HIV-Related Fatigue and Sleep Disturbance

Subjects: Infectious Diseases

Contributor: Tongyao Wang

HIV-related Fatigue: a subjective, unpleasant, potentially disabling, chronic symptom characterized by physical and/or psychological exhaustion.

HIV-related sleep disturbance: a disruption in the amount and quality of sleep that impairs functioning.

Keywords: fatigue ; HIV ; interventions ; nursing

1. Introduction

Symptom management is core to nursing science, and research on symptom management is a priority for people living with HIV (PLWH). Despite antiretroviral treatments being globally available, quality of life continues to remain poor for some PLWH due to their experiences of HIV-related symptoms. The term 'HIV-related symptom' has not been defined but has been used extensively in the nursing literature, which includes as many as 72 symptoms that were not problematic before the onset of HIV infection. We considered any new symptom that occurs after the initial infection to be an HIV-related symptom [1]. The prevalence rates of HIV-related fatigue and sleep remain high [2][3][4]; a national study (N = 1597) in 2017 showed that 65% of PLWH experienced worsening fatigue after the onset of HIV infection [5]. Meanwhile, more than half (56%) of PLWH reported daytime sleepiness or drowsiness from impaired quality of sleep as their second most distressing symptom from both the CNICS cohort (Centre for AIDS Research Network of Integrated Clinical System, N = 5370) [6] and Lee's Symptom and Genetics Project (N = 317) [7].

1.1. What Is HIV-Related Fatigue?

Fatigue is the most prevalent symptom among PLWH [8][9], and is defined as a subjective, unpleasant, potentially disabling, chronic symptom characterized by physical and/or psychological exhaustion (adapted from [10]). Fatigue has an adverse impact on the continuum of care; people may be too tired to get their medications from a pharmacy or to take them once they do get them [11][12]. When comparing case and control patients in South Africa after ≥5 months of first-line antiretroviral therapy (ART), Marconi et al. found fatigue predicted virologic failure independent of adherence measures [13]. HIV-related fatigue is multi-causal and strongly associated with psychological causes, particularly stress and stressful life events [14][15]. More recent work from Zuniga and colleagues (2020) showed in a sample of N = 32 PLWH that elevation in adiponectin, serum amyloid A, and soluble interleukin-1 receptor type II levels were highly predictive of fatigue. This could indicate that the chronic inflammatory processes of low-grade HIV within the cardiovascular system and the brain play a major role in the presence of fatigue [16].

1.2. What Are HIV-Related Sleep Disturbances?

Sleep disturbance among PLWH is another frequently reported symptom [17], which is uniquely different from populations with other diseases in terms of patterns and severity. HIV-related sleep disturbance is defined as 'a disruption in the amount and quality of sleep that impairs functioning' [17]. Lee et al. found that difficulty falling asleep (sleep onset >30min) and sleep fragmentation (wake after sleep onset >15% of the night) were the most common types of sleep disturbances in PLWH [18]. In the past 20 years, HIV-related sleep disturbances have slowly gained more attention due to their association with worsening of HIV-related symptom burden [19][20][21], disabling effects on overall health, and even failure to secure a job [22]. The etiology of HIV-related sleep disturbance remains poorly understood; however, sleep disturbances are a common side effect of many antiretroviral medications [15][23][24], and an Australian study (N = 522) found sleep disturbance was the most commonly reported ART side effect [25].

1.3. Breakthroughs on HIV-Related Fatigue and Sleep Disturbances Research

Breakthroughs in nursing science on understanding the unique etiology and pattern of each HIV symptom accelerated the progress of understanding fatigue and sleep disturbances and, thus, has the potential to improve focused interventions. One breakthrough for fatigue was the discovery by Barroso et al. [26] that HIV-related fatigue is chronic and persists for

years, tending to remain at the same level of intensity and impact on functioning for years. In a longitudinal five-year study of 128 PLWH, fatigue did not spontaneously remit, nor was there a response shift on the measurement tools, but the level of fatigue and its impact on impairment of functioning (ability to accomplish activities of daily living (ADLs) and independent ADLs) remained essentially unchanged over a three-year period. Those who experienced low, medium, or high intensity fatigue levels remained in the same intensity level, respectively, throughout the three years of data collection. This clearly documents the chronicity of fatigue and the urgency to find interventions to help PLWH.

A breakthrough in the treatment of sleep disturbances in PLWH was the discovery by Lee et al. [18]; in their cross-sectional design with 290 participants, Lee et al. found that the self-reported sleep quality was not related to quality of sleep objectively measured by wrist actigraphy and their overall HIV-associated symptom experiences. They advocated for greater effort in understanding patients' specific sleep problems and designing interventions accordingly [18]. Even a person with a mild or moderate symptom experience could suffer tremendously and experience a high level of distress over the symptom.

