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The use of prescription medication in 239 patients with multiple functional somatic syndromes

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ABSTRACT

Objective: To describe the use of prescription drugs and their association with patient characteristics in patients with multiple functional somatic syndromes (FSS) focusing on drugs generally recommended and not recommended in FSS treatment.

Method: Using data from a national prescription registry, we describe the drug use during a two-year period for 239 trial participants. Using regression models, we analyse the associations of patient characteristics with the patterns of use of antidepressants, anticonvulsants, opioids and sedatives.

Results: The use of prescription drugs was highly heterogeneous. Antidepressants were used at least temporarily by 34% (88/239), anticonvulsants by 7% (16/239), opioids by 26% (61/239) and sedatives by 20% (47/239) of the patients. Severe impairment due to multiple FSS was associated with use of opioids or sedatives (OR 6.49 (95% CI 2.68–15.68; $p < 0.001$)) but also with use of antidepressants or anticonvulsants (OR 3.42 (95% CI 1.35–8.65; $p = 0.009$)). Poor self-reported physical health, additional physical comorbidities and low socio-economic status were associated with use of opioids or sedatives only.

Conclusion: Antidepressants and anticonvulsants were modestly used. Opioids and sedatives were especially used by the severely affected patients. Balancing treatment expectations and enhancing patients' understanding of FSS may direct treatments towards more generally recommended drugs.

1. Introduction

Patients with numerous somatic symptoms not attributable to conventionally defined diseases are common in all clinical settings. These patients often fulfill criteria for one of the functional somatic syndromes (FSS) such as fibromyalgia (FM), irritable bowel syndrome (IBS) or chronic fatigue syndrome (CFS). When patients suffer from multiple symptoms from several bodily systems, they often qualify for several of these syndrome diagnoses simultaneously; multiple FSS [1,2]. Patients with multiple FSS represent a severely affected patient group with low functioning, poor quality of life and a high level of physical and psychiatric comorbidities [3–5].

Current evidence for the management of FSS suggests a multimodal treatment approach, including the use of pharmacotherapy [2,6]. In multiple FSS, the body of evidence as regards pharmacological treatment is limited [7], but pharmacological treatment guidelines exist for some FSS. Guidelines differ across syndrome diagnoses, and in FM, one of the most research-active areas, they even differ across continents and medical specialties [8–10]. Despite differences, shared among most recommendations is the use of certain centrally acting pain-modulating drugs, i.e. antidepressants or anticonvulsants, and a restriction for the use of opioids and sedatives [2,11–14]. However, as shown in studies of prescription patterns for outpatients with FM [15], IBS [16] and CFS [17], the use of pharmacological agents in clinical practice is highly diverse with little concordance with pharmacological treatment recommendations [15,18,19].

The use of pharmacological therapies in everyday clinical practice for patients with multiple FSS has not been described. Physicians have little evidence to rely on when choosing drug treatments. Initially, the choice may largely depend on physician-related factors such as physicians' specialty, interests and approach to the condition as shown especially for treatment of FM [15,20]. Physicians may also find inspiration for the treatment approach in the existing clinical treatment recommendations in FSS. However, in the more severely affected patients with long illness duration, physical or psychiatric comorbidities and several prior treatment attempts, numerous drug classes may be attempted often following a trial and error principle. The treatment choices at this point may largely depend on patient preferences and

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patient characteristics such as level of impairment and physical and psychiatric comorbidities rather than clinical recommendations.

In clinical practice, patients with multiple FSS may receive a variety of diagnoses. The diagnostic practice for this patient group is highly varied [21]. Depending on clinical setting and local diagnostic traditions, the patients may receive several FSS diagnoses, symptom diagnoses, diagnoses of somatoform disorders or receive no diagnosis at all [21]. Patients with multiple FSS are thus difficult to identify in patient registries. In this study, we describe multiple FSS by means of the research diagnosis Bodily Distress Syndrome (BDS) multi-organ subtype [5,22]. This diagnosis includes patients with multiple, impairing, long-lasting somatic symptoms from several organ systems and captures patients with multiple FSS [5,7,22].

The aim of this study was to describe the use of prescription drugs in patients with multiple FSS. Specifically, we aimed to describe the use of prescription drugs using data from a national prescription registry for 239 trial participants with multi-organ BDS during a two-year period prior to treatment at a specialised secondary care unit. We focused on 1) the overall use of prescription drugs, 2) the use and extent of use of psychotropic drugs and analgesics, and 3) the association of the use of generally recommended (antidepressants and anticonvulsants) and not-recommended (opioids and sedatives) drug classes with patients characteristics, in particular impairment in daily life due to multiple FSS and physical and psychiatric comorbidities.

