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Research Article

The Prevalence of Long-Term Opioid Therapy in Spine Center Outpatients Following Initiation of Tramadol: The Spinal Pain Opioid Cohort (SPOC)

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Abstract

Background: Opioid prescriptions for chronic spinal pain are generally high, even though long-term usage is associated with several risks. Tramadol has previously been the preferred opioid choice in Denmark, but recent concerns have been raised concerning the risk of developing an addiction. Unfortunately, evidence from long-term studies is lacking. The purpose of this study was to investigate the risk of long-term use of tramadol compared to other types of opioids over a 5-year follow-up period. **Methods:** The setting of this prospective cohort study was an outpatient healthcare Spine Center. Patient variables included clinical and registry data. The primary outcome parameter was Long-Term Opioid Therapy (LTOT) in the 5th follow-up year, indicated by 6+ opioid prescriptions per year. **Results**: For the primary outcome, we did not find any significant differences indicating tramadol to be more likely to develop LTOT status, but overall starters of tramadol had more prescriptions compared to starters of other opioids. Among tramadol starters, 25% shifted to other opioids during follow-up. A similar number in non-tramadol starters was 38%. The percentage of patients using 4-5 different opioids over the five years was significantly higher for the non-tramadol starters (8.8%) compared to tramadol starters (4.8%). **Conclusions:** The findings do not support tramadol starters to be more likely to develop LTOT status compared to other opioid starters. In fact, tramadol initiators and non-tramadols have a similar LTOT status 5 years following initiation opioids. The cautious conclusion could be that there are no clinically important differences in the risk of LTOT in tramadol versus non-tramadol opioids.

Keywords: Back pain; Neck pain; Cohort study; Opioids; Tramadol; Long-term opioid therapy; LTOT

Key Points

- Tramadol initiators had insignificantly more prescriptions during five years of observation period compared to other opioid starters.
- A significantly lower rate of tramadol initiators shifted to other opioids compared to other opioid starters.
- From these data tramadol initiators and non-tramadols seem to have a similar LTOT status 5 years following initiation opioids.

Introduction

Chronic low back pain is estimated to affect up to one billion people around the world according to the Global Burden of Disease Study of 2016 and has consistently been one of the major global causes of years lived with disability [1]. This is also the case for other types of spinal pain such as neck pain [2]. Unfortunately, a "silver bullet" for spinal pain does not exist [3-5], and the prescription of opioids has increased substantially over the past two decades [6]. Now it is one of the most commonly prescribed treatments for spinal pain although the fact that the majority of international guidelines recommend trying all relevant non-opioid treatments before any type of opioids [7,8]. Long-term usage of opioids – "Long-Term Opioid Therapy" (LTOT) – is associated with a range of risks regarding severe side effects. For example, it can result in addiction and a broad range of somatic and psychological side effects, including depression and anxiety [6-11]. Also, long-term usage is associated with generally reduced physical activity, lower rates of return to work in injured workers, and the risks associated with social isolation [12]. Despite the increased risk of addictive behavior associated with ongoing opioid treatment [13,14], no published spinal pain studies include follow-up data beyond one year [14]. Recently, our published study documented that previous opioid treatment - i.e., before a new acute spinal pain episode began - doubled the risk of LTOT during 5 years [15].

In Denmark, tramadol was introduced in 1993. It has a relatively low affinity for the μ-opioid receptor and is phenotypically distinct from other marketed opioids [16]. Therefore, it has been suggested that tramadol has a lower risk of developing addictive behavior. The usage of tramadol has been higher in Denmark compared to most other countries [17,18]. It peaked in 2014, but recently, public concerns have been raised regarding reported addictive properties similar to other opioids [18]. This has caused a gradual fall in prescriptions since 2017 [18]. Nonetheless, evidence from long-term studies is necessary to develop reference material documenting risks of potential problems related to tramadol addiction.

