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ORIGINAL ARTICLE

Patients' self-reported physical and psychological effects of opioid use in chronic noncancer pain—A retrospective cross-sectional analysis

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Abstract

Background: Strong opioids can have unintended effects. Clinical studies of strong opioids mainly report physical side effects, psychiatric or opioid use disorders. To date, too little attention has been paid to the psychological effects of opioids to treat patients with chronic noncancer pain (CNCP). This study aims to identify and measure (i) the nature and frequency of physical and psychological effects and (ii) the degree of physician counseling of patients with CNCP taking strong opioids.

Methods: Within a cross-sectional survey—conducted as part of a randomised controlled online intervention trial (ERONA [**E**xperiencing the **r**isk of overusing **o**pioids among patients with chronic **n**on-cancer pain in **a**mbulatory care])—300 German CNCP patients were surveyed via patient-reported outcome measures regarding on both the side effects from their use of strong opioids as well as their counselling experience.

Results: Among the patients' reported effects, the psychological outcomes of the opioids in CNCP were: feeling relaxed (84%), fatigue (76%), dizziness (57%), listlessness (37%), difficulty with mental activities (23%), dulled emotions (17%) and poor memory (17%). Ninety-two per cent of the patients reported having received

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information about opioid effects, and 46% had discussed cessation of the opioid medication with their physicians before commencing the prescription.

Conclusions: In addition to the well-known physical side effects, patients with CNCP taking strong opioids experience significant psychological effects. In view of these effects, discontinuation of opioid therapy should be discussed early to ensure their benefits do not outweigh their harm.

Significance: In this study, patients with non-cancer pain notice that opioids they have taken do not only cause physical side effects but also may have an impact on their psyche and their emotions and, thus, may also affect quality of life substantially.

Clinical trial number: DRKS00020358.

1 | INTRODUCTION

The use of opioids for non-cancer pain has a long history; but since its use was described in case reports before the 1990s (Portenoy & Foley, 1986), it has nowadays become common to prescribe opioids for chronic non-cancer pain (CNCP; Häuser et al., 2020). Although there is some low-quality evidence of long-term effectiveness of opioids for subgroups within this patient population (Nury et al., 2021; Petzke et al., 2020; Sommer et al., 2020; Welsch et al., 2020), knowledge about the long-term effects of opioids in CNCP is limited.

Understanding of side effects associated with opioid use in CNCP is largely based on industry-sponsored clinical trials. These focus on efficacy and safety; consideration of any adverse events relied on ad hoc reports from the patients and/or open questions made by the investigator (Els et al., 2017; Moore & McQuay, 2005). These randomized controlled trials (RCTs), therefore, risk underestimating the frequency of adverse events given they were not assessed systematically. In particular, side effects associated with the central nervous system, psychiatric diseases or less noticeable psychological changes may easily be overlooked in the absence of an adequate systematic survey (Furlan et al., 2006). In addition, patients with diagnosed mental disorders are also usually excluded from such studies even though depression, anxiety, post-traumatic stress disorders (PTSDs) or opioid misuse are prevalent in patients with chronic pain (Gatchel, 2004). Moreover, the observation period of these studies is frequently too short to draw conclusions about any potential effects of long-term use (Bialas et al., 2020). Many recent opioid studies have used an Enriched Enrollment Randomized Withdrawal (EERW) design which, due to pre-selection of responsive patients, may lead to an overestimation of opioid efficacy and an underestimation of harmful effects (Furlan et al., 2011). The main problem, however, is that all of these studies only report specifically surveyed or spontaneously reported side effects rather than all the effects that may occur. Recent research has shown that up to 25% of the patients with CNCP are at risk of developing behaviours indicative of opioid misuse or even abuse (Vowles et al., 2015). Clinical study reports may not capture such behavourial information leading to an alarming gap in the knowledge of psychological and/or psychiatric opioid effects.

Research studies on opioid use disorders have documented that opioids can be (mis)used by patients in psychiatric facilities for self-treating unpleasant feelings such as restlessness, fear, sadness or emotional emptiness (Garland et al., 2015). It is probable that this phenomenon also occurs in patients with CNCP (Bilal et al., 2019). A more complete knowledge of the psychological effects of strong opioids among prescribing physicians could raise awareness of the harmful effects of opioids. This could positively affect their prescribing behaviour and encourage them to initiate shared decision-making with their patients to balance the benefit versus harm of opioids.

As a first step towards a more complete understanding of the potential range of opioid (side) effects, the present study aimed to systematically collect self-reported information from patients with CNCP about the general, physical and psychological effects they experienced during their therapy with strong opioids as well as their experience of their physician's counseling regarding the benefits and harms of strong opioid use.

2 | METHODS

The ERONA (**E**xperiencing the **r**isk of overusing **o**pioids among patients with chronic **n**on-cancer pain in **a**mbulatory care) project—consisting of four prospective exploratory, RCTs with four independent study

populations—aimed to investigate experiential versus text-based educational formats (DRKS00020358). The full study protocol is published (Wegwarth et al., 2020). The data reported here are based on survey questions that were included in the RCT of patients with CNCP prior to their randomization to one of two educational interventions assessing the benefit-to-harm-ratio of strong opioids. The ethics vote was obtained from the Institutional Ethics Board of the Max Planck Institute for Human Development, Berlin (Germany) (Ethic Approval ID: pilot test A 2019-32; RCT A 2020-05).