2. Methods

This historical prospective study combines data from the Danish Registry of Medical Product Statistics [23] and two previous clinical trials on patients with multi-organ BDS [24,25]. Approval was obtained from the Danish Data Protection Agency (no 1-16-02-578-13).

2.1. Study population

The patient sample consists of 239 patients who were consecutively referred to a Danish specialised secondary care unit. In Denmark, all citizens have equal access to health care. The patients in this study are previous participants in two trials conducted from 2005 to 2009. All patients met criteria for multi-organ BDS of multiple somatic symptoms from several organ systems not attributable to other medical or psychiatric conditions causing a moderate to severe impairment in daily life with a minimum duration of two years. The diagnostic procedures have been described elsewhere [24]. Patient-rated questionnaires and data from a diagnostic research interview (Schedules for Clinical Assessment in Neuropsychiatry, SCAN) were obtained at the time of diagnosis.

2.2. Prescriptions

The Danish National Prescription Register holds information on all redeemed prescriptions administered as part of the Danish universal healthcare system [23]. The register does not contain information about over-the-counter sales, un-redeemed prescriptions or pharmacological treatments given during inpatient hospital admission.

The medication exposure window for this sample was the two-year period prior to treatment at a specialised secondary care unit.

Drugs were classified based on the WHO's Anatomic Therapeutic Chemical Classifications System (ATC) (March 30, 2017). Drugs were divided into subgroups based on organ system (1st level), therapeutic and chemical characteristics (2nd, 3rd and 4th levels).

2.2.1. Overall drug use

The number of prescriptions from each subgroup was calculated as total number of prescriptions and number of patients who received at least one prescription during the study period and with the median (IQR) of prescriptions. To evaluate the diversity of the drug use for the patients, we calculated how many drug categories (0–15) were used at least once per patient in the two-year period. The 15 categories correspond to the ATC classification but with the ATC category "N: Nervous system" divided into to two categories: 1) N02 Analgesics and N03 Antiepileptics and 2) Psychotropic drugs and others (N04-N07).

2.2.2. Use of psychotropic drugs and analgesics

The use and the extent of the use of psychotropic drugs and analgesics was characterised by description of all prescriptions from the ATC categories "N Nervous system" and "M Musculoskeletal system". For antidepressants, anticonvulsants and sedatives, we also presented the proportion of patients receiving these drugs who had a lifetime of anxiety or depression.

We define opioids as any opioid except for combination drugs (i.e. opioids in combinations with weaker analgesics).

We focused on the following: 1. Patients who redeemed at least one prescription, 2. Patients with only one prescription (treatment attempt), 3. Patients redeeming three or more prescriptions of the drug class (at least temporary use) and 4. Patients redeeming six or more prescriptions of the drug class (frequent use).

2.3. Associations between use of drug classes and patient characteristics

Focusing on the drug classes generally recommended in FSS treatment (antidepressants and anticonvulsants) and not recommended (sedatives and opioids), we defined mutually exclusive patterns of use of these drugs:

1. Opioids or sedatives: At least three prescriptions of opioids or sedatives, alone or in combination with other drugs.

2. Antidepressants or anticonvulsants: At least three prescriptions of antidepressants or anticonvulsants, alone or in combination with other drugs, but not in combination with more than two prescriptions of either opioids or sedatives.

3. Mixed short-term treatments of both opioids or sedatives and antidepressants or anticonvulsants: Short-term use of one of more of the drug classes opioids, sedatives, antidepressants or anticonvulsants defined as no more than two prescriptions of any of the four drug classes.

4. No use of opioids, sedatives, antidepressants or anticonvulsants.

The prescription data were linked to the data collected for research purposes in the two trials [24,25]. The collected variables originate from patient-rated questionnaires and from the SCAN interview [26]. The association of the following patient characteristics with prescription patterns was explored: Age, gender, education, work status, illness duration, somatic symptoms (Symptom Checklist (SCL) somatization score), physical and mental health (SF-36 Physical and Mental Component Summary (PCS and MCS) [27], social functioning (SF-36 SF) [27], impairment due to multiple FSS in daily life, physical comorbidity (number of well-defined physical diagnoses during the past 2 years during hospital admissions and ambulatory care obtained through the Danish National Patient Registry as described in another study [28]), physical comorbidities possibly explaining the extent of opioid use (as rated by at least two of three independent physicians) and psychiatric comorbidities: lifetime anxiety or depression (moderate to severe) and current severe health anxiety (severely disturbing or significantly interfering with everyday activities) [29].

We focus on the adjusted association of the three variables: lifetime anxiety or depression, number of physical comorbidities and impairment due to multiple FSS in daily life.

2.4. Statistics

Descriptive statistics were used to describe patients and prescriptions. Mean and standard deviation (SD) or median and interquartile range (IQR) were reported for continuous variables, and proportions were reported for categorical variables. Multinomial logistic regression models were used to assess the association between patient