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Classifying Medication Use in Clinical Research

par
Dorrie Rizzo

Département de psychologie, Cycles supérieures
Faculté des arts et sciences

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présentée par :
Dorrie Rizzo

a été évalué(e) par un jury composé des personnes suivantes :

Robert Haccoun
président-rapporteur

Julie Carrier
directeur de recherche

Eva Libman.
codirectrice

Marie Achille
membre du jury

Résumé

Les données sur l'utilisation des médicaments sont généralement recueillies dans la recherche clinique. Pourtant, aucune méthode normalisée pour les catégoriser n'existe, que ce soit pour la description des échantillons ou pour l'étude de l'utilisation des médicaments comme une variable. Cette étude a été conçue pour développer un système de classification simple, sur une base empirique, pour la catégorisation d'utilisation des médicaments. Nous avons utilisé l'analyse factorielle pour réduire le nombre de groupements de médicaments possible. Cette analyse a fait émerger un modèle de constellations de consommation de médicaments qui semble caractériser des groupes cliniques spécifiques. Pour illustrer le potentiel de la technique, nous avons appliqué ce système de classification des échantillons où les troubles du sommeil sont importants: syndrome de fatigue chronique et l'apnée du sommeil. Notre méthode de classification a généré 5 facteurs qui semblent adhérer de façon logique. Ils ont été nommés: Médicaments cardiovasculaire/syndrome métabolique, Médicaments pour le soulagement des symptômes, Médicaments psychotropes, Médicaments préventifs et Médicaments hormonaux. Nos résultats démontrent que le profil des médicaments varie selon l'échantillon clinique. Le profil de médicament associé aux participants apnéiques reflète les conditions de comorbidité connues parmi ce groupe clinique, et le profil de médicament associé au Syndrome de fatigue chronique semble refléter la perception commune de cette condition comme étant un trouble psychogène.

Mots-clés : classification des médicaments, le regroupement des médicaments, l'analyse factorielle, analyse en compSAHSntes principales, méthode

Abstract

Medication use data is usually collected in clinical research. Yet, no standardized method for categorizing these exists, either for sample description or for the study of medication use as a variable. The present investigation was designed to develop a simple, empirically based classification scheme for medication use categorization. We used factor analysis to reduce the number of possible medication groupings. This permitted a pattern of medication usage to emerge which appeared to characterize specific clinical constellations. To illustrate the technique's potential, we applied this classification system to samples where sleep disorders are prominent: Chronic Fatigue Syndrome and Sleep Apnea. Our classification approach resulted in 5 factors that appear to cohere in a logical fashion. These were labeled: Cardiovascular / Metabolic Syndrome Medication, Symptom Relief Medication, Psychotropic Medication, Preventative Medication, and Hormonal Medication. Our findings show that medication profile varies according to clinical sample. The medication profile for participants with Sleep Apnea reflects known comorbid conditions; the medication profile associated with Chronic Fatigue Syndrome appears to reflect the common perception of this condition as a psychogenic disorder.

Keywords : medication classification, medication grouping, factor analysis, principal components analysis, method

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Dédicace

I dedicate this thesis:

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Introduction

When clinical research involves recruitment from patient populations, we constantly have to reconcile the benefits of real-world relevance and ethical feasibility with the loss of experimental rigor. A very common "uncontrolled" variable is medication use. Most patients take at least one prescription medication and many take multiple prescription and over-the-counter medications. However, these are seldom recorded in a systematic manner; they are not taken into account with respect to their potential effects and side effects, nor are they examined as possible health status indicators. The overall focus of this project was to develop a method for handling medication use data that is typically collected in clinical research but is rarely analyzed or reported on. To illustrate the topic of medication in clinical research, the subject of sleep was selected as of general interest, and the present investigation focuses on the better understanding of medication profiles in individuals with sleep disorders. The present study addresses the following questions: Could a medication profile enhance the diagnostic process? Might the medications for some constellations of symptoms help identify an underlying untreated sleep disorder? What other story might a classification system reveal in individuals with various clinical disorders?

Although medication use data is usually collected in clinical research, no standardized method for categorizing these exists, either for sample description or use as a variable. In the present investigation we developed a simple, empirically based classification scheme to categorize medication. In order to illustrate the technique's potential, we applied the classification system to samples where sleep disorders are prominent. This study selected two clinical disorders to demonstrate how this classification system can be used: sleep apnea, chronic fatigue syndrome.

Review of the literature

Rationale for Medication Classification

Generally, in clinical samples, participants consume a combination of medications in a single day. There is a clear need to systematize such data to enhance our understanding of patient samples and to clarify to associated risk factors. For example, the literature shows that cardiovascular, diabetic and lipid-lowering medications tend to be associated statistically, and this medication constellation characterizes people at elevated risk for developing aspects of cardiovascular / metabolic syndrome (Grundy et al., 2006; Donahue, 2008).

Similarly, one would expect antidepressant, hypnotic and sedative use to be associated statistically, and in fact is characteristic of treatment for individuals with anxiety and depressive disorders, among other psychological/psychiatric diagnoses. Interestingly, this medication profile has also been associated with chronic fatigue syndrome (Creti, et al., 2010). We believe that it is important to be able to quantify and describe medication use in a way that is both logical and meaningful, as well as to understand the interrelationships among medications and other aspects of patient health and functioning. Nowhere is this more critical than in the area of sleep disorders, particularly sleep apnea/hypopnea syndrome (SAHS), where patients who tend to be at greatest risk are older and/or have other medical conditions for which they are taking medication. The medication profile might also be informative in a poorly understood condition like CFS, where etiology and pathophysiology are unclear, but judging from their medication a psychological/psychiatric diagnostic bias is apparent (Libman et al., 2007).

Previous studies

Reeves et al. (2006) was one of the first groups to point out that medication data were lacking in most studies. Although these researchers took medications into account in their own

study, these were classified only as to their sedative or stimulant properties. Of course, in any behavioral study one needs to know which sedatives or stimulants play a role in the findings.