2.1 | Study population and inclusion criteria

A total of 300 patients were recruited by an independent market research institution (IPSOS Health) from April 2020 to August 2020. They were contacted directly through their treating physicians, chronic pain support groups or pain prevention programmes. Patients were reimbursed for participation by IPSOS Health. Only patients that met the following criteria were included in the RCT: age over 18 years, pain not caused by cancer, pain lasting for at least 3 months or longer, pain score of 5 or greater on a numeric rating scale (NRS) of 0 ('no pain') to 10 ('worst pain imaginable'), a good understanding of the German language, and currently prescribed strong opioids. Strong opioids were defined as WHO level III opioids, which in Germany are subject to the German Narcotic Drugs Act (BtMG) and, therefore, require a prescription through a special BtM (narcotic drugs) prescription. Therefore the patients were asked: 'Are you currently treating your pain with an opioid for which you need a prescription according to the BtMG (e.g. morphine, Sevredol®, buprenorphine, Norspan®, Transtec®, Temgesic®, fentanyl, Durogesic®, oxycodone, Oxygesic®, Targin®, hydromorphone, Palladon®, Jurnista®, tapentadol, Palexia®)'? *[yes/no]*. Informed consent was obtained prior to the study.

2.2 | Survey questionnaire

The survey was introduced with a brief summary text, which, in addition to sharing the legal aspects, data protection and technical assistance available for the study, presented the prospective participant with an unbiased perception of the benefits and harms of opioid use.

The following patients' baseline epidemiological and clinical characteristics were recorded in the online-survey: age, gender, education, place of residence (north, south, east, west of Germany), duration of pain, number of pain locations, previous pain-related surgeries [none or once/twice or three times/more than three times], the analgesic drug therapy taken prior to starting with the strong opioid, and the non-drug based therapy that was accompanying the strong opioid therapy. The localization of pain was asked by the question 'Where exactly is the main chronic pain for which you are taking opioids located? Multiple responses are possible'.

Pain intensity was queried using a 11-point NRS from 0 (no pain) to 10 (worst pain imaginable). Pain related disability was rated according to the interference with daily activities, the ability to take part in recreational, social and family activities and the ability to work. The disability score was calculated according to von Korff (von Korff et al., 1992; 0 = no disability to 3 = maximal disability). Based on this score, incorporating pain intensity and the number of days with disability during the past 3 months, the severity of chronic pain was assessed, ranging between chronic pain grade (CPG) I (low pain intensity, little impairment) and IV (high pain-related impairment, severely limiting; von Korff et al., 1992). The history of the mental comorbidities was captured with the question 'Have you ever been diagnosed with depression, anxiety disorder, or post-traumatic stress disorder'? *[yes/no]*.

Our primary goal was to gain an insight into the physical and psychological effects of strong opioids as reported from the patients' perspective. As there are no standardized specific registers of potential side effects associated with opioid therapy, we examined textbooks, publications and guidelines for this information in order to compile a comprehensive list of such possible adverse events. Also, statements from patients concerning side effects were added. This list was then shortened by OW, CD and ES not only with regard to its clinical relevance (from our point of view, e.g. headache, sinusitis, xerostomia, infection, myoclonus are quite seldom) but also with regard to the limitations that are given by a survey from the patient's point of view (e.g. immunosuppression or respiratory disorders are difficult to assess for the patient). In addition, some variables that cover quite similar states were excluded, for example 'sedation', as it is quite similar to the item 'fatigue'. This resulted in 22 items that could be divided into three areas: (i) general, (ii) physical and (iii) psychological effects. On the basis of these items, statements were now generated that covered the content of the items as well as possible. In the pilot phase, the patients were asked to make suggestions for improvement here in particular. The items and the wording of the resulting opioid side effect list can be viewed in detail in Table S8. The order of the sentences can be seen in in the original survey list (Appendix S1). After a general introduction into the effects of opioids, patients were presented with each of the 22 effects with the sentence: 'Since taking the opioid...' and they were provided with the following possibilities to

answer: (1) 'I have observed this in myself' [Yes/No], (2) 'Friends/close acquaintances who also take opioids have told me about this'. [Yes/No], (3) 'My doctor told me about this or I read about it in information brochures' [Yes/No] and/or (4) 'None of these'. [Yes/No]. Although patients could choose one or more answers, the answer (4) excluded the other possibilities.

In addition, patients were asked about their counselling experiences associated with the opioid prescription with two questions: (1) 'Did the doctor who prescribed the opioid inform you about the opioid's benefits and harms before prescribing it'? [Yes/No] and (2) 'When the doctor prescribed the opioid to treat your pain, did you discuss with them when you should stop taking it'? [Yes/No]. The content of these questions was taken from the German interdisciplinary guideline on long-term administration of opioids in CNCP (LONTS; Häuser et al., 2020), which recommends an open discussion of the benefits and harms of the opioid therapy as well as to define a specific date to stop the opioid therapy already with the initial prescription.

The questionnaire used in this study was piloted with 13 patients presenting with CNCP. Their feedback was essential to the optimization of the survey questions.

2.3 | Statistical analysis

The survey did not permit any non-responses to the questionnaire items; thus, all surveys were complete. Categorical data were descriptively analysed by frequency distributions and percentages. For continuous data, mean and standard deviation were used where the values were normally distributed, whereas medians and IQR were used to describe data not normally distributed. The differences between subgroups were assessed using X^2-tests (for categorical variables) and correlations between opioid effects were described using the Pearson correlation coefficient. Binary logistic regression models were used to investigate whether differences between self-reported effects measures were confounded by covariates such as sociodemographic variables, pain intensity and duration, mental comorbidity or different therapeutic strategies. To adjust for multiple testing, a $p < 0.005$ was considered significant. Data were stored and analysed with IBM SPSS Statistics© (version 27).

