .001$); however, anxiety was not related to environmental QoL ($b = -0.61$, $SE = 0.36$, $t = -1.67$, $p = .10$). In sum, there was evidence that the association between PTSD

and QoL was completely mediated by anxiety in health, physical, psychological, and social QoL.

Analyses were conducted on the potential mediating effect of depression in the relationship of PTSD to QoL as well (Table 6). Depression completely mediated the relationship to overall QoL (a path: $b = 0.21$, $SE = 0.05$, $t = 4.16$, $p < .001$; b path: $b = -0.08$, $SE = 0.02$, $t = -4.56$, $p < .001$; c' path $b = 0.01$, $SE = 0.01$, $t = 1.54$, $p = .13$). The relationship of PTSD to health QoL was completely mediated by depression (a path: $b = 0.21$, $SE = 0.05$, $t = 4.16$, $p < .001$; b path: $b = -0.06$, $SE = 0.02$, $t = -2.56$, $p = .01$; c' path $b = -0.01$, $SE = 0.01$, $t = -0.96$, $p = .34$). PTSD's effect on physical QoL was completely mediated by depression (a path: $b = 0.21$, $SE = 0.05$, $t = 4.16$, $p < .001$; b path: $b = -1.68$, $SE = 0.38$, $t = -4.44$, $p < .001$; c' path $b = -0.21$, $SE = 0.16$, $t = -1.36$, $p = .18$). The effect of PTSD on psychological QoL was completely mediated by depression as well (a path: $b = 0.21$, $SE = 0.05$, $t = 4.16$, $p < .001$; b path: $b = -1.81$, $SE = 0.34$, $t = -5.37$, $p < .001$; c' path $b = 0.05$, $SE = 0.14$, $t = 0.38$, $p = .70$). The association between PTSD and social QoL was completely mediated by depression (a path: $b = 0.21$, $SE = 0.05$, $t = 4.16$, $p < .001$; b path: $b = -1.66$, $SE = 0.49$, $t = -3.36$, $p < .01$; c' path $b = -0.27$, $SE = 0.20$, $t = -1.33$, $p = .19$). One participant had incomplete data and a social QoL subscale could not be computed. Finally, depression completely mediated the effect of PTSD on environmental QoL (a path $b = 0.21$, $SE = 0.05$, $t = 4.16$, $p < .001$; b path: $b = -1.67$, $SE = 0.36$, $t = -4.69$, $p < .001$; c' path $b = 0.05$, $SE = 0.15$, $t = 0.33$, $p = .74$). Overall, depression completely mediated the relationship of PTSD to all forms of QoL.

MODERATED-MEDIATION EFFECTS ON QoL

Moderated-mediation models were used to further explore the association of PTSD to QoL using conditional process modeling. Sleep quality and nightmares were included as moderators of the a-path for all mediation models. As indicated by the Index of Moderated Mediation, sleep quality moderated the direct effect of PTSD to depression, indicating that moderated mediation had occurred, only in the models of physical ($b = 0.09$, $SE = 0.05$, 95% CI [0.00, 0.18]), psychological ($b = 0.09$, $SE = 0.05$, 95% CI [0.00, 0.20]), and environmental QoL ($b = 0.07$, $SE = 0.04$, 95% CI [0.00, 0.16]). The other depression models (e.g., overall, health, social, and environmental QoL) were not significant (Table 7). Sleep quality did not moderate the mediation effect of anxiety on the relationship of PTSD to overall, health, physical, psychological, social, or environmental QoL (Table 8). Nightmares did not moderate any of the mediation models (Tables 9 and 10). This included the mediation models involving anxiety on the subtypes of QoL and all of the depression mediation models.

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CHAPTER 4: DISCUSSION

SUMMARY AND DISCUSSION OF RESULTS

This study examined potential moderating and mediating factors in the relationship of PTSD and QoL. Consistent with previous findings, we found PTSD to be associated with anxiety, depression, and sleep disturbances. Sleep quality appears to moderate the relationship of PTSD to anxiety and depression. Nightmares nearly moderated the relationship of PTSD to depression and trended towards significance to anxiety. Additional analyses indicated the relationship between PTSD and depression was strengthened with better sleep quality (lower PSQI score).

