

ORIGINAL ARTICLE

## Utilization of pharmaceuticals among patients with temporomandibular disorders: A controlled study

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### Abstract

**Objective.** Pharmaceuticals are among factors that might be associated with temporomandibular disorders (TMDs), but knowledge about their utilization is limited. The purpose was to systematically register the regular use of medication in general among TMD patients and matched controls to enable comparisons to be made. **Material and methods.** Three hundred consecutive patients referred for diagnosis and treatment of TMDs and fulfilling the Research Diagnostic Criteria were examined prospectively and any medication recorded. Matched controls were registered parallel in time. The pharmaceuticals used were categorized according to the Anatomical Therapeutic Chemical Classification System (ATC). **Results.** Forty-four percent of the patients received a main diagnosis of “muscle disorder”, 39% “disk disorder”, and 17% “joint disorder”. Fifty-one percent of all patients used some medication on a regular basis compared to 36% of the controls ( $p < 0.001$ ). The average number of ATC categories used among all patients was 0.9 and among controls 0.5 ( $p < 0.001$ ). Of the female patients with the diagnosis “muscle disorder”, 23% used antidepressants (N06A), 6% tranquilizers (N05B), and 7% sleep medication or sedatives (N05C) significantly more frequently than controls. Of the female patients diagnosed with a “joint disorder”, 26% used antidepressants (N06A) significantly more frequently than controls. All other ATC categories differed non-significantly. **Conclusions.** The results suggest that the use of pharmaceuticals differs between patients and controls. TMD patients, particularly women diagnosed with “muscle” or “joint” disorders, appear to use drugs for depression more frequently than ordinary dental patients.

**Key Words:** Anxiety, depression, prospective study, stress

### Introduction

Temporomandibular disorders (TMDs) are characterized by pain and dysfunction of the masticatory system [1]. The collective term embraces a cluster of diagnostic subgroups. Currently, the most widely used classification system is the Research Diagnostic Criteria for TMD (RDC/TMD) [1]. The RDC/TMD axis I classifications are based on observable findings and provide standardized criteria for the process. The etiology of TMDs is not always clearly understood and may vary in different subgroups. Among the factors that might be associated with the signs and symptoms of TMDs are pharmacological substances. Recently, the use of female reproductive hormones has attracted considerable interest [2]. Women of reproductive age are much more likely to seek care for TMD than other age groups or than males [3]. Hormonal differences, including

exogenous hormones, have therefore been suggested as one possible explanation for this observation. Hormones might modulate the risk of TMD by several possible peripheral joint or central pain-related mechanisms [4,5].

Several other different pharmaceuticals might also be associated with the signs and symptoms of TMDs in various ways. For example, the fact that depression is overrepresented among TMD patients has been verified by psychometrics in numerous studies over the years and confirmed in recent clinical research [6,7]. The actual use of antidepressant medication in TMD patients has seldom been reported but could provide evidence for an association.

Additionally, anxiety and stress have been considered important factors in TMDs, particularly in certain subgroups. Research continues to establish an association between these conditions and certain

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TMD diagnoses by psychometrics [8] as well as by experimental methods [9,10]. Again, the consumption of tranquilizers and sedatives in TMD subgroups has not been reported.

Sleep disturbances are also known to exacerbate pain [11]. It has been suggested that myofascial pain is associated with sleep disturbance [12]. The prevalence of frequent sleep medication use in TMD samples has been described [13], but no comparative reports about the use of sleeping medicine in clinical series of TMD patients and controls have been published. Furthermore, general health has been reported to be impaired in cohorts of TMD patients [14]. If this is so, a more frequent use of pharmaceuticals in general among TMD patients compared to controls could be expected. Few clinical studies have addressed this issue.

Actual knowledge about the utilization of drugs among patients diagnosed with TMDs appears to be sparse. Utilization of certain pharmaceuticals might also be common in non-patient populations, but some differences in medication between patients and controls are possible and may vary in different subgroups. The purpose was therefore to systematically investigate the regular utilization of pharmacological substances in general among patients seeking treatment for TMDs and compare with controls.

