

# Mortality in a cohort of chronically fatigued patients

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## ABSTRACT

**Background.** Comprehensive studies of mortality among patients with chronic fatigue (CF) and chronic fatigue syndrome (CFS) have not been published, but several sources suggest that CFS is associated with an elevated risk for suicide.

**Method.** Data on 1201 chronically fatigued patients followed in a university-affiliated tertiary-care clinic for up to 14 years were submitted to the Center for Disease Control and Prevention (CDC) National Death Index (NDI) to evaluate all-cause and suicide-caused death rates against standardized mortality rates (SMRs). We used Life Table Analysis to examine the influence of sex and diagnoses of CFS and depression.

**Results.** All-cause mortality in chronically fatigued patients was no higher than expected, but suicide-caused death rates were more than eight times higher than in the US general population. The significant elevation in the SMR of suicide was restricted to those who did not meet criteria for CFS [ $SMR_{CF} = 14.2$ , 95% confidence interval (CI) 5.7–29.3 *versus*  $SMR_{CFS} = 3.6$ , 95% CI 0.4–12.9]. Among chronically fatigued patients who did not meet CFS criteria, those with a lifetime history of major depression (MD) had higher suicide-caused death rates than among their non-depressed counterparts ( $SMR_{MD} = 19.1$ , 95% CI 7.0–41.5 *versus*  $SMR_{NMD} = 5.6$ , 95% CI 0.1–31.4), although the difference was not significant.

**Conclusions.** CFS does not appear to be associated with increased all-cause mortality or suicide rates. Clinicians, however, should carefully evaluate patients with CF for depression and suicidality.

## BACKGROUND

Chronic fatigue (CF) is a common complaint in clinical settings that may result from diverse medical and psychological conditions. Chronic fatigue syndrome (CFS) is an illness characterized by at least 6 months of persistent and severe fatigue that is associated with unrefreshing sleep, myalgia, headache and neuropsychological disturbances. The case definition for CFS, developed by the Center for Disease Control and Prevention (CDC), allows a diagnosis of CFS to be considered only after other causes of fatiguing illness have been excluded, such as

hepatitis, cancer, neurological diseases and diabetes (Fukuda *et al.* 1994). By definition, persons with CFS are free of most major medical conditions and therefore might be expected to have mortality rates similar to, or lower than, those for the general population. However, most psychiatric conditions are not exclusionary and rates of depressive, anxiety and other psychiatric disorders are high among patients with CF (Wessely *et al.* 1996) and CFS (Krusei *et al.* 1989; Katon *et al.* 1991; Lane *et al.* 1991). It is not known whether major depression (MD), along with the profound life changes engendered by these conditions, results in elevated rates of suicide among individuals with CF and CFS.

Comprehensive studies on mortality among persons with chronically fatiguing illnesses have

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not been published, although one review found no increased mortality or suicide (Joyce *et al.* 1997). Nonetheless, reports of death and suicide attributed to CFS have been disseminated by the lay press and the internet (Australian Broadcast Corporation, 2001; Guardian Unlimited, 2001), highlighted in testimony from medical experts (Cable News Network, 2001), and reported in consumer-group publications (Chronic Fatigue and Immune Deficiency Syndrome Association of America, 1998; Allison Hunt Memorial Foundation, 1999). However defined, CFS is linked by these sources to an increased risk of suicide.

We analyzed data obtained on 1201 patients evaluated at a tertiary referral clinic over a period of 12–14 years to determine if CF or CFS carried an increased risk for mortality. We used the CDC's National Death Index (NDI) to confirm death. The main objectives were to evaluate whether all-cause mortality and suicide death rates differed significantly among patients with CF or CFS from those for the general US population.

## METHOD

### Setting and sample

Patients were adults seen at an academic referral center devoted to the evaluation and treatment of CF. All clinic patients were evaluated with a standardized, comprehensive review of their medical and psychiatric history, physical examination, and routine laboratory studies as recommended by the CDC (Fukuda *et al.* 1994). Other laboratory studies were obtained as clinically indicated. Patients were not required to meet the CDC's criteria for CFS to be seen at the clinic, but information was collected on each criterion in the case definition. Patients provided written, informed consent to use the data elements gathered during their clinic visits, a procedure that was approved by the institutional human subjects office.