The present study focuses on the risk of long-term tramadol use benchmarking other opioids in a 5-year follow-up. Three exploratory research questions were formulated:

1. What is the total number/percentage of prescriptions of tramadol compared to other opioids?
2. What are the number of opioid shifts and the total number of opioids used after the initial prescription of tramadol and other opioids?
3. What is the 5-year prevalence of LTOT for tramadol and other opioids?

Materials and Methods

Study Design and Setting

This is a longitudinal cohort study based on data collected from the daily clinical routine procedures of The Spine Centre of Southern Denmark during 2012-2013 and five years of follow-up, which later were enriched with registry data. The overall project is known as the Spinal Pain Opioid Cohort (SPOC). Further details of this have been published in a previous paper [19].

Study Participants

The study sample was low back pain patients aged between 18 and 65 who experienced a new pain episode lasting more than two months (but less than one year) and had their first outpatient visit at the Spine Center. Only patients who received their first opioid prescription during the actual pain episode were included in the cohort.

Referral from the primary healthcare service to the Spine Centre of Southern Denmark can only take place when a patient has had acute pain for 2 or more months. Before that, the patient must have undergone treatment with their General Practitioner (GP) in conjunction with a local physiotherapist or chiropractor. Typically, patients are seen at the Spine Centre 2-4 months after symptom debut involving typically 1-2 ambulatory consultations. Therefore, most analgesic treatments–including opioids-are initiated and monitored by the patient's GP both before and after the course of treatment at the Spine Centre.

Study Data

All clinical data were collected in the Spine Centre's electronic clinical registry (Spine Data) [20] and linked with data from the Danish national registers. We linked the data using the Danish Identity Number (known as the CPR number) assigned to all citizens at birth or immigration. We used data from the Danish National Prescription Registry (NPR) [21]. NRP records every single

prescription handed over the counter in all Danish pharmacies, and therefore, the opioid data presented are based upon a complete case analysis.

Descriptive and Clinical Variables

Several self-reported descriptive characteristics and clinical variables were included in the present study. These were only used to describe the opioid subgroups. The reported descriptive characteristics used in this study were sex, age, height, weight, and smoking, while the clinical variables were:

- Spinal pain intensity and radiating pain intensity were measured by a Numerical Rating Scale (NRS) from 0 ("No pain") to 10 ("Worst Pain Imaginable) [22].
- Pain-related disability was measured by the Roland Morris Disability Questionnaire [23,24].
- Health status was measured by EuroQol VAS ranging from 0 to 100 with a higher score indicating a better health status [25].

Opioid-related Variables

In addition to the above-described descriptive and clinical variables, several registry-based variables regarding opioids were included. These are outlined below.

Types of Opioids

The dispensed medications from the NPR were classified according to the Anatomical Therapeutic Chemical classification system (ATC: https://www.who.int/tools/atc-ddd-toolkit) [26]. We extracted the generally used opioids for spinal pain, which were available for oral or transdermal use from the NPR using the relevant ATC codes (Table 2). Several opioids had been rarely used for spinal pain in this cohort (including Hydromorphone, Ketobemidone, Pethidine, Tapentadol, Dextropropoxiphene, and Codeine) and were therefore not included in this study. Among all patients in the cohort, these opioids were prescribed to 40 patients for totally less than 100 prescriptions over the observation period.

Primary Outcome Parameter: LTOT

This study's primary outcome parameter was inspired by "The Copenhagen Criteria" definitions and related methods to register LTOT [13,27]. In our study, six or more opioid prescriptions in a one-year interval fulfilled the LTOT criteria during that follow-up period. The prevalence of patients fulfilling LTOT in the respective subgroups was calculated separately for all five years of follow-up. LTOT in the 5th year following opioid initiation was defined as the primary outcome parameter.

Definitions of Subgroups based on Opioid Prescriptions

To fulfill the aim of the study, we separated the cohort patients into four subgroups before initiating the analysis process:

Group 1: Patients who initiated non-tramadol opioids and did not shift to other opioids in 5 years.

Group 2: Patients who initiated non-tramadol opioids and did shift to other opioids in 5 years.

Group 3: Patients who initiated tramadol and did shift to other opioids in 5 years.