## Material and methods

Three hundred new consecutive patients, 15 years or older, were selected among referrals from dentists and medical practitioners to the Orofacial Pain Clinic, Sahlgrenska University Hospital, Mölndal. All participating patients fulfilled the inclusion/exclusion criteria for RDC/TMD axis I. Patient data were collected prospectively during a 19-month period (December 2002 to June 2004). Either of two dentists examined and classified the patients based on the anamnestic and clinical findings and on imaging, when available. The dentists were calibrated in the examination technique before the data were collected, and they discussed the findings before the final classification into one or more of the three diagnostic groupings according to the RDC/TMD. Additionally, based on clinical judgment, the patients' signs and symptoms were classified as being mainly of muscular, disk, or joint (hard tissue) origin, a main diagnosis, corresponding to RDC axis I diagnoses group I, II, and III, respectively.

The 300 controls, also 15 years or older and from the same geographical areas as the patients, all attended a general dental clinic for yearly routine examination. They were selected prospectively, matched for sex and age ( $\pm 5$  years), and registered parallel in time by a third dentist. To participate, none had to report subjective symptoms of TMDs

when questioned, but no calibrated examinations were performed.

The patients and controls were systematically questioned about their present use of pharmacological substances at the ordinary history taking. All were asked in a standardized way if they "used any medication on a regular basis including (women) oral contraceptives or other exogenous hormonal replacement". The answer was noted on a separate record together with the subject's age, gender, and TMD diagnoses, respectively, and, for the controls, confirmed absence of subjective TMD symptoms. Temporary use of medication such as painkillers, seasonal anti-allergic medication, or migraine medication as required was not included in the registration. All patients and controls signed a written informed consent form; none refused to participate. The Ethics Committee of Göteborg University granted ethical approval for the study.

The pharmacological substances were categorized according to the Anatomical Therapeutic Chemical Classification System (ATC) [15]. A three-digit code, based on FASS 2004 (Swedish Drug Compendium), was used, which implies 197 possible ATC categories.

The distribution of differences in use of pharmaceuticals between patients and matched controls was found to be symmetrical and tested with Student's *t*-test and signed rank test.

## Results

Of the 300 patients, 15 to 89 years, and the 300 matched controls, 15 to 84 years, 229 in each group (76%) were women and 71 (24%) men. The criteria for an RDC/TMD axis I diagnosis muscle disorder (I a/b) was fulfilled in 68% of all patients, a disk disorder (II a/b/c) was fulfilled in 45% and arthralgia/arthrosis (III a/b/c) in 35%. Twenty different combinations of RDC/TMD diagnoses occurred, and the group size ranged from 1 (Ia/IIc, IIa/IIIb, and Ib/IIIa) to 66 patients (Ia). A main diagnosis of "muscle disorder" was made for 132 patients (44%), "disk disorder" for 118 (39%), and "joint disorder" for 50 patients (17%).

More than half of all patients (51%) used some medication on a regular basis compared to 36% of the controls ( $p < 0.001$ ). The average number of reported drugs (ATC categories) used regularly among all patients was 0.9 (SD 1.2) and among controls 0.5 (SD 0.9) ( $p < 0.001$ ).

The most frequently used medications (ATC categories) among all female and male patients and controls are given in Table I.

In the main diagnostic group, "muscle disorder", female patients used drugs from 48 different ATC categories and male patients from 21. In the diagnostic groups, "disk disorder" and "joint disorder", females used drugs from 26 and 34 different

Table I. The most frequently used pharmaceuticals (ATC categories) among female and male patients and controls, respectively

Patients <sup>1</sup>		Controls	
Women ( <i>n</i> = 229)	Men ( <i>n</i> = 71)	Women ( <i>n</i> = 229)	Men ( <i>n</i> = 71)
G03A contraceptive 17	N06A antidepressant 10	G03A contraceptive 11	C07A beta receptor blocker 12
N06A antidepressant 17	C07A beta receptor blocker 6	H03A thyroid hormones 6	B01A anti-coagulants 7
M01A NSAID 6	M01A NSAID 6	C07A beta receptor blocker 5	A10A insulin 4
H03A thyroid hormones 5	N02A opioids 6		
	N05B ataraktika 6		
	N05C sedatives 6		
	H03A thyroid hormones 4		

<sup>1</sup>Users in percent.