It has been suggested that it is potentially important to take participants' medications into account in terms of their stimulant and sedative effects in psychobehavioral clinical studies related to our research area as well (Reeves, et al., 2006). In 2006, we also examined medications with respect to stimulating and sedating effects. We implemented this suggestion in a previous study (Rizzo, et al., 2007a, 2007b) by demonstrating that a sample with SAHS could be distinguished from a sample that declined further investigation of their sleep (Decliners) on the basis of the sedative/stimulant properties of their medication profile. Participants were two patient groups: (1) consecutive referrals to a sleep laboratory and (2) older adults in primary care. The relationship between stimulating and sedating medications and sleep/wake variables were explored for each group. Results showed that the medication profiles differed according to group as well as to experienced sleep/wake difficulties (Rizzo, 2007b). In that study: 1) 22% of the participants with SAHS used sedating medication versus 3% of those who did not have a diagnosis of apnea, 2) stimulating and neutral medication use were similar between groups, and 3) severity of sleepiness and insomnia symptoms were significantly correlated with the number of sedative medications use by participants with apnea. 20% of the participants with SAHS used sedating medication vs 3% of Decliners. Our conclusion of this study was that sedating medication use may reflect physicians' attempts to address sleep problems in SAHS and may serve as an additional diagnostic signal for SAHS.

The findings (a) contributed to our understanding of sleep disturbances and daytime complaints in patient samples, (b) underlined the importance of further investigating medication use in a more meticulous manner, and (c) raised the possibility of possible iatrogenic sleep

disorders, that is to say that sedatives may worsen the symptoms of untreated SAHS, for example.

Effective management of medication

The Emergence of E-files in Doctors' Offices

The effective management of prescription medication has long been a struggle for physicians. In fact, to manage medication use, a group of McGill University researchers have developed software called Moxxi (Tamblyn, et al., 2005). Moxxi in an integrated electronic prescribing and drug management system for primary care in which some of the functionalities include: display of patient demographics, display of active drugs by pharmacy systems, and integration of electronic prescriptions into pharmacy software. To date, one pilot study was performed to assess the acceptability of the software by physicians: 61.5% (n=28) strongly agreed that they would use the MOXXI system for most their patients (Tamblyn, et al., 2005). This type of system could be of interest to studies of medication use.

This tool was primarily designed to reduce errors related to prescribing (ex.: contraindications, interactions, etc.), however this type of system could be of interest to studies of medication use.

For example, pharmacists would update their patients' medication profiles in terms of active medications or discontinued medications; general practitioners are then able to access that information to have a better knowledge of prescriptions that have been filled. Since medication information is entered electronically, the data is ready to use and accessible to health workers who obtain a permit. Although this software is still being developed and trialed, our team of investigators inquired about data access by health researchers and what aspect of the software's

use was considered throughout its conceptualization. There appears to be "limited" profile access for researchers, in that names would be confidential and identified with a code.

A team of researchers studied the impact of electronic prescribing on the professionalization of community pharmacists and showed that e-files improve the collaboration between pharmacists and physicians due to its easy to use technology (Motulsky, Winsdale, Tamblyn, Sicotte, 2008). The potential of such a system to monitor medication profiles to enhance the diagnostic process has not yet been assessed.

Medication classification scheme in two clinical entities

To demonstrate how a medication classification system such as the one proposed in the present study might be applied, we have selected two clinical disorders: sleep apnea, a well defined primary sleep disorder with clear links to cardiovascular symptoms, and chronic fatigue syndrome, a poorly understood condition. We will describe sleep apnea in relative detail, because there is more known about its recognized association with medical illness. This constellation implies some interesting clinical and research possibilities for a medication profile derived by means of a user-friendly technique.

Sleep Apnea and Health

In the International Classification of Sleep Disorders (2001), obstructive sleep apnea (SAHS) is a dyssomnia of the intrinsic sleep disorders class "characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation". This breathing disorder, usually accompanied by very loud snoring and periodic lapses in breathing comes with a sensation of being unrefreshed in the morning due to the sleep disturbances. Typically, people wake up momentarily when these stops in breathing

occur, and blood oxygenation decreases, sometimes as low as 50%. They are often not aware of waking up in order to resume breathing.

To diagnose SAHS, patients are sent to a sleep laboratory to perform an overnight polysomnography. Once other medical or sleep disorders have been ruled out, SAHS is diagnosed when at least 5 respiratory disturbances greater than 10 seconds occur an hour. Traditionally, the main symptom the individual experienced was believed to be severe daytime sleepiness. Very recently, it has been demonstrated that daytime fatigue, as distinct from sleepiness, is an important symptom (Bailes, et al., 2008; 2010). Sleep apnea is treated with a nasal continuous positive airway pressure (CPAP) working by keeping airway open under air pressure so that unobstructed breathing becomes possible.

Consequences of this breathing disorder introduce a level of psycho-behavioural variability within the SAHS syndrome itself. One might appropriately assume that primary sleep disorders like SAHS, which restrict or disrupt sleep and cause some level of sleep loss, would result in substantial daytime sleepiness. Indeed, in clinical practice, case identification and referral for sleep disorder are typically centered on the evaluation of sleepiness, often employing the self-report Epworth Sleepiness Scale (Hardinge, Pitson, Stradling, 1995) to evaluate the severity of the condition. It has been found recently that daytime fatigue is as frequent a symptom as sleepiness (Hossain et al., 2005; Bailes et al., 2010) and perhaps of even greater clinical significance (Bailes et al., in press, 2008; 2010). Notably, there is a substantial number of individuals with sleep apnea who do not complain of the expected daytime sleepiness/fatigue symptoms (Young, et al., 1993). In fact, patients with SAHS may present with a wide array of symptoms. Although some may report direct signs, such as loud snoring and sleep disruption, others report symptoms such as insomnia, headache, body pain, and depression, conditions

which often improve with the treatment of SAHS and reflect the disorder's impact on other systems (Schwartz, Kohler, Karatinos, 2005; Sand, Hagen, Schrader, 2003). This variability in presentation of SAHS-related complaints is likely an important factor in the under-recognition of SAHS by primary care physicians.