Group 4: Patients who initiated tramadol and did not shift to other opioids in 5 years.

Statistical Modeling

Baseline characteristics of the cohort subgroups have been reported either as proportions or median values with the Inter Quartile Range (IQR). For continuous variables not normally distributed, we used the median and IQR. For the test of significance, we used Pearson's Chi-squared test, T-test and for the continuous variables, we used the k-sample equality-of-median test.

We used a logistic regression model to calculate the differences in dispensed opioid prescriptions between patients who initiated using tramadol or respective non-tramadol opioids. To account for the clustered nature of the data, we used a robust standard error estimator. We allowed interaction between subgroups and years; however, this was not statistically significant ($p=0.355$), and we examined the differences between the subgroups.

All differences were considered to be statistically significant at $p<0.05$. Analyses were performed using STATA version 16.1 (StataCorp, College Station, TX, USA).

Results

Descriptive Characteristics

Overall, SPOC included 8,356 patients. Hereof, 4,409 (53%) had one or more opioid prescriptions in a 4-years period before referral to the Spine Centre. Of these opioid users, many initiated opioid usage before the current pain episode, but a total of 2,183 (26%) patients received their first opioid prescription during the actual acute pain episode fulfilling the inclusion criteria in this study. Hence, the sample for the present study was 2,183 patients. Descriptive summaries for all included patients and the subgroups are shown in Table 1. Baseline data between subgroups do not demonstrate any clinically relevant differences. Generally, the patient's characteristics are similar to other published SpineData cohorts [20].

Baseline	All patients	Group 1: Only one non-tramadol opioid	Group 4: Only tramadol	p-value Group 1/4	Group 3: Initiation of tramadol and later non-tramadols	Group 2: Initiation of another opioid and later shift to different opioid(s)	p-value Group 3/2
Number of Patients	2,183	135	1,466		500	82	
Age, years; median (IQR)	49(38;61)	52(39;63)	47(37;58)	0.17	51(41;66)	56(42;69)	0.318
Females, n(%)	1,152(53)	73(54.1)	766(52.3)	0.685	268(53.6)	45(54.9)	0.830
Spinal pain intensity, (0-10)							
Median (IQR)	5(3;7)	4(2;6)	5(3;7)	0.273	5(3;7)	5(3;6)	0.136
Self-perceived general health, Health Thermometer, (0-100)							
Median (IQR)	50(30;70)	52(35;76)	50(31;71)	0.192	47(29;61)	45(26;67)	0.876
Radiating pain, (0-10)							
Median, (IQR)	4(1;6)	4(1;5)	4(1;6)	0.407	5(2;7)	5(1;7)	0.869
***Low Back Disability, RMDQ, (0-100)**							
Median, (IQR)	65(43;78)	65(43;74)	65(44;78)	0.840	70(48;83)	65(43;78)	0.159
Weight and height							
Weight, Median (IQR)	80(68;91)	78(66;89)	80(68;90)	0.734	81(69;94)	80(70;92)	0.752
Height, Median (IQR)	173(166; 180)	172(165; 180)	173(166;180)	0.722	173(167;180)	173(168;178)	0.785
Smoking							

Baseline	All patients	Group 1: Only one non-tramadol opioid	Group 4: Only tramadol	p-value Group 1/4	Group 3: Initiation of tramadol and later non-tramadols	Group 2: Initiation of another opioid and later shift to different opioid(s)	p-value Group 3/2
Yes, n(%)	671(30.7)	38(28.1)	438(29.9)	0.544	172(34.4)	438(29.9)	0.488
*Only data from low back pain patients included. IQR: Inter Quartile Range.							

Table 1: Baseline characteristics of included patients.

Research Question 1

Overall, a large subgroup of 2,026 patients (93%) had tramadol prescribed during the study period. Further, some patients received prescriptions for either morphine (n=372; 17%) or oxycodone (n=393; 18%) and relatively few patients received fentanyl/buprenorphine. The total number of dispensed opioid prescriptions to patients in the cohort was 16,492 during the 5-year observation period (Table 2).