As hypothesized PTSD was associated with worse QoL. Anxiety and depression each mediated the relationship of PTSD to health, physical, psychological, and social QoL; however, only depression mediated PTSD's effect on overall and environmental QoL. An integrated moderated-mediation model of the relationship of PTSD to QoL revealed sleep quality moderated three models: PTSD to physical, psychological, and environmental QoL when mediated by depression, such that the extent of the indirect effect of PTSD to QoL was dependent upon sleep quality. This association was strengthened by worse sleep quality (higher PSQI Global Score). Overall, the present study suggests the relationship of PTSD to QoL is best understood when examining comorbid symptoms.

These results suggest sleep disturbances play an important role in understanding the effect of PTSD on common comorbidities. It is well-documented that mental health disturbances significantly decrease sleep quantity and quality (Spoormaker & van den Bout, 2005; Taylor et al., 2005) as well as the bidirectional effect of sleep problems increasing mental health symptoms (Mellman, 2006; Alvaro et al., 2013). Thus, it is not

surprising that sleep quality moderated the effects of PTSD on both anxiety and depression. Additionally, nightmare presence was a nearly significant moderator of the relationship of PTSD and depression. It is possible this may be due to hopelessness associated with nightmares (Littlewood, Gooding, Panagioti, & Kyle, 2016). Hopelessness is common in depression and a sufficient cause of the disorder (Alloy, Abramson, Metalsky, & Hartlage, 1988). Hopelessness also has been documented as a mediating factor in the effect of nightmares on suicidal behaviors in patients with posttraumatic stress symptoms (Littlewood et al., 2016). Finally, nightmares were not a significant moderator of the relationship of PTSD to anxiety.

Anxiety and depression are commonly comorbid with PTSD (Spinoven et al., 2014; Ginzburg et al., 2010). Additionally, anxiety, depression, and PTSD are known to cause significant impairment on QoL (e.g. d'Ardenne et al., 2005). The present results largely support a model in which symptoms of anxiety and depression mediate the relation of PTSD on QoL. Indeed, this same pattern was supported for almost all of the subscales of the WHOQOL. This is largely consistent with results found in civilian survivors of motor vehicle accidents that anxiety and depression completely mediate the effect of PTSD on overall QoL (Gudmundsdottir, Beck, Coffey, Miller, & Palyo, 2004). Depression mediated all aspects of QoL. These results are in line with findings from Araújo and colleagues (2014) that depression severity is an important component of QoL in patients with PTSD. These results provide support for the importance of assessing comorbid conditions in patients with PTSD.

The results of the moderated-mediation analyses provide a novel understanding of the effect of PTSD on QoL and the importance of sleep quality in this relationship. These

results suggest that among patients with low and moderate sleep disturbances, depression is a mediator of the relationship of PTSD to physical and psychological QoL. The negative indirect effect indicates that greater PTSD was associated with greater depression, which is then associated with lower QoL. However, this relationship is not significant for patients with the greatest levels of sleep disturbance.

STRENGTHS, LIMITATIONS, AND FUTURE DIRECTIONS

Though PTSD is known to impact QoL, there is a paucity of knowledge regarding this relationship in individuals who have tried but not responded to treatment for PTSD or how PTSD is related to different aspects of QoL, particularly among service members and veterans. This study was strengthened by the choice of measures. Clinician-administered measures assessed mental health symptom severity. The WHOQOL-BREF provided a measure of the various aspects of QoL allowing a more comprehensive examination of the associations of PTSD to facets of QoL. Finally, the study utilized a unique and hard to sample group, which allowed for an understanding of QoL in military patients with treatment-resistant PTSD. Thus, the present study provides important insight into the effects of treatment-resistant PTSD on QoL in military-related populations. However, the limitations of the study should be considered when evaluating these results.

