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Prolonged Fatigue in Ukraine and the United States: Prevalence and Risk Factors

Abstract

Background: Prolonged, severe, unalleviated fatigue may be disabling whether it occurs on its own or in conjunction with medical or psychiatric conditions. This paper compares the prevalence and correlates of prolonged fatigue in general population samples in Ukraine versus the US. **Methods:** Population surveys were conducted in 2002 in both Ukraine (Ukraine World Mental Health [WMH] Survey) and the US (National Comorbidity Survey-Replication; NCS-R). Both surveys administered the Composite International Diagnostic Interview (CIDI 3.0), which contained modules assessing: neurasthenia (prolonged fatigue); mood, anxiety, and alcohol/drug use disorders; chronic medical conditions; and demographic characteristics. Multivariable logistic regression was used to examine risk factors in each country. **Results:** The lifetime prevalence of prolonged fatigue was higher in Ukraine (5.2%) than the US (3.7%). In both countries, one-fifth of individuals with prolonged fatigue had no medical or DSM-IV psychiatric condition. Also in both settings, fatigue was significantly associated with socio-demographic characteristics (being female, not working, and married before) as well as early onset and adult episodes of mood/anxiety disorder. Fatigue prevalence in Ukraine increased with age, but decreased in the US at age 70. Unique risk factors for fatigue in Ukraine included lower socio-economic status, Ukrainian versus Russian ethnicity, and cardiovascular disease. Unique risk factors in the US were parental depression/anxiety, adult episodes of alcohol/drugs, pain conditions, and other health problems. **Conclusions:** The lifetime prevalence of prolonged fatigue in Ukraine was 40% higher than that found in US data. In addition, fatigue prevalence increased sharply with age in Ukraine perhaps due to limited social and medical resources and greater comorbidity.

Keywords

prolonged fatigue, neurasthenia, chronic fatigue syndrome, prevalence, Ukraine, comorbidities

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Prolonged fatigue in Ukraine and the United States: Prevalence and risk factors

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Abstract

Background: Prolonged, severe, unalleviated fatigue may be disabling whether it occurs on its own or in conjunction with medical or psychiatric conditions. This paper compares the prevalence and correlates of prolonged fatigue in general population samples in Ukraine versus the U.S.

Methods: Population surveys were conducted in 2002 in both Ukraine (Ukraine World Mental Health [WMH] Survey) and the U.S. (National Comorbidity Survey-Replication; NCS-R). Both surveys administered the Composite International Diagnostic Interview (CIDI 3.0), which contained modules assessing: neurasthenia (prolonged fatigue); mood, anxiety, and alcohol/drug use disorders; chronic medical conditions; and demographic characteristics. Multivariable logistic regression was used to examine risk factors in each country.

Results: The lifetime prevalence of prolonged fatigue was higher in Ukraine (5.2%) than the U.S. (3.7%). In both countries, one-fifth of individuals with prolonged fatigue had no medical or DSM-IV psychiatric condition. Also in both settings, fatigue was significantly associated with sociodemographic characteristics (being female, not working, and married before) as well as early onset and adult episodes of mood/anxiety disorder. Fatigue prevalence in Ukraine increased with age, but decreased in the U.S. at age 70. Unique risk factors for fatigue in Ukraine included lower socio-economic status, Ukrainian vs Russian ethnicity, and cardiovascular disease. Unique risk factors in the U.S. were parental depression/anxiety, adult episodes of alcohol/drugs, pain conditions, and other health problems.

Conclusions: The lifetime prevalence of prolonged fatigue in Ukraine was 40% higher than that found in U.S. data. In addition, fatigue prevalence increased sharply with age in Ukraine perhaps due to limited social and medical resources and greater comorbidity.

Key words: prolonged fatigue, neurasthenia, chronic fatigue syndrome, prevalence, Ukraine, comorbidities

Introduction

Prolonged, debilitating fatigue without clear etiology is embodied in two similar conditions, neurasthenia and chronic fatigue syndrome (CFS). Both conditions feature disabling medically unexplained fatigue that is associated with the unusual symptom of post-exertional fatigue (or exhaustion). Neurasthenia appears in the ICD-10 [1] and is characterized by at least 3 months of persistent and distressing feelings of exhaustion after minor mental or physical effort. Also required is one additional symptom (muscular aches, sleep disturbance or irritability) and an inability to recover from exhaustion through rest or relaxation. By comparison, CFS [2] requires 6 months of unremitting fatigue and 4 out of 8 secondary symptoms of which the most frequently reported are cognitive difficulties, sleep disturbance, and post-exertional malaise [3]. An early report by Farmer et al. [4] found that 97% of CFS subjects also met ICD-10 criteria for neurasthenia (without exclusion criteria).