Sleep apnea is under-recognized in primary care and, therefore, under-diagnosed and undertreated by sleep disorder specialists (Larsson, Lindberg, Franklin, & Lundback, 2003). Undiagnosed sleep apnea in Western countries is believed to be up to 5% of adults (Young, Peppard, Gottlieb, 2002). Addressing the need for treatment for up to 5% of the population is a far-fetched vision, but facilitating the detection of sleep apnea may help increase its diagnosis.

In recent years, there have been numerous studies highlighting the association of physical and psychological health aspects with sleep disorders. For example, in 1999, Spiegel, Leproult and Van Cauter examined the impact of sleep debt on health. They concluded that carbohydrate metabolism and endocrine function are both adversely affected by insufficient sleep. This adverse effect might be particularly salient in the context of age-related "metabolic syndrome", which is characterized by of obesity, hypertension, hyperlipidemia, and/or diabetes. Recent epidemiological data showed that SAHS can be involved in the initiation or the progression of several cardiovascular diseases (ex.: Bradley & Floras, 2009). Furthermore, there is compelling experimental evidence that SAHS can raise blood pressure which, in turn, increases cardiovascular risk; treatment of SAHS by continuous positive airway pressure (CPAP) can lower blood pressure. In addition, CPAP treatment has been found most effective in patients with increased blood pressure (Bradley & Floras, 2009).

Difficulties in identifying SAHS

In the middle-aged work force, approximately 4% of men and 2% of women have SAHS (Coughlin et al., 2004), and only 20-60% of cases are believed to be identified in the older population (Ancoli-Israel S, et al., 1991; Ancoli-Israel & Coy, 1994; Ancoli-Israel, et al., 1996; Lichstein, Reidel, Lester, Aguillard, 1999). There is a need for clear practice guidelines to identify patients who are likely to have sleep apnea as well as other sleep disorders (Reuveni, et al., 2004). In a previous study, we found a very high rate of sleep apnea (77% women, 98% men) in a self-selected sample. These individuals volunteered upon reading a poster about a sleep study recruiting people who were feeling sleepy, fatigued or have insomnia, with no knowledge of the presence of a sleep disorder (Bailes et al., 2005). Primary care physicians receive very little training in sleep disorders (Chung, Jairam, Hussain, & Shapiro, 2001), and even among sensitized practitioners, referral rates to sleep clinics for SAHS evaluation fall well short of the expected population rate (Kramer, Cook, Carlisle, Corwin, & Millman, 1999).

In a previous study we demonstrated that a self-report measure which evaluates sleep disorder symptoms in older primary care patients can be used to derive a symptom constellation or "profile" that could identify patients who should be referred to a sleep clinic (Bailes et al., 2007). This brief self-report measure, the Sleep Symptoms Checklist which produces symptom severity ratings in four domains, was designed as a practical diagnostic tool, useful in a busy general practice office. Adding patients' medical status as medication use information to this instrument may further enhance the physician's ability to direct at-risk patients to appropriate sleep laboratory screening, and this will be made easier with the emergence of e-files by looking at medication data that is already available.

The potential usefulness of a research focus on medications has already been illustrated in such epidemiological studies as evaluation of the impact of prescription cost on population

health (Clark et al., 1995), the use of pharmaceutical data in the identification of patterns of chronic disease status (Von Korff, Wagner, Edward & Saunders, 1992), and prediction of one year mortality rates (Charlson, Pompei, Ales, & MacKenzie, 1987).

Sleep apnea and Metabolic Syndrome Components

Recent epidemiological studies demonstrated that SAHS contributes to the onset or progression of many cardiovascular diseases (Bradley & Floras, 2009), thus increasing the popularity of medical studies trying to understand sleep disorders. For example, studies showed a greater prevalence of dyslipidemia among individuals with SAHS as compared with those without SAHS (Ip, et al., 2000; Schafer, et al., 2002; McArdle, Hillman, Beiling, Watts, 2007).

As the concept of metabolic syndrome attracted increased attention in recent years, clear parameters were needed in order to establish this collection of disorders as a bona fide syndrome. One investigation demonstrated several parameters including medical treatment (ie. medication) for lipids and blood pressure as a parameter for diagnosing the metabolic syndrome (Handelsman, 2009). This suggests that researchers can use medication data as an indirect way to identify SAHS (ie.: as a proxy measure). In fact, one study has already been carried out to investigate exposure to various prescription drugs as a proxy measure of disease (Grad, et al., 1999). The Charleson Comorbidity Index was originally designed as a classification tool for comorbid conditions measuring the risk of 1-year mortality attributable to comorbidity in hospitalized patients (McGregor, et al., 2005, Charlson, et al., 1987). The Index served as a validated tool for predicting mortality in longitudinal studies. In other words, the tool was developed for describing the effect of all other diseases an individual might have other than the primary disease of interest. In the case of possible SAHS, if a person is taking medication for

hypertension in combination with the presence of a sleep complaint, then this may lead to the physician wanting to further investigate his-her patient's sleep.

In addition, in past studies, researchers were interested in determining if routine health care data from large automated databases could be used to generate inexpensive but valid measures of health status. An example is a study using the "Illness Scale" by Mossey and Roos (1987), who used insurance claims data to measure health status and the Chronic Disease Score (CDS) was used by Von Kroff et al. (1992) in an investigation where automated outpatient pharmacy data were used to measure chronic disease status among prescription drug users for overall health status.

Chronic Fatigue syndrome (CFS)

There are no diagnostic clinical signs or laboratory markers for CFS. There is no specific pathophysiology, etiology, diagnostic tests or treatments linked to CFS (Libman et al., 2007). Concerns also arise about whether people with CFS are consuming medications to manage symptoms due to untreated CFS (ie. disability, pain). CFS is a syndrome with many uncertainties by both the patient and the caregiver. This syndrome can severely affect a person's social life and functioning. The International Classification of Sleep Disorders' only mention of CFS is the following: "Patients with the chronic fatigue syndrome (postinfectious neuromyasthenia) have similar findings to patients who report the onset of fibromyalgia following a febrile illness."

