Observational Study

OPRM1 Gene Interaction with Sleep in Chronic Pain Patients Treated with Opioids

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Background: The experience of chronic non-cancer pain (CNCP) is one of the most common reasons individuals seek medical attention. Patients with CNCP frequently experience concomitant sleep-related problems.

Objectives: The aim was to evaluate sleep problems in opioid naïve CNCP patients, before and after opioid titration, analyzing the influence of OPRM1 gene variants.

Study Design: A prospective, cohort, observational study.

Setting: This study was performed at the Pain Unit of the Alicante University General Hospital.

Methods: Pain and Medical Outcomes Study Sleep questionnaire (MOS-Sleep) were assessed at baseline and 3 months after opioid titration in 231 opioid naïve CNCP patients. Sleep data was compared with a matched-control group (n = 64). Morphine equivalent daily doses, adverse events, and drugs prescribed for pain were also registered. OPRM1 polymorphism rs1799971 was analyzed by RT-PCR. Ethics Committee approved the study and results were analyzed by R software.

Results: After 3 months of opioid titration, patients with CNCP (63 ± 14 years, 64% female, VAS 74 ± 17 mm) significantly decreased pain intensity, anxiety and depression, and increased quality of life. Sleep problems were significantly more frequent in females (P = 0.002). Age, quality of life, anxiety, and depression all influenced sleep disturbances and problems indices, which were significantly different from the control group. Furthermore, the OPRM1 118-GG genotype was also associated with significantly lower sleep adequacy, and more sleep problems.

Limitations: Total number of subjects studied was relatively small and most patients were on other non-opioid centrally-acting medications.

Conclusions: Opioids decreased CNCP severity, improving patients' psychological areas, and quality of life. However, patients with OPRM1 118-GG genotype indicated an increase in sleep problems and worsening sleep pattern while taking opioids.

Key words: OPRM1, pharmacogenetics, MOS-Sleep, opioids, chronic noncancer pain, sleep related problems, sleep problem index SLP-6 and SLP-9

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The experience of chronic noncancer pain (CNCP) is one of the most common reasons individuals seek medical attention, as it is a major issue in clinical practice due to activity limitations, and associated work disability worldwide (1). Patients with CNCP frequently experience concomitant sleep-

related problems that can increase depression, anxiety, hospitalizations, mortality, and/or other chronic medical conditions, as well as impair social functioning (2,3). Experimental studies suggest that sleep problems and pain might be reciprocally related since pain disturbs sleep continuity/quality and poor sleep further exacerbates pain (4).

Even more, there is controversy on whether chronic opioid therapy has a beneficial or deleterious effect on sleep quality, efficiency, and duration. Opioid use could affect sleep by acting on both sleep- and wake-promoting systems at the pontine reticular formation and the substantia innominata within the basal forebrain (5,6). Opioids can decrease adenosine levels in the pontine reticular formation by opioid receptor mu 1, encoded by the OPRM1 gene agonist, and subsequently result in dose-dependent sleep problem side effects (7,8). Polymorphisms on the OPRM1 gene can alter the density and function of the receptor and, consequently, receptor-signaling efficacy that might contribute to individual variations in response to opioids (9,10). A related study produced different results regarding OPRM1 polymorphisms and opioid sleep side effects (11). Similarly, polymorphisms in the OCT1 gene encoding for a morphine transporter have been shown to increase the risk of respiratory depression in Caucasian children when compared to African/American children, probably due to a lower morphine clearance in Caucasian children (12). However, one of the major challenges in pharmacogenetics is translating these results into clinical practice.

The present study examined the presence of sleep-related problems in opioid-naïve patients that required opioids to treat CNCP and the influence that OPRM1 rs1799971 (A118G) polymorphism could have on pain and sleep parameters.

Methods

Study Design

A prospective, cohort, observational study was performed from September 2012 through September 2014 in ambulatory, opioid-naïve patients with moderate to severe CNCP. The aim was to analyze the relationship between sleep and pain measurements, physical and mental health, and pain pharmacological therapy prescribed at baseline interviews and 3 months after opioid titration. All patients were titrated using the same protocol adapted to the patient based on clinical need, and initial prescription of oral morphine or fentanyl patch. Pregabaline or gabapentine were added, if

needed, as a first step neuromodulator.