Opioids	Number of Patients(%)	Number of Prescriptions (Mean/Patients)
Morphine (N02AA01) + (NO2AA51)	372(17.0)	1,800(4,8)
Oxycodone (N02AA05) + (N02AA55)	393(18.0)	2,428(6,2)
Fentanyl(N02AB03)	41((1.9)	219(5,3)
Buprenorphine (N02AE01)	58(2.6)	433(7,5)
Tramadol (N02AX02)	2,026(92.5)	11,612(5,7)
Total		16,492(7,6)

Table 2: The number of dispensed prescriptions distributed for each opioid among patients.

While not statistically significant, the tramadol initiators had a greater number of opioid prescriptions in all subgroups compared to non-tramadol users (mean 7.7 compared to 6.1, p=0.839). Generally, patients who only used one type of opioid during the follow-up period had a lesser number of dispensed prescriptions, however, the tramadol initiators did demonstrate a statistically higher usage (tramadol/non-tramadol; 5.1/ 3.3); (p=0.000).

Regarding patients who used 3-5 different opioids during the 5-year period the mean number of dispensed prescriptions was 27.1 for tramadol initiators and 18.3 for other opioid users (Table 3).

	Number (n) of patients	Total (n) pre-description	Tramadol; (n) pre-description	Other opioids; n prescriptions	Total n opioids prescribed (n patients): (n prescriptions)	Mean (n) pre-description
Group 1: Only one non-tramadol opioid	135	446				3.3
Group 2: Initiation of non-tramadol opioids and later other opioids	82	884	276	608	2 opioids: (63):(535) 3-5 opioids: (19):(349)*	8.5 18.3 10.8

Group 3: Initiation of tramadol and later other opioids	500	7,734	3,908	3,826	2 opioids: (406):(5191) 3-5 opioids: (94):(2543)*	12.8 27.1 15.4
Group 4: Only tramadol	1,466	7,428	7,428			5.1
Total	2,183	16,492	11,612	4,880		
*10 individuals-equally distributed among groups 2 and 3-have received 4 or 5 opioids in the observation period; in total 432 prescriptions.						

Table 3: Dispensed opioids and number of prescriptions in the subgroups.

Research Question 2

As shown in Table 3, a total of 1,966 patients initiated tramadol during the 5-year observation period. Of these, 1,466 patients (74.6%) (Group 4) did not shift to other types of opioids during the follow-up period. The remaining 500 tramadol patients (25.4%) (Group 3) shifted to other types of opioids at a later date. Out of 1,966 tramadol initiators, 94 patients (4.8%) used 3-5 different opioids during the follow-up. Among the remaining 217 non-tramadol initiators, 135 patients (62.2 %) kept using this "first choice" opioid during the entire treatment period (group 1) and 82 (37.8%) shifted to other types of opioids during follow-up (group 2). A total of 19 patients in this non-tramadol group (8.8%) used 3-5 different opioids during the follow-up period. A similar number was found in the tramadol group (4.3%). The difference was statistically significant (p=0.000) (Figure 1).