Complaints expressed by CFS sufferers are often misinterpreted as depression, laziness, somatoform or "in her/his head". Patient complaint is the only tool caregivers have to make a diagnosis. Unfortunately, caregivers cannot make an easy diagnosis or detection of CFS and are left with a limited arbitrary diagnostic procedure when dealing with the syndrome. Nevertheless,

having studied CFS participants in several of our studies, one characteristic was salient to us: their medication use. Medication became a topic of interest since we also had collected this data in previous studies, but, except for sedative/stimulant effects, had not explored the implication further. Currently, CFS diagnoses are done with an elimination process when no medical, psychiatric or drug can explain the presence of prolonged fatigue for at least 6 months along with a constellation of other symptoms (Boneva, 2009; Dinos et al., 2009). Individuals with CFS are not routinely sent for evaluation of sleep disorders. It is widely recognized that there is a high percentage of undiagnosed sleep disorder in individuals with CFS in both study participants and clinical patients (Creti et al., 2010). There is some controversy whether individuals with CFS symptoms and primary sleep disorder fit the diagnosis of CFS (Libman et al., 2009).

Lombardi et al. (2009) report: "Chronic fatigue syndrome is a debilitating disease of unknown etiology that is estimated to affect 17 million people worldwide." The prevalence of CFS is estimated between 400 and 2500 adults per 100 000 population. An analysis by the World Health Organization looked at 14 countries and showed that the prevalence of disabling fatigue to be 1.69% of the population and that significant costs are related to the inability to work and to the medical care needed (Dinos et al., 2009).

In a recent study of sleep characteristics, individuals with CFS reported on their use of medications compared with healthy individuals (Boneva, et al., 2009). Their study shows that participants with CFS are faced with a "polypharmacy" problem. More specifically, more than 90% of people with CFS used at least one drug or supplement with an average use of 5.8 drugs per person. They compared individuals with CFS to "well" persons and persons with "CFS-like symptoms" and found that individuals with CFS use significantly more medication, especially antidepressants. Interestingly, this group also raised the question of iatrogenic effects of

medication use as a key motive for looking at medication profiles in clinical practices. Reeve's team coded patient verbatim data, and then categorized them with the help of a physician review panel. In the present study, we intend to classify medication information from physician reports into categories predetermined by the Canadian Compendium of Pharmaceuticals and Specialties (CPS) (electronic version, 2004) as the basis for the classification and coding procedure.

Recent studies report a viral basis for CFS (ie., XMRV, MLV) (eg.: Lombardi et al., 2009; Vallings et al, 2009), but some data fail to support those findings (Erlwein et al, 2010)..

The Present Study- Background

Excluding individuals who take medication reduces ecological validity. Ignoring medication and its effects can confound the results. The number of different medications consumed by participants is often large and varied; available classificatory systems group medications based on a priori clinical criteria rather than on an empirical basis. Knowing what medications individuals take is vital because of their effects and side-effects on the variables of interest (e.g. Brownlee et al., 2003).

The two clinical entities selected for the present study manifest nocturnal sleep disorder and both have daytime sleepiness and fatigue as prominent symptomatology. The aim was to demonstrate that individuals with common symptoms could be reliably distinguished from each clinical entity on the basis of medication profile alone. Clearly, rich details may be lost when there is no empirically sound way of grouping extensive lists of medications used by different clinical samples into a manageable number of categories.

In the present study our goal was to develop a simple, empirically based classification system for the diverse medications that research participants may be using. The procedure

represents a standardized method to code drug use data to help with sample descriptions and to enable researchers to use medication as a variable in clinical research.

Our study will compare individuals with SAHS, CFS and Healthy Controls to demonstrate that a specific medication profile may be developed for each clinical group.

Our ongoing research required that we incorporate medication use into the analyses. This forced us to examine how medications could be combined into meaningful groupings to use in our project. Because this led us to a novel way of conceptualizing medication use in clinical research, in the present paper our goal is to share the results of our experience by demonstrating how researchers can develop a simple, empirically based classification system for the diverse medications that their research participants may be using. Thus, here we describe and illustrate a procedure that represents a standardized method to code drug use data in clinical research. The aim is to help with sample descriptions and to enable researchers to use medication as a variable in clinical research.

What distinguishes this approach from the various existing systems is that it groups medications on an empirical basis, reflecting the attributes of the samples in question, rather than on the basis of clinical criteria, as do most conventional systems (e.g., the US National Drug Code Directory updated by the FDA/Center for Drug Evaluation and Research (UDHHS, 2008); the American Hospital Formulary Service Drug Information (AHFS DI) from the American Society of Health-System Pharmacists (ASHP); the WHO's Anatomical Therapeutic Chemical (ATC) Classification System). Thus, our technique both allows for the reduction of the number of medication groupings as well as permits the researchers to see the pattern of medication usage in specific clinical constellations.

In the present investigation, we used an existing data base for older individuals recruited from the community and from primary care, as well as a sample of individuals with CFS (Table 1). The data base included uncoded, self-report information on what medications, prescription and over-the-counter, each participant was taking. We first developed a simple, empirically based classification scheme for medication use categorization. To illustrate the technique's potential, we then applied this classification system to two samples where sleep disorders are prominent (SAHS, CFS) and on samples of control subjects. We predicted that:

- SAHS will be more associated with medication related to the metabolic syndrome
- CFS will be more associated with psychotropic medications;
- Healthy Controls will take fewer of the medication classes associated with clinical samples.

The present study

We plan to (a) develop a classification method to arrive at a medication profile, and (b) to demonstrate how such a profile could be used to (c) identify individuals with apnea and (d) distinguish these, on the basis of their medication profile, from another clinical disorder that shares many aspects of apnea symptomatology.