With regard to prevalence, the most recent U.S. population-based study of neurasthenia [5] estimated lifetime prevalence at 4.9%. CFS lifetime prevalence is considerably lower with a generally accepted U.S. estimate of about .5% [6, 7]. Both CFS and neurasthenia have been prospectively linked to prior stressful life events [8-11]. More generally, debilitating prolonged fatigue is a common feature in a wide variety of conditions, such as chronic inflammatory, infectious, neurological, and psychiatric diseases as well as cancer [12].

Prolonged fatigue has also been studied in aging populations and may be an early indicator of the onset of medical conditions. Two large sample investigations in the elderly (ages 65-85) [13, 14] found a high prevalence (18-24%) of self-reported persistent fatigue or lack of energy that was linked to physical and role impairments. Furthermore, subjective reports of tiredness after

activities in the elderly have been found in several studies [reviewed in 15] to be a strong independent predictor of functional decline, disability, and death.

Aims

The purpose of this study was to compare the prevalence of prolonged fatigue in Ukraine and the U.S. using data obtained from the neurasthenia module of Composite International Diagnostic Instrument (CIDI). More specifically, this paper examined the lifetime prevalence of neurasthenia in these two countries, and their age-of-onset distributions, patterns of comorbidity, and sociodemographic correlates. A secondary question concerned the relationships of comorbid conditions to fatigue in the elderly. Throughout the text, the term “prolonged fatigue” will be used as a more generic term for neurasthenia and CFS.

Methods

Ukraine Sample

The Ukraine World Mental Health Survey (WMH; 16) and the National Comorbidity Survey-Replication (NCS-R; 17) have been described previously. Briefly, the Ukraine WMH implemented a four-tiered stratified cluster design to obtain a nationally representative sample of 4,725 adults aged 18 and older (response rate 78.3%). The sample was administered the paper-pencil version of the CIDI 3.0, which contains two parts in order to reduce respondent burden. All 4,725 respondents received Part I, which assessed mood and anxiety disorders and alcoholism. Part I respondents who met criteria for one or more disorders and a random sample (16%) of the remaining respondents were administered Part II (N = 1,720). The analysis of prolonged fatigue used the Part II sample. Weighting procedures allow the generalization of findings to the population of adults in Ukraine (see *Data analysis*).

U.S. Sample

The NCS-R was a national probability sample assessed with the computerized version of the CIDI 3.0 in 2002-2003 (data available from www.icpsr.org). The NCS-R used a multi-stage cluster sampling design. A total of 9,282 respondents aged 18 and older participated in Part 1 of the NCS-R (response rate = 73.0%). The Part II sample (N=5962) was the focus of our analysis of prolonged fatigue. Weighting procedures allow the generalization of findings to the population of adults in the United States (see *Data Analysis*).

Instrument

The CIDI 3.0 is a widely administered and reliable structured diagnostic tool designed for use by lay interviewers. More detail on the CIDI can be obtained elsewhere [18] including translation details used for the Ukraine CIDI [16].

Prolonged fatigue

Using the Neurasthenia Module of the CIDI, prolonged fatigue was operationalized as follows: (a) several months or more of weakness, tiredness or exhaustion while performing minor everyday physical or mental tasks, (b) the tiredness or weakness was not alleviated by resting or relaxing, (c) during the months or years when the problems were most severe, the respondent got tired most or nearly every day, and (d) the tiredness had “a lot” or “extreme” impact on work, social life and/or personal relationships. Lifetime prevalence rates were derived from participants who fulfilled these criteria.

In comparison to previous studies [e.g., 19], our inclusion criteria specified symptom severity in addition to presence or absence of each symptom. Information on severity and frequency of symptoms may yield more accurate prevalence estimates because symptoms are assessed in a precisely defined and reproducible manner [3]. To ensure that the prevalence of prolonged

fatigue was not driven largely by individuals reporting a cancer diagnosis, which is strongly linked to fatigue [e.g., 20], we also created a version of the prolonged fatigue diagnosis that eliminated individuals who reported ever being diagnosed with cancer. There were no other medical or psychiatric exclusion criteria.

