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## Medication Use by Persons with Chronic Fatigue Syndrome: Results of a Randomized Telephone Survey in Wichita, Kansas

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### Abstract

**Background:** Chronic fatigue syndrome (CFS) is characterized by profound fatigue, which substantially interferes with daily activities, and a characteristic symptom complex. Patients use a variety of prescribed and self-administered medications, vitamins, and supplements for relief of their symptoms. The objective of this study was to describe utilization of medications and supplements by persons with CFS and non-fatigued individuals representative of the general population of Wichita, Kansas.

**Methods:** We used a random-digit dialing telephone survey to identify persons with CFS in the general population of Wichita, Kansas. Subjects who on the basis of telephone interview met the CFS case definition, and randomly selected non-fatigued controls, were invited for a clinic evaluation that included self-reported use of medications and supplements. Sex-adjusted odds ratios and 95% confidence interval were estimated to measure the association between CFS and use of various drug categories.

**Results:** We clinically evaluated and classified 90 subjects as CFS during the study and also collected clinical data on 63 who never described fatigue. Subjects with CFS reported using 316 different drugs compared to 157 reported by non-fatigued controls. CFS subjects were more likely to use any drug category than controls ( $p = 0.0009$ ). Pain relievers and vitamins/supplements were the two most common agents listed by both groups. In addition CFS persons were more likely to use pain relievers, hormones, antidepressants, benzodiazepines, gastro-intestinal, and central nervous system medications (Sex-adjusted odds ratios range = 2.97 – 12.78).

**Conclusion:** Although the reasons for increased use of these agents were not elucidated, the data indicated the CFS patients' need for symptom relief.

### Background

Chronic fatigue syndrome (CFS) poses unique challenges for health care providers and patients. Population-based prevalence estimates range from 142 to 560 per 100,000 adults [1,2], which implies that the illness may affect at least 800,000 adults in the United States <http://eire.cen>

[sus.gov/popest/data/national/tables/asro/NA-EST2002-ASRO-01.php](http://sus.gov/popest/data/national/tables/asro/NA-EST2002-ASRO-01.php). Their median duration of illness range from 2 to 7 years [1,2], a quarter of them are unemployed or receiving disability, and fewer than 20% have received medical care for CFS [1-3]. However, CFS is an exclusionary diagnosis based on a characteristic but non-specific

symptom complex [4]. No diagnostic physical signs or laboratory abnormalities and no single cause for CFS have been identified, and the pathophysiology of the syndrome remains ill defined. Thus, treatment efforts are directed at symptom relief, with the goal of the patient regaining some level of pre-existing function and wellbeing. Many health care providers prescribe pharmacologic therapy to relieve fatigue and bothersome symptoms (e.g., pain or unrefreshing sleep). Individuals suffering from CFS for prolonged periods may become frustrated with a lack of acceptable recovery and self-medicate with over the counter (OTC) medications and other supplements. However, both prescribed and OTC medications can cause untoward side effects, which may lead to new symptoms and exacerbate overall disability. Remarkably, no population-based studies have documented use of medications by persons with CFS.

The objective of this study was to describe use of medications and supplements by persons with CFS and non-fatigued individuals representative of the general population of Wichita, Kansas. We wished to determine if persons with CFS used more medications and supplements than non-fatigued persons and to determine the nature of medications/supplements used by the two groups. We found a high level of medication/supplement use by both groups and use of selective medications by individuals with CFS.

## Methods

The study adhered to human experimentation guidelines of the U.S. Department of Health and Human Services and of the Centers for Disease Control and Prevention Institutional Review Board. All participants were volunteers who gave informed consent for the telephone interview and clinical evaluation.

## Study Design

The study has been described in detail [1,3,4]. Briefly, in 1997 we used random-digit-dialing phone interviews to screen for fatigue among 56,146 adults 18 to 69 representing the Wichita population. We then conducted detailed telephone interviews with 3,528 who reported fatigue lasting for at least 1 month and 3,634 non-fatigued persons. Fatigued individuals who, based on telephone interview, met criteria for CFS (termed CFS-like) [4] and randomly selected non-fatigued adults were further evaluated clinically. A committee of physicians reviewed all the clinical data and identified the fatigued subjects who could be classified as CFS individuals. In 1998, 1999, and 2000, all previously interviewed subjects were re-contacted by telephone and newly identified CFS-like subjects and previously examined participants were evaluated clinically. Thus, new CFS cases were identified throughout the 3-year follow-up period [1]. This analysis considered

information from individuals identified as CFS during any year of the study.