Study 1: Development of the Classification System

Method

Participants: Phase 1

To develop the classification system, we used 473 subjects from our database of participants who had been recruited for a series of sleep and fatigue related studies carried out in our laboratory. Overall sample characteristics are presented in Table 1.

Chronic fatigue syndrome (CFS) sample. (Libman, et al., 2007). Ninety-seven participants with CFS were part of a larger study of sleep disorders in this population (Fossey, et al., 2004; Creti, et al., 2004). These participants were diagnosed by a neurologist (see study 2 for specific criteria).

Older primary care sample (Bailes, Baltzan, Alapin, Fichten, & Libman, 2005). Forty-seven participants were older adults (ages 55 and over) recruited from primary care waiting rooms at three family practice centers in Montreal for a study of sleep disorders.

Older community sample (Fichten, Libman, Creti, Bailes, & Sabourin, 2004). Two hundred and three participants were recruited from the community through media publicity consisting of press releases, presentations, and mailings to seniors' groups and notices in community clinics and residences for older adults. Individuals with daytime fatigue and/or sleepiness and/or insomnia were sought for a study of sleep disorders.

Sleep clinic sample (Bailes, et al., 2008). Seventy-two participants were consecutive new patients referred for evaluation of possible sleep disorder at two hospital based sleep clinics in Montreal. They were recruited from sleep clinic waiting rooms.

Healthy control sample (Bailes, et al., 2006). Fifty-four control group subjects were individuals with no diagnosed medical or psychiatric condition. They were recruited from the community through posters, announcements and personal contacts.

Table 1

Sample Characteristics for the Medication Profile of Comparison Groups

Sample		Chronic Fatigue Syndrome (CFS)	Older Primary Care	Older Community	Sleep Clinic	Control Group
n	Males	22	24	77	46	15
	Females	75	23	126	26	39
Mean age[1]	Males	44.4(8.7)	70.9(10.4)	64.8(11.4)	54.0(11.4)	45.9(11.2)
	Females	46.5(11.2)	66.4(11.1)	65.7(10.7)	54.4(11.2)	45.3(10.3)

Procedure

Data on medication use were collected as a routine part of our research protocol. These were grouped into the 43 specific therapeutic classes provided in the Canadian Compendium of Pharmaceuticals and Specialties (CPS) (electronic version, 2004). There are other systems derived for different purposes and used in different countries. Examples are the US National Drug Code Directory updated by the FDA/Center for Drug Evaluation and Research (UDHHS, 2008), and the American Hospital Formulary Service Drug Information (AHFS DI) from the American Society of Health-System Pharmacists (ASHP). We used the Canadian Compendium of Pharmaceuticals and Specialties (CPS) (electronic version, 2004) as the basis for the classification and coding procedure for its convenience, availability, ease of use, and relevance to the Canadian health care system.

Medications were classified into one of the 43 specific CPS therapeutic classes. Unused therapeutic classes (i.e., if no participants took any medication in this class) were excluded, leaving 27 therapeutic classes (see Table 2). Medication use was coded by indicating the number of different drugs used in each CPS therapeutic class for each participant. If the participant did not take a medication in a certain class, this was scored as "0". A "1" was scored when a participant took one medication in a particular class. A score of "4" indicated that a participant took four different medications within the class. For example, if a participant took separate Vitamin A, C, D and calcium pills, they obtained a score of "4" in the "Vitamins" class.

Table 2

Number of Medications Taken in Each CPS Therapeutic Class Ranked by Popularity

CPS Therapeutic Classes	Number of Participants Taking Medications Within a Class	Maximum Number of Different Medications Taken by a Participant Within a Class	Total Number of Medications Taken in Each Class
Cardiovascular drugs	116 / 24.3%	5	199
Analgesics	71 / 14.9%	3	79
Lipid lowering agents	61 / 12.8%	2	63
Thyroid hormones	61 / 12.8%	1	61
Antidepressants	58 / 12.1%	2	64
Hypnotics and sedatives	40 / 8.4%	3	52
Gastrointestinal agents	36 / 7.5%	2	37
Sex hormones	34 / 7.1%	3	42
Vitamins and Minerals	33 / 6.9%	4	57
Anticonvulsants	30 / 6.3%	2	32
Diabetes therapy	28 / 5.9%	3	37
Diuretics	23 / 4.8%	1	23
Anticoagulants	18 / 3.8%	2	19
Corticosteroids, inhaled (incl. Asthma therapy)	16 / 3.4%	2	18
Osteoporosis therapy	16 / 3.4%	1	16
Prostatic hyperplasia therapy	15 / 3.1%	2	19
Respiratory system agents	12 / 2.5%	2	15
Antihistamines	11 / 2.3%	1	11
Antispasmodics	6 / 1.3%	1	6
Anemia therapy and Hematopoietics	3 / 0.6%	1	3
Antipsychotics	3 / 0.6%	1	3
Antiparkinsonian agents	2 / 0.4%	1	2
Corticosteroids, systemic	2 / 0.4%	2	3
Ophthalmologicals	2 / 0.4%	1	2
Immunosuppressive agents	1 / 0.2%	2	2
Mania therapy	1 / 0.2%	1	1
Rheumatic disease therapy	1 / 0.2%	1	1

Results

Data from all subjects were combined for this study and are presented in Table 2, which presents the number of medications taken in each CPS therapeutic class, including multiple

medications taken by individual participants. To organize the data into more manageable classes for further analysis, we first reassigned medications taken 3 or fewer times into an "other" class, and then carried out a principal components factor analysis with varimax rotation on the remaining classes. This converged in 5 iterations and resulted in 5 factors. Examination of the scree plot, scree elbow curves, and eigenvalues (see Figure 1) indicated that a five factor solution was the most parsimonious. Factor loadings of magnitude less than .4, with the eigenvalue greater than 1 criterion, were suppressed simply because we applied a general and rigorous cutoff rule for factor analysis. These can be seen in Table 3. A guideline for identifying significant factor loadings based on sample size. Significant (based on a .05 significance level) factor loadings based on sample size go as follows: n=350—.30; n=250—.35; n=200—.40; n=150—.45; n=120—.50; n=100—.55; n=85—.60; n=70—.65; n=60—.70; n=50—.75.(Hair, Babin, et al., 2003).