All patients who followed standard treatment at the Pain Unit of Alicante University General Hospital, were recruited during clinical visits, and received information on the design and purpose of the study. The hospital ethics committee approved the study and all participants signed informed consent forms. Research was performed in accordance with the ethical standards as stated in the 1964 Declaration of Helsinki and its later amendments.

Patient Population and Data Collected

A total of 231 participants were preselected based on the inclusion criteria of 1) age of over 18 years old, 2) a diagnosis of CNCP that required appropriate opioid analgesia to ensure pain relief, 3) minimal adverse events experienced. Only those requiring opioid treatment were included in the study. Exclusion criteria included: 1) age under 18 years old, 2) patients with oncologic pain, and 3) patients with significant psychiatric disorders that could interfere with the proper development of the study. Controls included 1) recruitment at the same ambulatory visit, 2) age, and 3) matched-pair stratified by age and gender from patients relatives without pain.

All patients were interviewed at the first visit where demographic data and pain history was collected. Clinical interviews were performed to evaluate physical health, drug use, and medical history. Validated scales and questionnaires completed at each visit were used to evaluate the clinical situation for each patient. All questionnaires were self-administered, but monitored by the presence of an expert clinician. Also, a matched-pair control stratified by age and gender from patients relatives without pain (n = 64), was established to check healthy population sleep patterns within similar environmental and with similar habits, was included in the study.

Pain severity was determined using a standardized self-reported Visual Analogue Scale (VAS), with 0 indicating 'no pain,' and 100 mm indicating 'the worst possible pain." Pain severity was classified as mild (VAS ≤ 30 mm), moderate (VAS 40–60 mm) or severe (VAS ≥ 70 mm).

Quality-of-life related to health measures developed by the EuroQol-VAS was also assessed in this study. Scores ranged from 0 (the worst health status) to 100 (the best health status). The Hospital Anxiety and Depression (HAD) scale was used to assess both anxiety and depression by each patient answering 7 questions

with the scores categorized as normal (0-7 scores), mild (8-10 scores), moderate (11-14 scores), and severe (15-21 scores).

Evaluation of sleep disturbance required assessment of multiple sleep dimensions (13). While not a diagnostic tool, the Medical Outcomes Study Sleep (MOS-Sleep) questionnaire has been utilized in patients with chronic diseases, which provides support for the feasibility, reliability, and validity of this scale (14). Patients were asked to report how often each particular sleep symptom or problem was applicable to them on a 6-point categorical scale ranging from "all of the time" to "none of the time." The 12 questions aim to evaluate sleep, with derived subscales for the domains of sleep disturbance (4 questions), quantity of sleep (1 question scored as the average hours slept per day: 0–24 hours), snoring (1 question), awakening due to short of breath or with headache (1 question), sleep adequacy (2 questions), and somnolence (3 questions). The question regarding time it takes to fall asleep uses a 5-point categorical response scale ranging from "0 to 15 minutes" to "more than 60 minutes." This questionnaire also allows for the calculation of global "sleep problem indices" (SLP-6 and SLP-9, scored from 0-100) that provide a measure applicable to overall sleep quality. Higher scores indicate the presence of sleep problems, not including the issue of adequacy of sleep. Respiratory impairment is based on the presence of snoring and awakening with shortness of breath or with a headache (3,15).

Medications

Analgesic medication (simple analgesic, tramadol, opioids, and adjuvant) use was obtained from the institution's electronic prescribing application. As the number of available opioid medications is increasing, it is necessary when comparing patients taking different agents to compare equivalent doses. For this purpose, oral morphine equivalent daily doses were estimated using available references (16).

A questionnaire with a list of most frequent adverse drug reactions (selected according to opioids Summary of Product Characteristics frequency as "very common" and "common") and a blank field to add any other adverse event was developed in our unit. A questionnaire that included insomnia and daytime somnolence as sleep-related problems and was also administered to the patients. Results were compared to suspected adverse drug reactions from the Spanish Pharmacovigilance System related to pain pharmacology treatment (n = 3476) at the same study time period.