### Identification of deaths

Personal identifiers (name, social security number, date of birth, and sex) and date of the initial clinic visit were submitted to the NDI for patients who were first evaluated prior to 2002. Matches were determined based on the

probabilistic match score provided by the NDI. Also provided for each potential match were the date of death and an ICD-9 or ICD-10 code indicating all causes of death for patients who died prior to 31 December 2001, which, at the time of the analysis in 2003, were the most recent data available. ICD-10 codes were translated into corresponding ICD-9 codes for analytic purposes because the software had not yet been upgraded to recognize ICD-10 codes. Although only the primary cause of death was considered in the analysis, we carefully inspected both the primary and the ancillary death codes to ensure that all suicide-caused mortality was captured.

### Diagnoses

CFS status was assessed at the initial clinic visit according to the 1994 CDC criteria (Fukuda *et al.* 1994) using self-report items on the pattern, intensity and timing of fatigue and the ancillary symptoms. Retained in the current study were patients who endorsed problematic fatigue with an onset date at least 6 months prior to the examination. The presence of exclusionary diagnoses was determined by a physical examination and the attending physician's interview and review of the medical history, and by follow-up medical evaluations such as polysomnography. A trained research assistant administered the National Institute of Mental Health Diagnostic Interview Schedule Version III-A, a structured interview that assigns current and lifetime psychiatric diagnoses based on DSM-III-R criteria (Robins & Helzer, 1985). Lifetime and current MD were determined using the structured psychiatric interview.

Patients who were chronically fatigued but did not meet the CDC case definition of CFS were excluded for the following reasons: (1) fatigue that was lifelong, remitted with rest, did not result in a substantial decrease in function, or was associated with an insufficient number of ancillary symptoms, (2) the presence of an exclusionary medical condition (i.e. one that could cause fatigue), including polysomnographically verified sleep disorders, or (3) the presence of an exclusionary psychiatric condition, consisting of a history of psychosis, eating disorder or alcohol or substance abuse within 2 years prior to the fatigue onset.

## Data analysis

Patients who reported at least 6 months of fatigue and were not missing data for key variables (date of birth, social security number, sex, race, date fatigue began, initial examination date, and CFS and lifetime MD diagnoses) were considered in the analyses. Of the 1395 patients undergoing their index clinic visit between December 1988 and December 2001, 1201 (86%) met these criteria and were included in the final sample.

We computed standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) for all-cause mortality and suicide by comparing observed death rates in the referral clinic cohort to general population rates in the USA from 1960 to 1999. SMRs were adjusted for sex, race, age and calendar time. We computed SMRs for the entire cohort and stratified by sex, fatigue duration prior to clinic entry, and CFS and depression diagnoses.

Follow-up time began at the date of the first clinic visit and ceased on the date of death or 31 December 2001, whichever was earlier. We set the start of follow-up time at the date of clinic entry because it was the time when patients first came under observation. If we had started the follow-up period at the reported onset of fatigue, we would have introduced a bias due to incomplete observation of risk. Instead we chose to assess differences in the duration of fatigue prior to clinic entry by performing a stratified SMR analysis. Patients were stratified according to quartile of fatigue duration: <2, 2–3.9, 4–7.9 and  $\geq 8$  years prior to clinic entry.

All analyses were conducted using the Life Table Analysis System version 1.0d (Waxweiler *et al.* 1983) developed by the National Institute for Occupational Safety and Health. Stratified SMRs were tested for heterogeneity or trend using methods developed by Breslow & Day (1987).