1.4. Gaps in Our Understanding

We are currently unable to account for the lack of impact of more recent changes in HIV treatment, such as the 'test and treat' approaches or the single formulation of the triple combination therapy, which clearly improved adherence to medications but did not improve symptoms. The current intervention literature does not allow for assessment of whether changes in antiretroviral treatment changed the degree of symptom severity, duration, or impact, according to treatment modalities. Although the advent of and access to combination ART has drastically reduced morbidity and mortality rates, PLWH continue to suffer from multiple chronic HIV-related symptoms [27].

Authors have no way of distinguishing if the onset of new symptoms can be ascribed to the presence of the HIV infection alone or other issues such as the aging processes, developing comorbidities, or any other physical and psychological changes that may occur along their illness trajectory. At this point, we cannot say with certainty what drives the persistence of a particular symptom or multiple symptoms after the initial onset of HIV infection. Authors know, however, from longitudinal data that fatigue and sleep disturbances will persist for years and will not improve spontaneously without any meaningful interventions [28][29][30]. The literature is very clear that with the onset of HIV infection, PLWH begin and continue to experience fatigue and sleep disturbances. All these symptoms may be interrelated and have approached or exceeded prevalence rates of 50% in various samples of PLWH [5][31][32][33][34][35]. Symptom management has been a long-term goal of HIV nursing care through the examination of biological, social, and behavioral underpinnings of symptoms. Cognitive behavioral therapy for insomnia (CBT-I) is the first-line therapy recommended by the American Academy of Sleep Medicine for insomnia [36]. However, the effectiveness of other behavioral interventions warrants more evidence [37]. Due to the lack of symptom management strategies without medications, the authors focused on the studies that tested behavioral and biological interventions led by nurse investigators to ameliorate one or both symptoms in order to understand their effectiveness and long-term impact.

2. Fatigue Management Strategies

Fatigue management studies (*N* = 7) took diverse approaches, including exercise, cognitive behavioral therapy (CBT), the use of symptom management guidelines, and treating a co-morbid symptom with the goal of reducing fatigue. There were two studies which examined exercise programs to reduce HIV-related fatigue [38][39], and two studies that examined CBT, delivered in person [40] or via an app [41]. One study examined the use of symptom management guidelines with hospitalized patients living with HIV and fatigue [42]; one study examined the treatment of depression to determine the effects of reducing depression on fatigue [43]; and one study examined the treatment of sleep disturbances to determine the effect of reducing sleep disturbances on fatigue [44]. The Zhu et al. [42] study was conducted in China; the other six were conducted in the US. Four studies were randomized controlled trials (RCTs), two studies were pilot RCTs, and one was a pre-/post quasi-experimental design. Sample sizes ranged from 30 to 234. In those studies that reported this information, intervention doses varied widely, from three times/week for 12 weeks to treatments at two, four, and six weeks. Data were collected at baseline and then at widely varying intervals, with one study collecting data for a year, while most stopped data collection after three months or less post-intervention. Two studies used the HIV-Related Fatigue Scale, and the other five studies each used different fatigue measures, making comparison of results difficult.

In a randomized controlled trial, Barroso et al. (2016) analyzed data from a sample of people living with HIV who were randomized to receive enhanced usual care for depression, or a depression treatment model called measurement-based care (MBC). Participants (*n* = 234) in this depression treatment trial who experienced a stronger depression response (greater improvement in depression scores) had larger decreases in fatigue. However, even among those who demonstrated a full depression response, nearly three-quarters continued to have either moderate or severe fatigue,

supporting the belief that these are two separate constructs and must be treated as such. The treatment group experienced improvements in depression.

We also found two exercise interventions for fatigue management. The Jaggers et al. study implemented a supervised exercise program of aerobic and resistance training [39], and while there was a decrease on the POMS (Profile of Mood States) fatigue sub-scale from pre- to post-intervention, it was not statistically significant. Goulding et al. [38] enrolled a sample of older people to complete 12 weeks of moderate intensity exercise, then randomized them to complete another 12 weeks of moderate or high intensity exercise [38]. High intensity exercise was associated with greater improvements in vitality/fatigue in weeks 13–24 compared to moderate intensity.

In the area of mind/body interventions, CBT also showed potential to improve fatigue. Doerfler and Goodfellow [40] found that individual CBT when compared to usual care was effective in reducing fatigue in PLWH on ART; however, the intervention did not have a sustained effect at the 90-day measurement. In the second study using CBT, Barroso et al. [41] developed an app based on cognitive behavioral stress management (CBSM). At three months, findings showed an improvement in fatigue, with completers (those who completed at least 80% of the intervention modules) having a sustained, significant reduction in fatigue intensity and impairment of fatigue-related functioning.

Another two studies used behavioral-educational strategies to manage fatigue. Zhu et al. (2018) implemented an HIV symptom management guideline in an inpatient unit in Shanghai, China, with fatigue being one of the targeted symptoms. Frequency of fatigue was lower in the intervention group but was not statistically significant [42]. Finally, in a randomized controlled pilot study, Lee, Jong, and Gay [44] tested a behavioral-educational intervention to reduce fatigue through education about daytime behaviors and nighttime sleep behaviors. Participants were living with HIV, between 45–75 years old, unemployed, and fatigued. At the conclusion of the study, the intervention group had significantly improved fatigue severity scores and symptom burden over time, especially in the frequency of fatigue.