3 | RESULTS

3.1 | Patient flow

The patient recruitment process took place via practitioners or patient groups; therefore, the absolute number of patients who were initially invited to participate and the possible reasons for their exclusion cannot be validly estimated. Altogether, the practitioners and patient groups reported having access to about 2700 patients with CNCP on opioid therapy. Assuming that between 30% and 40% of these patients were approached, between 810 and 1080 patients may have been invited to participate in our trial. In total, 362 patients started the trial online, 18 were excluded due to ineligibility (e.g. pain <3 months, treatment other than strong opioids) and 44 dropped out of the survey prematurely before randomization to an intervention arm, leaving 300 patients who were randomized to either of the two intervention arms.

3.2 | Characteristics of patients and their pain

Almost the same number of women and men were represented in the study cohort (Table 1). Most of the study participants were middle aged, and their place of residence was distributed evenly across Germany (Table 1). Their level of schooling and qualifications roughly corresponded to those of the general German population (Table 1; Bundeszentrale für Politische Bildung, 2020). Patients who reported having back pain were the largest group in the sample (33%) and 7.3% of the patients reported a mental comorbidity (already received diagnosis of depression, fear, or PTSD; Table 2). Whereas our study population was characterized by reports of severe pain, it was apparently seldom accompanied by 'typical' characteristics of pain chronification such as mental comorbidity, multiple surgeries or sites of pain in the body.

3.3 | Opioid prescription and education process

Most patients (57%) reported that a general practitioner or a general internist prescribed the strong opioid; 23%, an orthopaedic surgeon and 10%, a pain specialist (for more details, see Table 3). At the outset of the opioid therapy, 54% of patients reported that their physicians did not discuss a termination time point of the treatment with strong opioids (Table 3).

Ninety-two per cent of patients reported to have received oral or written information about the effects of strong opioids from the prescribing physician (Table 3). For each physical side effect, the percentage of patients who had heard of that effect from their physician exceeded the percentage of those who experienced this effect (Figure 1). For psychological effects, there was a mixed

TABLE 1 Demographic patient characteristics.

	N (%[a])
Gender	
Female	146 (48.7)
Age (in years)	
<20	0 (0.0)
20–39	28 (9.3)
40–59	172 (57.3)
60–79	100 (33.3)
≥80	0 (0.0)
Region of household	
North Germany	65 (21.7)
South Germany	76 (25.3)
East Germany	75 (25.0)
West Germany	84 (28.0)
Highest level of schooling	
Lower secondary education	47 (15.7)
Middle school	136 (45.3)
High school	117 (39.0)
Professional qualification	
None	27 (9.0)
Practical vocational training	189 (63.0)
Bachelor/master	70 (23.3)
Dissertation/habilitation	14 (4.7)

[a]Percentages are rounded and may not total 100%.

TABLE 2 Clinical patient characteristics

Duration of pain [months]	
Median [IQR]	20.5 [10.0; 36.0]
Min; max	4; 180
Pain intensity	
Median [IQR]	7.0 [6.0; 8.0]
Min; max	5; 9
Localization of pain [*n*; %[a]]	
Back pain	100 (33.3)
Small joints[b]	52 (17.3)
Hip	42 (14.0)
Head	41 (13.7)
Lower extremities	40 (13.3)
Shoulder	20 (6.7)
Belly/intestines	17 (5.7)
Upper extremities	9 (3.0)
Genital organs	7 (2.3)
Chest	3 (1.0)
Others[c]	10 (3.3)
Numbers of pain localization categories [*n*; %]	
One	250 (83.3)
Two	50 (16.7)
Three or more	0 (0.0)
Mental comorbidity[d] [*n*; %]	
Yes	22 (7.3)
No	278 (92.7)
Von Korff disability score [*n*; %]	
0	0 (0.0)
1	26 (8.7)
2	108 (36.0)
3	166 (55.3)
Von Korff CPG [*n*; %]	
I	0 (0.0)
II	24 (8.0)
III	26 (8.7)
IV	250 (83.3)
Number of days on which normal activities could not be done because of pain (during the last 90 days)	
Median [IQR]	45.0 [20.3; 60.0]
Min; max	0; 90
Previous surgeries for pain [*n*; %]	
No or once	219 (73.0)
Twice or three times	71 (23.7)
Three times	10 (3.3)

Abbreviation: CPG, chronic pain grade.

[a]More than 100%, as multiple answers were possible.

[b]Joints other than hip and shoulder.

[c]Other places of pain; muscles and bones in general.

[d]Already received professional diagnosis of depression, fear disorders or post-traumatic stress disorder.

situation: While for some effects, the attending physician informed patients more often about these than it was experienced (e.g. listlessness 49% vs. 37%, dulled emotions 38% vs. 17%), for other psychological effects it was the reverse (e.g. feeling relaxed 57% vs. 84%, fatigue 59% vs. 76%; details, Figure 1). General opioid effects were more often described to patients than being experienced: loss of opioid effectiveness (40% vs. 21%), the desire to increase the dose (51% vs. 19%) and even the potential of opioids causing worse pain (29% vs. 6%). Acquaintances and friends who also took opioids were rarely reported to be a source of opioid knowledge (Figure 1).