## Data Collection

During the clinical evaluation subjects underwent a standardized physical examination, were administered the Diagnostic Interview Scheduling for DSM-IV psychiatric disorders [4], and provided blood and urine samples for routine clinical laboratory screening to fulfill evaluation criteria recommended by the CFS case definition [4]. At each clinic visit, subjects enumerated their medication use, including prescription, OTC medications, and supplements/ vitamins. Hereafter, these agents will be referred to as "drugs" unless otherwise specified.

## Statistics

We assessed differences in the prevalence of drug categories using the Fisher's exact or  $\chi^2$  tests. Continuous variables were tested by the Wilcoxon rank-sum test or Student's t-test. We fitted the logistic regression model to estimate odds ratios and 95% confidence intervals to measure the association between CFS and drug categories, adjusting for sex. All tests were 2-sided and p-values were considered significant if they did not exceed .05. We utilized SAS version 8.1 (SAS Inc., Cary, NC) for all analyses.

## Results

### Description

Over the 4-year study period, 90 persons were classified as CFS during at least one clinic evaluation. In this study, we also considered longitudinal data for 63 clinically evaluated individuals who did not report fatigue in the first year of the study. Table 1 describes demographics in both groups. There were no significant differences between CFS and non-fatigued subjects with respect to age, race/ethnicity, income, or education. However, subjects with CFS were more likely than non-fatigued subjects to be female (85.6% versus 57.1%,  $p = .0001$ ). Median duration of CFS was 6.9 years, the median age at onset was 36.5 years, and 79.3% reported a gradual onset.

### Overall use of medications/supplements (drugs)

The CFS group reported use of 1174 medications identifying 316 distinct drugs. There were 130 drugs reported only once. The most frequently reported single drug was an OTC acetaminophen preparation, being cited in 51 (4.3%) of the 1174 reports. Acetaminophen, however, was a component of a total of 81 (6.8%) reported drugs. Pain medications also included 82 (6.9%) reports of anti-inflammatory agents including non-steroidal anti-inflammatory agents, with the most common being ibuprofen (22 reports, 1.9%), COX-2 inhibitors and aspirin. Narcotics and tramadol were reported in 16(1.3%) and 22 (1.8%) instances, respectively. There were an additional

**Table 1: Demographic characteristics of subjects with chronic fatigue syndrome (CFS) and non-fatigued subjects in Wichita, Kansas**

Characteristic*	CFS subjects (n = 90)	Non-fatigued subjects (n = 63)
Age (mean years, SD)	44.4 (10.3)	43.3 (13.5)
Female (%)	85.6	57.1
Race/ethnicity (%)		
White	90.0	93.7
African American	2.2	4.8
American Indian	5.6	0.0
Hispanic	1.1	0.0
Other	1.1	1.6
High School education (%)	62.2	74.6
Income ≥ \$40,000	42.2	54.1

\* No significant differences between CFS and non-fatigued subjects except for female sex ( $\chi^2$  test,  $p < .0001$ )

**Table 2: Categories of drugs, according to name of medication reported, used by subjects with CFS and non-fatigued subjects in Wichita, Kansas**

Drug Category	Name/type of medication
Pain reliever	Tramadol hydrochloride, acetaminophen, narcotics, NSAIDs, (including OTC preparations)
Supplements/vitamins	Calcium, potassium, vitamins, dietary supplements
Hormones	Estrogen, progesterone, levothyroxin, prednisone
Antidepressants	Tricyclics, other (specific serotonin reuptake inhibitors, buspirone)
Allergy	Oral antihistamines, nasal steroids
Gastrointestinal	Antacids, H <sub>2</sub> blockers, proton pump inhibitors
Antihypertensive	Calcium channel blockers, acetylcholine esterase inhibitors
Cardiac	Agents used in absence of history of hypertension (eg. beta-blockers)
Cold/sinus	Antihistamines/decongestants, cough suppressants
Muscle relaxants	Carisoprodol, cyclobenzaprin
Asthma	Inhaled bronchodilators (BD), inhaled corticosteroids, oral BD
Diabetes	Oral, insulin
Lipid-lowering agents	HMG-CoA reductase inhibitors
Sleep	Primary hypnotics (zolpidem tartrate, temazepam)
Diuretics	Triamterene, hydrochlorothiazide, furosemide
Benzodiazepines	Benzodiazepines
Antibiotics	Antibacterials, antifungals, antivirals
Migraine	Sumatriptan succinate, isometheptene Mucate/dichloralphenazone/acetaminophen
Central nervous system	Gabapentin, chromium picolinate

25 (2.1%) reports of "OTC pain relievers" without further identification.