The study was under powered due to a small sample size. This may be due to the treatment-resistant sample, which requires patients who have already undergone treatment and continue to have clinically significant symptom levels to consent to experimental treatment as part of a medication trial. The sample size was decreased further due to incomplete participant data. Sleep quality analyses were particularly

susceptible to low power because of a lack of completed PSQI assessments or assessments which were incorrectly completed (45.1% usable data). Thus, some non-significant analyses may have been due to Type II error rather than non-significant effects. Future studies would benefit from a greater sample size.

Additionally, patients with PTSD are poor reporters of their sleep quality and often overestimate the time it takes for them to fall asleep and underestimate the time spent asleep (Spoormaker & van den Bout, 2005). Future research would benefit from the use of an objective rather than a subjective measure of sleep quality, such as actigraphic measured sleep. Further, recall bias may have affected these results by using self-report measures that examine sleep quality and psychological symptoms over a period of time. A future study utilizing methods such as EMA may provide a better understanding of the effect of mental health on QoL.

While this study provides important clarity to the effects of PTSD on QoL in a sample of treatment-seeking patients with treatment-resistant PTSD, the results lack generalizability to the larger QoL research in military-related populations with PTSD. The results of this study are most applicable to patients who are military-related and both treatment-seeking and treatment-resistant. These results may be least generalizable to patients who are not seeking treatment as it is possible there may be a difference in these patients compared to non-treatment-seeking patients in that the current sample has hope of symptom improvement. Thus, these results should be replicated within a more general sample of military patients with PTSD (e.g. non-treatment-resistant PTSD sample) to increase the generalizability of these results.

It should also be noted that QoL is lower in military-related populations than civilian populations for many reasons including aspects related to military service and the deployment experience (Wallace et al., 2010). Aspects of the deployment experience (e.g., sleep deprivation (Taylor et al., 2014) as well as repeated deployments and combat exposure (e.g. Hoge et al., 2004; Kok, Herrell, Thomas & Hoge, 2012; Xue et al., 2015) and reintegration stressors (Marek et al., 2012) may lead to disparate effects in regards to the effects of sleep disturbances, anxiety, and depression in the relationship of PTSD to QoL compared to the civilian population. Therefore, future studies should compare the effect of PTSD to QoL in military and civilian samples.

IMPLICATIONS FOR CLINICAL PRACTICE

Despite these limitations, the present study provides important insights into moderating and mediating factors in the relationship of PTSD to QoL. These results demonstrate the potentially important role sleep plays in understanding the comorbidity of PTSD, anxiety, or depression. Additionally, this study provides support for the significant impact of anxiety and depression in the relationship of PTSD and QoL among people with treatment-resistant PTSD. Further, the moderated-mediated effect informs the conceptual model of factors involved in this relationship.

This study helps delineate the role of comorbid diagnoses in the effects of PTSD and, thus, the importance of considering these symptoms in treating patients with treatment-resistant PTSD. Additionally, this study increases the understanding of patients with PTSD who do not respond to SSRI or SNRI treatment for their PTSD. These findings are particularly important as they identify that symptoms of depression continue to be critical to the understanding of the effect of PTSD on QoL in patients who were

treated with anti-depressants. Further, this study extends the existing literature of the effect of PTSD on QoL by identifying anxiety and depression as complete mediators of this relationship. Thus, it is critical to evaluate and address potential comorbid conditions in patients with treatment-resistant PTSD.

These results provide important clinical considerations for the treatment of PTSD, specifically treatment-resistant PTSD. Sleep, including sleep quality and nightmares, are not only common symptoms of PTSD but also may increase comorbid symptoms of anxiety and depression in patients with treatment resistant PTSD. By targeting sleep disturbances in treatment for PTSD, patients may see greater reductions in symptoms of comorbid anxiety and depression than treatment for PTSD alone, perhaps leading to increased functioning and QoL. Further, it is important to consider the additional effect of comorbid conditions when evaluating QoL in PTSD populations. Thus, focusing on anxiety and depression symptoms in the treatment of PTSD may provide a clinically significant increase in QoL.

