Acta Pharm. **72** (2022) 529–545
https://doi.org/10.2478/acph-2022-0035

Original research paper

Therapeutic alliance impact on analgesic outcomes in a real-world clinical setting: An observational study

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Accepted March 19, 2022
Published online March 20, 2022

ABSTRACT

A good therapeutic alliance is relevant for healthcare providers exposed to patients' suffering, especially since patients and physicians may understand the painful experience differently. Our aim was to explore the impact of therapeutic alliance on analgesic outcomes in a real-world interdisciplinary pain unit (PU). A cross-sectional observational study was conducted on outpatients (n = 69) using opioids on a long-term basis for the treatment of chronic non-cancer pain, where clinical pharmacologists and pharmacists advised patients about their opioid treatment. Responses to the patient-doctor relationship questionnaire (PDRQ), sociodemographic and clinical information (pain level, quality of life and hospital use) were collected, whereas pharmacology data (analgesic prescription, adverse events, and compliance) were obtained from electronic health records. Patients were predominantly middle-aged (75 % women, 72 % retired), experiencing moderate pain (VAS 40–70 mm) on average, and under a high morphine equianalgesic dosage (95 ± 88 mg per day, mainly tapentadol or fentanyl). Patients with better PDRQ outcomes, and therefore better therapeutic alliance, showed lower pain intensity than patients with worse PDRQ outcomes (pain intensity: high scores 60 ± 47 mm and medium scores 60 ± 45 mm *vs*. low scores 80 ± 75 mm, $p < 0.01$). Along with this, pain intensity was lower when patients affirmed that, thanks to the healthcare providers, they "gained new insight", "felt better", or "felt content with their doctor's treatment". What's more, patients who affirmed "I benefit from the treatment" experienced increased pain relief (benefit 40 ± 30 *vs*. non-benefit 19 ± 26 mm, $p = 0.010$) and improved quality of life (benefit 33 ± 25 *vs*. non-benefit 18 ± 16 mm, $p = 0.031$). However, there was a percentage of patients who did not fully understand the provided information, which is something to be taken into account to improve in clinical routine. Therapeutic alliance supported by pharmacist experts on pain management can be an effective strategy to improve analgesic outcomes. Further efforts are needed to improve communication strategies for pain management. Future directions of research should include the analysis of the role of the pharmacist in poly-professional consultations as related to the advice of patients about their medication, and the mutual trust with the patients.

Keywords: therapeutic relationship, pharmacy, analgesics, opioid, global health, compliance

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INTRODUCTION

The quality of the therapeutic relationship, or alliance between the physician and the patient, could play a fundamental role in collaborative health decision-making (1). This parameter is based on accessibility, empathic understanding, and communication that promotes confidence and constructive sharing of the emotional state (2, 3). Formerly, physicians' insights were limited to the patient's pathology and did not take other aspects of the patient-doctor relationship into account. This, together with the briefness of the medical appointment, could cause misunderstandings for patients and affect the patterns of behavioural adherence (4). In fact, health providers' reactions to poor performance can affect subsequent long-term compliance (5) and turn it poorer, which can lead to a worsening of drugs' safety and the appearance of side-effects (6). This is particularly relevant in chronic medical conditions (7), such as chronic non-cancer pain (CNCP), for which high inter-individual variability in therapeutic response is reported.

Pain is the most common physical symptom in primary care, accounting for a large proportion of patients suffering from reduced quality of life and work disabilities and causing higher costs to the health care system (8). Moreover, opioids cause debilitating adverse effects (AEs) (9) which can alter the quality of life and jeopardize the vital prognosis. Their long-term use at high doses can increase opioid-related hospitalization (10) as well as raise the risk of prescription opioid use disorder (11). Tellingly, as opioid use has risen to epidemic proportions, there are more and more cases of accidental overdoses and deaths in CNCP long-term use of opioids (12).

Our aim was to explore the impact of therapeutic alliance on analgesic outcomes and analgesic compliance from CNCP ambulatory patients in a real-world interdisciplinary Pain Unit setting. This is an important priority for research, especially for patients under long-term opioid prescription.

EXPERIMENTAL

Study design

A cross-sectional observational study was conducted at the Pain Unit (PU) of the Alicante General University Hospital (Alicante, Spain) on chronic pain ambulatory patients under opioid treatment between July 2015 and October 2015. The Ethics Committee Board of the Alicante General University Hospital approved the study of free programming software in May 2014. The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki. Once the aim and confidentiality of the study were explained to the patients, informed consent was obtained, and questionnaires were self-administered. This study adheres to the STROBE guidelines.