3. Sleep Disturbance Management Strategies

Seven studies, examining six interventions on sleep disturbances, met our inclusion criteria. Two of the seven studies analyzed the ‘Sleep B.E.T.T.E.R’ intervention, first conducting an efficacy trial [45] and then an RCT [44]. Overall, nurse-led interventions to address HIV-related sleep disturbances were composed of two mechanisms targeting the biological response or sleep hygiene behaviors. Three biological response studies included acupuncture treatment [46], 30-day caffeine withdrawal [47], and transcranial direct current stimulation (tDCS) [48]. The other three psychoeducational intervention studies on sleep hygiene included SystemCHANGETM-HIV intervention [49], Brief Behavioral Treatment for Insomnia [50], and ‘Sleep B.E.T.T.E.R’ [44]. The total number of participants ranged from 12 to 120 across all studies and the studies took place between 2001 and 2019. One study, ‘Sleep B.E.T.T.E.R.’, included only women living with HIV and the others included all genders. Of note, the ‘Sleep B.E.T.T.E.R.’ intervention was tested in two separate studies [44][45], one with women-only participants, and the other with all gender participants; nevertheless, both studies demonstrated significant improvement in sleep quality. The length of the interventions ranged from 4 to 10 weeks with varied frequency and doses of intervention over time.

Three interventions were developed primarily to target the biological components of sleep quality. In 2001, the first HIV-related sleep disturbance quasi-experimental study in our search was conducted by a nurse and a professional acupuncturist. They recruited 21 participants and provided five weeks of individualized acupuncture treatment [46]. Not only did they find a 32% improvement in sleep quality, they also learned that as the acupuncturist developed a personal treatment plan for each individual, pain was the most common patient-reported cause for poor sleep [46]. Improvements in length of sleep ($p = 0.05$) and total minutes of awakening ($p = 0.05$) were statistically significant, but no change was found in the amount of time that people needed to fall asleep, also called sleep latency ($p = 0.87$) [46]. In 2003, Dreher conducted an RCT to test the effects of a 30-day gradual caffeine withdrawal on sleep quality in 120 PLWH. Participants with 90% caffeine reduction experienced a 35% significant improvement in sleep quality compared with participants who had a 6% caffeine reduction [47]. In 2019, Cody et al. tested another two biological interventions, using speed of processing training (SOPs, an interactive computerized exercise to improve speed and accuracy to visual stimuli) or transcranial direct current stimulation (tDCS) over five weeks (1 h twice a week) in older adults (ages > 50) living with HIV, and neither of these interventions improved sleep quality [48]. tDCS is defined as a non-invasive procedure to slightly change the membrane potential of neurons with a static, direct electrical current to stimulate the brain [51].

An additional four intervention studies tested used educational and coaching sessions to promote sleep hygiene behaviors and therefore improve quality of sleep. In 2013, the ‘SystemCHANGETM-HIV intervention’ was tested; it was comprised of ten weekly sessions on different topics of HIV management, including sleep hygiene and behavioral

modification strategies based on the SystemCHANGE theory. The theory encourages small environmental or behavioral changes with a goal of improving overall health [49]. The randomized controlled trial recruited 40 participants but showed no significant effect in sleep outcomes [49]. In 2018, Buchanan et al. developed the intervention called the Brief Behavioral Treatment for Insomnia (BBTI) based on three principles, including sleep restriction, stimulus control, and circadian mechanism. The interventionist worked with each participant to practice these principles and provided sleep hygiene education as well. The BBTI was the first intervention study to primarily facilitate behavioral change by working with everyone to agree on a set schedule of sleeping and rising. In the feasibility test of the intervention in 12 clinically diagnosed insomnia patients, intervention participants demonstrated fewer symptoms of insomnia and had a statistically significant increase in clinical sleep outcomes [50]. Furthermore, they also found that the BBTI was well accepted and rated favorably by PLWH. Another intervention, the 'Sleep B.E.T.T.E.R' (Bedroom, Exercise, Tension, Time to sleep, Eating, drinking and drugs, Rhythm) program, was designed in 2008 to address sleep disturbance issues by providing a 30-minute instructional session on sleep hygiene and advising participants to practice sleep hygiene in the following week (*N* = 30 female participants only); the post-intervention actigraphy results showed a significant reduction in sleep disturbance only, and minimal improvement in overall sleep [45]. Later in 2019, Lee and her colleagues extended the 'Sleep B.E.T.T.E.R' intervention to 60 min by providing additional sleep hygiene devices, such as a white noise fan, eye mask, or caffeine-free tea, and adding weekly booster sessions over four weeks [44]. When the modified intervention was tested in an RCT (*N* = 55), participants experienced significantly improved sleep quality.

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