## RESULTS

As of 31 December 2001 the mean amount of time our sample patients were followed was 9 years (s.d. = 4 years). Nearly 80% of the patients had been followed for at least 5 years. The mean age of the clinic patients at their initial evaluation was  $48 \pm 13$  years, and the majority were female (77%). The sample was 94%

Caucasian, which is typical of the clinic, even though the greater metropolitan area is approximately 75% Caucasian. Over half the sample met all the 1994 diagnostic criteria for CFS (53%); 55% met criteria for lifetime MD. At the time of assessment the group with CF not meeting CFS criteria more frequently met criteria for current MD than did the CFS group (24% v. 14%). Among the 560 patients in the group with CF not meeting criteria, 135 (25%) were excluded from the CFS group by not meeting the symptom criterion, 36 (7%) were excluded for medical conditions, 30 (6%) were excluded for psychiatric or substance abuse conditions, and 329 (62%) had more than one exclusion.

Among the 1201 clinic patients, 38 (3%) were deceased. The most common causes of death as listed by the NDI were cancers ( $n=9$ , 24%), suicide ( $n=9$ , 24%) and heart disease ( $n=3$ , 8%). Two deaths each (5%) occurred from renal failure, human immunodeficiency virus (HIV) complications, chronic obstructive pulmonary disease, and chronic liver disease, and one each (3%) from cerebrovascular disease, pneumonia, effects of alcohol dependence, asthma, motor vehicle accident, phlebitis, atherosclerosis, diaphragmatic hernia, and stroke.

Table 1 shows the SMRs for our sample according to cause of death and sex. Overall, chronically fatigued patients did not experience all-cause mortality at higher rates than the general US population (SMR = 0.9, 95% CI 0.6–1.2) and the SMRs for males and females were similar ( $p=0.51$ ). The overall SMR for suicide was 8.6 (95% CI 3.9–16.3). The SMRs for suicide were elevated in both men (8.9, 95% CI 2.9–20.8) and women (8.2, 95% CI 2.2–21.0), but did not differ according to sex ( $p=0.91$ ).

Table 1 also shows the SMRs for the clinic sample according to cause of death and diagnosis of CFS. The SMRs for all-cause mortality in patients with CF not meeting criteria and those with CFS were 1.0 and 0.7, respectively. Neither SMR differed significantly from 1, nor were the ratios different from each other ( $p=0.22$ ). The SMRs for death due to suicide were elevated for both patients with CF and CFS when compared to expected rates (SMR<sub>CF</sub> = 14.2, SMR<sub>CFS</sub> = 3.6). However, the

Table 1. Standardized mortality ratios (SMRs) for all chronically fatigued patients according to sex or diagnosis

	All-cause mortality			Suicide		
	Observed deaths	SMR	95% CI	Observed deaths	SMR	95% CI
Sex						
Male	15	1.0	0.6–1.8	5	8.9	2.9–20.8
Female	23	0.8	0.5–1.3	4	8.2	2.2–21.0
All patients	38	0.9	0.7–1.3	9	8.6	3.9–16.3
Diagnosis of CF <sup>a</sup>						
With MD	14	1.1	0.6–1.8	6	19.1	7.0–41.5
Without MD	10	1.0	0.5–1.8	1	5.6	0.1–31.4
All CF patients	24	1.0	0.7–1.5	7	14.2	5.7–29.3
Diagnosis of CFS						
With lifetime MD	10	0.9	0.4–1.6	1	3.2	0.1–18.0
Without lifetime MD	4	0.5	0.1–1.2	1	4.0	0.1–22.2
All CFS patients	14	0.7	0.4–1.2	2	3.6	0.4–12.9

CI, confidence interval; MD, major depression.

<sup>a</sup> Chronic fatigue (CF) not meeting criteria for chronic fatigue syndrome (CFS).

SMR was significant only for chronically fatigued patients who did not meet the CDC criteria for CFS ( $p < 0.01$ ) (i.e. did not meet fatigue or symptom severity criteria or had an exclusionary condition). Among these chronically fatigued patients, further stratification by lifetime MD revealed a larger SMR for depressed than non-depressed patients (19.1, 95% CI 7.0–41.5 *v.* 5.6, 95% CI 0.1–31.4), but the difference was not significant ( $p = 0.23$ ).

