Research protocol

Administrative information

Title: A questionnaire-based study investigating the prevalence of sleep problems and psychological symptoms among patients with musculoskeletal pain compared to a general practice population

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Introduction

Chronic pain is a major health concern worldwide. The global prevalence of chronic pain was estimated to 30.3 % in a systematic review from 2012(1). Musculoskeletal (MSK) pain comprises a great amount of the chronic pain conditions, being the commonest reported cause of long-term illness in the Danish adult population(2). From 2000-2005, the prevalence of moderate to severe chronic noncancer pain in Denmark was around 16%, whereas the prevalence of mild chronic noncancer pain was 20.2%(3). Focusing on (GP) practice alone, musculoskeletal pain forms the largest diagnostic group accounting for 2/3 of all painful conditions and 14 % of all consultations(4–6).

It has been shown that chronic pain affects daytime activities, such as the ability to exercise, perform household chores, and attend social activities(7), entailing that a substantial proportion of chronic pain sufferers reports a significantly poorer health-related quality of life compared to pain-free peers(3,8). Furthermore, pain appears to have a major impact on employment status, as seen in a study by Breivik *et al.,* where 19 % of the participants had lost their job as a consequence of their pain problem(7). This creates a major economic burden, not only on the individual but also on society(9). Therefore, it is important to identify potential contributing factors or comorbid conditions associated with the onset and course of pain, more specifically of MSK pain as this constitutes a major part of chronic pain conditions, as these may be important targets for treatment.

A growing number of studies support the idea of a noticeable link between musculoskeletal pain and sleep problems(10–13). Significantly more patients with chronic MSK pain suffer from clinical insomnia compared to healthy controls(10,13), however, no unequivocal differences have been seen when focusing on objective polysomnographic sleep parameters(13). Not only is sleep disturbance an independent risk factor for the development of chronic widespread pain(14), it also worsens the long-term prognosis of existing MSK pain(15) and the number of tender points in fibromyalgia(12). As described, the influence of sleep on pain is well-established but the presence of a bidirectional

relationship is more controversial, as it is inconclusive whether pain has the same impact on sleep problems(15,16).

Sleep is not the only parameter that may influence the course of pain. Studies have demonstrated that depression is associated with more pain complaints, more intense pain, longer duration of pain, and the persistence of pain(17,18). This might be because patients with comorbid depression are less likely to comply with pain rehabilitation and therefore are more likely to relapse(17). The same trend is seen when looking at anxiety, another psychological symptom, which also increases the risk for pain incidence at follow-up(16,18). Not only does psychological disorders influence the onset of pain, but the results of one study revealed that pain also predicted the onset of psychological disorders, suggesting a bidirectional relationship between the two(19).

A plausible link between MSK pain and psychological symptoms is the stress response system, as proposed by Palagini *et al*. in a review published in 2016. Besides the connection between pain and affective disorders, this study also found a complex relationship between affective disorders and insomnia probably attributable to the HPA stress system(20). These findings are important, as they might indicate a reciprocal relationship between all three parameters (MSK pain, sleep problems, and psychological symptoms). However, at present there is a lack of research examining the interaction between these factors in patients with MSK.

Therefore, the primary aim of this study is to investigate the prevalence of sleep problems among adolescents and adults with musculoskeletal pain compared to the background population in general practice. Our main hypothesis is that patients with musculoskeletal pain have more sleep problems compared to the background population in general practice.

In addition, we will explore the prevalence of psychological symptoms; in particular anxiety and depressive symptoms, among adolescents and adults with musculoskeletal pain compared to the background population in general practice. Moreover, whether psychological symptoms are more common among MSK pain patients with concurrent sleep problems will also be explored. Our hypothesis is that patients with comorbid MSK pain and sleep problems have more psychological symptoms compared to patients with MSK pain alone.