Participants

Participation was open to all the ambulatory CNCP patients seen in the PU (n = 69). The patients were selected by a pharmacist from the researcher team in the waiting room before any medical practice was conducted. Inclusion criteria were being an adult (≥ 18 years old) under long-term analgesic use (using tramadol or any major opioid for at least six months or longer, controlled by the PU), the previous diagnosis of CNCP verified by

record review according to medical standard care, agreement to complete various questionnaires, and an adequate mental status for properly filling them out. For the purposes of this study, participants were classified using ICD-9 or ICD-10 diagnosis codes according to the etiology of the pain. Here, nearly half of patients have mixed neuropathic-nociceptive symptoms. Patients with other conditions that may or may not be pain-related (*e.g.*, restless leg syndrome, cerebrovascular disease, paraplegia), and those receiving opioids for fibromyalgia, were not included.

Procedure

An interdisciplinary team composed of two pharmacists, a nurse, an occupational therapist, and a biologist, all experts in the management of CNCP, took over the recruitment and inclusion of the subjects. A consecutive sampling method was used within the allocated recruitment timeframe for the study. Once a week for three months, the first 5–6 patients arriving in the PU waiting area were informed about the purpose of the study. Interested individuals singed the informed consent and were asked to complete a routine questionnaire on their own, in a separate room. The questionnaire consisted of both historical clinical assessment measures and the questionnaires designed for this study. Furthermore, steps were taken to establish recruitment days at times when some of the physicians were not present, thus preventing them from knowing that patients were being interviewed after their clinical consultation. The PU has six different anesthetists who are distributed weekly in a rotating schedule. In this way, all data (clinical and therapeutic alliance) were collected at a single time point.

Clinical and pharmacology outcomes

Clinical interviews were performed as a clinical routine in the PU to evaluate the physical health, effectiveness, and safety profile of drug use. Here, socio-demographical parameters (age, sex, ethnicity, marital status, family support, education level, and income) were collected. After the physician interview, in the same session, questionnaires related to doctor-patient relationship and communication were completed independently, though with the support of the research team experts on pain management led by a pharmacist.

Pain drug prescriptions were obtained from Electronic Health Records (EHRs) and grouped in non-opioid analgesics (*e.g.*, acetaminophen, NSAIDs), weak opioids (codeine, tramadol) or strong opioids (*e.g.*, fentanyl, morphine, buprenorphine, tapentadol, oxycodone, hydromorphone), and oral morphine equivalent daily dose (MEDD, mg per day) was calculated using available references (13) by a pharmacist. After that, the patient was asked about his/her adherence (compliance/non-compliance) and for confirmation that prescriptions were dispensed at the pharmacy correctly. The percentage of use of each analgesic was counted over the total sample period. As it is usual for these patients to be polymedicated (four or more drugs prescribed) (6), the use of neuromodulators (anticonvulsants such as pregabalin and gabapentin) was also registered, those being the most concomitant drugs in CNCP.

Clinical outcomes variables

Effectiveness variables. – Pain intensity and relief was recorded according to a VAS paper version consisting of a 100 mm horizontal line anchored by two extremes, from 0 (no

pain or not relief, resp.) to 100 mm (the worst pain or main relief, resp.) (14, 15). Pain (intensity or relief) was classified as mild (< 40 mm), moderate (40–70 mm) or severe (> 70 mm) (16). The quality of life of the patient was evaluated with the VAS-EuroQol scale. This scale consists of a vertical line from 0 (the worst health status) to 100 mm (the best) (17), where the patient points to their current health status and classifies it according to the previously identified pain level on the VAS scale.

Safety variables. – Patients were encouraged to report all suspected AEs due to pain medication (any noxious, unintended, or undesired effect of a drug that occurs at dosages used in humans for prophylaxis, diagnosis, or therapy) (18). All the AEs were registered during the medical visit, using the following list of the most frequently occurring issues following analgesic medication use, as acknowledged in the summary of product characteristics (19): xerostomia, constipation, dizziness, dry skin, headache, somnolence, insomnia, weight change, loss of appetite, depression, nervousness, pruritus, nausea, edema, vomiting, erectile dysfunction, loss of libido and erythema. A field was also left open in the list for free text additions. In the case that an AE was suspected to be an adverse drug reaction, the pharmacist took over the corresponding notification. Furthermore, the pharmacist classified all the AEs related to pain treatment according to the medical dictionary for regulatory activities (MedDRA, version 20.0) (20).