Figure 1

Scree Test Graph For Medication Factor Loadings

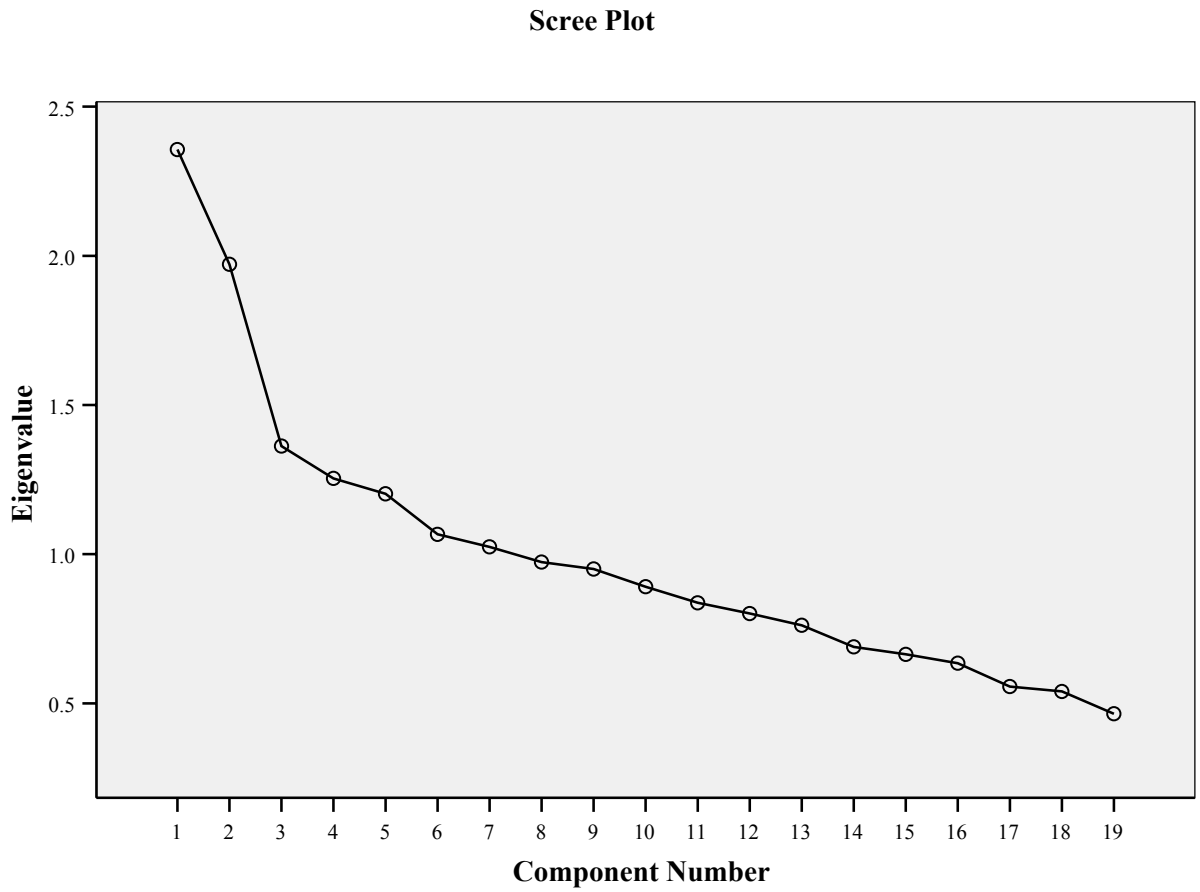

Table 3

Medication Factor Loadings Based on CPS Therapeutic Class Frequencies

CPS Medication Classes	Factor 1: Cardiovascular/ Metabolic Disorder Medication	Factor 2: Symptom Relief Medication	Factor 3: Psychotropic Medication	Factor 4: Preventative Medication	Factor 5: Hormonal Medication
Cardiovascular drugs	0.75				
Lipid lowering agents	0.74				
Anticoagulants	0.66				
Diabetes therapy	0.64				
Diuretics	0.42				
Gastrointestinal agents		0.63			
Respiratory system agents		0.58			
Corticosteroids, inhaled (incl. asthma therapy)		0.56			
Antihistamines		0.54			
Antispasmodics		0.47			
Analgesics					
Anticonvulsants			0.74		
Hypnotics and sedatives			0.65		
Antidepressants			0.41		
Vitamins and Minerals				0.70	
Osteoporosis therapy				0.63	
Thyroid hormones					0.68
Sex hormones					0.60
Prostatic hyperplasia therapy					

Published guidelines for sample size in factor analysis include 2 options: 1) Absolute N and 2) N (number of participants) :p (observed variables) ratio. In both cases, higher is better. When adopting the "absolute N" approach, the literature recommends several minimum sample sizes: N= 400 (Aleamoni 1976) or a sample size evaluated with a suggested scale (50—very poor; 100—poor; 200—fair; 300—good; 500-very good; 1000 or more—excellent).Generally, larger samples minimize the probability of error as in other statistical analysis, but other rules about good statistical analyses may not apply to this method (e.g., increasing generalizability of the results). The second approach - N:p suggests a that increasing the ratio also increases the quality of the analysis. A recommendation of a minimum ratio of 5:1-10:1 has been

recommended (Gorsuch 1983; Nunally 1978 respectively) In this study, we used a sample size of n=473 and a total of 20 variables, translating to a ratio of 23.7:1.