Furthermore, we want to compare patients with localized MSK pain to those with widespread pain (WSP) to explore the occurrence of sleep problems and psychological symptoms. According to The American College of Rheumatology criteria, WSP is defined as pain in both the left and right side of the body, pain above and below the waist, and pain in the axial skeleton(21). This definition of WSP is also applied in this study. We hypothesize that patients with widespread pain have more sleep problems compared to those with localized MSK pain.

Methods

Study design

The study is a cross-sectional questionnaire-based study, which will be conducted in the autumn of 2017 in a general practice in Thisted, Denmark. All patients aged 12 years and over consulting the practice during the study period will be asked to complete the questionnaire. The questionnaire assesses

demographic parameters as well as the presence of musculoskeletal pain, sleep problems, and psychological symptoms. The patients will be divided into two groups based on their replies: A group with musculoskeletal pain and a control group representing the background population in general practice with no musculoskeletal pain.

Setting
The study will take place in a general practice in Thisted, a town comprised of 13.363 inhabitants (2017), in Northern Jutland, Denmark. Three general practitioners own the practice, which has a patient population of approximately 6.000 patients. The staff (doctors, nurses, and a medical laboratory technician) sees around 150 patients in total each day. The study will be conducted during the autumn of 2017.

Participants
Participants included in the study are all patients aged 12 years and over visiting the general practice regardless of the cause (e.g. care-seeking, health checks, blood sample collection) on the days the questionnaires are distributed. Both patients visiting the doctors, nurses, or the medical laboratory technician will be asked to complete the questionnaire. Based on the replies of the questionnaires, the patients will be divided into two separate groups. The first group will consist of patients with musculoskeletal pain, whereas the second group will be the control group representing the background population in general practice with no musculoskeletal pain. To be included in the MSK pain group, patients must have experienced pain at least once a week in at least one location during the preceding month. Furthermore, pain has to negatively interfere with the patient's usual activities (e.g. work, studying, housework). Patients are excluded from the MSK pain group if their pain is due to a condition/disease that cannot be classified as musculoskeletal. Consequently, patients who mark either the head or the abdomen as their only pain site will be excluded from the MSK pain group, unless they clearly state that their pain is due to a musculoskeletal condition such as tension type headache or the like. The exclusion criteria are created in order to prevent that an underlying condition, such as a comorbid, active cancer, is the cause of the patient's sleep problems and psychological symptoms, and not MSK pain. The rationale behind this is that if you for instance look at cancer patients, a great number of these patients experience sleep disturbances(22,23), anxiety(24,25), and depressive symptoms(26), which consequently could affect the results of the study.

In regards to the participation rate, this will be determined by calculating the percentage of patients eligible for inclusion who returned the questionnaire out of all the patients who visited the general practice on the days the questionnaires were distributed.

Sample size
The sample size was calculated on the basis of the primary hypothesis as well as the primary outcome of sleep disorders assessed by the Athens Insomnia Scale. (AIS-8). The sample size is based on a study by Paparrigopoulos *et al.* examining the prevalence of insomnia using the Athens Insomnia Scale in a representative,

nonclinical sample of the Greek population, in which participants with a chronic disease had a higher prevalence of insomnia compared to participants without a chronic disease, as 15.5 % of participants without a chronic disease suffered from insomnia against 42.8 % of those with chronic disease(27). This difference of approximately 25 percentage points is statistically significant and forms the basis of our sample size calculation. We expect a slightly higher prevalence of insomnia in our control group with no musculoskeletal pain (also referred to as the background population of general practice) as it consists of patients consulting the GP (some of them might suffer from chronic diseases which affect sleep). Therefore, we estimate that 20 % of the patients with no musculoskeletal pain will be classified as insomniacs based on the AIS-8.

Paparrigopoulos *et al.* found 42.8 % of the participants with chronic disease suffered from comorbid insomnia. We expect that a lower proportion of MSK pain patients will suffer from sleep problems, as some may have acute MSK pain, rather than chronic. Consequently, our sample size is based on the estimation that 35 % of the patients with MSK pain will be classified as insomniacs according to the AIS-8. This will ensure the study is sufficiently powered to detect a potentially smaller difference in proportions between the control and MSK pain group.