The non-fatigued group reported 157 unique drugs among 417 reports. There were 87 drugs reported only once. Sixteen reports (3.8%) identified ibuprofen in any form, but 38 (9.2%) reports included some type of non-steroidal anti-inflammatory agents. Acetaminophen containing agents totaled 11 (2.6%) and there was a single report of narcotic analgesic use. Fifteen (3.6%) reports listed unidentifiable "OTC pain relievers

### **Prevalence of drug categories in CFS and non-fatigued subjects**

The subjects' reports of drugs were divided into 19 categories. These categories and examples of specific agents and their drug families are described in Table 2.

Pain relieving drugs and supplements/vitamins were the two drug categories most frequently reported by CFS and non-fatigued subjects. However, CFS subjects used 7 categories of drugs more frequently than the non-fatigued individuals. The 7 categories were: pain relievers, supplements/vitamins, hormones, antidepressants, gastrointestinal agents, central nervous system drugs, and

**Table 3: Prevalence of drug category use among CFS and non-fatigued subjects in Wichita, Kansas**

Drug Category	CFS subjects (n = 90)	Non-fatigued subjects (n = 63)	p-value
Pain reliever	87.8	47.6	<.0001
Supplements/Vitamins	62.2	42.9	.0180
Hormones	52.2	20.6	<.0001
Allergy	44.4	30.2	.0740
Antidepressants	41.1	11.1	<.0001
Gastrointestinal	32.2	14.3	.0115
Cold/sinus	30.0	22.2	.2851
Central nervous system	24.4	4.8	.0012
Antihypertensive	21.1	14.3	.2826
Antibiotics	16.7	14.3	.6902
Diuretics	13.3	7.9	.2958
Lipid-lowering	12.2	9.5	.6012
Muscle relaxants	12.2	4.8	.1152
Asthma	12.2	6.4	.2292
Benzodiazepines	11.1	1.6	.0273
Sleep	7.8	3.2	.3087
Cardiac	6.7	7.9	.7613
Migraine	4.4	6.4	.7178
Diabetes	4.4	1.6	.6492
Any category	97.8	82.5	0.0009

**Table 4: Associations between drug categories and CFS status and sex in CFS subjects using drugs in Wichita, Kansas**

Drug category	CFS versus Non-fatigued OR*, (95% CI)	Female versus Male OR (95% CI)
Pain relievers	6.51 (2.85–14.88)	2.26 (0.97–5.28)
Supplements/vitamins	1.68 (0.84–3.38)	2.84 (1.29–6.32)
Hormones	2.97 (1.35–6.51)	9.51 (2.71–33.34)
Antidepressants	4.62 (1.85–11.53)	2.38 (0.82–6.95)
Gastrointestinal	2.67 (1.12–6.36)	1.28 (0.49–3.38)
Central nervous system	6.85 (1.85–25.30)	0.83 (0.26–2.62)
Benzodiazepines	12.78 (1.39–108.34)	0.28 (0.07–1.15)

\*OR, odds ratio; CI, confidence interval; † Odds ratios were adjusted for other variables in the table since they were all included in the logistic regression model

benzodiazepines (Table 3). CFS subjects reported a median of 5 drug categories reported compared with 2 reported by non-fatigued persons (p value < 0.0001).

#### **Association between CFS and drug categories adjusted for sex**

Since women were much more common in the CFS group and gender might account for the differences between drug use patterns, we used logistic regression models to measure the association between CFS illness and drug use, adjusting for sex. Only significant results are reported (Table 4). Female sex was only associated with use of supplements/vitamins, and hormones. However, the association of CFS with supplement/vitamins was no longer significant after female sex was considered. To assess

whether the association of sex with drug categories was the same among CFS and non-fatigued subjects, we fitted additional logistic regression models including an interaction term representing the joint effect of CFS and female sex. No significant interaction terms were detected.

#### **Drug use and duration of illness**

We assessed whether duration of illness among CFS subjects was associated with drug category use and found no association with any drug category, except muscle relaxants. Subjects reporting muscle relaxant use had a shorter duration of illness than those not reporting use (median = 4.1 and 7.8 years, respectively, p = .0402).

### **Drug use and change to non-fatigued state**

Of the 90 subjects ever classified with CFS, 65 underwent at least one subsequent clinical evaluation [5]. Of those, 50 reported persistent fatigue at follow-up but 15 reported they were no longer fatigued. We questioned whether drug use differed between the two groups. The median difference between the number of medications was 1. The only drug category associated with persistent CFS was gastrointestinal medications (60% among subjects who ever changed to a non-fatigued state versus 28% of subjects who remained in the CFS group,  $P = 0.0230$ ).

### **Discussion**

This study clearly documented that, within the general population, persons with CFS were significantly more likely to use medications than non-fatigued individuals. However, CFS and control subjects used similar types of drugs.