We decided on principal component factor analysis with varimax rotation rather than cluster analysis for two key reasons: (a) cluster analysis, which can involve different techniques that yield very different results (Gorsuch, 1983), would also have made the data look more complex than factor analysis, and (b) it would not have permitted computing scores for each subject (Gorsuch, 1983; 1997), thereby limiting the utility of the method for clinical research.

The 5 factors, labeled: Cardiovascular / Metabolic Syndrome Components Medication, Symptom Relief Medication, Psychotropic Medication, Preventative Medication, and Hormonal Medication, appear to cohere in a logical fashion (see Table 3). For example, Osteoporosis therapy and Vitamins and minerals loaded on Factor 4; this indicates that when participants use a medication for bone loss, for example, they are likely to take calcium or glucSAHSmine as well. Thus, the findings suggest that this method resulted in a series of medication groupings that cluster in a meaningful, valid way.

The 473 participants summed 867 individual medications that they were taking of which only 57 are supplements. Overall (n=473), medication use averaged 1.83 per person and the 5 most frequently used medication categories were Cardiovascular Drugs (24.3%), Analgesics (14.9%), Lipid Lowering Agents (12.8%), Thyroid Hormones (12.8% and Antidepressants (12.1%). Table 2 provides a list of all the medication categories and ranked by their popularity. To further understand the relationship between our medication variables, we performed a linear regression model predicting medication use by study groups. We found that the adjusted R^2 of our model is 0.251 with the $R^2 = .407$. Therefore, the linear regression explains 40.7% of the variance in the data. F=2.618 with 22 degrees of freedom suggests that the test is highly

significant, thus we can assume that there is a linear relationship between the variables in our model.

Study 2: Validating the Classification System - An Illustrative Example

Method

To evaluate empirical validity, in Study 2 we examined how meaningful these groupings are in a different sample of subjects.

Subjects

Subjects were a subset of those participating in Study 1. We selected those 107 individuals from our data set who, after the initial assessment, were sent for a polysomnographic evaluation at a sleep laboratory to determine their sleep disorder status. Participants' diagnoses fell into three groups: Chronic Fatigue Syndrome (CFS) with no Sleep Apnea/Hypopnea Syndrome (SAHS, n=23) aged 42.2 ±10.3, Sleep Apnea/Hypopnea Syndrome (SAHS) with no CFS (n=50) aged 59.7 ±11.6 , and a healthy comparison sample (Controls, n=34) aged 51.3 ±8.6.

The selection criteria for each group are as follow:

- CFS sample (n=23): The CFS sample was recruited from physician referrals and CFS support groups. For each participant, two independent assessments of CFS were made. Participants arrived with a diagnosis from their own physician. The research team physician (neurologist) confirmed the original CFS diagnosis by using a standardized diagnostic instrument based on Fukuda et al.'s (1994) diagnostic criteria. None had ever been referred to a sleep laboratory and none had been diagnosed with a primary sleep disorder such as sleep apnea/hypopnea (Creti et al., 2004).

- SAHS sample (n=50): Participants underwent a 30-min assessment by the team respirologist (to evaluate medical reasons for nighttime and daytime complaints); and one night of PSG in a sleep laboratory to evaluate breathing and/or movement disorders. A nocturnal PSG assessment was carried out in a supervised sleep laboratory from 10 p.m. to 7 a.m. Monitoring included three leads EEG, EOG, bilateral anterior tibialis, and chin EMG, ECG, pulse oximetry, nasal and oral airflow with thermistor and nasal pressure cannulae, and respitrace bands for the measurement of respiratory effort. All signals were acquired on a digital data management system (Sandman, Nellcor-Puritan Bennett & Tyco, Ottawa, Canada). An apnea event was scored when there was a cessation of breathing for 10 or more seconds. The cut-off criterion for defining a case with significant SAHS was 10 or more events per hour of EEG sleep (Bailes et al., 2005).
- Healthy Comparison sample (n=34): Participants undergo polysomnographies resulting in no diagnosis for sleep disorders.

The ratio of male to female participants was 2.3:1 for individuals with SAHS, .05:1 for individuals with CFS and .31:1 for Healthy Controls, $\chi 2 = 34.42$, $p = .000$, indicating sex differences among the samples. Similarly, the comparison on age was significant, $F(2,104) = 25.21$, $p < 001$. In spite of these findings, we decided not to covary sex or age because this example is presented for illustrative purposes only. A series of 1-way analysis of variance comparisons (ANOVA) was performed to compare the scores of the three groups on the five medication factors.

Results

For our clinic samples (CFS and SAHS, n=73), their medications summed up to 210 individual medications. In other words, use of medications by clinical samples averaged 2.88 per person. More specifically, 78.3% of the CFS sample (n=23) takes at least one medication with an average of 1.91 medications per person (range 0-8), where Hypnotics ranked the highest in popularity. 86% of the SAHS sample (n=50) takes at least one medication with an average of 3.32 medications per person (range 0-9), where Cardiovascular medication ranked highest in popularity (accounting for 30.7% of the total medication used by individuals with SAHS). As for Controls (n=34), they used a total of 20 individual medications, translated to an average use of .59 medications per person (range 0-2). The most popular medication category used by Controls was Thyroid Hormones.

The factor analysis we then ran gave us groupings of medication categories (factors) that permitted is to statistically analyze the data of all 27 medication categories (listed in Table 2) that were being used by the overall sample.

Table 4 shows significant differences among the three samples on medication factors: ANOVA and post-hoc results show that, as expected, individuals with CFS had significantly higher scores on the Psychotropic medication factor and individuals with SAHS had significantly higher scores on the Cardiovascular/metabolic syndrome components medication factor than the other two groups. In addition, individuals with SAHS had higher scores than the Control group on Preventative as well as on the Symptom relief medication factors.