Hospital use and compliance. – Hospital admissions and any changes of drug prescription (as compared to their previous PU visit, whether due to pain or other reasons), were registered. In addition, patients were asked for their compliance and any reasons for stopping their treatment. Treatment adherence was evaluated due to the patient's verbal statement and reviewing EHRs, since there is a section in the patient's pharmacotherapeutic record where the health providers can check whether the patient has collected the medication from the pharmacy and on what date. Thus, subjects were classified into three groups: (*i*) compliant, (*ii*) non-compliant, and (*iii*) a mixed group: patients who claim to have complied with the treatment but mark reasons for stopping the analgesic treatment on the questionnaires. Some of these possible answers were: AEs, lack of effectiveness or others. If they accepted the treatment, possible reasons were: it seemed to be the best option, acceptance of the doctor's decision, expected benefits from the treatment or other reasons. The compliance questionnaire included items such as whether patients have accepted the treatment or not, and if so, what the reason for abandoning the prescriptions was.

Therapeutic alliance

Patient-doctor relationship questionnaire (PDRQ). – This validated questionnaire with closed questions is a brief activity consisting of thirteen questions developed to assess the patient's experience with the therapeutic aspects of the patient-doctor relationship in their primary care settings (21, 22). It is a valuable tool for monitoring the patient-doctor relationship based on communication, satisfaction with treatment, or accessibility to the doctor. Every question is answered with either the affirmative ("yes") or the negative ("no"). PDRQ has no threshold scores that correspond to a qualitative rating, and thus gives only descriptive information related to the total percentage of affirmative or negative responses. Patients answered the PDRQ questionnaire once since this was a cross-sectional study.

In order to avoid "social desirability bias", which is defined as the tendency of survey respondents to give overly positive self-descriptions (23), patients were clustered depend-

ing on their scores on the PDRQ questionnaire: low (< 60 % of positive answers), medium (61–90 % of positive answers) and high (> 91 % of positive answers). Differences in pain intensity, pain relief, quality of life, treatment compliance and number of AEs were analyzed within each of these three groups.

Understandability of prescription information. – Finally, a non-validated test was used to assess the level of comprehension of drug information provided by the health professionals (doctor, pharmacist, or nurse) involved in the study related to the analgesic prescription. This also assessed whether any family member had been under opioid treatment. It consisted of thirteen questions, where patients could answer either "yes" or "no", except for the question regarding the knowledge of what an opioid is. In that case, patients could answer "not at all", "partially" and "yes completely".

Statistical analyses

Data are presented as mean ± standard deviation (SD) when normally distributed, and as median (interquartile range) (P25-P75) for parameters with the non-parametric distribution. Categorical data were expressed by percentages. Data distribution was analyzed with Kolmogorov-Smirnov's normality test with correction of statistical significance using the Lilliefors test. It was estimated that this descriptive 3-month study would be sufficient to achieve an approximate sample of 65–75 patients due to the daily PU patient attendance rates (24). This is an approximate sample number similar to other observational studies that use qualitative questionnaires.

Comparisons of data exhibiting parametric distributions between any two given groups were conducted using the *t*-test analysis, and for analyses between three groups, an ANOVA test was carried out. Furthermore, analysis of data with non-parametric distributions was done using the U Mann-Whitney and Kruskal-Wallis tests for comparison between two and three groups, resp. Chi-square ($\chi 2$) tests were performed for categorical data.

Binary logistic regression was carried out to analyze opioid adherence, and multiple linear regression was performed according to "sequential entry" (25). Thus items (age, sex, pain intensity, pain relief, quality of life, and number of AEs, education level, PDRS and understanding of the information) that could theoretically impact the dependent variable (pain intensity) were entered in a given order based on theory, logic or practicality.

Value $p < 0.05$ was considered statistically significant. Effect size Cohen's d (*d)* was calculated, with values categorized as follows: < 0.2 "small effect", < 0.5 "medium effect", > 0.8 "large effect". For Kruskal-Wallis analyses, effect size Eta squared (η^2) was also calculated, with values categorized as < 0.04 small effect, < 0.110 medium effect and > 0.140 large effect.

All statistical analyses were carried out using free programming software**,** R program, version 3.2.4 (26).

RESULTS AND DISCUSSION

Socio-demographical and clinical variables

A total of 88 patients were pre-screened to enter the study. After the exclusion of 19 patients due to various reasons (missing data from questionnaires or main pain diagnosis

being fibromyalgia), a total of 69 patients were analyzed. All participants were referred to our PU for regular pain management mostly due to somatic pain (85 %). Non-specific low back pain was the most common type (associated with radiculopathy, spinal stenosis, or another specific spinal cause), followed by gonalgia and other musculoskeletal pain (hip pain or due to other cervical joint dysfunctions).