This study highlights the importance of considering QoL as a clinical outcome for patients with treatment-resistant PTSD. This model may provide evidence that addressing these symptoms can more efficiently improve QoL and assist clinicians in forming case conceptualizations. Further, it provides an understanding of how these common clinical concerns may interact and, thus, can be used to inform treatment planning.

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Table 1. Demographics

Variable	Total Sample (<i>N</i> = 51)	Prazosin Exclusions (<i>N</i> = 24)
Mean Age (Years)	37.6	37.25
Gender		
Male	44 (86.3%)	20 (83.3%)
Female	6 (11.8%)	4 (16.7%)
Race		
White	36 (70.6%)	16 (66.7%)
Black or African American	6 (11.8%)	2 (8.3%)
Asian	1 (2.0%)	0 (0.0%)
Native American or Alaskan Native	1 (2.0%)	1 (4.2%)
Hawaiian or Other Pacific Islander	1 (2.0%)	1 (4.2%)
Other	4 (7.9%)	1 (4.2%)
Branch		
USA	23 (45.1%)	16 (66.7%)
USN	10 (19.6%)	1 (4.2%)
USMC	8 (15.7%)	4 (16.7%)
USAF	6 (11.8%)	3 (12.5%)
Other	4 (7.9%)	
Rank		
Junior Enlisted (E1-E3)	1 (2.0%)	1 (4.2%)
NCO (E4-E9)	42 (82.4%)	20 (83.3%)
Junior Officer (O1-O4)	5 (9.8%)	3 (12.5%)
Senior Officer (O5-O9)	2 (3.9%)	0 (0.0%)
Other	1 (2.0%)	0 (0.0%)
Duty Status		
Active Duty	26 (51.0%)	14 (58.3%)
Retired	24 (47.1%)	10 (41.7%)
Other	1 (2.0%)	0 (0.0%)

Table 2. Average Baseline Characteristics

Variable	Participants (<i>N</i> = 51)		Prazosin Exclusions (<i>N</i> = 24)	
	% or M	SD	% or M	SD
Percent who met PTSD Criteria	80.40%		95.7%	
PTSD*	62.31	16.19	74.83	22.23
Anxiety	22.67	8.40	24.00	8.67
Depression	21.96	7.69	22.00	9.65
PSQI	15.91	3.53	17.25	4.06
Nightmares*	5.90	3.42	7.83	3.73

Note. **p* < .05

Table 3. Correlation of PTSD, Anxiety, and Depression to QoL Subscales

	<i>M (SD)</i>	PTSD	Anxiety	Depression	Quality of Life					
					Overall	Health	Physical	Psych.	Social	Environ.
PTSD	1.53 (.50)		.62***	.51***	-.11	-.34*	-.46***	-.30*	-.42**	-.28†
Anxiety	31.88 (10.29)			.62***	-.22	-.49***	-.54***	-.48***	-.54***	-.35*
Depression	2.60 (1.57)				-.53***	-.45***	-.65***	-.66***	-.56***	-.60**
Quality of Life										
Overall	3.44 (1.06)					.49***	.51***	.57***	.34*	.47***
Health	1.21 (.30)						.75***	.61***	.22	.46***
Physical	49.06 (19.96)							.73***	.51***	.64***
Psych.	46.02 (18.17)								.59***	.46***
Social	46.48 (24.03)									.43**
Environ.	66.18 (17.86)									

Note. † $p = .05$, * $p < .05$, ** $p < .01$, *** $p \leq .001$

Table 4. Relationship of PTSD to Anxiety and Depression Moderated by Sleep Quality and Nightmares

Predictor	β	p	95% CI	
			Lower	Upper
Anxiety x Sleep Quality	-0.05	.07	-0.10	0.00
Anxiety x Nightmares	-0.02	.16	-0.06	.01
Depression x Sleep Quality*	-0.07	.01	-0.12	-0.02
Depression x Nightmares+	-0.03	.05	-0.06	0.00

Note. + $p = .05$, * $p < .05$.