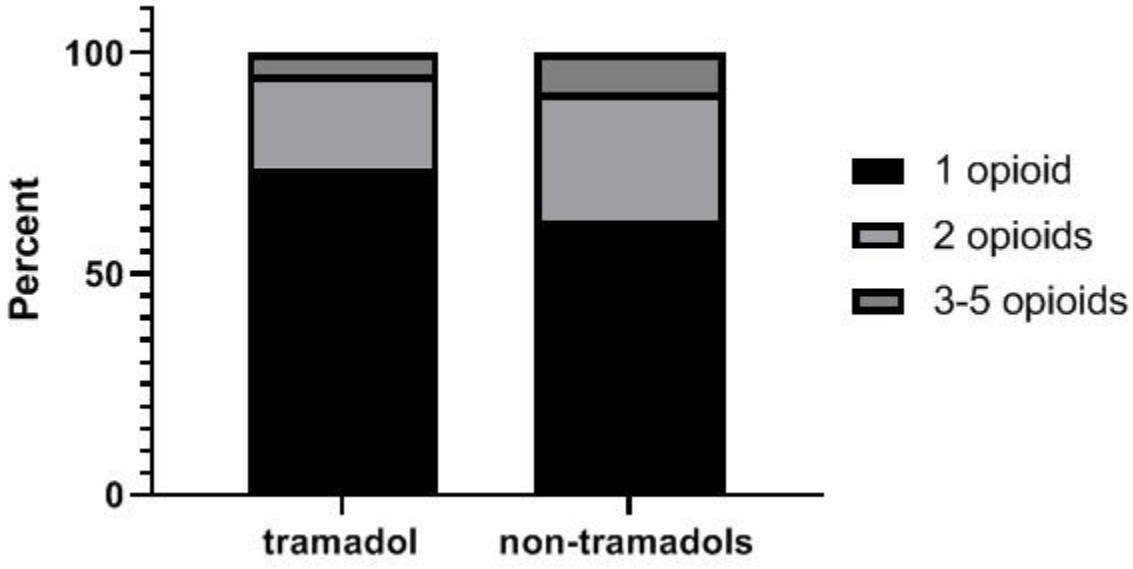

Figure 1: Tramadol initiators benchmarking other opioids initiators. The proportion of patients who shift to alternative opioids during 5-year follow-up.

Figure 1 illustrates the percentage of patients who started with tramadol but shifted to other opioids (25.4%) compared to other opioids shift (37.2%).

Data indicate patients who shift to other opioids are at risk of requiring many more prescriptions during the follow-up period. As Figure 2 illuminates, there is an accelerated risk of developing LTOT for every shift. Patients given 4-5 different opioids received 8-9 times more prescriptions than patients with only one type of opioid, irrespective of which type.

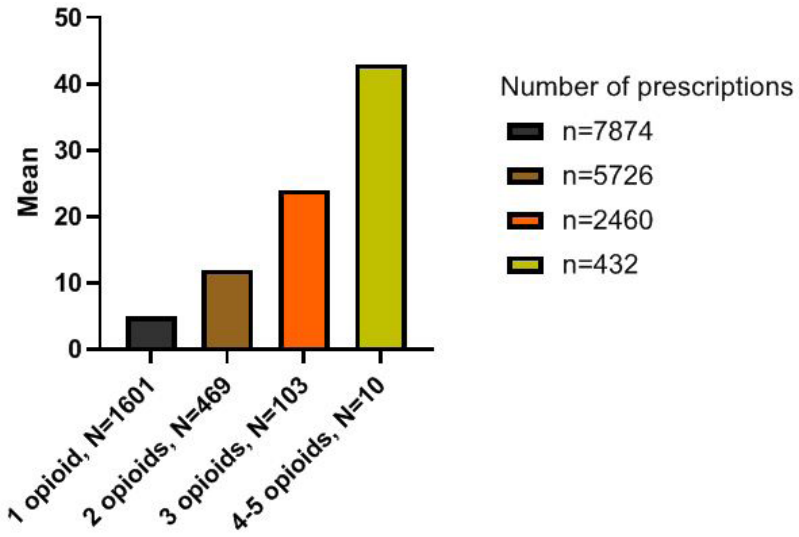

Figure 2: Differences in mean numbers of dispensed prescriptions related to the number of shifts in opioids.

Research Question 3

Figure 3 shows the prevalence rates of patients who received 6+ opioid prescriptions (LTOT) in one or more years during the 5-year follow-up period. Tramadol and non-tramadol benchmarking are separated in the figure, and the prevalence rates are independently calculated for each one-year interval. The prevalence of LTOT in the tramadol group was 12.9% in the first year compared to a non-tramadol opioids prevalence of 5.1%. The primary outcome parameter - LTOT prevalence in the 5th year after inclusion – was similar between the groups; LTOT in tramadol patients was 3.6% compared to 3.7% in other opioid patients. Overall, we did not find any statistically significant differences indicating tramadol users to be more likely to develop LTOT status (OR=1.31 (0.86:1.99; p=0.24)).