We also examined whether the SMRs for all-cause mortality or suicide increased with fatigue duration prior to clinic entry (results not shown). We found no evidence that the SMR for all-cause mortality increased with fatigue duration ( $p_{\text{trend}} = 0.51$ ). Although the rate of death due to suicide was significantly elevated in most strata when compared to expected rates (SMR range 7.7–9.2), the rate of suicide did not increase with fatigue duration ( $p_{\text{trend}} = 0.91$ ).

## DISCUSSION

This study is the first to examine SMRs among a well-defined population of fatigued patients. We found that overall mortality was not higher than expected in our sample of 1201, mostly female, chronically fatigued Caucasian clinic patients. Suicide, however, occurred at a higher rate than in the general population, but this increase was significant only among those who did not meet

diagnostic criteria for CFS. The SMR for suicide was higher among non-CFS patients with lifetime MD episodes than among their non-depressed counterparts, although this finding did not reach statistical significance.

Because neither death nor suicide has ever been rigorously examined among individuals with CF and CFS, we cannot directly compare our findings to other data. However, in a study comparing depressed CFS patients with depressed patients without CFS, the CFS group experienced less worthlessness and higher self-esteem than the purely depressed group (Powell *et al.* 1990). Similarly, others have found that chronically fatigued adolescents without MD endorsed many secondary symptoms of depression but were less likely than depressed psychiatric clinic patients to report primary depressive symptoms such as depressed mood, guilt and suicidality (Smith *et al.* 1991).

In our study, the co-occurrence of a CFS-exclusionary condition or MD disorder appeared to increase the risk of suicide among chronically fatigued patients. MD is a well-recognized risk factor for suicide (APA, 1994) and is itself not exclusionary for CFS. Yet it often co-exists with other psychiatric diagnoses (APA, 1994) that preclude a diagnosis of CFS, such as mania, melancholia, psychosis, eating disorders and substance abuse (Fukuda *et al.* 1994). These exclusionary diagnoses increase the

risk of suicide (Bongar, 1991) and may explain the greater SMR for suicide in the CF patients not meeting CFS criteria. In addition to psychiatric illnesses, other risk factors for suicide include chronic, debilitating medical illness and dissatisfaction with medical care (Bongar, 1991). By definition, the chronically fatigued group not meeting the CFS case definition had a higher proportion of patients with debilitating medical illness, and may have contained a higher proportion who were disappointed and dissatisfied with their health care because of failure to be diagnosed with CFS after an extensive medical work-up.

This study has several additional limitations. First, for a study of this type, our sample size was relatively small and the follow-up period short. A related issue is that SMRs may be inflated if patients recovered and were no longer fatigued during the follow-up period. However, in our previous work using self-reported disability measures with follow-ups averaging 1·7 years, we showed that the rate of recovery was low in our clinic population (Bombardier & Buchwald, 1995). Second, the reliance of the NDI on state death certificates has led some early researchers to question the accuracy and completeness of suicide as a cause of death (Nelson *et al.* 1978; Taylor, 1982). However, the NDI has very high sensitivity in detecting true deaths (Fisher *et al.* 1995), and more recent work suggests adequate reliability for suicide (Rockett & Thomas, 1999). Third, our results may not be generalizable to primary-care or community-based samples of fatigued patients because of our tertiary-care setting and the under-representation of non-Caucasians in the sample. Finally, we used the index examination date as the date when the follow-up period began rather than the date of reported fatigue onset. To do otherwise would have systematically biased the true mortality rate due to incomplete observation of risk. Nonetheless, we examined the duration of prior fatigue in a stratified analysis and saw no effect of longer fatigue duration on all-cause or suicide mortality.

In summary, the all-cause mortality rate among this sample of 1201 chronically fatigued clinic patients followed for up to 12–14 years was similar to that of the general population. The subgroup that failed to meet the CFS case definition experienced greater than expected

rates of death by suicide. Larger non-clinical samples and longer periods of follow-up might provide a different view, but these data underscore the need for clinicians to not dismiss the potentially serious consequences of a chronically fatiguing condition, especially when accompanied by major depression.

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## DECLARATION OF INTEREST

None.

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