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Prevalence and Factors Associated with Opioid Prescription in Swiss Chronic Hemodialysis Patients

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Abstract: Pain is a common symptom in patients on chronic hemodialysis (HD) but the prevalence of opioid prescriptions in this population has been poorly studied outside the United States. This study assesses the prevalence of opioid prescription in two Swiss dialysis centers. Prescriptions and clinical characteristics were retrospectively retrieved from the medical records of patients on HD for at least six months, treated at Lausanne University Hospital (academic center, AC), and the private center Clinique Cecil (PC) for the study. A total of 117 patients were included; 29.1% received at least one opioid prescription during the study period. Significantly more patients received an opioid prescription in the AC (39.1%) than in the PC (14.6%, $p = 0.004$). Univariate logistic regression analysis showed that center (Odds Ratio (OR) 3.76; Confidence Interval (CI) 1.48–9.6; $p = 0.006$), neuropathic pain (OR 2.99; CI 1.28–6.98; $p = 0.011$), benzodiazepine prescription (OR 2.72; CI 1.14–6.46; $p = 0.024$), polyneuropathy (OR 2.71; CI 1.14–6.46; $p = 0.024$) and amputation (OR 4.23; CI 1.1–16.1; $p = 0.034$) were associated with opioid prescription. The center was the only independent predictive factor in the multivariate analysis. Our results show that opioids are regularly prescribed to Swiss dialysis patients, although important differences exist between centers. The latter finding might suggest that opioid prescribing is more related to the prescriber than to the patient's condition, but larger-scale studies are necessary to confirm this.

Keywords: end-stage kidney disease; hemodialysis; pain; opioids

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1. Introduction

Hemodialysis (HD) is the most frequently applied treatment for patients suffering from end-stage kidney disease (ESKD). Hemodialysis is lifesaving but can be complicated by a number of undesirable effects, such as pain [1–5]. In fact, pain is a commonly reported symptom in ESKD patients, with a prevalence of around 50% of patients on chronic HD [3]. Pain in HD patients has multiple causes and may be difficult to control with conventional pain treatment. such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen [5–8]. In addition, NSAIDs are generally not recommended in advanced chronic kidney disease (CKD), given their associated risks of gastric ulcers and bleeding, making them particularly unsuitable in this population that receives systemic anticoagulation on a regular basis. Moreover, in patients with residual renal function, NSAIDs favor water- and salt-retention and the loss of residual diuresis [9]. Therefore, the next step of the World Health Organization (WHO) analgesic ladder is often the introduction of opioids [7]. However, kidney failure changes the pharmacokinetics of some opioids and/or their metabolites, thus increasing the risk of accumulation [10,11]. On the other hand,

hemodialysis partly eliminates some opioids, which can result in a reduced antalgic effect during and after the dialysis session, or even withdrawal symptoms [10–13]. It is, therefore, recommended to use opioids with caution in HD patients. Conversely, insufficient treatment of pain has often been reported in the HD population [2,5,6,14,15].

Unfortunately, there are currently no guidelines on when and how to prescribe opioids safely in HD patients [16,17]. Although the general prevalence and outcomes of opioid prescription have been widely reported in CKD patients, data for patients on HD are limited and are largely restricted to US dialysis centers [18,19]. In addition, factors explaining differences in prescription patterns between centers have been poorly studied.

The aims of this study were, therefore, to (1) assess the prevalence of opioid prescription in HD patients from a European region, and (2) to compare prescription patterns between an academic and a private dialysis center in Switzerland.

2. Materials and Methods

2.1. Study Design and Participants

We performed an observational, retrospective study at the Lausanne University Hospital (academic center, AC) and the private dialysis center, Clinique Cecil (private center, PC), between September 2017 and September 2018. Clinique Cecil is located in the same city, not far from Lausanne University Hospital (distance between the two centers: 2.5 km).

Patients on HD for at least six months, and who were treated at AC or PC during the complete study period, were included in the cohort after obtaining their written informed consent. This study was approved by the local ethical committee and conducted according to the principles of the Declaration of Helsinki.