Table I presents all socio-demographical and clinical variables in detail. The mean age of the participants was 62 ± 15 years, 74 % female and 100 % of Caucasian ethnicity. Most of them enjoyed family support, with 74 % living with another person and 62 % being married. A third of participants had completed education at the primary level, with the rest having completed further schooling. Two-thirds were retired with incomes less than 1.000 euros per month, *i.e.*, slightly above the minimum monthly wage in Spain. Additionally, 30 % of the patients came to the emergency room and 13 % of patients were hospitalized due to their uncontrolled pain. 36 % of the patients needed to change analgesic drugs, and 25 % stopped their pain treatment due to AEs from the last PU visit.

Mean pain intensity was found moderate (VAS 60 ± 30 mm), while pain relief (VAS 30 ± 30 mm) and quality of life (VAS 29 ± 24 mm) reached mild levels. Lower pain intensity was significantly associated with higher pain relief and quality of life [R^2 adjusted = 0.324: pain intensity = 10.570 + (–0.2794) × quality of life + (–0.3520) × pain relief + (–0.342) × PDRQ]. Here, an increase in quality of life (1 point) was associated with a decrease in pain intensity (0.27 points). Similarly, an increase in pain relief (1 point) was associated with a decrease in pain intensity (0.35 points). Again, an increase in the PDRQ questionnaire score (1 point) was correlated with a decrease in pain intensity (0.34 points).

Analgesic prescription and drug side-effects

All patients were on long-term analgesics treatment, and more than half of the sample was under a neuromodulator prescription, such as pregabalin, gabapentin, or duloxetine. Most of the prescribed opioids were major opioids such as tapentadol (31 %), followed by fentanyl (21 %) and buprenorphine (12 %) and the mean MEDD was 95 ± 88 mg per day. Tramadol was prescribed to 13 % of the sample population, usually in combination with another major opioid. More details are shown in Fig. 1.

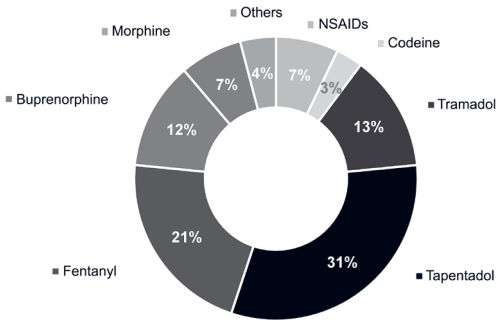

Fig. 1. Summary of NSAIDs (non-steroidal anti-inflammatory drugs) and opioids prescribed in our ambulatory chronic non-cancer pain patients.

Table I. Demographical, clinical variables, morphine equivalent daily dose and reasons to leave the opioid treatment

Total no. of participants	69
Age (year)	62 ± 15
Sex (female, %)	74
Married	43 (62)
Widowed	17 (25)
Single	4 (6)
Separated or divorced	3 (4)
NA	2 (3)
Level of education	
Primary school	22 (32)
Secondary school	9 (13)
Bachelor/intermediate associate degree	15 (22)
Superior associate degree	5 (7)
Diploma program	3 (4)
Bachelor's degree	2 (3)
Other studies	11 (16)
Occupation	
Retired	50 (72)
Unemployed	9 (13)
Active	4 (6)
Homemaker	3 (4)
NA	3 (4)
Incme	
< 1000 €	52 (75)
> 1000 €	11 (16)
NA	6 (9)
Clinical outcomes	
Pain intensity (VAS, 0–100 mm)	60 ± 30
Pain relief (VAS, 0–100 mm)	30 ± 30
Quality of life (VAS, 0–100 mm)	29 ± 24
MEDD (mg per day)	95 ± 88
Hospital use due to pain	
Emergency visit	21 (30)
Hospital admission	9 (16)
Change of medication	25 (36)
Hospital use due to other causes	
Emergency visit	11 (16)
Hospital admission	6 (9)
Change of medication	10 (14)
Treatment compliance	56 (81)
Reasons to stop treatment	
Adverse reactions	4 (25)
Lack of effectiveness	3 (19)
Other reasons	6 (38)
NA	3 (19)

MEDD – morphine equivalent daily dose, NA – no answer, VAS – visual analogue scale