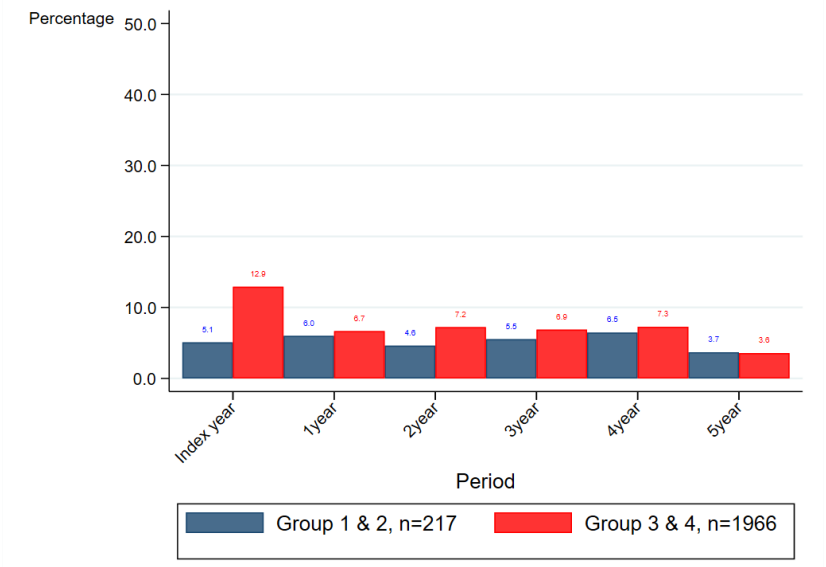

Figure 3: Differences in Long-Term Opioid Therapy in 5 years following initiation of tramadol compared to other opioids. OR=1.31 (0.86:1.99; *p*=0.24); Group 3&4=initiation of tramadol / Group 1&2=initiation of other opioids.

Discussion

Only a few published studies have analyzed potential variations in the long-term impact of using different opioids in naïve users with spinal pain conditions [28,29]. In this study, we examined the general risk profile of tramadol for long-term use - the opioid of choice among Danish clinicians for spinal pain patients - for the first time thereby benchmarking other opioids in opioid naïve low back pain patients.

Discussion of Research Questions

Tramadol Usage (Research Question 1)

Generally, patients that began their treatment with tramadol received a higher number of prescriptions – non-statistically significant - regardless of whether they continued with tramadol or switched to other opioids during the entire follow-up period. From a clinical point of view, it is not possible to determine from our data whether approximately an extra 1.6 prescriptions per patient over a 5-year period has any clinical relevance. In fact, tramadol initiators and non-tramadols have a similar LTOT status 5 years following initiation opioids.

The reasons why patients initiating their treatment with tramadol have a relatively higher average drug usage is unknown. It has been suggested that tramadol due to its pharmacological characteristics results in increased dependence and addictive behavior as well as the likelihood of developing LTOT status [30]. Another possible reason for the noted difference regarding the number of prescriptions may be due to a systemic nature. Tramadol has both nationally and internationally been marketed as a "weak" opioid with an expected reduced risk of developing dependence and addiction. That might have resulted in an image among doctors as being a "lower risk" mild opioid, which may have led to being less restrictive attitude in writing prescriptions. Such a potential mistaken perception may well have resulted in a generally increased number of prescriptions in the individual patient before discontinuation due to a slackened attention amongst prescribers to the risk of initiating addiction in individual patients [30].

Shifts in Usage of Different Opioid Types (Research Question 2)

Among patients in which tramadol was the first choice, a minority of patients shifted to other preparations compared to the non-tramadol group (25% versus 38%). The relatively small proportion of patients that shifted from tramadol to non-tramadol opioid medications over five years may reflect that the expected analgesic effect of the medication was met by a greater number of tramadol patients combined with a relatively low incidence of intolerable side effects. However, the study does not include any systematically gathered data regarding side-effects. A priori, one might expect that the frequency of shifting from tramadol to other medications would be higher because as many as 10% of the general population in Denmark do not have a normal function of the enzyme genotype CYP2D6 [31,32]. After intake, the "prodrug" tramadol is metabolized in the liver by this enzyme and becomes a metabolite with a high affinity for the μ-opioid receptor. A reduced metabolism could result in a lesser analgesic effect of tramadol [33], but this theoretically reduced analgesic effect in about 10% of users was not reflected by a significant shift from tramadol to other opioids.