3.4 | Alternative pharmacological and non-pharmacological therapies

Seventy-nine per cent of patients reported that they took alternative analgesics before they started a strong opioid, with the vast majority (78% of all patients) reporting the use of non-steroidal anti-inflammatory drugs.

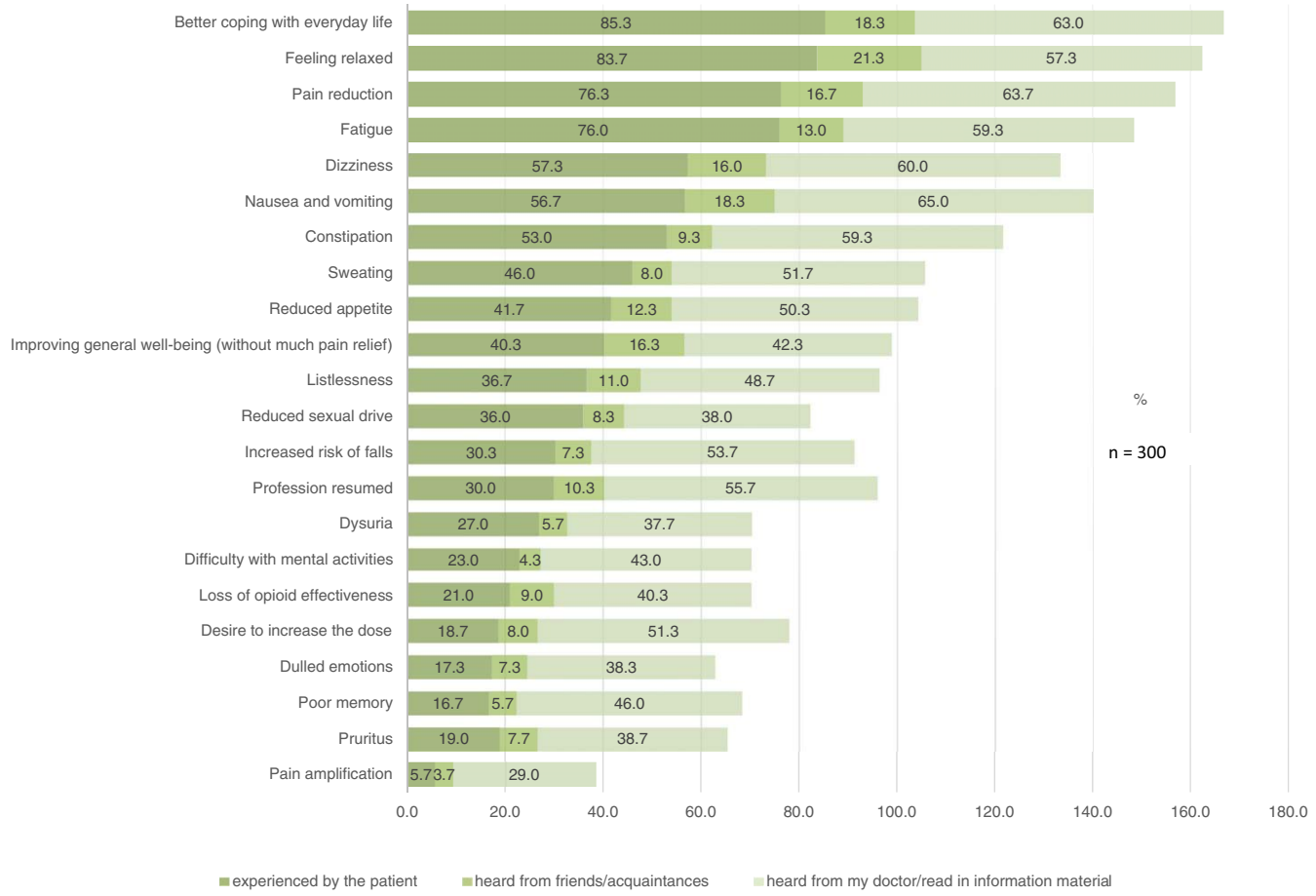

FIGURE 1 Overview of opioid (side) effects and differentiation according to source of knowledge

Weak opioids were only tried in 1 out of 4 patients (25%) before commencing a strong opioid. Co-analgesics were reported to be used as follows: muscle relaxants (15%), anti-depressants (3%) and anti-epileptic drugs (2%; Table 3). More than two thirds of the patients (69%) had tried or concurrently used non-drug based alternative approaches to relieve their pain. Half of them received or had received physical or/and manual therapy. Under a third of the patients (28%) reported practicing relaxation techniques or mindfulness. Only four patients (1.3%) received or had received psychotherapeutic treatment (Table 3).

3.5 | General effects of the opioids

Seventy-six per cent of patients reported opioid mediated pain relief. Patients with a mental comorbidity reported less pain reduction: 50% versus 78% without mental comorbidity ($p < 0.005$). Patients who reported an ability to better cope with everyday life (85%) exceeded those reporting a reduction in pain (76%). An improvement in general well-being irrespective of pain relief was experienced by 40% of the patients with CNCP. Almost a third of patients (30%) said that they had started working again after taking the opioid (depending on the von Korff CPG: II = 79%, III = 85%, IV = 24%; $p < 0.005$). A decrease in opioid effectiveness was reported by 21% of the patients and 19% of patients wanted to increase the dose; this opioid outcome correlated significantly ($r = 0.572$, $p < 0.005$, $n = 300$). An increase in pain while taking the opioid was reported by 6% of patients. The influence of demographics and clinical strata on this data is shown in Table S4.