In conclusion, the proportion of sample 1 (the background population of general practice with no musculoskeletal pain) is set at 0.2, the proportion of sample 2 (the patients with musculoskeletal pain in general practice) is set at 0.35, and the ratio between the sample sizes is set at 0.14, as musculoskeletal pain accounts for 14 % of all consultations in general practice(5). This gives us a final sample size of 598, and at least 73 patients from the sample need to suffer from musculoskeletal pain.

Recruitment

The employees in the general practice will hand out questionnaires to every patient aged 12 years and over visiting the clinic during week 45 and 47 in 2017. The questionnaires will be distributed Monday-Thursday. Using the sample size calculation as point of departure, the recruitment period will last for eight days. However, in the end of the first week, we will evaluate whether the recruitment procedure needs to be repeated for the second week in order to reach the sufficient sample size. The data from the questionnaires will be typed in continually to create an overview of the sample size and to help determine when the adequate sample size has been achieved.

Outcomes

Primary outcome

The primary outcome of this study will be sleep problems as evaluated by the Athens Insomnia Scale (AIS-8). The prevalence of sleep problems will be compared between two separate patient groups in general practice: Patients with MSK pain and patients with no MSK pain representing the background population.

Other outcomes

In addition to the primary outcome, the study includes one exploratory outcome. This outcome will be psychological symptoms assessed by the Hospital Anxiety

and Depression scale (HADS). The occurrence of psychological symptoms will be evaluated and compared within the two above-mentioned groups. Furthermore, the occurrence of psychological symptoms will be compared between patients with comorbid MSK pain and sleep symptoms and patients with MSK pain alone.

Data collection

The questionnaire is based on existing and validated surveys and is constructed to determine demographic parameters, including age, sex, height, and weight, pain, sleep problems, anxiety symptoms, and depressive symptoms. We have chosen to look at depression and anxiety, as these are the most common mental disorders among adults in Europe(28). The sleep questionnaire is translated using the dual-panel translation method(29). First, the questionnaire is translated from English into Danish by a panel consisting of 5-7 bilingual people native to the target language and at least one native speaker of the source language. Subsequently, a lay panel working as a focus group assesses the translated version of the questionnaire, without having access to the original version. The lay panel should also consist of 5-7 persons and contain people of different genders and age groups.

The dual-panel translation method has been compared to the commonly used forward-backward translation method in a previous study(30). In this study, they made two separate translations of the Rheumatoid Arthritis Quality of Life Instrument using the dual-panel method and the forward-backward method respectively. They found no difference between the two translations in regards to the psychometric performances of the questionnaires. However, lay people and patients preferred the wording of the dual-panel version to the forward-backward version, which is why this method was chosen in this study.

The final version of the entire questionnaire will be piloted in the clinic before the initiation of the actual study. For the piloting process, a minimum of 15 patients will be asked to complete the questionnaire. Subsequently, they are asked to give their feedback on the questionnaire and evaluate if any of the items were unclear and need to be rephrased. Their comments will be taken into consideration and the questionnaire corrected before the study start, if necessary. Additionally, the questionnaire will be piloted in adolescents aged 12-14 years old before the initiation of the study to determine whether this age group understands the items well enough to provide reliable answers to the questions. If not, the age criteria will be redefined.

A structured pain questionnaire was designed to assess different aspects of musculoskeletal pain. Patients are asked to mark the exact location of their pain on an outlined manikin of the human body. In this study, we use a pain manikin developed by van den Hoven *et al.* who found that a manikin generally produces the same results as written questions containing descriptions of anatomical areas(31). The questionnaire also contains a question about pain frequency measured on a Likert-type scale (which consisted of the answers: *pain seldom, monthly, once a week, more than once a week, almost daily)* as well as a question about pain duration. Average pain intensity and worst pain during the preceding week are evaluated using a visual analogue scale ranging from 0 to 10. Furthermore, patients are asked about the cause of their pain, if known, and

whether they have consulted their general practitioner for the pain. They are also asked to assess if pain has a negative influence on their daily activities, and whether they take any pain-relieving medication.