Table 5. Mediation Effects of Anxiety on the Relationship between PTSD and QoL
95% CI

Effect	N	b	95% CI	
			Lower	Upper
Overall	51			
Total		-0.01	-0.02	0.01
Direct		0.00	-0.02	0.02
Indirect (mediation)		-0.01	-0.03	0.00
Health	51			
Total		-0.02	-0.04	-0.00
Direct		-0.00	-0.02	0.02
Indirect (mediation)		-0.02	-0.03	-0.00
Physical	51			
Total		-0.57	-0.89	-0.25
Direct		-0.25	-0.63	0.13
Indirect (mediation)		-0.32	-0.66	-0.09
Psychological	51			
Total		-0.33	-0.63	-0.03
Direct		-0.00	-0.36	0.35
Indirect (mediation)		-0.33	-0.66	-0.13
Social	50			
Total		-0.62	-1.01	-0.23
Direct		-0.21	-0.67	0.25
Indirect (mediation)		-0.41	-0.81	-0.11
Environmental	51			
Total		-0.30	-0.61	0.00
Direct		-0.11	-0.49	0.27
Indirect (mediation)		-0.20	-0.58	0.03

Note. * $p < .05$.

Table 6. Mediation Effects of Depression on the Relationship between PTSD and QoL

Effect	<i>N</i>	<i>b</i>	95% CI	
			Lower	Upper
Overall	51			
Total		-0.01	-0.02	0.01
Direct		0.01	-0.00	0.03
Indirect (mediation)		-0.02	-0.03	-0.01
Health	51			
Total		-0.02	-0.04	-0.00
Direct		-0.01	-0.03	0.01
Indirect (mediation)		-0.01	-0.03	-0.00
Physical	51			
Total		-0.57	-0.89	-0.25
Direct		-0.21	-0.53	0.10
Indirect (mediation)		-0.36	-0.65	-0.17
Psychological	51			
Total		-0.33	-0.63	-0.03
Direct		0.05	-0.23	0.33
Indirect (mediation)		-0.38	-0.69	-0.18
Social	50			
Total		-0.62	-1.01	-0.23
Direct		-0.27	-0.68	0.14
Indirect (mediation)		-0.35	-0.67	-0.10
Environmental	51			
Total		-0.30	-0.61	0.00
Direct		-0.05	-0.25	0.35
Indirect (mediation)		-0.35	-0.67	-0.16

Note. * $p < .05$.

Table 7. Sleep Quality Moderation of the Depression Mediation Model

Effect	<i>N</i>	<i>b</i>	SE	95% CI	
				Lower	Upper
Overall	23	0.00	0.00	-0.00	0.01
Health	23	0.00	0.00	-0.00	0.01
Physical*	23	0.09	0.05	0.00	0.18
Psychological*	23	0.09	0.05	0.00	0.20
Social	23	0.07	0.06	-0.03	0.21
Environmental*	23	0.07	0.04	0.00	0.16

Note. * $p < .05$.

Table 8. Sleep Quality Moderation of the Anxiety Mediation Model

Effect	<i>N</i>	<i>b</i>	SE	95% CI	
				Lower	Upper
Overall	23	0.00	0.00	-0.00	0.01
Health	23	0.00	0.00	-0.00	0.01
Physical	23	0.06	0.04	-0.02	0.15
Psychological	23	0.07	0.05	-0.01	0.17
Social	23	0.03	0.04	-0.03	0.13
Environmental	23	0.07	0.05	-0.02	0.17