OPRM1 Genotyping

Approximately 8 mL of blood was collected from each participant. Genomic DNA was isolated from a 1-mL aliquot with a QIAmp Blood DNA kit according to the manufacturer's instructions. Real-time polymerase chain reaction (RT-PCR) analysis was used to genotype OPRM1 rs1799971 (A118G) gene polymorphism. All PCR amplifications were carried out in a RT- PCR Rotor Gene Q (Qiagen) using specific TaqMan probes MGB® (Applied Biosystems). The amplification parameters were as follows: initial 10 minute denaturation at 95°C, 45 cycles for 15 seconds at 92°C, 90 seconds at 60°C, and 1 minute final extension at 60°C. Results were analyzed by Q-Rex software.

Statistical Analyses

Quantitative data are presented as mean ± standard deviation. Relative frequencies of genotypes and alleles were calculated for each group, and chi-square analyses were conducted to compare the distribution of genotypes and alleles.

Bivariate correlations of each of the MOS-Sleep subscales with age, weight, pain intensity, quality of life, and anxiety and depression were analyzed using the Pearson correlation matrix. Effect size of correlations were considered small if $r < 0.29$, moderate if $r > 0.30-0.49$ and large if $r > 0.50$ (17). To determine the socio-demographic and clinical parameters associated with each MOS-Sleep subscale score, linear regression analyses were performed. Final linear regression models were selected using stepwise forward selection.

Comparisons for continuous or categorical variables between baseline and final data were conducted using independent t-tests or chi-square tests, respectively. For interaction analyses, genotypes were also classified into dichotomous variables according to the different gene models (dominant, codominant, recessive, and log-additive).

A *P* value < 0.05 was considered statistically significant. In all cases, multiple testing was adjusted using Bonferroni correction. Statistical analyses were carried out with R software package version 3.2.0.

RESULTS

Patients

Clinical and pharmacological data collected at the beginning of the study and at 3 months of opioid titration are shown in Table 1.

All participants (n = 231 participants, 63 ± 14 years old, 64% female, 100% Caucasian, BMI 29 ± 5 Kg/m²) were referred to treatment for moderate to severe pain with musculoskeletal CNCP, mainly in the lower back. Seven percent of patients were excluded from the study, mostly due to loss of follow-up. The final study sample was of 215 patients. Controls (n = 64, 61 ± 10 years old, 59% female, 100% Caucasian) of age and gender were similar to CNCP patients. The population was demographically representative of the patients that are seen at the Pain Unit of the Alicante University General Hospital.

Clinical and Pharmacological Data

Clinical parameters and drug use are shown in Table 1.

Patients included in the study received: 39% simple analgesics (9% NSAIDs, 30% acetaminophen), 25% tramadol/acetaminophen, 17% non-regular use opioids (mostly morphine). Most patients (70%) were taking other concomitant drugs such as anticonvulsants (42% pregabalin, 12% gabapentin), benzodiazepines (17%) or antidepressants (13% duloxetine) (Supplementary Table 1). All medications were prescribed at dosages recommended by the summary product characteristics datasheet and the influences on sleep (mainly drowsiness and insomnia) were described in the datasheet. Influence on sleep by concomitant drugs was analyzed

Table 1. *Clinical and pharmacological data at the beginning of the study (baseline) and at 3 months of opioid titration (final).*

	Baseline*	**Final**	***P*-value**
VAS (0-100 mm)	74 ± 17	55 ± 25	0.000
EQ-VAS (0-100 mm)	48 ± 13	65 ± 23	0.007
HAD-Anxiety (0-21 scores)	8 ± 5	6 ± 5	0.001
HAD-Depression (0-21 scores)	8 ± 5	7 ± 5	0.016
Opioid prescription, %			
Fentanyl	2	22	0.012
Oxycodone	8	17	0.014
Morphine	2	5	0.001
Tapentadol	1	10	0.165
Buprenorphine	4	2	0.242
Hydromorphone	1	1	0.562

VAS: Visual Analog Scale; HAD: Hospital Anxiety and Depression Scale. Data is presented as mean ± standard deviation or as %. * Opioid treatment at baseline visit was sporadic (non-regular prescription) use. *P* value < 0.05 is bold.

at the final visit. At the end of the study, tramadol use was significantly decreased to 15% (*P* = 0.014) with a significantly increased use of major opioids such as fentanyl (22%, *P* = 0.012), oxycodone (17%, *P* = 0.014) and tapentadol (10%, *P* = 0.001). Final morphine equivalent daily dose was 55 ± 49 mg/day with a maximum of 70 ± 54 mg/day. No significant differences were found in the use of simple or adjuvant analgesics.