Sleep problems are measured using the Athens Insomnia Scale (AIS-8)(32,33). This questionnaire consists of 8 items and focuses on sleep quality and quantity as well as daytime functioning by assessing different aspects of insomnia. The first five items assess difficulties with sleep induction, awakening during the night, early awakening in the morning, total sleep duration, and overall sleep quality, whereas the last 3 items deal with the sense of well-being, overall functioning, and sleepiness during the day. The items are scored on Likert-type scales ranging from 0 (no problem at all) to 3 (very severe sleep problem). The total score lies between 0-24 with a cutoff score of 6(34). The responders are requested to rate the item positive if it occurred at least three times per week during the last month. The internal consistency of the AIS-8 is high with a Cronbach's alpha on 0.89. The external validity of the AIS was measured against the total score of the Sleep Problems Scale. The correlation with this scale is very high with a Pearson's correlation coefficient on 0.90 ($p < 0.001$). Furthermore, the test-retest-reliability is very satisfactory (0.89)(33).

To access anxiety and depressive symptoms, the Hospital Anxiety and Depression scale (HADS) has been chosen. HADS is a self-report questionnaire, which consists of two subscales: An anxiety subscale (HADS-A) and a depression subscale (HADS-D). The questionnaire consists of 14 items in total, which evaluate anxiety and depressive symptoms, such as worrying, feeling tense, frightened, restless, cheerful, and loss of interest in appearance. Participants evaluate how often they felt each of these items during the past week. Responses are scored from 0-3, meaning possible scores from each subscale range from 0–21. Studies have demonstrated an optimal cutoff value of 8 for each of the subscales(35). Scores from 8–10 indicate mild anxiety/depression, scores 11–14 moderate anxiety/depression, and scores ≥15 indicate severe anxiety/depression(36,37).

A systematic review, which assessed the validity of HADS, found a mean Cronbach's alpha coefficient of internal consistency on 0.83 for HADS-A and on 0.82 for HADS-D(35). In this review, they also conclude that the validity of HADS is good to very good (correlation between 0.60-0-80) when compared to other commonly used questionnaires such as Beck's Depression Inventory and SCL-90. HADS has previously been translated into Danish using the forward-backward translation method and the translated version has been cross-culturally validated(38).

Even though the AIS-8 and HADS were originally developed for and validated in an adult population, several studies have used one of these scales to assess either sleep problems(39,40) or anxiety and depressive symptoms in adolescents(41,42). Furthermore, both of these scales have been validated as satisfactory screening instruments in adolescent populations(43,44).

Data management
All data will be entered electronically by one person. Personal data will be stored in REDCap by permission of Datatilsynet (Project ID: 2017-215). REDCap is a web application that securely stores data in accordance with the data protection law. Personal data will be anonymised for the final article. After completion of the study, all original questionnaires will be destroyed.

Statistical methods
The primary analysis to detect differences in proportion of insomniacs between the control group and the MSK pain group will be investigated using a Chi-squared test of independence. This test will also be applied to detect differences in proportion of insomniacs between patients with localized versus widespread pain. Unpaired t-tests will be used to analyze all continuous data from HADS, if normally distributed, to detect differences in anxiety and depressive symptoms between the primary groups (patients with MSK pain and the control group) as well as the subgroups (patients with MSK pain alone versus patients with MSK pain and comorbid insomnia and patients with localized MSK pain versus WSP). Results for continuous variables will be reported as means with SD (as appropriate). Furthermore, we will calculate the proportion of patients from each group with a score greater than the HADS cut-off score. All proportions will be stated as percentages. For all analyses, the level of statistical significance will be set at $p < 0.05$. Data is analyzed using the SPSS software.
Missing data in HADS will be managed using the "half rule" method, which means that the patient's subscale mean (for the HADS-A and HADS-D respectively) will be used to fill in the missing data(45). Patients will be excluded from the study if they have failed to answer the questions, which allocate them to either the MSK pain group or the control group.