2.2. Data Collection and Analysis

Prescription records and clinical characteristics were retrospectively retrieved from the computed medical records. Handwritten prescriptions of opioids were also recorded. According to Swiss law (article 47 of "l'Ordonnance sur le Contrôle des Stupéfiants (OCStup)), opioids must be prescribed on a specific form in a so-called "carnet à souches" that is delivered by the health care authorities. A copy of the handwritten form must be kept in the carnet à souche for each patient. In our study, these copies were retrieved in both centers. Hereafter, we analyzed overall opioid prescriptions and compared the prescription patterns in the AC and PC. We differentiated between chronic prescription and short-term prescription, as defined in the literature [20]. Chronic prescription was defined as $\geq$90 days on opioids within a one-year timeframe, whereas short-term prescription corresponded to 1 to 89 days. We also compared the different types of opioid molecules prescribed. In multivariable analysis, we assessed the associations between different clinical variables and opioid prescription.

2.3. Statistical Analysis

Data were checked for normality using the Shapiro–Wilk test, expressed as mean $\pm$ standard deviation or median (interquartile range), as appropriate. Variables that were not normally distributed were log-transformed.

Qualitative variables were expressed as a number and relative frequencies. Baseline variables were compared between opioid and non-opioid users and between the two centers, using the chi-squared test for categorical and Student's *t*-test for normally distributed continuous variables.

Associations between predefined clinical variables and opioid use were first assessed in univariate regression analysis. It is of note that opioid use included both short- and long-term prescriptions, as the numbers were too small to analyze short-term and long-term use separately.

In a second step, factors significantly associated with opioid use in univariate analysis were introduced in the multivariate regression analysis. Analyses were performed with

STATA 15 (StataCorp LLC, College Station, TX, USA). A *p*-value of <0.05 was considered to be statistically significant.

3. Results

3.1. Baseline Demographics

At screening, 136 patients fulfilled the inclusion criteria. A total of 117 respondents accepted the invitation to participate, signed informed consent forms, and were included in the analyses. The baseline characteristics of these 117 patients are shown in Table 1. The mean age, and in particular the age group of 65 years and above was relatively larger in the PC (p = 0.003) group. The majority of patients were male (59%) and more than 75% were of European descent. Thirty-eight percent of patients had diabetes and 26% suffered from polyneuropathy. The main causes of pain reported in the patients' files were osteoarticular pain (42.7%), followed by neuropathic pain (29.9%). Regarding treatment, benzodiazepines and antidepressants were significantly more frequently prescribed at the AC. Except for cancer and amputation (both more frequently encountered at the AC), there were no statistically significant differences in comorbidities and types of pain between the two centers.

Table 1. The baseline characteristics of patients included in the study.

Characteristics	All (n = 117)	Academic Center (n = 69)	Private Center (n = 48)	p-Value
Age (mean ± SD)	63.3 ± 14.8 years	60.1 ± 15 years	68.5 ± 13 years	0.02
Minimum number of physicians in charge		11	2	
Age group years				
20–44	14 (12%)	11 (15.9%)	3 (6.3%)	0.112
45–64	44 (37.6%)	31 (44.9%)	13 (27.1%)	0.05
65+	59 (50.4%)	27 (39.1%)	32 (66.7%)	0.003
Female	47 (40.2%)	23 (33.3%)	24 (50%)	0.07
Male	70 (59.8%)	46 (66.7%)	24 (50%)	0.07
Ethnicity				
European	93 (79.5%)	51 (73.9%)	42 (87.5%)	0.073
Asian	11 (9.4%)	8 (11.6%)	3 (6.3%)	0.33
African	10 (8.6%)	7 (10.1%)	3 (6.3%)	0.459
Other	3 (2.6%)	3 (4.4%)	0 (0%)	0.143
Dialysis duration years (mean ± SD)	4.9 ± 5.5 years	4.72 ± 5.02 years	5.16 ± 6.18 years	
Dialysis duration > 5 years	42 (35.9%)	26 (37.7%)	16 (33.3%)	0.630
Fistula	94 (80.34%)	57 (82.6%)	37 (77.1%)	0.459
Tobacco history	51 (43.6%)	34 (49.3%)	17 (35.4%)	0.137
Alcohol history	17 (14.5%)	12 (17.4%)	5 (10.4%)	0.292
Treatments:				
Antidiabetics	35 (29.91%)	22 (31.88%)	13 (27.08%)	0.577
Antihypertensives	88 (75.21%)	51 (73.91%)	37 (77.08%)	0.696
Antidepressants	16 (13.68%)	15 (21.74%)	1 (2.08%)	0.002
Benzodiazepine	31 (26.50%)	23 (33.33%)	8 (16.67%)	0.044
Immunosuppressants	9 (7.69%)	6 (8.70%)	3 (6.25%)	0.625
Diuretics	65 (55.6%)	32 (46.4%)	33 (68.8%)	0.017
Comorbidities:				
Diabetes	45 (38.46%)	28 (40.58%)	17 (35.42%)	0.572
Hypertension	96 (82.05%)	57 (82.61%)	39 (81.25%)	0.851
Cancer	6 (5.13%)	6 (8.70%)	0 (0%)	0.036