Pain duration at baseline was more than 1 year and intensity was mostly severe (VAS$_{basal}$, 74 ± 17 mm). At 3 months of opioid titration, pain intensity was significantly reduced from baseline value (VAS$_{final}$, 55 ± 25 mm, *P* < 0.001). Furthermore, mean HAD scores for anxiety and depression that were initially mild (8 ± 5 scores for both scales) also decreased significantly upon opioid titration (6 ± 5 and 7 ± 5 scores, respectively).

Sleep-Related Problems Analysis

Results from MOS-Sleep questionnaire are presented in Table 2.

At baseline, patients vs. controls, showed sleep disturbance scores of 47 ± 31 vs. 29 ± 22 (*P* = 0.000) and sleep adequacy scores of 47 ± 38 vs. 61 ± 33 (*P* = 0.010). Quantity of sleep scores were 5.8 ± 1.7 vs. 6.8 ± 1.1 (*P* = 0.000) with more "awaken short of breath or with headache" (24 ± 28 vs. 14 ± 23, *P* = 0.015). SLP-6 scores were 42 ± 26 vs. 27 ± 18 (*P* = 0.000) and SLP-9 scores were 43 ± 25 vs. 27 ± 17 (*P* = 0.000) (Table 2 and Fig. 1). No differences in any of the sleep dimensions were found in CNCP patients upon 3 months of opioid titration (Table 2).

Analysis by linear regression demonstrated that pain severity was associated with higher SLP-6 scores (b = 1.16, 95% CI = 0.60-1.72, *P* < 0.001) and lower "sleep adequacy" (b = -1.62, 95% CI = -3.22-0.20, *P* < 0.001).

Bivariate correlations analyses showed that age, anxiety, and depression had a significant small-moderate effect size in "sleep disturbance" and moderate with "sleep adequacy," and SLP-9 (Table 3). No influence of analgesic medication (simple analgesic, tramadol, opioids) or adjuvant (antidepressants or benzodiazepines) was found with any of the MOS-Sleep items (data not shown).

Patient's Self-Reported Adverse Events

Adverse events reported by patients were similar to those typically reported for opioids. Daytime somnolence was reported in 22% of the patients rating significantly higher depending on pain severity (*P* = 0.033). Also, sleep problems were more frequently reported by females (*P* = 0.002).
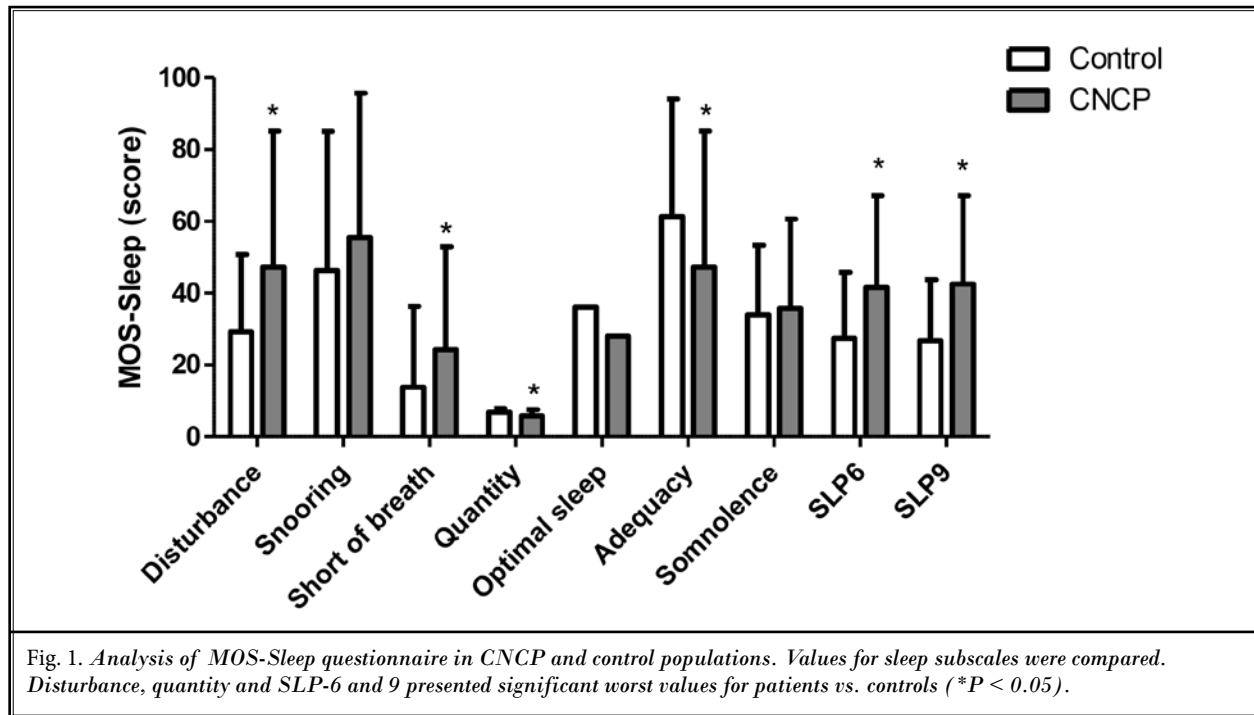
Fig. 1. *Analysis of MOS-Sleep questionnaire in CNCP and control populations. Values for sleep subscales were compared. Disturbance, quantity and SLP-6 and 9 presented significant worst values for patients vs. controls (*P < 0.05).*

