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Opioids Increase Sexual Dysfunction in Patients With Non-Cancer Pain

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ABSTRACT

Introduction: Long-term opioid therapy has been found to have a strong impact on the hypothalamic-pituitary-gonadal axis that can be manifested clinically by sexual dysfunction (SD). This event is rarely reported and thus unnoticed and undertreated.

Aim: To analyze the presence of SD in a large group of patients receiving long-term opioids.

Methods: A descriptive, cross-sectional pilot study of sexual health was conducted for 2 years in 750 consecutive ambulatory patients with chronic non-cancer pain (CNP) receiving opioids for at least 12 months. Cases that reported SD and matched controls were included. Standardized questionnaires and medical record reviews were used to assess rates of pain at diagnosis, daily morphine equivalent doses, and opioid adverse effects.

Main Outcome Measures: Sexual function was determined by the Female Sexual Function Index (FSFI; scores = 2−36) and the International Index of Erectile Function erectile function domain (IIEF-EF; scores = 1−30).

Results: Thirty-three percent of 33% of 750 patients with CNP recorded SD based on their spontaneous notification at the pain unit. Men reported SD significantly more frequently than women (33% vs 25%, respectively, $P < .05$), although they reported having a regular partner (84% vs 70%, $P = .03$) and a sexually active life (69% vs 34%, respectively, $P = .00$) significantly more often. FSFI scores were significantly influenced by sexual activity in lubrication and arousal. IIEF scores were significantly determined by age in satisfaction with sexual intercourse and overall satisfaction. The morphine equivalent dose was significant higher in men than in women (38%; median = 70 mg/d, interquartile range = 43.1−170, 115.5 ± 110.3 mg/d vs median = 60 mg/d, interquartile range = 30−100.6, 76.67 ± 63.79 mg/d, $P = .016$) at the same mean intensity of pain ($P = .54$), which correlated to FSFI scores ($r = -0.313$, $P = .01$).

Conclusion: SD is prevalent in patients with CNP and higher in men who received a significantly higher mean opioid dose at the same intensity pain level than women. The morphine equivalent dose was correlated to SD intensity. Evidence-based interventions to support sexual activity and function in CNP are needed.

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Key Words: Long-Term Opioid; ADRs; Sexual Dysfunction; Chronic Non-Cancer Pain; Erectile Function; International Index of Erectile Function; Female Sexual Function Index

INTRODUCTION

Chronic non-cancer pain (CNP) persisting longer than 6 months affects 15% to 30% of the population. However, approximately 20% of these patients do not derive sufficient pain relief from traditional measures and might benefit from therapy with opioids. However, the use of opioids has been impeded by concerns about systemic side effects and fear of regulatory action. Fortunately, clinical experience has shown that this apprehension

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is exaggerated and that opioids can be used effectively over prolonged periods without inducing unacceptable side effects.[1–4] Nonetheless, the occurrence of endocrine side effects, including sexual dysfunction (SD; ie, erectile dysfunction, decreased libido)[5,6] can become an important issue if patients with CNP, especially young people, are treated for prolonged periods.[7,8]

Sexual function is considered an important domain of quality of life and is vulnerable to disruption through illness and injury, including chronic pain. There are only a small number of empirical studies on chronic pain, presumably because of the complexities of the field. Also, because of their multifactorial etiology, there is no single, universally accepted management algorithm for women and men diagnosed with this entity and thus are rarely considered for treatment despite its high frequency and persistence.[9]

Some studies have documented androgen insufficiency associated with hypogonadotropic hypogonadism by long-term opioid use leading to inadequate production of sex hormones, particularly testosterone.[10] Interestingly, the effects of opioids on testosterone might depend on the specific opioid used.[11] Bliesener et al[11] studied the hormonal effects of opioid maintenance and found that individuals taking buprenorphine had significantly higher plasma testosterone levels and less SD compared with patients receiving methadone. It is unclear whether these results can be extrapolated to patients with pain, but it underscores the importance of potential medication-dependent hormonal side effects. Apart from circulating testosterone levels, neuropeptides can modulate sexual behavior in patients with prescribed opioids by acting mainly in the hypothalamic nuclei, in the medial preoptic area, and in the spinal cord. However, it is often unclear whether neuropeptides influence the anticipatory phase (sexual arousal and/or motivation) or the consumption phase (performance) of sexual behavior, except in some cases of opioid peptides.[12]

Another major barrier to the development of clinical research has been the absence of well-defined end points and outcomes, which in turn reflects the current lack of consensus on the definition and diagnostic framework for assessing and treating SD.[13,14] The questionnaires used most often are the Female Sexual Function Index (FSFI)[15] and the International Index of Erectile Function (IIEF), which have been designed as clinical trial assessment instruments but their use in CNP remains to be investigated.[16]

Long-term opioid use can contribute to impaired sexual function and decreased libido, which might not be clinically recognized as opioid-related symptoms. Patients initiated or maintained with opioids should be queried about symptoms that might suggest hypogonadism, and additional data appear necessary to formulate guidelines regarding the diagnosis and management of SD. Options include rotating or decreasing the dose or type, stopping opioid therapy, or adding hormonal supplementation in the form of androgen replacement therapy.[17,18]

AIMS

The present study analyzed the presence of SD of a large group of patients receiving long-term opioids. This could serve to assist and standardize diagnosis and guide opioid treatment in CNP.

METHODS

A descriptive, cross-sectional pilot study of sexual health was conducted in 750 consecutive patients with CNP receiving long-term opioids. The ethics committee of the Alicante Department of Health, General Hospital (Alicante, Spain) approved the study. Once the aim of the study and confidentiality of the information obtained were explained and informed consent was obtained, questionnaires were self-administered.

SD was recorded based on a patient's spontaneous notification during routine clinical visits. Patients with CNP receiving oral and/or transdermal opioid treatment for at least 1 year were eligible for participation. Patients' ages ranged from 18 to 80 years. None of the patients were taking hormone medication (supplementation or deprivation) or phosphodiesterase type 5 inhibitors. Patients who reported SD before the onset of chronic pain were excluded from the study.

A study physician obtained data on the patients' medical history: sociodemographic data (regular partner, marital status, sexual active or not, and employment status), medical data (age, body mass index [BMI], blood pressure, and heart rate), the most common comorbidities (hypertension, diabetes, dyslipidemia, and obesity), and drugs prescribed. Civil or marital status was registered as married, single, divorced, or widowed. The existence of a regular partner, which included the civil status of "married" but also unmarried with a regular relationship, was registered.

A group of 53 patients with CNP under chronic opioid treatment who did not report SD was included as the control group (49% men).

Pain severity was determined using a commonly used self-reported visual analog scale (VAS), with 0 indicating "no pain" and 10 indicating "the worst possible pain." Pain severity also was classified as mild (VAS $\leq$ 3 cm), moderate (VAS 4–6 cm), or severe (VAS $\geq$ 7 cm). Quality of life related to health measurements developed by the EuroQol-VAS was used in this study. Scores ranged from 0 (worst health status) to 100 (best health status). The Hospital Anxiety and Depression Scale was used to assess anxiety and depression by seven questions and scores that were categorized as normal (0–7), mild (8–10), moderate (11–14), and severe (15–21). All questionnaires were self-administered but supported by the presence of an expert clinician.

Also, patients were encouraged to report all suspected opioid adverse events (any noxious, unintended, or undesired effect associated with the analgesia prescription) using patient self-completed forms.