Table 1. *Cont.*

Characteristics	All (*n* = 117)	Academic Center (*n* = 69)	Private Center (*n* = 48)	*p*-Value
CHF	20 (17.1%)	11 (15.9%)	9 (18.8%)	0.691
COPD	9 (7.7%)	3 (4.4%)	6 (12.5%)	0.104
Polyneuropathy	31 (26.5%)	18 (26.1%)	13 (27.1%)	0.904
Amputation	10 (8.6%)	9 (13%)	1 (2.1%)	0.037
Types of pain				
Muscular pain	8 (6.84%)	6 (8.7%)	2 (4.17%)	0.340
Osteoarticular pain	50 (42.74 %)	28 (40.58%)	22 (45.83%)	0.572
Headache	4 (3.42%)	2 (2.9%)	2 (4.17%)	0.710
Thoracic pain	3 (2.56%)	3 (4.35%)	0	0.143
Neuropathy	35 (29.91%)	20 (28.99%)	15 (31.25%)	0.792
Vascular access pain	3 (2.56%)	2 (2.9%)	1 (2.08%)	0.784
Wound pain	7 (5.98%)	5 (7.25%)	2 (4.17%)	0.490

CHF, cardiac heart failure; COPD, chronic obstructive pulmonary disease.

3.2. Prevalence of Opioid and Non-Opioid Antalgic Prescription, and the Distribution of Different Opioids among Patients

Among the 117 included patients, 98 (83.8%) received at least one prescription for pain relief within the study year. The most frequently prescribed antalgic drug was acetaminophen (82.1%), followed by opioids (29.1%). NSAIDs were not frequently prescribed (15%). Both acetaminophen and opiates were more frequently prescribed at the AC (see Figure 1). Out of the 34 patients who received at least one opioid medication prescription, nine patients (7.7%) had a chronic prescription (>90 days within the study year). Of note, two patients had initially received a short-term prescription, followed by chronic prescription later on in the study period. A total of 27 out of 69 patients (39%) of the AC received at least one opioid prescription within the study year, versus only 7 patients (14.6%) at the PC ($p = 0.004$). Only one of them had a chronic prescription at the private center, while 8 patients were on chronic opioid prescription at the academic center, accounting for 11.6% of all patients from that center. Of all patients who received at least one opioid prescription, 32 (94%) were also treated with acetaminophen. Only 2/34 took a combination of opioids, acetaminophen and NSAIDs.