Table 2. *MOS-Sleep questionnaire results at baseline and at 3 months of opioid titration (final).*

MOS-Sleep items	Control	Baseline	Final	*P-value	#P-value
Sleep disturbance	29 ± 22	47 ± 31	43 ± 31	0.000	0.234
Snoring	46 ± 39	56 ± 40	57 ± 40	0.153	0.827
Awaken SOB or with headache	14 ± 23	24 ± 29	25 ± 30	0.015	0.912
Quantity of sleep	6.8 ± 1.1	5.8 ± 1.7	6.1 ± 1.8	0.000	0.319
Optimal sleep (yes, %)	36%	28%	24%	0.205	0.490
Sleep adequacy	61 ± 33	47 ± 38	55 ± 38	0.010	0.153
Somnolence	34 ± 19	36 ± 25	40 ± 25	0.775	0.181
SLP-6	27 ± 18	42 ± 26	38 ± 26	0.000	0.211
SLP-9	27 ± 17	43 ± 25	39 ± 24	0.000	0.279

MOS-Sleep: Medical Outcome Study Sleep questionnaire; SOB: short of breath; SLP: Sleep Problem Index. Data is presented as mean ± standard deviation. *P*-value < 0.05 is bold. *P value from U-Mann Whitney test Control vs CNCP baseline. #P value from U Mann Whitney test CNCP baseline vs CNCP final visits.

In addition, a total of 168 suspected adverse drug reactions related to pain pharmacology therapy were noted by physicians from which a total of 25 (15%) were related to sleep: insomnia (n = 3, 2%), nightmares (n = 6, 4%), somnolence (n = 14, 8%), and others sleep related problems (n = 2, 1%). Compared to the Spanish Pharmacovigilance System, 150 (5%) suspected adverse drug reactions were reported as related to sleep problems in similar percentages to our results.

OPRM1 Genotype and Sleep Problems Correlation

Genotypic and allelic frequencies in this study were in equilibrium with Hardy-Weinberg. The frequency of the OPRM1 (rs1799971, A118G) AA genotype was 63%, AG 32% and GG 5%. MOS-Sleep questionnaire results at baseline and final visit were compared according to the OPRM1 genotype (Fig. 2).