3.6 | Physical effects of opioids

The most common physical side effect patients with CNCP experienced as a result of opioid use was dizziness (57%) and nausea/vomiting (57%) followed by constipation (53%). Other physical effects experienced included sweating (46%), reduced appetite (42%), reduced sexual drive (36%), increased risk of falls (30%), dysuria (27%) and pruritus (19%). The overall influence of demographic and clinical characteristics on the physical effects was limited and is shown in detail in Table S5. It is notable that dizziness did not necessarily increase with age (20–39 years: 54%, 40–59 years: 58%, 60–79 years: 57%; $p > 0.05$) while the fear of falling did, although this was

TABLE 3 Characteristics of opioid prescribing and additional therapies

Prescriber of the strong opioid [*n*; %[a]]	
General practitioner	119 (39.7)
Orthopaedist	68 (22.7)
General internist	53 (17.7)
Pain specialist	30 (10.0)
Rheumatologist	27 (9.0)
Others	3 (1.0)
Education about opioids before prescribing [*n*; %]	
Yes	277 (92.3)
Discontinuation time of opioid defined prior to prescription [*n*; %]	
Yes	139 (46.3)
Other analgesic drug therapies before strong opioid [*n*; %]	
Yes	236 (78.7)
Analgesic medication groups before strong opioid [*n*; %[b]]	
Non-opioids/NSAIDS	234 (78.0)
WHO II opioids	74 (24.7)
Muscle relaxants	44 (14.7)
Anti-depressants	10 (3.3)
Anti-epileptic drugs	7 (2.3)
Others	1 (0.3)
Other analgesic non-drug therapies parallel to opioid therapy [*n*; %]	
Yes	208 (69.3)
Non-drug therapies parallel to opioid therapy [*n*; %[b]]	
Physical therapy/manual therapy/occupational therapy	151 (50.3)
Massage/baths/cold/warm therapy	95 (31.7)
Relaxation procedures[c]	84 (28.0)
Injections with local anaesthetics	33 (11.0)
Acupuncture	32 (10.7)
Mindfulness training	12 (4.0)
Transcutaneous electrical nerve stimulation	5 (1.7)
Psychotherapy	4 (1.3)

Abbreviation: NSAID, non-steroidal anti-inflammatory drug.

[a]Percentages are rounded and may not total 100%.

[b]More than 100%, as multiple answers were possible.

[c]For examplem Progressive Muscle Relaxation according to Jacobsen, autogenic training, yoga, hypnosis, biofeedback.

not statistically significant (20–39 years: 25%, 40–59 years: 27%, 60–79 years: 37%; $p > 0.05$). Increased disability was associated with a higher rate of the following effects: dizziness (von Korff disability score 1: 19%, 2: 45%, 3: 71%, $p < 0.005$), nausea/vomiting (disability score 1: 42%, 2: 46%, 3: 66%, $p < 0.005$) and constipation (disability score 1: 26%, 2: 45%, 3: 62%, $p < 0.005$).

3.7 | Psychological effects of opioids

Eighty-four per cent of patients reported feeling relaxed after taking the opioid. Fatigue was reported by 76%. Further psychological effects patients reported included the following: listlessness (37%), difficulty with mental activities (23%), dulled emotions (17%) and poor memory (17%). Demographic variables (e.g. age, gender, education) did not have any influence on the psychological effects reported (Table S6). The extent of psychological effects correlated with the duration of the pain and also on self-reported pain intensity and disability (Table S6). Patients with a higher pain intensity (>7 on the NRS scale) reported fatigue more often than those with lower pain intensity (86% vs. 71%; $p < 0.005$). And the higher the disability grade, the more common were the following side effects: fatigue (disability score 1: 54%, 2: 67%, 3: 68%, $p < 0.005$), difficulty with mental activities (disability score 1: 4%, 2: 17%, 3: 30%, $p < 0.005$), dulled emotions (disability score 1: 4%, 2: 9%, 3: 25%, $p < 0.005$) and poor memory (disability score 1: 8%, 2: 8%, 3: 24%, $p < 0.005$). Patients with and without mental comorbidity did not differ in their reported frequency of psychological effects.

The entire range of patient with CNCP self-reported general, physical and psychological opioid side effects is shown in Figure 1, which also indicates the patient source of information regarding that side effect, that is, personally experienced, heard from their physician/read in the doctors' patient information or heard from friends/acquaintances.

3.8 | Covariate analysis

Logistic binary regression analysis showed that those patients with CNCP on strong opioids but presenting with no mental comorbidities had a fivefold higher probability of coping better with everyday life (OR: 5.1, 95%-CI 1.4–18.5; $p = 0.012$; Table S7). Gender, professional qualifications, duration of pain, pain intensity, psychotherapy or mindfulness training did not increase the probability of coping better with everyday life since taking the opioid (details are presented in Table S7).

4 | DISCUSSION AND CONCLUSIONS

In this study, we have surveyed patients with CNCP prescribed opioids for chronic pain participating in the ERONA study with a comprehensive register of opioid side effects reported here. Although randomized placebo-controlled studies are required to generate exact data on

the frequency of effects and side effects of opioid medicines, the data presented here do raise awareness of the fact that the opioid mode of action in CNCP is not based solely on pain relief as more patients indicate they cope better with everyday life (84%) than they experience pain relief (76%). Two fifths (40%) of the patients even state that their improvement in general well-being is not simply due to pain relief. Thus, psychological effects of opioids in CNCP also need to be carefully assessed. This topic has been approached cautiously in this study—the data on the psychological effects of opioids are more qualitative in nature, and, consequently generate more questions than answers.