Table 9. Nightmare Moderation of the Depression Mediation Model

Effect	<i>N</i>	<i>b</i>	SE	95% CI	
				Lower	Upper
Overall	51	0.00	0.00	-0.00	0.01
Health	51	0.00	0.00	-0.00	0.00
Physical	51	0.05	0.03	-0.03	0.11
Psychological	51	0.05	0.04	-0.03	0.12
Social	50	0.04	0.03	-0.04	0.10
Environmental	51	0.05	0.03	-0.03	0.11

Table 10. Nightmare Moderation of the Anxiety Mediation Model

Effect	<i>N</i>	<i>b</i>	SE	95% CI	
				Lower	Upper
Overall	51	0.00	0.00	-0.00	0.00
Health	51	0.00	0.00	-0.00	0.00
Physical	51	0.02	0.02	-0.02	0.06
Psychological	51	0.02	0.02	-0.02	0.06
Social	50	0.03	0.03	-0.02	0.09
Environmental	51	0.01	0.02	-0.02	0.05

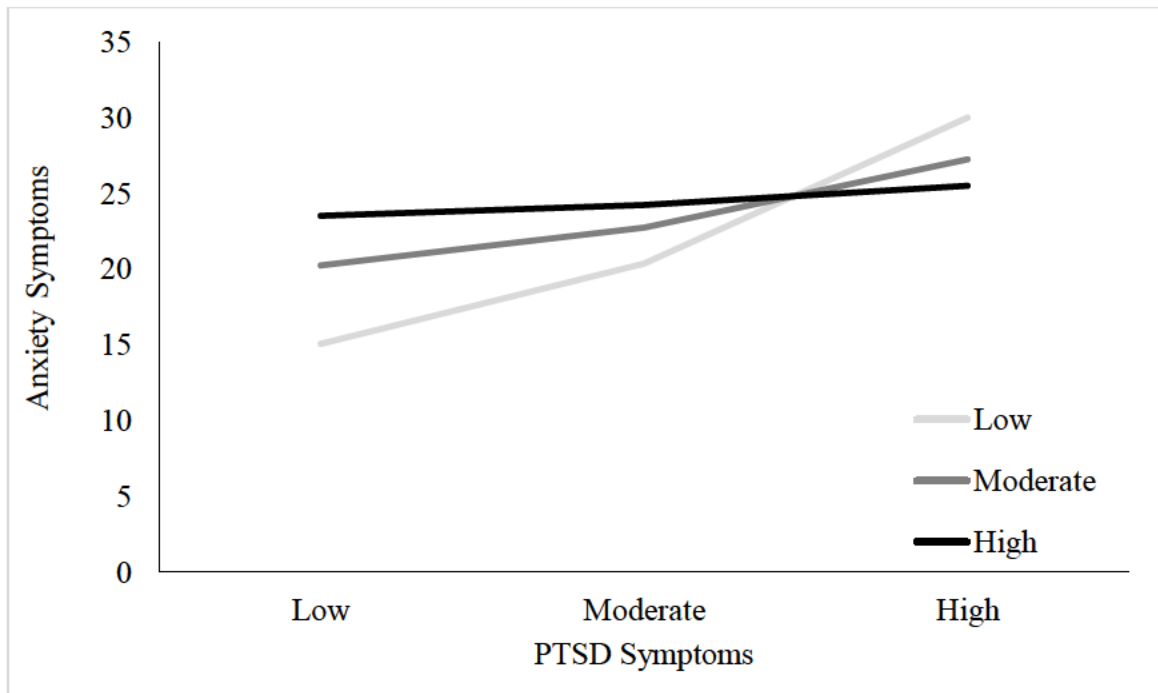


Figure 1. Moderating Effect of Sleep Quality in the Relationship of PTSD and Anxiety