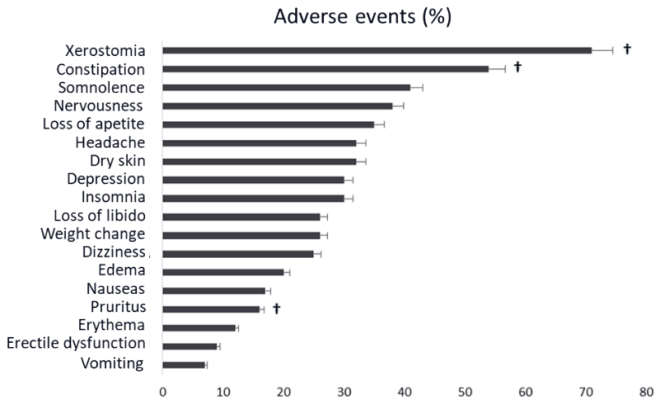

Fig. 2. Frequency of adverse events (%) (X-axis) of the ambulatory chronic non-cancer pain patients. (n = 69). Data are represented as mean ± SD (n = 69). Higher frequency of adverse events compliance *vs*. non-compliance (✝ $p < 0.05$); Fisher's exact test.

The median number of AEs was 5 (IQR [4–8]) per person. The most frequent MEDRA--defined systems affected were general (36 %), psychiatric (19 %), nervous (19 %) or gastrointestinal disorders (15 %). The most frequent AE was xerostomia (dry mouth), which was reported by 71 % of the patients, followed by constipation (54 %), somnolence (41 %), nervousness (38 %), or loss of appetite (35 %). Vomiting (7 %) and sexual dysfunction (9 %) showed the lowest prevalence. All the results concerning AEs are illustrated in Fig. 2.

Compliance with analgesic prescription

Related to the compliance, most of the patients accepted the opioid prescription (91 %) because they "expected benefits" (41 %), "thought it was the best option" (25 %), or "accepted the doctor's decision" (19 %). Patients who had previous knowledge of "what an opioid is" (34 % "partially" and 11 % "completely") showed a 15 % higher degree of analgesic compliance in contrast to patients who "did not previously know about the concept of opioid" (86 % *vs*. 71 %, p = 0.261), as can be seen in Supplementary Digital Content 1. However, no statistically significant differences were evidenced between compliance and the level of pain intensity. A binary logistic regression was carried out to analyze the influence of socio-demographical variables on analgesic drug "compliance" and "decision to accept the treatment" (both questions included in the "treatment compliance" questionnaire), without resulting in any statistically significant relations.

Therapeutic alliance

Patient-doctor relationship questionnaire. – PDRQ results showed that most of the patients (96 %) perceived that their doctor was "dedicated to helping" them and felt that they "can talk to their doctors", and thus found the doctor to be "easily accessible". Within these results, more than 90 % reported that the "doctor helps them" and thus had gained their "trust", resulting in "agreement on the nature of my medical symptoms". Furthermore, 82 % of patients stated that "thanks to my doctor, I feel better". Finally, a total of 65 % reported

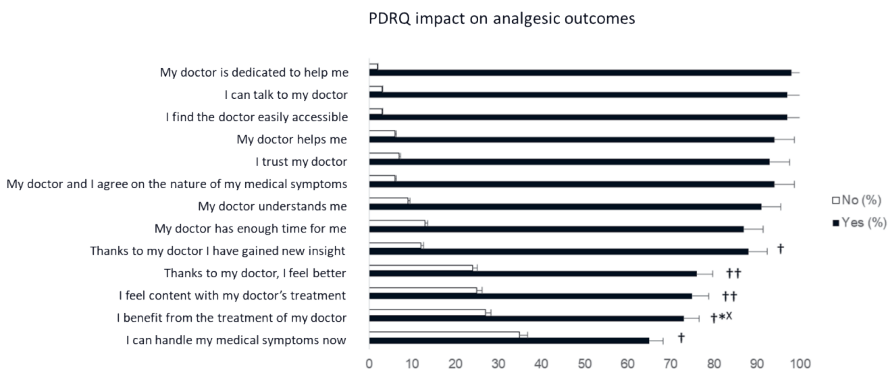

Fig. 3. Therapeutic alliance assessed by patient-doctor relationship questionnaire's (PDRQ) and analgesic outcomes impact related to pain intensity, relief and quality of life. The X-axis represents the % of "yes" and "no" answers. Data are represented as mean ± SD (n = 69). Less pain intensity ($^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$); higher pain relief ($^{*}p < 0.05$); higher quality of life ($^{X}p < 0.05$); Fisher's exact test.

that they could "handle their medical symptoms now". Fig. 3 shows the relation of PDRQ responses on clinical outcomes (pain intensity, relief and quality of life).