Risk factors

Demographic characteristics, childhood onset (early childhood) factors, and adult episodes of psychiatric and medical conditions (adult risk factors) were included in the analysis. We considered seven demographic variables, five of which were identical in the two samples: sex, age (18-49, 50-69, 70+), employment status (currently working or not currently working), education (high school or less, beyond high school) and marital status (married before but not currently, currently married, or never married). Ethnicity and socio-economic status were constructed differently for the two samples: (1) Ethnicity in the U.S. was dichotomized into white vs non-white; ethnicity in Ukraine was based on whether the interview was conducted in Ukrainian versus Russian; (2) socioeconomic status was assessed in the U.S. by household income of $\geq \$65,000$ versus $< \$65,000$ and in Ukraine by a rating of family financial status as adequate (enough money for durables), inadequate (not enough money for clothing) and very inadequate (not enough money for food).

Four early childhood factors were analyzed using identical variables for the U.S. and Ukraine, namely, (1) early onset (aged 19 or earlier) of DSM-IV alcohol or drug abuse (substance use disorder), and of mood or anxiety disorders (depression, dysthymia, (2) generalized anxiety disorder, panic disorder, social phobia and agoraphobia, (3) parental anxiety or mood disorder (depressive episodes lasting 2+ weeks that interfered with life activities or episodes of nervousness or anxiety lasting 1+ month or anxiety/panic attacks), and (4) parental alcoholism

(alcohol problems that interfered with life activities during a significant portion of the respondent's childhood). The WMH-CIDI contained special probes designed to maximize recall of age of onset.

Five adult risk factors were measured identically in the two samples: (1) adult episodes (age 20+) of DSM-IV drug or alcohol abuse (substance use disorder); (2) mood or anxiety disorder (disorders are identical to list in previous paragraph); (3) cardiovascular health problems (stroke or heart attack within the last 12 months or lifetime diagnosis of heart disease or high blood pressure); (4) pain conditions (arthritis or rheumatism, chronic back or neck problems, frequent/severe headaches or any other chronic pain condition over the past 12 months); and (5) other major health conditions (asthma, tuberculosis, other chronic lung disease, diabetes, ulcer, thyroid disease, neurological disorders, epilepsy, kidney disease, and liver disease).

Data analysis

To approximate the population distributions for both Ukraine and the U. S. on key socio-demographic variables and to account for differential probability of selection and non-response bias into part II, the sample was weighted [16,34,35]. Statistical analyses were conducted using R statistical software [21] to adjust for the stratified sampling design and sample weights. Odds ratios and 95% confidence intervals were obtained from binary logistic regression analyses. Multivariable analyses were conducted in three steps in order to model the temporal progression of potential risk of prolonged fatigue: (1) Step 1 included the significant ($p < 0.05$) demographic risk factors; Step 2 added the significant childhood risk factors while retaining significant risk factors from Step 1; and (3) Step 3 added the adult risk factors while retaining significant risk factors from Steps 1 and 2.

Results

Demographic characteristics

Table 1 shows the demographic characteristics of the Ukraine and the U.S. samples. Both samples were relatively evenly split between male and female respondents, while the Ukraine sample had more years of education but with greater unemployment. Parental, childhood and adult mental and physical health risk factors tended to be similar between the two samples, though some modest differences are noted in the table.

Prevalence of Prolonged Fatigue

The lifetime prevalence of neurasthenia, i.e., prolonged fatigue was 5.2% (SE=0.7%; 89/1720) in Ukraine and 3.7% (SE=0.2%; 213/5692) in the U.S. ($p<.05$). Information on age of onset and recency of prolonged fatigue was available for 59.8% ($n=53$) of fatigue cases in Ukraine and 91.9% ($n=196$) of cases in the U.S. In Ukraine, the median age of onset was 34.16 (range 10 - 73; IQR 20.4 – 44.87). A total of 2.8% (SE=0.3%; 48/1720) of cases reported prolonged fatigue in the year prior to interview. Among U.S. cases with prolonged fatigue, the median age of onset was 32.6 (range 6 - 81; IQR 22 - 41). A total of 1.9% (SE=0.2%; 108/5692) of cases reported prolonged fatigue in the year prior to interview. Lifetime prevalence decreased only minimally to 5.0% (SE=0.7%; 85/1720) in Ukraine and 3.4% (SE=0.2%; 194/5692) when excluding individuals with a lifetime diagnosis of cancer. The diagnostic criteria without physical or mental health exclusions are used throughout the remainder of the manuscript.