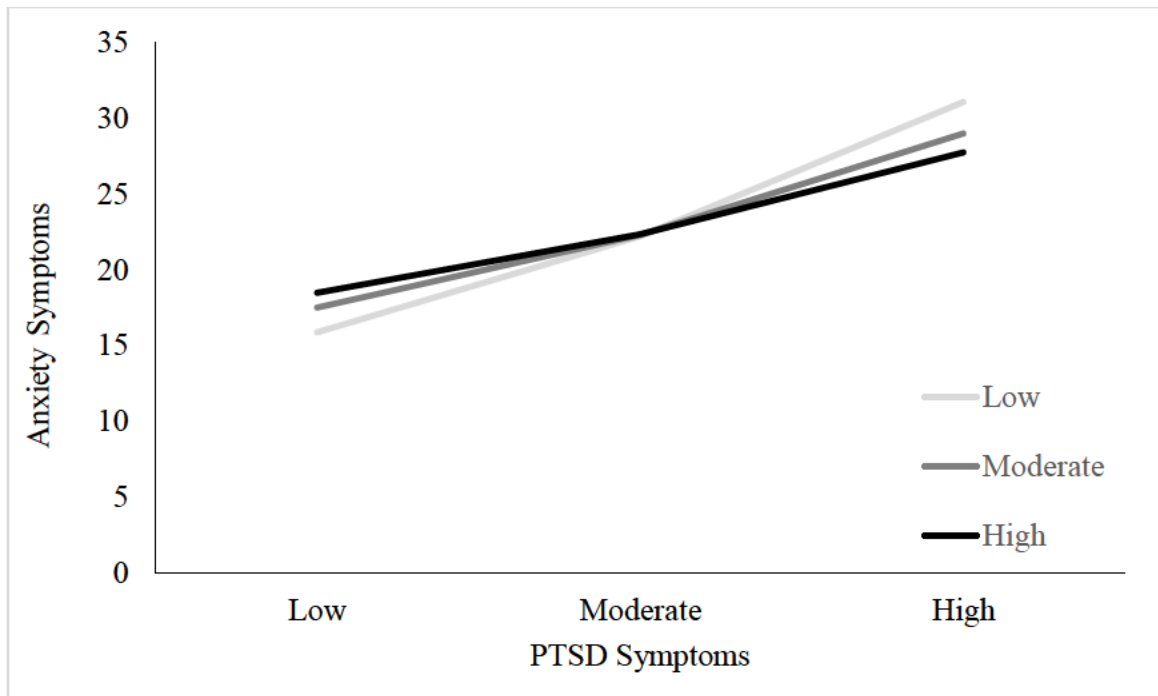


Figure 2. Moderating Effect of Nightmares in the Relationship of PTSD and Anxiety