A total of 39 % of the PDRQ questions evidenced a statistically significant association with improved pain clinical outcomes. As we expected, patients who affirmed, "I benefit from the treatment of my doctor" reduced significantly their pain intensity by 35 % ("yes" *vs.* "no", 53 ± 30 *vs.* 81 ± 20 mm, resp., $p = 0.010$, $d = 1.079$ – large effect) and experienced both higher pain relief (52 %, 40 ± 30 *vs.* 19 ± 26 mm, $p = 0.010$, $d = 0.675$ – moderate effect) and quality of life (46 %, 33 ± 25 *vs.* 18 ± 16, $p = 0.0310$, $d = 0.638$ – moderate effect). Similarly, pain intensity was significantly lower when patients affirmed that: (*i*) "thanks to my doctor, I gained new insight" (29 %, 57 ± 29 *vs.* 80 ± 23 mm, resp., $p = 0.024$, $d = 0.574$ – moderate effect) or with a much higher significance "feel better" (29 %, 55 ± 31 *vs.* 77 ± 20 mm, resp., $p = 0.004$, $d = 0.756$ – moderate effect), (*ii*) "I feel content with my doctor's treatment" (33 %, "yes" *vs.* "no", 54 ± 30 *vs.* 80 ± 17 mm, resp., $p = 0.002$, $d = 0.826$ – large effect), where a strong significance was obtained, or (*iii*) "I can handle my medical symptoms now" (21 %, 54 ± 31 *vs.* 68 ± 28 mm, resp., $p = 0.049$, $d = 0.5$ – moderate effect). These results are illustrated in Fig. 3. Supplementary materials comprise Digital content 2 representing statically significant questions of PDRQ questionnaire with pain intensity (VAS scale, mean standard deviation), and Digital content 3, where a summary of the relation between PDRQ questionnaire and clinical variables (pain intensity, relief and quality of life) is given.

Differences between patients' clinical, safety, and compliance variables were analyzed according to the level they reported on the PDRQ questionnaire (patient-doctor relationship: low, medium or high). Patients with low PDRQ scores showed higher pain intensity (80 ± 75 mm) than patients with medium and high scores (60 ± 45 mm and 60 ± 47 mm, resp., $p < 0.01$, medium effect size $\eta^2 = 0.114$) (data not shown). On the other hand, we did not find statistically significant differences in pain relief, quality of life, treatment compliance or number of AEs depending on the level of the PDRQ questionnaire score.

Understandability of prescription information. – In this case, 76 % of patients stated that the "level of comprehension of the information was easy to understand". Up to 65 % of the

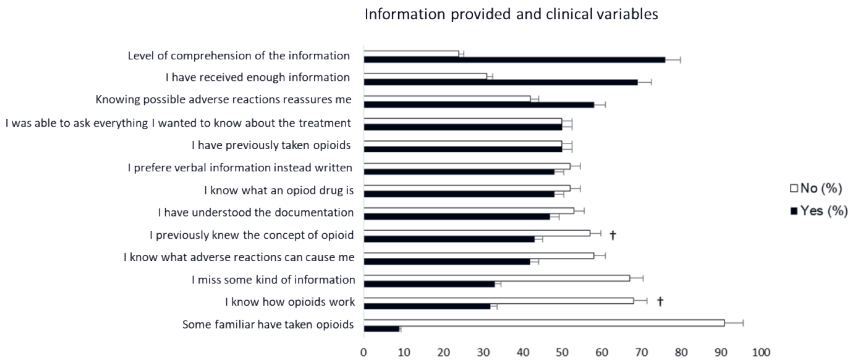

Fig. 4. Patients' comprehension of the prescription information provided, and analgesic outcomes impact related to pain intensity, relief and quality of life. Data are represented as mean ± SD (n = 69). Patients without previous use of opioids referred less pain intensity ($^{\dagger}p < 0.05$); Fisher's exact test.

patients felt that they had "received enough information", and 58 % of patients reported that "knowing possible adverse reactions reassures me". Regarding the treatment, half of the sample population stated, "I had previously taken opioids" before the current prescription and that "I was able to ask everything I wanted to know about the treatment". Furthermore, half of the patients "preferred verbal information instead of written". In fact, more than half of the population did not "understand the information in the given documents" and 30 % "were missing certain types of information". It is notable that patients that "previously knew about the concept of opioids" (43 %) or stated "I know what an opioid drug is" (32 %) reported higher mean pain intensity (21 % and 25 %, resp.) compared with the rest of the patients who did not have previous knowledge of opioids. Although a statistically significant difference was not found, probably due to the sample size, a clear tendency is observed, where a better knowledge was associated with higher pain intensity. A summary of these results is shown in Fig. 4.