ATC categories, respectively, while males used drugs from 8 and 7 categories, respectively. The distribution of the 20 most frequently used pharmaceuticals (ATC categories in alphabetic order and users in percent) in the main diagnostic and control groups (female/male) and *p* values for the differences is given in Table II. No other pharmaceuticals were used by more than 4% in any diagnostic or control group, female or male, and differences between patients and controls were non-significant. More frequent use of medication in female patients compared to controls was found in the main diagnostic group “muscle disorder” for tranquilizers (N05B) (*p* < 0.05), sleep medication or sedative (N05C) (*p* < 0.05), and antidepressants (N06A) (*p* < 0.001). Female patients, diagnosed with a “joint disorder”, also used antidepressants (N06A) significantly more frequently than controls (*p* < 0.01). Differences between patients and controls in the use of all other ATC categories were non-significant in all main diagnostic groups.

## Discussion

The most striking finding was the difference in use of antidepressant medication between TMD patients and controls, significant among female patients diagnosed with “muscle” or “joint” disorders. The observation could be considered confirmative of earlier research where a comorbidity of depressive symptoms, based on self-reports and TMDs, is a frequent finding [16,17]. Depression, as recognized by a physician, has also been found to be associated with symptoms of TMDs in non-patient populations [18]. Patients with a muscular diagnosis exhibit greater depression than those with articular problems, as judged psychometrically [19], and when differentiated with RDC/TMD [20]. In the present study, the difference was non-significant if the main problems were disk related, possibly suggesting a different psychological background. The causal link between depression and certain facial pain conditions is controversial. Low doses of tricyclic antidepressants have been proven useful in the treatment of TMD pain [21,22]. Depression might precede, follow, or share a common cause with certain TMDs

or care seeking. The primary reasons for the prescription of the antidepressant medication among the patients in this study were not TMDs, as revealed at the history taking. The temporal relationship cannot be decided with certainty: the relation might be bi-directional.

Also, the overrepresentation of the use of sedative and tranquilizers among patients with muscular problems, particularly among women, was remarkable. This is not a surprising finding in the light of earlier research by other methods, psychometrics and self-reports, about the psychological characteristics of these patients [16,23]. Also, in non-patient samples, signs of TMDs have been found to be associated with self-reported stress related to health and pain [24].

More patients than controls used sleeping medicine, again particularly so among women with symptoms of presumed muscular origin. A positive relationship between sleep disturbances and pain severity has been reported in TMD patients [13]. Sleep quality has been found to be worse among patients with masticatory muscle pain than in those with intracapsular problems [25]. It has frequently been noted that it might be the perception of sleep quality rather than real sleep performance that is impaired [26]. Experimental deprivation of sleep in healthy men has been found not to interact with jaw muscle pain [27]. In another study [28], the use of benzodiazepine was found to improve sleep quality and sleep architecture but not to affect pain in TMD patients. The relation between sleep disturbances and TMD thus seems uncertain, but some patients obviously complain of poor sleep.

Depression, anxiety, stress, and disturbed sleep are common findings among patients diagnosed with TMD [8,29], and the results are consistent with these data. Sleep disturbances assessed with validated questionnaires have been found to be among the predictors of poor treatment outcome in TMDs [30]. Also, anxiety and depressive components are involved in the risk of developing chronic jaw pain [31]. Depression, anxiety, stress, and perhaps disturbed sleep might share underlying neurochemical mechanisms of importance for certain facial pain

Table II. Distribution of the most frequently used pharmaceuticals (ATC categories in alphabetical order) in the main diagnostic groups and controls respectively and *p*-values for significant differences

ATC category <sup>1</sup>	Main diagnosis								
	Muscle disorder			Disk disorder			Joint disorder		
	Patients	Controls	<i>P</i> <sup>3</sup>	Patients	Controls	<i>P</i>	Patients	Controls	<i>P</i>
	Women n = 100 (44/16) <sup>2</sup>	Women n = 100 (44/16)		Women n = 94 (28/13)	Women n = 94 (28/12)		Women n = 35 (55/18)	Women n = 35 (56/17)	
Men n = 32 (44/18)	Men n = 32 (43/16)	Men n = 24 (23/12)	Men n = 24 (25/11)	Men n = 15 (46/19)	Men n = 15 (46/20)				
%	%	%	%	%	%	%	%		
A02B gastric.	6 0	1 3		3 0	1 0		3 0	3 0	
A10A insulin	1 0	0 9		0 0	0 0		3 0	0 0	
A12A calcium	0 0	0 0		1 0	0 0		3 0	0 7	
B01A anticoag.	3 6	1 13		0 0	0 4		14 0	6 0	
C03A tiazider	1 0	1 0		0 0	0 0		6 0	0 0	
C07A betabloc.	3 6	8 16		3 4	1 8		9 7	9 13	
C08D calc. antag.	0 6	0 0		0 0	0 0		0 0	0 0	
C10A chol. redu.	3 3	0 3		1 0	0 4		11 0	0 0	
G03A anti-conc.	8 0	9 0		30 0	18 0		6 0	0 0	
G03C oestrogen	3 0	6 0		2 0	1 0		14 0	3 0	
H03A thyr. horm.	6 6	4 3		1 4	4 0		11 0	14 0	
J01A tetracyklin	0 0	0 0		0 4	0 0		0 7	0 0	
L02B antihorm.	0 6	1 0		0 0	0 0		0 0	0 0	
M01A NSAID	9 9	5 0		2 0	2 0		6 7	6 0	
N02A opioides	6 9	2 3		0 4	3 0		3 0	3 0	
N03A antiepilep.	2 3	0 0		0 0	0 0		3 7	6 7	
N05B tranquil.	6 9	0 0	*	1 0	0 0		0 7	0 0	
N05C sleep/sed.	7 9	0 0	*	2 4	0 0		3 0	3 0	
N06A antidepr.	23 19	0 6	***	6 0	2 0		26 7	0 0	**
R03B obstr. resp	2 0	1 0		2 4	1 0		0 0	0 0	