Most subscales were not influenced by genotype,

Table 3. *Correlation analysis of MOS-Sleep Subscale scores with clinical parameters.*

R Spearman	Sleep disturbance	Snoring	Awaken SOB	Quantity of sleep	Optimal sleep	Sleep adequacy	SLP-6	SLP-9
Age	**-0.21**	0.09	-0.11	0.11	0.13	**0.26**	**-0.17**	**-0.25**
P-value	0.011	0.305	0.198	0.180	0.133	0.002	0.044	0.003
Weight	-0.10	0.11	0.16	-0.04	0.12	-0.02	0.10	0.04
P-value	0.543	0.493	0.300	0.805	0.428	0.883	0.506	0.783
Pain	-0.01	-0.04	0.08	-0.05	0.02	-0.05	0.05	0.05
P-value	0.906	0.676	0.329	0.553	0.810	0.548	0.547	0.575
Quality of life	-0.12	0.02	-0.10	**0.20**	0.1568	**0.25**	0.006	**-0.19**
P-value	0.154	0.848	0.270	0.024	0.063	0.002	0.945	0.022
Anxiety	**0.35**	0.10	**0.27**	**-0.24**	**-0.20**	**-0.45**	**0.15**	**0.43**
P-value	< 0.000	0.301	0.001	0.006	0.020	< 0.000	0.075	< 0.000
Depression	**0.29**	**0.18**	**0.18**	**-0.18**	**-0.18**	**-0.32**	0.08	**0.31**
P-value	0.001	0.046	0.030	0.038	0.033	0.000	0.335	0.000

SOB: Short of breath; SLP-6 and SLP-9: Sleep problem indices 6 and 9. Values correspond to r Spearman correlation coefficients. *P*-value < 0.05 are written in bold. Significant correlations are highlighted in grey.

except for "sleep adequacy" where the 118-GG genotype presented significantly lower values (AA 75 ± 40, AG 63 ± 44 and GG 18 ± 17 scores, *P* = 0.024 for co-dominant model; AA-AG 72 ± 6, GG 18 ± 9 scores, *P* = 0.011 for recessive model; and *P* = 0.012 for log-additive model). In the same way, SLP-6 and 9 were significantly higher for the OPRM1-GG genotype indicating a severe sleep pattern. No association was found between the type of opioid prescribed and the sleep-related indices (data not shown).

Discussion

In this study, after 3 months of opioid titration, participants showed a significant decrease in pain intensity, anxiety and depression, and an increase in quality of life that was associated with higher daytime somnolence but without any significant difference in sleep dimensions. Genotype GG for OPRM1 polymorphism A118G was associated with a severe sleep pattern. Our findings highlight the elevated levels of sleep-related problems in the CNCP population vs. controls, and the influence of female gender, pain severity, anxiety, and depression on sleep quality without the influence of opioid prescription dose.

Sleep and pain present a multidimensional relationship. Pain disturbs sleep and disturbed sleep aggravates pain (18,19). Thus, relieving pain could improve sleep, although, when opioids are involved, this is not uniformly the case (20,21). While some studies demonstrated that the use of opioids improved sleep quality,

onset, and terminal insomnia (22); some studies suggested that opioids might cause the inhibition of the rapid eye movement and the non-rapid eye movement phases of sleep, contributing to pain exacerbation (23). Opioids have complex effects on breathing that are particularly prominent during sleep. They reduce upper airway muscle activation, predisposing a patient to snoring and upper airway obstruction. In opioid-naive subjects, it has been observed that opioids depress hypoxic and hypercapnic ventilatory drives, leading to hypoventilation (24). With chronic opioid use, breathing periodicity becomes evident, probably by changing the balance between hypoxic and hypercapnic ventilatory drives (25). MOS-Sleep scores confirmed respiratory impairment rates were higher than those in the control population. Rates were also higher in patients who have other chronic diseases such as for painful diabetic peripheral neuropathy (26), or systemic lupus erythematosus (21). Our CNCP population presented higher scores for sleep disturbance and sleep problem indices with less quantity and adequacy of sleep than the control group without any change after opioid titration. Thus, in our sample, chronic musculoskeletal pain found mainly in the lower back, could have a higher influence on sleep pattern profiles than opioid treatments.