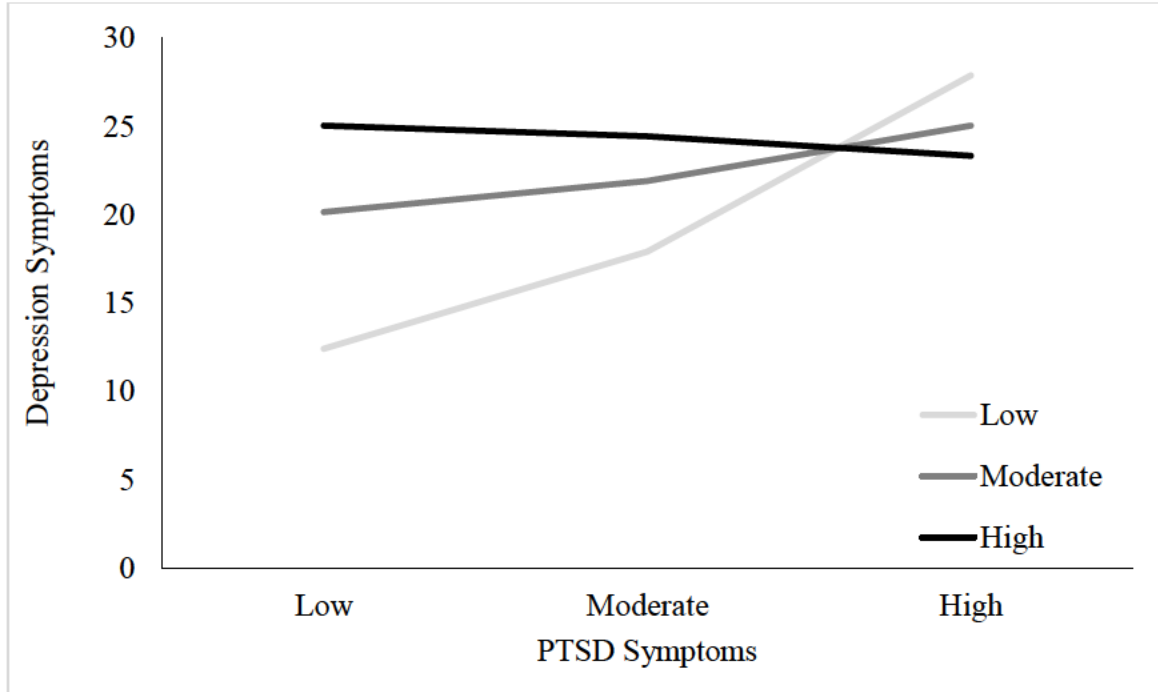


Figure 3. Moderating Effect of Sleep Quality in the Relationship of PTSD and Depression

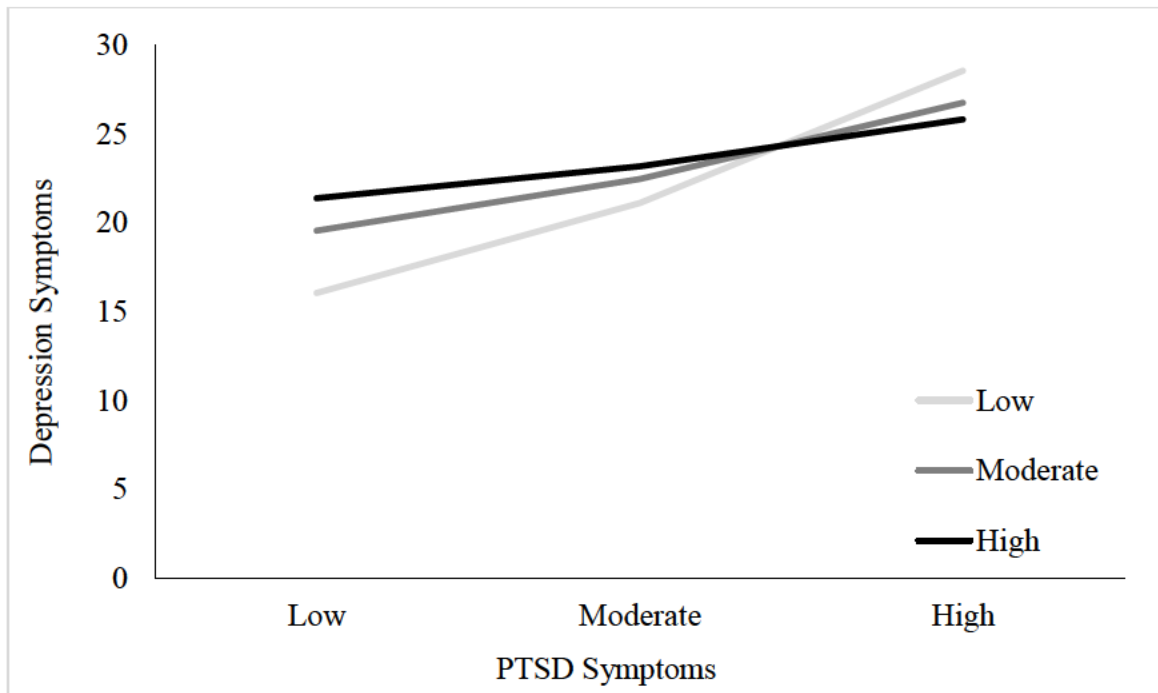


Figure 4. Moderating Effect of Nightmares in the Relationship of PTSD and Depression

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