We have tried to develop items that cover the effects of strong opioids on the human psyche (Table S6; Figure 1). In doing this, we accept at this early stage of investigating psychological side effects of opioids that the depiction of the same potential side effect may influence response rates, depending on positive or negative wording. If the sedating opioid effect is described positively as 'feeling relaxed' four of five patients (84%) agree, but if it is referred to more negatively as 'dulled emotions' only 17% of the patients select this description. This example illustrates how difficult it is to establish measures that reliably capture psychological effects in patients with CNCP. This raises also the question whether a psychological effect of opioids is indeed beneficial or harmful. For example, although a relaxing opioid effect is not negative per se, experiencing such a (desirable) effect may increase the urge to use the medication to regulate emotions and stress, thus amplifying the risk of misuse. Sometimes it will only be possible for a professional observer, for example, a psychological diagnostician, to distinguish between these. In the context of this study, it is not possible to differentiate whether negative emotional states are the result of the opioid therapy or are independent of it. But since, according to Ballantyne et al. (2019), a negative self-reinforcing cycle of negative emotional states and opioid reward can occur in this context, it is not necessarily expedient to differentiate between cause and effect in this instance; however, it is important for the practitioner to be attentive as this vicious circle may lead to opioid dependence or even opioid use disorder (Ballantyne et al., 2019).

A possible neuropsychological side effect of opioids is cognitive impairment. 'Difficulty with mental activities' and 'poor memory' are described by 23% and 17% of the patients of this survey, respectively. The correlation between chronic opioid use and cognition is still inconsistent in the literature despite a large body of research; whereas some reviewers describe minimal or no significant impairment in cognitive functioning (Akhurst et al., 2021; Ersek et al., 2004), others found reduced attention, vigilance, working memory and psychomotor speed (Allegri et al., 2019; Jamison & Edwards, 2013) depending on the characteristics of the opioid (e.g. the chemical structure, formulation, dosing, treatment phase: beginning or steady state, comedication of anti-depressants/anti-epileptic drugs) or the patient (e.g. age, previous damage to the brain; Jamison & Edwards, 2013; Strassels, 2008). Regardless of the study situation, it is important to identify those patients who suffer some form of cognitive impairment associated with opioid use. Pask et al. suggest a brief screening tool to assess attention, language, orientation, psychomotor function, verbal working and delayed episodic memory—especially in older adults using opioids (Pask et al., 2020). Such neuropsychological monitoring could be an important future obligation in the long-term prescription of opioids for CNCP.

Considering physical effects, the frequencies reported here are higher than in the literature. 'Dizziness' was reported to be experienced in 57% of this patient cohort, whereas estimates emerging from meta-analyses and the scientific literature suggest a range of 8% to 33% (Furlan et al., 2006; Moore & McQuay, 2005; Nury et al., 2021). This pattern was also observed for 'nausea/vomiting' (57% vs. 15%–21%), 'pruritus' (19% vs. 4%–13%) 'constipation' (53% vs. 15%–27%; Furlan et al., 2006; Moore & McQuay, 2005; Nury et al., 2021). The main reason for the high physical side effect rates in this study could be our direct enquiry about these effects, whereas the side effect data from clinical studies often arise as spontaneous ad hoc reports (unless the primary study outcome parameter included the side effect). In addition, whereas RCTs take a snapshot during a certain observation period, this investigation asked whether the effect occurred over the entire span of taking the strong opioid. Thus, long-term side effect rates may be underestimated in RCTs. Open-label, follow-up phases of clinical studies or studies with EERW (enriched enrolment with randomized withdrawal) design may also lead to an underestimation of side effects because patients who have discontinued treatment due to physical effects are no longer included in the group of long-term users.

Promisingly, the percentage of patients indicating that they had received information about opioids and their effects from their prescribing physician in this study was very high and more than 90%. We did not find comparable data in the literature. However, it should be noted that we did not directly examine the nature and quality of the information provided by the doctor. Importantly, just under half of the physicians in this investigation discussed the duration of opioid therapy, which is key to a shared and informed decision process with patients. Here, too, we have not yet found any published comparative data. But, shared decision-making can be challenging in chronic pain patients, requiring high quality communication and long-term empowerment (Spies et al., 2006). To support this process, written patient information on opioids for CNCP is necessary, for example, in Germany provided by the German Medical Association (AWMF, 2021; Bundesärztekammer, 2021).

The study presented here was performed as an online survey to a cohort of patients prescribed with opoids. This certainly limits the representativeness of the patient sample. As the patients were relatively young, no gender predominated, the pain scores were high and chronification parameters were rare, these factors may modulate the relative frequencies of the listed side effects, but not necessarily their qualitative presence, especially of the psychological side effects. But a psychometric validation of an opioid side effect questionnaire should certainly be carried out on a more representative collective.

The undefined period that opioids had actually been taken and the lack of differentiation between opioid preparations is a major shortcoming of this study. Especially if the patients are on low-dose opioids, well below nationally recommended maximum doses, or on high doses with a greater likelihood of unwanted side effects, this will probably also affect the occurrence of psychological side effects. Future studies should address how opioid doses contribute to the perception of psychological side effects: for example, if the opioid sedation ranges from 'feeling relaxed' at low doses to 'dulled emotions' at higher doses or if the psychological effects of opioids are perceived as more beneficial at higher doses to manage the negative emotional states and opioid dependence becomes more entrenched.