A number of studies demonstrated the effectiveness of using long-acting opioids to achieve adequate pain control as significantly higher than that found when using a placebo. Long-acting opioids also improved sleep quality, duration of sleep, sleep onset insomnia,

and terminal insomnia, diminishing the need for sleep medication (27). However, most opioid-treated patients were taking 1 or 2 other centrally-acting medications, such as other neurodepressive drugs, such as benzodiazepines, antidepressants, or GABA analogues as anticonvulsants that could modify sleep-related adverse events (28,29). Some studies reported that pregabalin improves sleep disturbance in patients with chronic pain syndromes; however, the use of some anticonvulsants or analgesics can contribute to an increase in daytime somnolence, in a dose-dependent manner that can affect pain perception in wakefulness (30). In our study, the use of anticonvulsants, antidepressants, and anxiolytics was not related with lower values of optimal sleep when compared with patients not under those treatments.

Sleep problems are associated with some risk factors including: elevated weight, smoking, more than 60-65 years old, male gender, or cardiovascular disorders. In our study, age, quality of life, anxiety, and depression significantly influenced sleep disturbance with worsening sleep problems indices; however, no changes were observed upon opioid titration.

Genetic variations in the OPRM1 gene have been associated with variation in opioid responses in different settings including acute post-operative pain, CNCP, and cancer-related pain (31,32). The most studied SNP in the OPRM1 gene is the non-synonymous exonic A118G (rs1799971) polymorphism that has been associated with needing increased doses of morphine to achieve pain control in cancer patients (33,34), and following surgery (35,36). However, this has not been confirmed either in the European Pharmacogenetic Opioid Study (n = 2294) (37) or, in a recent meta-analysis (38) that indicated only weak associations with increased morphine dose requirements. In regards to adverse events, the G-allele variant presented less sedation and nausea or vomiting that was especially associated to fentanyl-induced post-operative effects (31,35,39). Also, it G-allele has been associ-
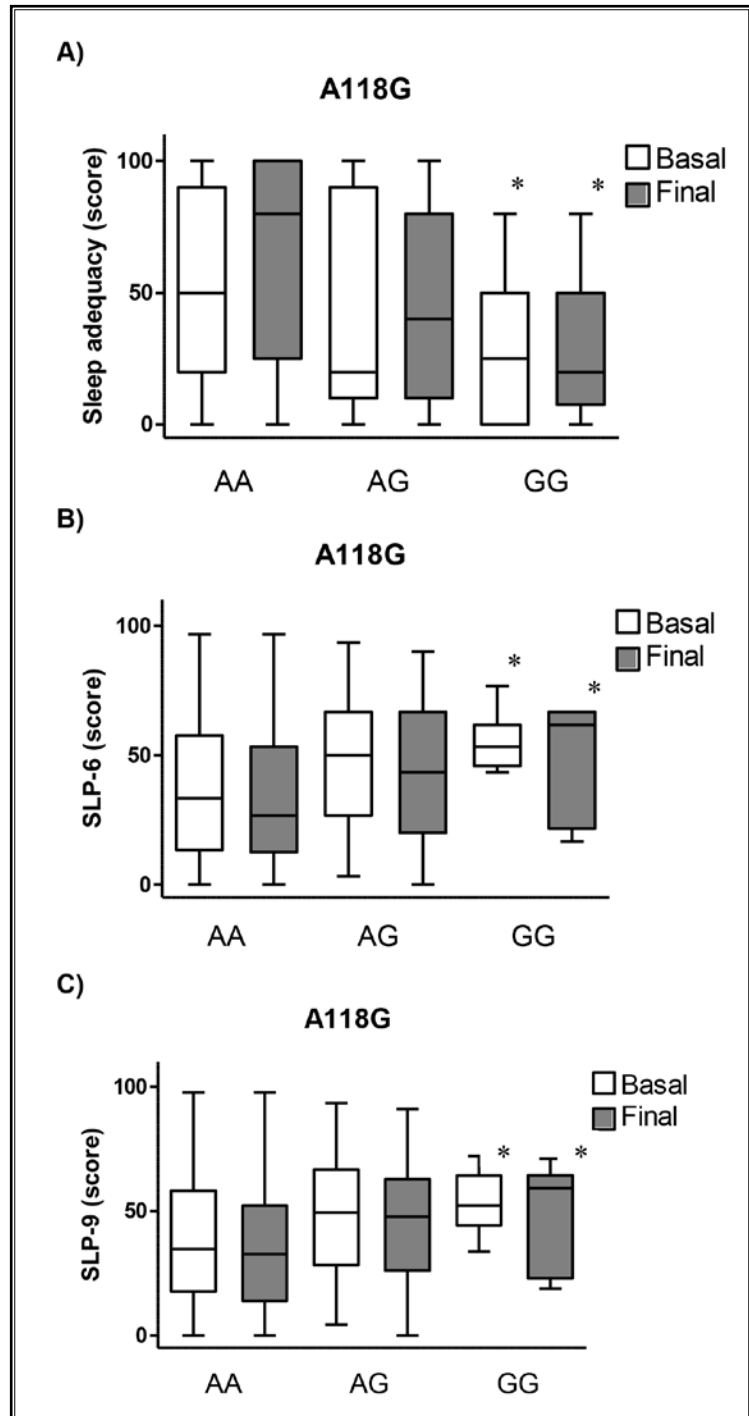