Table 4

Factor Mean Scores and Test Results for the CFS, SAHS, and Control Groups

Medication Factors	Group	Mean	SD	n	df	F	Sig. p =	Post-Hoc
Cardiovascular/Metabolic Disorder Medication								
	SAHS	1.20	1.25	50	2	23.23	0.000	SAHS>CFS,C
	CFS	0.00	0.00	23				
	Control	0.09	0.29	34				
Symptom Relief Medication								
	SAHS	0.54	0.61	50	2	3.33	0.040	SAHS>C
	CFS	0.52	1.16	23				
	Control	0.15	0.44	34				
Psychotropic Medication								
	SAHS	0.38	0.75	50	2	9.67	0.000	CFS>SAHS,C
	CFS	0.87	0.81	23				
	Control	0.09	0.29	34				
Preventative Medication								
	SAHS	0.18	0.44	50	2	3.67	0.029	SAHS>C
	CFS	0.04	0.21	23				
	Control	0.00	0.00	34				
Hormonal Medication								
	SAHS	0.10	0.30	50	2	1.30	0.276	
	CFS	0.13	0.34	23				
	Control	0.24	0.50	34				

Discussion

Our study outlines a procedure for dealing with medication data which is routinely collected in many clinical research studies and which largely go unreported. We found that coding a wide array of medications based on a well-known classification system (in this case, the Canadian CPS) into therapeutic classes was a useful first approach to bring order to the chaos. In this study we demonstrate this 3-step method:

(1) identify which therapeutic class each medication belongs to,

(2) discard low frequency therapeutic classes, and

(3) carry out principal components factor analysis.

Deriving factors permitted us to study medication use as a variable in clinical research. Group comparisons yielded differences using the medication factors which would not have been discernable had we attempted to look at medications on a drug-by-drug basis. For example, we found that participants diagnosed with Sleep Apnea/Hypopnea Syndrome (SAHS) took significantly more medications in the Cardiovascular/metabolic syndrome category than did either those with CFS or healthy controls. The literature shows that untreated SAHS is strongly associated with cardiovascular medication (cf. Otake, Delaive, Walld, Manfreda, & Kryger, 2008), and with hypertension, insulin resistance, and cardiovascular events, including stroke and arterial fibrillation (Hirshkowitz, 2008, Chowdhuri, Crook, Taylor, & Badr, 2008). Because our data reflect medication use prior to the sleep disorder diagnosis, we are now able to evaluate whether treatment of the SAHS might result in less medication and improved cardiovascular status. Of course such diagnostic and treatment implications need to be verified for other medical conditions.

Our findings show that in a single day, our participants generally consumed a combination of medications. The use of factor analysis allowed us to reduce medications in the various CPS therapeutic classes into five coherent groupings. Notably, the system allows one to include multiple anxiolytics, antidepressives, and over the counter medications, for example, and to see the *pattern* of medication usage in any particular clinical constellation. It has already been shown that use of cardiovascular, diabetic and lipid-lowering medications tend to be associated statistically, and are characteristic of people at elevated risk for developing cardiovascular / metabolic disorders (Grundy et al., 2006; Donahue, 2008). It has been shown antidepressants,

hypnotics and sedatives are also associated statistically and are characteristic of treatment for individuals with Chronic Fatigue Syndrome (Creti, et al., 2010).

What is of particular interest in the present study is that not only do the constellations of medications describe the two samples in a meaningful way, but in the case of SAHS, medication usage reflects known comorbid conditions, which might be useful to assist in the diagnosis of this condition. On the other hand, the medication profile characteristic of CFS appears to reflect the common perception of this condition as a psychogenic disorder. Furthermore, the profile does not have the same diagnostic usefulness as the SAHS profile; for CFS, the medications used might even exacerbate existing symptoms.

A recent study of CPAP adherence reported that treating the sleep disorder was an effective way of managing both daytime sleepiness and hypertension (Gagnadoux et al., 2009). One might wonder if the reverse is the case as well; Are the medications for metabolic syndrome being consumed as an indirect way to treat the apnea? How often are the consequences of an unrecognized condition (apnea) being treated rather than the disorder itself?

The factors derived in the present study likely reflect medication use patterns only in clinical samples characterized by disrupted sleep or chronic fatigue. Most likely, other clinical samples will have very different medication profiles. It may well be that the same medications may group into different factors with other disorders. This may be considered a limitation of the present investigation, we believe that the benefits of this technique, which allows us to discover, in an empirical manner, the constellation of medications that group together in various clinical categories, outweighs the disadvantages. As is the case in our own samples, in other disorders, as well, the procedure may enhance the diagnostic process or, as in the case of CFS, reflect a possible distortion by the medical community in prematurely labeling the illness as psychogenic.

Thus, a prognostic model's external validity can be determined for its planned use or purpose (Iezzioni, 1999).

A definite limitation is that the technique itself is not fully descriptive. For example, medications that were popular in all samples, such as analgesics, did not load on any of the derived factors, and therefore did not differentiate groups. Therefore, such medications must be noted and handled separately in statistical procedures. Another limitation is that most of the frequencies in our samples were low and, thus, extreme scores may have had undue influence on the results.

Therefore, our findings are illustrative of an easy way to implement a three-step method to derive empirically based medication classification categories for use in clinical research, rather than as a conclusive classificatory system.

It is notable that the medication profiles derived in the present study were the result of a secondary analysis of data for the two samples. The next step is to include the medication classification system as part of the initial study design. Our team is embarking on a longitudinal project evaluating sleep apnea and metabolic syndrome, with the aim of determining which condition predicts the other. This will allow us to examine medication profiles for individuals diagnosed with SAHS or with metabolic syndrome aspects , to evaluate what differences exist between these two groups. The design also permits a re-evaluation of the profile two years after original diagnosis to add a longitudinal perspective. with enhanced diagnostic possibilities.

Conclusions

In conclusion, the findings of this study add to the meager literature on medication profiles and their relationship to clinical disorders. Our method of drug classification suggests that factor analysis: (a) affords an empirical means of deriving medication profiles for clinical

samples in health-related research and, (b) offers a useful and simple method for handling medication data in an intuitively appealing way, (c) adds a descriptive dimension that might enhance diagnostic process or reveal a distorted diagnostic bias.

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Annexe