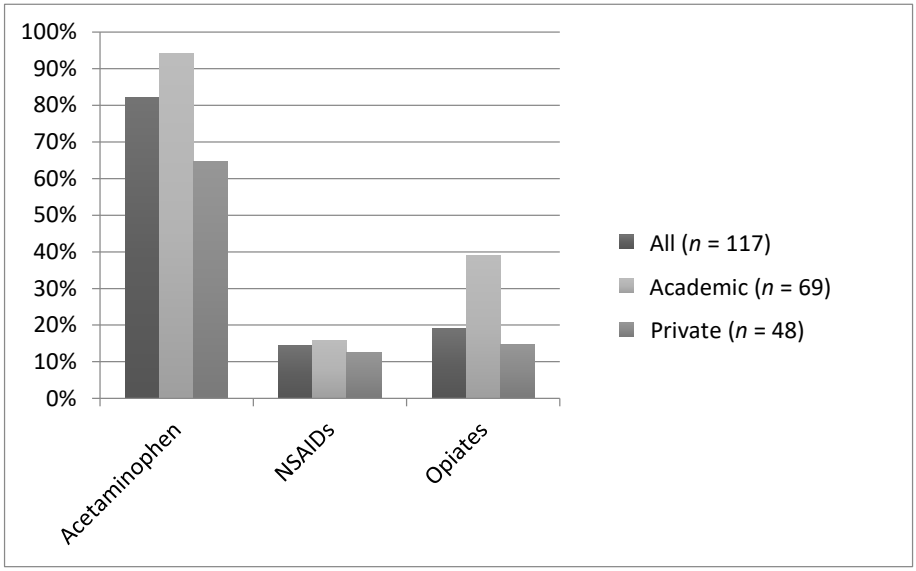

Figure 1. Acetaminophen, NSAID and opiate consumption per center. Bars represent the percentage of patients that received an analgesic drug during the study period in the academic center of Lausanne University Hospital versus the private dialysis center Clinique Cecil.

The most commonly prescribed opioids were tramadol chlorhydrate (44.1% of all 34 opiate prescriptions) and buprenorphine (41.2%). Fentanyl was the third most commonly prescribed opioid (20.6% as a patch; 14.7% sublingually). An overview of the number and type of opioids prescribed at each center is shown in Figure 2.

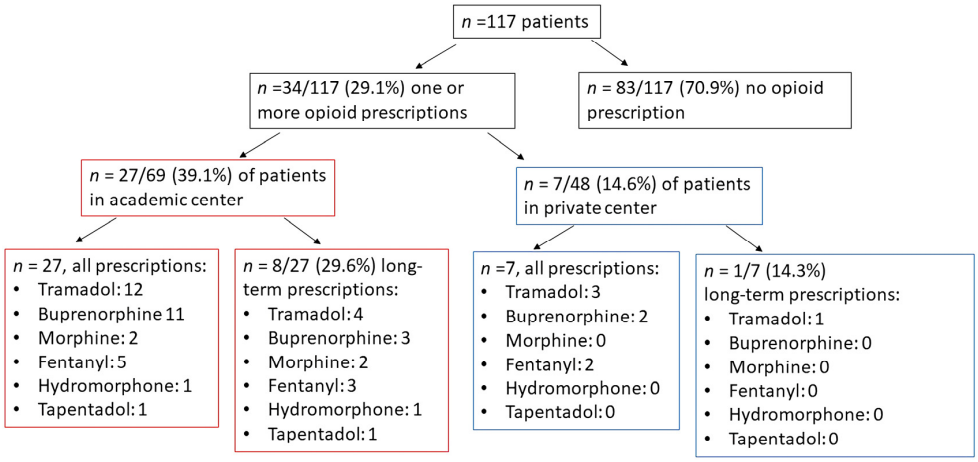

Figure 2. Overview of opioid prescription. Summary and general overview of the type of opioids in the two centers, for both short- and long-term prescriptions.

Opioids were prescribed by two nephrologists in the private center (one man and one woman, aged 45–50). In the academic center, opioids were prescribed by the head of the chronic dialysis unit (aged 48), by two certificated house officers between 35 and 40 years old, and by seven residents between 30 and 35 years old. The head of dialysis and house officers were men. Among the residents, five were women and two were men.

3.3. Factors Associated with Opioid Prescription

In univariate logistic regression analysis, being on dialysis at the academic center (AC vs. PC: OR, 3.70; CI, 1.48 to 9.6; $p = 0.006$), neuropathic pain (OR, 2.99; CI 1.28 to 6.98; $p = 0.011$), benzodiazepine prescription (OR, 2.72; CI, 1.14 to 6.46; $p = 0.024$), polyneuropathy (OR, 2.72; CI 1.14 to 6.46; $p = 0.024$) and amputation (OR 4.23; CI 1.1 to 16.1; $p = 0.034$) were all significant determinants of opioid prescription (Table 2). It is of note that cancer was not associated with opioid prescription; in fact, none of the six patients with cancer received any opioid prescription.