The data (Figure 2) demonstrate that patients' shift of opioid preparations generally impacts the total number of prescriptions for individual patients throughout the entire observation period. Every shift results in nearly a doubling of the total number of prescriptions dispensed. This development is not linear but approximates an exponential development. In all, 1,601/2,183 (73%) of patients continued with one medication during the entire period, and when collated the mean number of prescriptions is 4.9. Patients that shift to other opioids are at risk of requiring many more prescriptions during the follow-up period. As Figure 2 illuminates, there is an accelerated risk of developing LTOT for every shift. Patients given 4-5 different opioids received 8-9 times more prescriptions than patients with only one type of opioid, irrespective of which type. Shifting to another opioid-irrespective of type - independently constitutes a relative risk of requiring more opioid prescriptions through a 5-year period.

Risk of LTOT after Tramadol Initiation (Research Question 3)

Figure 3 illustrates that in the first follow-up year, more than twice as many patients with 6+ prescriptions are seen in the tramadol group compared to the non-tramadol group, but during all the following observation years, no significant differences are registered between groups. Overall, the apparent difference in first year seems not to result in a relatively increased LTOT through the course of the study and is likely of no clinical relevance.

Clinical Implications

From this study, the results indicate that clinicians should consider that tramadol has a similar risk profile regarding LTOT status as to other opioids. Furthermore, clinicians should be aware of whether an individual patient is presenting with a clear desire to shift from one opioid to another as any shift, irrespective of the opioid medication may well result in a significantly increased use of opioids. A shift to the third prescription – or more - significantly increases the likelihood of developing LTOT. Based on the results in this study, it would be relevant to focus future research activities on identifying the subset of patients with chronic pain for whom opioid use is safe and effective [33,34] and identifying which patients have a higher risk profile for developing LTOT. Also, future analyses of the potential predictive value of social and psychologi-

cal factors on opioid patients' general prognosis would be relevant to carry out [9,12,35].

Strengths and Limitations

Overall, the strength of this study is the relatively high number of included patients, all of whom experienced the pain of spinal origin and obtained their very first dispensed opioid prescriptions during the five-year observation period based on a high-quality Danish National Prescription Register. Additionally, all patients were included from the same organizational system, which involved only one health care unit. In other words, we included a relatively homogeneous group in the study. Furthermore, by using the links to national registers during the entire study period, we were able to obtain a complete and precise data set for all patients regarding their ongoing use of opioids. However, a number of limitations also need to be taken into consideration. In the study, there is a relatively skewed distribution between tramadol starters and those initiating other opioids (90% versus 10%). There is a risk that some important differences in the LTOT risk profiles among the studied opioids are not identifiable in the presented results.

Conclusion

Overall, we did not find a significant difference in the primary outcome parameter, i.e. LTOT status in the 5th follow-up year regarding tramadol and other opioids. The total number of prescribed prescriptions was higher (non-significantly) in the tramadol group. Conversely, a higher number of shifts (significantly) between opioids in the non-tramadol group was observed. Additionally, the percentage of patients that ended up using 4-5 different opioids over the five-year follow-up period was significantly lower for the tramadol initiators group compared to the other opioid initiators. The cautious conclusion could be that there are no clinically relevant differences regarding the risk of LTOT phenomena in tramadol compared to non-tramadol opioids.

Declarations

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Ethical Statement

The Scientific Committee of the Region of Southern Denmark gave ethics approval to collect and use these data for quality assurance and research purposes (project ID S-200112000-29). The database was also registered with the Danish Data Protection Agency (2008-58-0035). The project was also registered in ISRCTN: https://doi.org/10.1186/ISRCTN69685117.

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