Only about one in ten individuals with prolonged fatigue in Ukraine (9.0%) and the U.S. (11.2%) had no other lifetime physical conditions. Less than one in four individuals with prolonged fatigue in the U.S. (23.2%) and less than half in Ukraine (39.7%) had no lifetime psychiatric disorders. We note, however, that these conditions were not necessarily comorbid in that they did not always occur simultaneously within the same individual.

Bivariate Risk Factors Associations

In both the U. S. and Ukraine, demographic risk factors were significantly associated with risk of prolonged fatigue (Table 2). In both countries females, individuals not working, individuals married before (divorced or widowed) and those with lower socio-economic status were at increased risk of prolonged fatigue. Race and education were not significant factors in the U.S., but were significant in Ukraine (higher rates of prolonged fatigue in the less educated and in Ukrainian speakers). Importantly, while age was significantly related ($p < .001$) to fatigue in both samples, the pattern of significance was quite different. In Ukraine, fatigue risk increased linearly across age categories, whereas in the U.S. cohort, there was a sharp decrease in risk in the age 70+ cohort (Figure 1).

In the United States, all four childhood risk factors, including both parental variables, were strongly related to lifetime risk of prolonged fatigue with odds ratios ranging from 1.7 (Early onset Alcohol/Drug) to 3.8 (Early Onset Mood/Anxiety). In Ukraine, only one of the four risk factors was significant (Mood/Anxiety; OR=2.7 (1.8, 4.0). As with childhood risk factors, all five adult risk factors showed significant associations with lifetime prolonged fatigue risk in the U. S. In Ukraine, three of the five adult risk factors were associated with prolonged fatigue risk: mood/anxiety disorder, cardiovascular health problems and pain conditions (Table 2).

Multivariable analysis

In the multivariable analysis, four demographic variables remained significantly associated with lifetime risk of lifetime prolonged fatigue after adjusting for the other significant demographic variables in each sample. Two of the four demographic variables (female and age) were significant in both samples (Female: U.S., $p < .001$, UK: $p < 0.01$; Age: U.S., $p < .001$, UK: $p < .05$), while marital status ($p < .01$) and employment status ($p < .001$) were significant in the U.S.,

whereas language ($p<.05$) and income ($p<.001$) were significant in Ukraine.

After controlling for other childhood and demographic risk factors, only 2 of the 4 risk factors remained significant for lifetime prolonged fatigue in the U.S. sample: Early Onset Mood/Anxiety ($p<.001$) and Parental Anxiety/Depression ($p<0.001$). Early Onset Mood/Anxiety was the only significant childhood risk factor in the Ukraine sample ($p<.001$).

Finally, only adult mood/anxiety disorders was a significant risk factor for prolonged fatigue in multivariable models for both the U.S. ($p<.001$) and Ukraine ($p<.01$). Cardiovascular diseases was a significant predictor ($p<.001$) in Ukraine, while adult substance use disorder, pain and other chronic health conditions were significant predictors ($p<.01$) in the U.S. Based on significant risk factors in the multivariable models, Figures 2a and 2b show the cumulative risk for prolonged fatigue as the total number of risk factors increases in both the U.S. (ten possible risk factors) and Ukraine (seven possible risk factors) samples.

Discussion

This paper presented findings on the epidemiology of lifetime prolonged fatigue, using a neurasthenia assessment in the Ukraine (Ukraine-World Mental Health Survey [Ukraine-WMH]) and in the U.S. (2003 National Comorbidity Survey-Replication [NCS-R]). The lifetime prevalence of neurasthenia (i.e., prolonged fatigue) was found to be 5.2% in Ukraine, about 40% higher than that found in the U.S. data (3.7%). The female: male ratio for prolonged fatigue prevalence was about 2:1 in both populations. The 12 month interference with activities such as housework and ability to work were similar between Ukraine and the U.S., but interference with close relationships and social life was actually greater ($p<0.01$ and $p<0.01$, respectively) in the U.S. We also found that a higher number of risk factors (e.g., adult mood and anxiety) was

predictive of a higher percentage of individuals reporting fatigue symptoms that fulfilled criteria for neurasthenia. In addition, prolonged fatigue prevalence spiked in the age 70 and over group in Ukraine, while U.S. rates declined for the elderly.

Increased risk of prolonged fatigue was linked to females, individuals not working, individuals married before (divorced or widowed) and those with lower socio-economic status. In the U.S., whites had higher rates of prolonged fatigue than non-whites. The risk factors for prolonged fatigue were largely similar between the U.S. and Ukraine, but with higher risk for individuals with alcohol abuse history in the U.S. sample and for those with lower education in Ukraine.