Table 2. Prevalence and univariate associations between patients' characteristics and opioid prescription.

Characteristics	Overall Opioid Prescription (in % of Total, *n* = 34)	OR	(95% Conf. Interval)		*p* Value
Center (academic versus private)		3.76	1.48	9.6	0.006
Age group, years					
20–44	20.6	2.81	0.9	8.77	0.074
45–64	32.4	0.72	0.31	1.68	0.454
65+	47.1	0.83	0.37	1.84	0.641
Male (vs. female)	67.7	1.6	0.69	3.71	0.271
Race					
European	79.4	0.99	0.37	2.67	0.99
Asian	8.8	0.91	0.23	3.65	0.891
African	8.8	1.05	0.26	4.33	0.945
Other	2.9	1.23	0.12	14	0.869

Table 2. *Cont.*

Characteristics	Overall Opioid Prescription (in % of Total, n = 34)	OR	(95% Conf. Interval)		p Value
Dialysis duration > 5 years	44.1	1.64	0.72	3.71	0.237
Vacs. Access	82.4	1.2	0.43	3.37	0.726
Tobacco history	44.1	1.03	0.46	2.3	0.941
Alcohol history	14.7	1.02	0.33	3.16	0.972
Treatments:					
Antihypertensives	67.7	0.58	0.24	1.41	0.228
Antidepressants	20.6	2.13	0.72	6.29	0.17
Benzodiazepine	41.2	2.72	1.14	6.46	0.024
Immunosuppressants	8.8	1.24	0.29	5.28	0.769
Diuretics	38.2	0.37	0.16	0.84	0.018
Comorbidities					
Diabetes	38.2	0.99	0.43	2.24	0.974
Hypertension	82.4	1.03	0.36	2.92	0.957
CHF	11.7	0.56	0.17	1.81	0.332
COPD	2.9	0.28	0.03	2.36	0.244
Polyneuropathy	41.2	2.72	1.14	6.46	0.024
Amputation	17.6	4.23	1.11	16.12	0.034
Causes of pain					
Muscular pain	29	0.33	0.04	2.78	0.307
Osteoarticular pain	55.9	2.12	0.95	4.78	0.068
Headache	2.9	0.81	0.08	8.05	0.856
Thoracic pain	2.9	1.23	0.11	14	0.869
Neuropathic pain	47.1	2.99	1.28	6.98	0.011
Wound	11.7	3.56	0.75	16.83	0.11

Values are expressed as percentages of the total number of patients having an opioid prescription, regardless of the center (n = 34). Statistical significance was defined as $p < 0.05$. CHF, cardiac heart failure; COPD, chronic obstructive pulmonary disease.

In multivariate logistic regression analysis, including all variables with significant associations in univariate analysis, the only independent predictive factor of opioid prescription was being on dialysis at the academic center (OR, 3.6 CI, 1.29 to 10; p = 0.014) (Table 3). We performed a sensitivity analysis that also included factors with a p-value of between 0.05 and 0.1 (age range 20–44 and osteoarticular pain). The results were unchanged, with the center remaining the only factor associated with opioid prescription in a multivariable analysis.

Table 3. Multivariate logistic regression analysis between patients' characteristics and opioid prescription.

Variable	OR	[95% Conf. Interval]		p Value
Center (academic vs. private)	3.6	1.29	10	0.014
Benzodiazepine (yes vs. no)	1.93	0.74	5.04	0.177
Polyneuropathy (yes vs. no)	1.94	0.68	5.49	0.213
Neuropathic pain (yes vs. no)	2.24	0.8	6.24	0.123
Amputation (yes vs. no)	2.41	0.57	10.25	0.233

The variables significantly associated with opioid prescription in univariate analysis were included in the multivariate model. Statistical significance was defined as $p < 0.05$.

4. Discussion

Our results show a high prevalence of opioid prescription in patients from two Swiss dialysis centers, with ~30% of them on short-term opioid prescriptions and 15% on chronic opioid prescriptions. However, there were important differences in prescription patterns between the two participating centers: opioid prescription occurred twice as often at the AC as at the PC. In multivariate analysis, the variable of location of the center was the only factor that independently predicted opioid prescription, whereas the presence

of comorbidities, such as polyneuropathy or amputation, did not. The most frequently prescribed opioids were tramadol, buprenorphine and fentanyl.