<sup>1</sup>Anatomical Therapeutic Chemical Classification System.<sup>2</sup>Mean age, years/S.D.<sup>3</sup>\*0.05; \*\*0.01; \*\*\*0.001.

conditions [32]. The precise nature of this relationship has not been established.

No other medication was overrepresented among the patients diagnosed with TMDs. The utilization of hormonal replacement therapy did not differ significantly between patients and controls, contrary to some earlier findings [4,33,34], but supportive of others [35]. Our findings of a similar utilization of exogenous hormones among patients and controls do not, of course, exclude the possibility of a hormonal modulation of signs and symptoms of TMDs. Use of oral contraceptives did not differ significantly either; also a controversial finding [34,36,37].

Contrary to our clinical experience, no difference in use of medication related to thyroid dysfunction was found between patients and controls. Hypothyroidism may be associated with both myalgia and arthralgia [38]. Thyroid diseases may have an impact on oral health [39], but little is known about the consequences for TMDs. Symptom perception may differ between individuals and constitute a decisive factor in care-seeking in this as well as other conditions [40].

The significantly more frequent use of pharmaceuticals in general among patients compared to controls is not unexpected. Epidemiological studies have shown that impaired general health is a strong risk factor for reported TMD symptoms [14] and should therefore correspond to an increased use of pharmaceuticals. Subjects with TMDs use health care services frequently [41].

Patients may neglect to report disorders they consider beyond the boundaries of the dental sphere or they may consider themselves in a good state of health at an ordinary history taking. Questions about the use of medication might be more concrete. It is unlikely that the willingness to report drug utilization differs between patients and controls. Prescriptions of specific pharmaceuticals may vary over time and regions and, above all, be related to age and gender [42], as was also observed in this study. It was therefore considered important that the controls be from the same community, registered in parallel, and matched in relevant aspects. One weakness is that subclinical signs of TMDs in controls cannot be excluded since no calibrated examinations were performed, but none were actively seeking treatment and all had to deny subjective TMDs symptoms to participate. The classification of the medications used according to the ATC is in line with the recommendations of the World Health Organization [15]. It does not imply that all pharmaceuticals in one category are identical in, for example, side effects, but it is the best available way to reduce the data.

Little is known about the prevalence of pharmacological substances in general among patients diagnosed with TMDs. For descriptive purposes,

300 patients and 300 controls were considered manageable numbers. About 60 patients could be expected to be examined in the smallest of three groups, divided by presumed etiological origin, in about 18 months at our clinic [43]. The other two groups could be twice as large in the same period of time. A power analysis revealed that if 30% of the patients and 10% of the controls used a particular substance, the probability of finding a difference is 79% at  $n=60$ . At a frequency of 15% and 1%, respectively, the probability is 85%. If 10% of the patients and 1% of the controls used a particular substance, the probability is only 60% at  $n=60$ . This implies that infrequently used drugs require larger groups to find any differences with an acceptable power, and our data are thus weak in this respect.

In conclusion, the results suggest that the use of pharmaceuticals differs between TMD patients and controls. Patients, particularly women diagnosed "muscle" or "joint" disorders, appear to use drugs for depression more frequently than ordinary dental patients do.

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