In a recent U.S. population study [5], the adjusted prevalence rate for lifetime neurasthenia without exclusionary criteria was 4.9%. Our lifetime estimates of 3.7-5.2% without exclusionary criteria are in a comparable range. Our use of symptom severity criteria may have increased the ability to screen those individuals with clinically significant symptoms.

The Impact of Life Events

Stressful life events have been prospectively linked to both CFS and neurasthenia [8-11]. In Ukraine, psychological risk factors for prolonged fatigue may in part be a long-range consequence of a number of potentially traumatic events that have occurred in that region. These events include the social and economic dislocations following the dissolution of the Soviet Union in the 1990s, and a large number of industrial, mining, and transport accidents [16], most notably the Chernobyl nuclear plant accident in 1987.

In related work, new pilot data based on a discrete catastrophic life event (9/11 responders to the World Trade Center attacks in the U.S.) suggest that the prevalence of prolonged fatigue is unusually high in this group [22]. Paths from major life events to prolonged fatigue (via

mediation or moderation) may include sleep disturbance, poor social support, ongoing stress, depression, anxiety [23], and/or medical comorbidities [12]. However, it is not clear how these intervening variables may exert their putative effects on fatigue severity and incidence. For instance, stress may directly lead to fatigue or be mediated by sleep disturbance. Furthermore, it is unclear whether factors such as social support might be able to alter the strength of the life events–fatigue relationship (i.e., as a moderator).

Psychiatric and medical morbidities

Childhood and adult psychiatric risk factors including mood/anxiety disorder and alcohol abuse were identified for prolonged fatigue. Because the symptom of fatigue occurs in mood and anxiety disorders, it has been proposed that prolonged fatigue states such as neurasthenia and CFS may be somatic variants of psychiatric disorders [24]. However, fatigue appears to be qualitatively different in prolonged fatigue states because it is worsened by physical and mental effort, including exercise [25]. By comparison, exercise is a moderately effective treatment for depression and anxiety [26]. Furthermore, although fatigue may be a feature of anxiety and depressive disorders, prolonged fatigue can occur in the absence of psychiatric disorder [6, 23].

The high prevalence of chronic medical comorbidities in both the Ukraine and U.S. samples suggest additional influences on prolonged fatigue states. For instance, fatigue is a frequent complaint in cardiovascular disease [27], with exertion fatigue particularly prominent in heart failure [28]. In addition, fatigue may constitute the first clinical manifestation of heart disease [27]. Similarly, fatigue in the less distinct conditions of neurasthenia and CFS may capture important elements, including pre-clinical manifestations, of other diseases especially in older populations [29].

Prolonged fatigue and the elderly

Figure 1 shows the sharply higher percentage of individuals with prolonged fatigue in the age 70 and over group in Ukraine (11.1%) as compared to a much lower rate in the U.S. elderly subgroup (1.9%). One partial explanation for this higher fatigue prevalence in Ukraine is that fewer public and private resources are available for health and other services to the elderly. Even for those elderly with “relative-responsible” families who are providing care, there are often feelings of profound social and psychological isolation [30]. Less social support has also been linked to neurasthenia [23].

Furthermore, the post- Soviet decline in health and the increase in chronic medical illness such as heart disease, diabetes, and cancer [30, 31] may disproportionately impact the elderly. As such, prolonged fatigue may reflect advancing heart disease as well as undiagnosed preclinical conditions, physical declines with age, and sedentary activity levels [15].

Limitations

The size of the U.S. sample was nearly twice as large as the Ukraine cohort which increased the ability to identify significant risk factors and may account for some of the differences between the two groups. However odds ratio estimates suggest that sample size may not be the only explanation. Findings in the over 50 group may reflect survivor bias [32], a significant concern in regions with life expectancy <70, as found in the Ukraine. In addition, memory for fatigue symptoms and episodes over the lifespan is subject to recall bias that may inflate the severity of remembered symptoms [33].

Conclusion

Prolonged fatigue as diagnosed with neurasthenia criteria shows considerably higher prevalence in the Ukraine in comparison to the U.S. Fatigue was associated with both medical and psychiatric comorbidities, with only a small minority reporting “pure” fatigue without

comorbid conditions. Fatigue prevalence was sharply higher in the elderly in Ukraine in comparison to the U.S.

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