The number of opioid prescriptions was high and may have important clinical consequences, as overdosage or chronic opioid prescriptions are associated with an increased risk of adverse events [2,10–13]. However, opioid exposure was lower compared to previous studies performed in the United States. Kimmel et al. reported that more than 60% of patients on HD had received at least one opioid prescription per year in their survey [19]. Davison et al. also reported a higher prevalence of opioid prescription in HD patients (35.9%) [8]. Although we found important center-based differences, the number of chronic prescriptions at the Lausanne University Hospital remained lower than those found in the United States [18,19]. There was also a difference in trend between the Swiss centers and those in the USA, concerning the type of opioid prescribed. Tramadol and buprenorphine were by far the most commonly prescribed opioid molecules at the two Swiss centers, whereas the most commonly prescribed opioid molecules in the United States are hydrocodone (not approved in Switzerland), followed by oxycodone [19]. It is of note that tramadol and buprenorphine are considered to be relatively safe choices in ESKD and HD patients. Buprenorphine demonstrates a non-renal clearance and is not significantly dialyzed, favoring its use in HD patients [10,12,13].

We have no clear explanation for the lower prevalence of opioid prescription in our study as compared to the US. First of all, the low number of participants limits its generalizability, and our results should be interpreted with caution as they may be a poor reflection of the real prevalence of opioid prescription in Swiss dialysis centers. In addition, the cited US studies were performed between 2006 and 2010; since that time, regulations concerning opioid prescription have been tightened in the US. Apart from these considerations, the fact that one-third of the HD patients in our study received an opioid prescription in the previous year merits all our attention and calls for actions to lower this number.

In order to shed light on the reasons for opioid prescription in the population cohort of our study, we looked at the associations between opioid prescription and several predefined variables. Neuropathic pain, polyneuropathy, and the use of benzodiazepines, as well as previous amputations were significant predictors of opioid prescription in univariate but not in multivariate models. It may seem odd that neuropathic pain and polyneuropathy were associated with the prescription of opioids, as these pain types are normally not controlled with opioids [21]. This finding is possibly explained by pain that is difficult to treat, incentivizing physicians to prescribe pain-relieving molecules that would normally not be recommended. In addition, molecules such as gabapentin and pregabalin can accumulate in patients with CKD and may have unpredictable adverse effects [22]. Benzodiazepine prescriptions were not often associated with opioid prescriptions in the literature. Their co-prescription in our study could suggest that an important number of HD patients who were included suffered from both somatic and psychological symptoms. Besides this, many HD patients suffer from insomnia [21].

The only predictor that was associated with opioid prescription in the multivariate analysis was the dialysis center. The reason why there was such a difference between the two centers remains unclear. Previous US studies reported correlations between the location of a particular dialysis center, whether in a metropolitan region or a rural region, and the chronic prescription of opioids [19]. According to these studies, opioids are more commonly prescribed in rural regions. However, in our study, both the AC and PC are located in the city center of Lausanne and are quite similar in size, implying that factors other than region or size must explain the difference in opioid prescriptions between those two centers. In a study by Baillie et al., female HD patients received opioid prescriptions more frequently than male patients, while Kimmel et al. showed that patients who were on HD for more than 5 years were more likely to receive an opioid prescription [18,19]. This was not the case in our study population, as neither the sex of the patient nor the duration of HD explained the differences demonstrated between the two centers.

Another hypothesis to explain the two centers' differences in prescription may be a difference in comorbidities burden in the cohorts. There were significantly more patients with amputations or cancer in the academic center, although these factors were not associated with opioid prescription in multivariate analysis, but the lack of power of our study clearly limits definite conclusions.