Another important shortcoming of the current study is that it lacks a control group not taking opioids. We tried to compensate for this by explicitly asking patients about the *effects of the opioid*. However, in this setting it is not possible to distinguish—especially with regard to the psychological side effects—whether the side effects described are also influenced by other parameters such as the chronic pain disorder itself or, if present, other centrally active drugs such as anti-depressants or anti-epileptic drugs.

Another limitation is that it is not possible to distinguish whether the effects are related or unrelated. For example, pain relief may lead to relaxation, or relaxation may lead to a decrease in the level of pain or they may even be interdependent. A prospective and long-term study design would be necessary to shed light on these important potential interactions. To be informative, such future studies on psychological side effects of opioids in CNCP should compare information provided by prescribed specific opioid preparations and doses to ascertain any dependencies.

The low prevalence of psychiatric comorbidities is another aspect to be viewed critically. The way in which we enquired about this certainly leads to a high degree of diagnostic confidence in the patients with this diagnosis, but not necessarily in those patients not diagnosed with psychiatric comorbidities and thus there may be a significant underdiagnosis in this category of respondents.

In summary, we need a realistic and differentiated profile of positive and negative effects of long-term opioid use, to adequately educate patients about potential physical and psychological effects of treatment with strong opioids and to lay out the foundation for a shared decision-making process about the desired balance between the benefits and harms among patients with CNCP and their physicians in line with current guideline recommendations.

CONFLICT OF INTEREST

See ICMJE form for Conflicts of Interests declared by CS. All other authors declare no competing interests.

AUTHOR CONTRIBUTIONS

OW conceived the project and was involved in preparing the manuscript. ES and NDB were involved in planning the study. ES analysed the data and drafted this manuscript. OW, CSp, and JJM sourced the funding for the project. CSp, JJM and RH supervised the project. FP, CD, JJM, NDB, MS, CS and OW reviewed and edited the manuscript. CD sensitized ES to the psychological effects of opioids in daily clinical work with chronic pain patients. All authors read and approved the final version of the manuscript.

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REFERENCES

Akhurst, J., Lovell, M., Peacock, A., & Bruno, R. (2021). A systematic review and meta-analysis of cognitive performance among people with chronic use of opioids for chronic non-cancer pain. *Pain Medicine*, *22*(4), 979–993. https://doi.org/10.1093/pm/pnab005

Allegri, N., Mennuni, S., Rulli, E., Vanacore, N., Corli, O., Floriani, I., De Simone, I., Allegri, M., Govoni, S., Vecchi, T., Sandrini, G., Liccione, D., & Biagioli, E. (2018). Systematic review and meta-analysis on neuropsychological effects of long-term use of opioids in patients with chronic noncancer pain. *Pain Practice*, *19*(3), 328–343. https://doi.org/10.1111/papr.12741

AWMF. (2021). *AWMF-Register Nr. 145/003. Patientenversion der wissenschaftlichen Leitlinie "LONTS" Langzeitanwendung von Opioiden bei chronischen Nicht Tumor-bedingten Schmerzen (Patient version of the scientific guideline "LONTS" Long-term use of opioids in chronic non-cancer pain)*. Retrieved May 3,

2021, from https://www.awmf.org/uploads/tx_szleitlinien/145-003p1_S3_LONTS_2020-10.pdf

Ballantyne, J. C., Sullivan, M. D., & Koob, G. F. (2019). Refractory dependence on opioid analgesics. *Pain*, *160*, 2655–2660. https://doi.org/10.1097/j.pain.0000000000001680

Bialas, P., Maier, C., Klose, P., & Häuser, W. (2020). Efficacy and harms of long-term opioid therapy in chronic non-cancer pain: Systematic review and metaanalysis of open-label extensions trials with a study duration ≥26 weeks. *European Journal of Pain*, *24*, 265–278. https://doi.org/10.1002/ejp.1496

Bilal, M., Chatila, A., Siddiqui, M. T., Al-Hanayneh, M., Shah, A. R., Desai, M., Wadhwa, V., Parupudi, S., Casey, B. W., Krishnan, K., & Hernandez-Barco, Y. G. (2019). Rising prevalence of opioid use disorder and predictors for opioid use disorder among hospitalized patients with chronic pancreatitis. *Pancreas*, *48*(10), 1386–1392. https://doi.org/10.1097/MPA.0000000000001430

Bundesärztekammer (BÄK). (2021). *Patienteninformation: Opioide bei chronischen Schmerzen (Patient information: Opioids for chronic pain)*. Retrieved May 3, 2021, from https://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/pdf-Ordner/Patienteninformationen/opiode-bei-chronischen-Schmerzen.pdf

Bundeszentrale für Politische Bildung (BPB). (2020). *Bildungsstand der Bevölkerung (Educational level of the population in Germany)*. Retrieved October 20, 2020, from https://www.bpb.de/nachschlagen/zahlen-und-fakten/soziale-situation-in-deutschland/61656/bildungsstand

Els, C., Jackson, T. D., Kunyk, D., Lappi, V. G., Sonnenberg, B., Hagtvedt, R., Sharma, S., Kolahdooz, F., & Straube, S. (2017). Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: An overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews*, *10*(10), CD012509. https://doi.org/10.1002/14651858.CD012509.pub2

Ersek, M., Cherrier, M. M., Overman, S. S., & Irving, G. A. (2004). The cognitive effects of opioids. *Pain Management Nursing*, *5*(2), 75–93. https://doi.org/10.1016/j.pmn.2003.11.002