We are not aware of comparable population-based reports of medication use by people with CFS or with fatiguing illnesses. CFS-associated reports are primarily medication trials and were recently reviewed by Whiting et al [6]. It is likely not a coincidence that of the few population reports regarding medication use in general, most describe use of pain and sleep medication since problems with pain and sleep are commonly reported to medical practitioners. However, most medications identified in this study may not reflect treatment of fatigue or other symptoms of CFS. The exceptions are medications for pain (ranked as number 1 in this study) that would influence arthralgia, myalgia, and headaches; medications for post-nasal drip associated sore throat, which might include allergy medications (#5); muscle relaxants (#10), which could influence myalgia; sleep medications (#14), which obviously would be used for sleep disturbances; benzodiazepines (#16), which could influence sleep disturbances, muscle aches, headaches, and possibly exertion-related symptoms; and CNS medications (#19), which could influence headaches, sleep disturbances, and cognitive problems associated with CFS. The drugs that were used equally by the two groups could simply reflect treatment of age-related illnesses. We are left with the unanswered question of why CFS subjects use more supplements/vitamins, hormones, antidepressants, and gastrointestinal drugs than do non-fatigued subjects or why they reported use of any drug only on one occasion.

This question highlights a major limitation of the study in regard to assignment of medication use, because we did not obtain the subject's perception concerning the problem(s) that prompted medication use. In particular, no specific questions addressed methods of combating fatigue per se. In addition, we did not address non-pharmacologic approaches to symptom relief, such as acu-

puncture. Since CFS patient perception of the adequacy and efficacy of medical care also affects therapy, absence of their perceptions may also influence our findings [7].

Comparable data for medication use in general in the United States are difficult to find. Medication use in Norway from 1988 to 1989 [8] provides an interesting point of comparison. In our data set, pain medications were the most frequently utilized drugs, whereas in the Norwegian study they were the second most commonly used drugs by both men and women. An antibiotic was the medication most commonly used by Norwegian men and anxiolytics were the most frequently used medication in women. These differences in ranking of drug use may have little meaning because in both studies, the lists of the 10 most frequently used agents contained the same medications.

Identification of medication use patterns may also rely on identification of the symptoms or problems under therapy. As reported by Mäntyselka et al. [9], use of pain medications for non-acute pain is common. Another report from a study of general practice use of non-steroidal anti-inflammatory drugs (NSAIDs) in the United Kingdom found prescribing rates ranging from 220 to over 700 per 1000 patient visits [10]. In both of these reports, the patients sought care for the primary complaint of pain. Even though pain was a common complaint, but not necessarily the primary problem in the current study, almost 90% of CFS subjects used pain medication. It is not clear why CFS subjects used more acetaminophen and central nervous system acting drugs than did the non-fatigued subjects. Medication use for pain is complex, as demonstrated by Mäntyselka et al [9], in that use of sedatives and anxiolytics accompanied the use of analgesics; use of these categories of drugs was also seen in our study.

Vitamin and dietary supplements constituted the second most frequently identified category of drugs used by CFS and non-fatigued subjects. These agents may be obtained directly by the individual or prescribed by a health care provider. As reviewed by Messerer et al. [11], supplement use in the United States population-at large ranged from 21% to 55%. In a previous analysis of vitamin/supplement use by 30 CFS subjects attending a referral clinic, 89% of patient subjects versus 40% of control subjects reported use of these agents [12].

Use of medications in general populations [13] and in the pain and supplement studies described above supports greater use by women. We determined similar overall differences between men and women in our study, but CFS- and sex-influenced odds ratios of medication use were independent. In other words, medication use by women is more common than by men and CFS is more common

in women, but medication use in CFS is not dependent on the subject being female.

### Conclusion

These observations support the concept that the morbidity associated with CFS leads patients to seek relief of illness by the use of prescription and non-prescription medications and supplements. Changes in fatigue status did not correlate with changes in use of common medications, however. The pursuit of symptom relief in the absence of supportive clinical trials is a strong indication of the desire of CFS patients to improve or to alleviate their symptoms and should serve as impetus for further research into the origins, consequences, and treatment of fatiguing illnesses.

Examination of the processes that lead to more medication use in general by individuals with fatigue is of high priority in terms of public health in general.

### Competing interests

None declared.

### Authors' contributions

JFJ and RN identified the study questions. JFJ identified the drug categories, assembled and interpreted the data, reviewed the literature, and prepared the manuscript. RN organized the data and performed the statistical analyses in addition to preparing the final manuscript. WCR identified the need for the study, participated in its design, coordinated the completion of the project, and helped to prepare the manuscript.

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