Finally, the marked difference between the number of prescribing physicians may explain the difference in opioid prescriptions between the two dialysis centers. At the Lausanne University Hospital, an academic training hospital, twelve physicians (residents, fellows and attending nephrologists) were involved in patient care at the dialysis center in 2018. This number does not include the nephrologists who were on call during the weekends. At Clinique Cecil, however, only 2 trained nephrologists were involved in patient care. In Switzerland, the nephrologist usually also fulfills the role of general practitioner and is, therefore, the health professional who introduces or renews all drug prescriptions, whether these are linked to dialysis or not. This is not necessarily the case in other countries. In the United States, for example, a recent study showed that physicians who prescribed opioid medication in HD patients were nephrologists in only 20% of the cases [16]. In non-dialysis populations, the number of prescribing physicians is a well-recognized risk factor for opioid over-prescription [23]. Our data suggest that this may also be the case in the dialysis population, but larger-scale studies are necessary to confirm this hypothesis as the doctors at the AC might all follow the same strategy on pain management as the division chief, even though there were no internal guidelines.

Whatever the cause of the differences between the centers in terms of opioid prescription, our study unfortunately only includes a small number of patients and, thus, lacks the statistical power to draw definite conclusions concerning the comparison between the two centers and the results of the multivariable analysis. In Switzerland, there are no central databases that compare with the US Renal Data System and the Centers for Medicare and Medicaid Services in the United States, which makes it extremely time-consuming to collect data on this important subject. Hence, this study should be seen as a hypothesis-generating study, one that will hopefully stimulate future nationwide projects. In addition, our study illustrates that there is no clear agreement on how pain should be treated in hemodialysis patients, probably due to the lack of well-established guidelines. It is essential to carefully weigh the benefit–risk ratio of opioids in this population. Patients suffering from pain, for whom the first steps of the WHO ladder are not sufficient, should receive more effective antalgic treatments in order to maintain a good quality of life [1,2]. Different tools exist to determine the risk associated with an opioid prescription in a particular patient. The "Opioid Risk Tool" is one of them, but it has not as yet been validated in the dialysis population, to the best of our knowledge [24]. Validated tools and specific guidelines for pain management in patients with ESKD are necessary to assist nephrologists and other physicians who are taking care of these patients.

Our study has several limitations and strengths. As mentioned, the small number of patients is its major limitation. Another limitation is that our data were based on prescriptions found in the computed medical files and on handwritten prescriptions. Therefore, we may have missed some prescriptions. We believe that this occurred only rarely, if at all, as the nephrologists of the Lausanne University Hospital and the Clinique Cecil are the only prescribers of pain treatment in HD patients. On the other hand, this aspect may also be seen as a strength in our study; each prescription was acquired individually for each patient, including handwritten prescriptions, in opposition to larger studies relying on big data collection where a great many mistakes and biases may occur. Thirdly, this retrospective study did not assess the baseline pain level and the response to treatment, nor if the patients actually took their medication or not. Finally, this study included only one academic and one private center. Our results can, therefore, not be generalized to all academic and private centers, and larger-scale studies are once again needed to confirm our findings. Among the strengths of this study, we can mention the participation of two different centers located in the same city, which allowed us to assess the role of physicians independently of the

geographical location. It is also worth mentioning that even if this study serves merely as a hypothesis generator, it is the first of its kind conducted in Switzerland.

5. Conclusions

In conclusion, the prevalence of opioid prescription in hemodialysis patients was high in the two included Swiss dialysis centers, albeit lower than reported in American studies. No definite conclusion can be drawn as to what caused such large differences in prescription patterns between the centers, but these differences illustrate that there is a need for more data on pain management in HD patients. The general prevalence and outcomes of opioid prescription have been widely reported, but data for patients with ESKD remain very limited. Switzerland is no exception, as this is, to the best of our knowledge, the first study performed on this subject in Switzerland. Future studies should evaluate the prevalence and consequences of opioid prescriptions in HD patients at a national and international level, and registries should be encouraged to collect data on this important issue. In our opinion, this is the best way toward clear recommendations on opioid prescription in HD patients. This will ultimately result in better patient care, improved quality of life, and the alleviation of pain while avoiding over-prescription and adverse effects in the vulnerable HD population.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the Commission Cantonale d'Ethique de la Recherche sur l'Etre Humain (CER-VD) (protocol code: 2018-01141 and date of approval: 8 October 2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

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Conflicts of Interest: The authors declare no conflict of interest.

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