Furlan, A., Chaparro, L. E., Irvin, E., & Mailis-Gagnon, A. (2011). A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Research and Management*, *16*(5), 337–351. https://doi.org/10.1155/2011/465281

Furlan, A. D., Sandoval, J. A., Mailis-Gagnon, A., & Tunks, E. (2006). Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. *Canadian Medical Association Journal*, *174*(11), 1589–1594. https://doi.org/10.1503/cmaj.051528

Garland, E. L., Hanley, A. W., Thomas, E. A., Knoll, P., & Ferraro, J. (2015). Low dispositional mindfulness predicts self-medication of negative emotion with prescription opioids. *Journal of Addiction Medicine*, *9*(1), 61–67. https://doi.org/10.1097/ADM.0000000000000090

Gatchel, R. J. (2004). Comorbidity of chronic pain and mental health disorders: The biopsychosocial perspective. *American Psychologist*, *59*(8), 795–805. https://doi.org/10.1037/0003-066X.59.8.795

Häuser, W., Bock, F., Hüppe, M., Nothacker, M., Norda, H., Radbruch, L., Schiltenwolf, M., Schuler, M., Tölle, T., Viniol, A., & Petzke, F. (2020). Koautoren für die Konsensusgruppe der 2. Aktualisierung der S3-Leitlinie LONTS. Empfehlungen der zweiten Aktualisierung der Leitlinie LONTS. Langzeit-anwendung von Opioiden bei chronischen nicht-tumorbedingten Schmerzen. *Der Schmerz*, *34*(8), 204–244. https://doi.org/10.1007/s00482-020-00472-y

Jamison, R. N., & Edwards, R. R. (2013). Risk factor assessment for problematic use of opioids for chronic pain. *Clin Neuropsychol*, *27*(1), 60–80. https://doi.org/10.1080/13854046.2012.715204.

Moore, R. A., & McQuay, H. J. (2005). Prevalence of opioid adverse events in chronic non-malignant pain: Systematic review of randomised trials of oral opioids. *Arthritis Research & Therapy*, *7*, R1046–R1051. https://doi.org/10.1186/ar1782

Nury, E., Schmucker, C., Nagavci, B. L., Motschall, E., Nitschke, K., Schulte, E., Wegwarth, O., & Meerpohl, J. J. (2021). Efficacy and safety of strong opioids for chronic non-cancer pain and chronic low back pain: a systematic review and meta-analyses. *Pain*. Epub ahead of print. https://doi.org/10.1097/j.pain.0000000000002423

Pask, S., Dell'Olio, M., Murtagh, F. E. M., & Boland, J. W. (2020). The effects of opioids on cognition in older adults with cancer and chronic noncancer pain: A systematic review. *Journal of Pain and Symptom Management*, *59*(4), 871–893.e1. https://doi.org/10.1016/j.jpainsymman.2019.10.022

Petzke, F., Welsch, P., Klose, P., Sommer, C., & Häuser, W. (2020). Opioids for chronic low back pain. An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least four weeks double-blind duration. *European Journal of Pain*, *24*(3), 497–517. https://doi.org/10.1002/ejp.1519

Portenoy, R. K., & Foley, K. M. (1986). Chronic use of opioid analgesics in non-malignant pain: Report of 38 cases. *Pain*, *25*(2), 171–186. https://doi.org/10.1016/0304-3959(86)90091-6

Sommer, C., Klose, P., Welsch, P., Petzke, F., & Häuser, W. (2020). Opioids for chronic non-cancer neuropathic pain. An updated systematic review and metaanalysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least four weeks duration. *European Journal of Pain*, *24*(1), 3–18. https://doi.org/10.1002/ejp.1494

Spies, C. D., Schulz, C. M., Weiss-Gerlach, E., Neuner, B., Neumann, T., von Dossow, V., Schenk, M., Wernecke, K. D., & Elwyn, G. (2006). Preferences for shared decision making in chronic pain patients compared with patients during a premedication visit. *Acta Anaesthesiologica Scandinavica*, *50*(8), 1019-1026. https://doi.org/10.1111/j.1399-6576.2006.01097

Strassels, S. A. Cognitive effects of opioids. *Current Pain and Headache Reports*, *12*(1), 32–36. https://doi.org/10.1007/s11916-008-0007-4

von Korff, M., Ormel, J., Keefe, F. J., & Dworkin, S. F. (1992). Grading the severity of chronic pain. *Pain*, *50*(2), 133–149. https://doi.org/10.1016/0304-3959(92)90154-4

Vowles, K. E., McEntee, M. L., Julnes, P. S., Frohe, T., Ney, J. P., & van der Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*, *156*(4), 569–576. https://doi.org/10.1097/01.j.pain.0000460357.01998.f1

Wegwarth, O., Spies, C., Schulte, E., Meerpohl, J. J., Schmucker, C., Nury, E., Brockmann, D., Donner-Banzhoff, N., Wind, S., Goebel, E., Ludwig, W. D., & Hertwig, R. (2020). Experiencing the risk of overutilising opioids among patients with chronic non-cancer pain in ambulatory care (ERONA): The protocol of an exploratory, randomised controlled trial. *British Medical Journal Open*, *10*(9), e037642. https://doi.org/10.1136/bmjopen-2020-037642

Welsch, P., Klose, P., Petzke, F., & Häuser, W. (2020). Opioids for chronic osteoarthritis pain. An updated systematic review and metaanalysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least four weeks double-blind duration. *European Journal of Pain*, *24*(4), 685-703. https://doi.org/10.1002/ejp.1522

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