Fig. 2. *Analysis of MOS-Sleep questionnaire according to OPRM1 genotype. Values for sleep adequacy (A), SLP-6 (B) and SLP-9 (C) at basal and final visit according to genotype were compared. GG individuals presented significant lower sleep adequacy at basal and final visit (*P < 0.05) and higher values for SLP-6 and SLP-9 indexes (*P < 0.05) than AG or AA individuals.*

ated with better sleep quality among males and might influence a change in insomnia side effects in patients with opioid dependence on methadone maintenance therapy (11,40). In our population, participants with the 118-GG genotype presented significantly lower sleep adequacy, and more sleep-related problems.

Limitations

Several considerations should be taken with regards to the limitations of the present study. First, the total number of subjects studied was relatively small and this can affect the ability to find genotypic differences. Second, most participants were on other non-opioid centrally-acting medications that might have independently contributed to sleep disorders such as irregular breathing, daytime sleepiness, and vigilance, thus, it is difficult to ascribe the alterations found to opioids alone. However, regardless of the relative contribution of opioids versus other medications, CNCP patients are frequently prescribed several centrally-acting medications.

Considering the study findings that the OPRM1 118-GG genotype is associated with vulnerability to sleep problems, we discovered the influence of pain on sleep and how opioid treatment could decrease CNCP severity, leading to an improvement in quality of life being. This information could be used to implement personalized strategies in CNCP patients in order to minimize sleep problems.

Given the importance of sleep quality for the patients, it is highly relevant to include sleep quality assessments when evaluating the efficacy of treatments for CNCP, and this aspect of treatment efficacy should be given greater consideration by clinicians. Further studies with elevated patient numbers, and a control group should be performed in order to assess sleep problems in CNCP under opioid treatment population.

Acknowledgments

Supplementary Table 1. *Opioid and concomitant drug use at baseline and final visits.*

Drug	Baseline visit		Final visit		Product information MEDD		Effect on sleep
	% of patients	MEDD prescribed (mg/day)	% of patients	MEDD prescribed (mg/day)	Recommended (mg/day)	Maximum (mg/day)	
Opioids							
Fentanyl	2	62±51	22	78±42	90-360	86±63	DrowsinessVF/InsomniaF
Oxycodone	8	47±33	17	64±41	20-400	85±58	DrowsinessF/InsomniaF
Morphine	2	23±18	5	27±11	30-60	48±46	DrowsinessF/InsomniaNF
Tapetandol	1	81±34	10	92±46	40-200	95±37	DrowsinessVF/InsomniaF
Buprenorphine	4	90±47	2	70±20	30-240	109±72	DrowsinessF/InsomniaF
Hydromorphone	1	40	1	60±28	40	80	DrowsinessVF/InsomniaF
Coadyuvants							
Pregabalin	42	174±8			150-600	nd	DrowsinessVF/InsomniaF
Duloxetine	13	46±28			60	120	DrowsinessVF/InsomniaF
Gabapentin	12	1200±543			300-900	3600	DrowsinessVF/InsomniaF

MEDD: Morphine equivalent daily dose; nd: not determined; VF: very frequent (>1/10); F: frequent (from >1/100 to <1/10); NF: not frequent (from >1/1000 to <1/100).

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