Summary

Our data shows that CNCP patients with a better therapeutic alliance showed less pain intensity. The pain was significantly lower when patients affirmed that, thanks to their healthcare, they gained new insights, felt better, and felt content with or perceived benefits from the treatment. These patients reported two times higher pain relief and quality of life. Thus, certain aspects of a good therapeutic alliance could improve analgesic outcomes in "real world" CNCP patients who attend a multidisciplinary hospital PU. Here, the role of the pharmacist is thought to be crucial due to a large number of drugs co-prescribed and the nature of the AEs related to opioids and/or co-adjuvants prescribed at PU regular patients. The pharmacists allowed the prompt detection of adverse drug reactions and confirmed the adherence to treatments. Also, it is noteworthy the role they can play in other aspects of personalized medicine such as drug interactions or pharmacogenetics (27–29), as proved in previous studies of our unit. However, additional effort needs to be made to improve the comprehension of the prescription information provided. Surprisingly, patients who were asked in the interview about their knowledge of opioids and affirmed

to be knowledgeable about opioid medications had more intense pain. This aspect should be analyzed in greater depth.

Our results are promising, especially for pain management in which specific therapeutic objectives and expectations need to be shared between patients and healthcare providers (30) in order to avoid unresolved issues when prescribing medication (31). All of the therapeutic alliance parameters can contribute to increased enablement of patients to comply with prescription routines (32) and to perceive the effectiveness of the health care received (29, 30).

A strong aspect of our data is that it is derived from CNCP real-world ambulatory hospital patients, with long-term attendance at the PU, at least 6 months, and high mean opioid doses. They were mostly adult women, retired, with a basic level of education, low income, and under a multidrug analgesic treatment due to their pain intensities. This is a representative sample of our PU, where most patients are old women, as has been observed in previous studies of our unit (29, 35). Subjects showed a median of the five most typical AEs in analgesic therapy, as well as the regular rates of hospital frequentation (35). It has previously been highlighted that there is a female predominance in our CNCP population (36). Literature data strongly suggest that men and women can differ in their pain responses (37, 38), potentially due to different modulation of the endogenous opioid system and sex hormones (39). Additionally, different narratives by patients of different genders could be a factor to take into account (40). Understanding this nuanced role of gender in communicating pain could help health professionals to develop more holistic practices promoting equality in healthcare systems (41). Due to this experience, we have incorporated a gender perspective in pain research (42).

Related to the patient-doctor therapeutic alliance, more than 90 % of the sample population considered the doctor to be trying to help them and accepted their opioid treatment, and perception of the doctor's accessibility was positive in nearly all our patients sampled. Patients who felt better, felt happy with the treatment, or perceived that they could control their symptoms better, reported significantly lower pain intensity. The same relation was observed with the responses to the prompt "thanks to my doctor I feel better". As in our study, previous data associate a better patient-doctor relationship with optimal pain management (43, 44), medication adherence and improved quality of life (45, 46). In fact, a better relationship helps to raise fewer complaints about the doctor's work (47). In addition, the patient-centred care approach involves understanding the individual's experience of their illness (48), sharing power and responsibility, and developing a relationship based on care, sensitivity, and empathy. Emotions and empathy are as of yet little studied and therefore it becomes difficult to really evaluate their effectiveness (49), despite their strong importance in therapeutic alliance strategies. Positive incentives for exemplary doctor-patient relationships would help restore this essential element to healthcare practices (50).

What's more, expanded training, providing clearer guidelines, and assessment of physicians' communication skills could help to improve the comprehension of the information provided by medical professionals to their patients (51). This should be incorporated properly as a routine (52, 53), being that it is essential in healthcare centered around patient care (2, 52). Our data evidence that improvement in the provision of drug information to patients leads to a not significant 15 % higher tendency to comply with medication routines. However, there is a need to improve the understandability of the prescription information provided in the given documents, and of patients' perspectives on AEs. Health care profes-

sionals should review patients' prescriptions, especially in cases of polymedication use patterns (54), and seek to understand patients' questions to assure optimal care, particularly for the elderly population. Therefore, the prescriber is required to inform the patient about the therapeutic and collateral effects that the therapy may cause, hence trying to involve and empower patients.

Finally, and surprisingly, our most opioid-informed CNCP reported significantly higher pain intensity. Some data showed that patients engaged in discussion about opioid safety when they reported greater anxiety or worry (24). This once again demonstrates how the communication is relevant and often challenging (55). Thus, the goal of achieving good clinical practice is essentially based on prescriptive appropriateness and on accurate counselling before and during therapy (56). Such discussions require a high degree of skill.

Limitations of the study. – Firstly, this is a cross-sectional survey of a small sample of patients in one particular hospital, where part of the information was self-reported without validated testing. This could compromise external validity and binary logistic regression results. Secondly, it also should be noted that those attending tertiary care pain clinics differ from patients in primary care, as they exhibit higher levels of psychosocial dysfunction, comorbidities, and polymedication practices related to their pain prescriptions. Concomitant non-painkiller drugs could be responsible for side-effects or loss of adherence, making a more detailed analysis that takes these aspects into account necessary. Furthermore, previous pathologies not related to pain were not analyzed. For this reason, these factors could influence our findings, such as clinical variables or treatment adherence; so all these factors should be addressed in further studies. Thirdly, research was limited by the small sample size attended by different physicians and pharmacists (operating from morning to afternoon) where the influence of some social aspects, such as how family members lived together, or a detailed salary were not registered. Without analyzing these variables, the likelihood of response or performance bias cannot be quantified. Furthermore, a higher pain relief due to medication could bias the healthcare-patient communication. In this way, a lower pain intensity could improve the communication and results of the PDRQ questionnaire. Finally, the trustfulness of the questionnaire outcome is questionable and could limit the reliability of the conclusions. Along with this, the PDRQ questionnaire is constituted by closed questions and these do not include the relationship to other healthcare professionals such as pharmacists or nurses, but the physicians. This could be a limitation and the questionnaire which should be more comprehensive and include relationships to other healthcare providers as well. In contrast, one of the greatest strengths of the study is the real-world environment that provides real perceptions of CNCP patients attended by inter-professional teamwork in a real PU environment. On the other hand, the use of a larger sample and a longitudinal study rather than a cross-sectional design would improve future studies and can help to achieve more reliable data.

CONCLUSIONS

Our results suggest that in addition to the pharmacological treatment, the improvement of the relationship between patients and their healthcare providers may contribute to positive outcomes in terms of pain intensity relief and quality of life improvement in patients with CNCP and long-term opioid use. These results also suggest that a good

patient-healthcare professionals relationship may be an important factor for improving patient adherence to pain treatment and should be taken into account. More exhaustive studies are considered necessary to back up our results in other clinical settings and to assess how the information provided about prescriptions impacts clinical outcomes and attitudes, since patients with better knowledge of opioids referred to higher pain intensity. It may be hypothesized that medical treatment should be accompanied by more empathy by the healthcare staff and better information regarding treatment to be provided.

Acknowledgments. – The authors acknowledge Mrs. Andrea Flor, Fernanda Jiménez, and Alicia López (nurses of Pain Unit) for their help, M-del-Mar Inda Ph.D. Sci (pain researchers) for their support in data management and statistical analysis, and Maila Sepri for her invaluable help reviewing this article.

Supplementary materials are available upon request (supplementary material 1: percentage of compliance ("yes" or "no") according to the patients' previous knowledge of what an opioid is ("yes", "no", or "partially"); supplementary material 2: the statistically significant relationship between patient-doctor relationship questionnaire's (PDRQ) and visual analogue scale (VAS) pain intensity (mean, standard deviation); supplementary material 3: clinical outcomes [pain and quality of life--related to affirmative or negative answers of patient-doctor relationship questionnaire (PDRQ)].

Funding source. – The authors did not receive support from any organization for the submitted work.

Conflict of interest. – All authors declare there is no conflict of interests and certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Author's contribution. – Conception and design: J. Barrachina, C. Margarit, J. Muriel, and AM Peiró, administrative support: T. Zandonai, J. Muriel, P. Ballester, E. Cutillas, and AM Peiró, provision of study materials or patients: C. Margarit, E. Cutillas, and AM Peiró, collection and assembly of data: J. Barrachina, B. Andreu, T. Zandonai and AM Peiró, data analysis and interpretation: J. Barrachina, B. Andreu, T. Zandonai, P. Ballester, J. Muriel and AM Peiró, Manuscript writing: all authors, final approval of the manuscript: all authors.

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