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ORIGINAL REPORT

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Tramadol use in Norway: A register-based population study

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Abstract

Purpose: Increasing use of tramadol for chronic non-cancer pain is concerning since tramadol users may be at risk of developing recurrent opioid use with increasing opioid consumption and co-medication. Therefore, we investigated a complete national cohort of tramadol users.

Methods: The study population (154 042 adult individuals in Norway, who redeemed ≥ one tramadol prescription in 2012) was stratified into four groups according to their opioid use 2 years before their first tramadol prescription in 2012 and followed until 2016. Information on all dispensed opioid analgesics, benzodiazepines (BZDs), and BZD-related Z-hypnotics were retrieved from the Norwegian Prescription Database.

Results: Six percent of opioid naïve tramadol users (no opioid use 2 years before tramadol use in 2012) became recurrent users (received opioids annually during 4-year follow-up), almost doubled their mean opioid consumption (66 to 108 defined daily doses [DDD]). One-quarter proceeded to strong opioids or was co-medicated with BZDs, one-third with Z-hypnotics. Among former weak opioid users, 39.8% became recurrent users, 18.7% proceeded to strong opioids, mean opioid consumption increased slightly, one-third used BZDs, or Z-hypnotics concurrently. Among former strong opioid and users in palliative care; 61%, 70% became recurrent users and developed a similar prescription pattern (high and increasing mean opioid consumption, 301 to 318, 413 to 430 DDD); half of them proceeded to strong opioids and/or used BZDs or Z-hypnotics concurrently.

Conclusions: Many patients who developed recurrent opioid use received prescriptions which substantially conflicted with existing guidelines and might lead to problematic opioid use.

KEYWORDS

benzodiazepine, co-medication, epidemiology, opioid consumption, pharmacoepidemiology, problematic drug use pattern, recurrent opioid use, tramadol, Z-hypnotics

1 | INTRODUCTION

In 1977, tramadol was introduced as a "safe" painkiller with low risk of addiction.[1] Lack of evidence regarding long-term effectiveness and adverse effects including tramadol's abuse potential was disregarded.[2] Tramadol was approved by the US Food and Drug Administration as the only nonscheduled opioid available in 1995.[3] Since recent research has shown that tramadol has a more pronounced potential for abuse and drug overdose than formerly anticipated,[3-6] tramadol has been rescheduled to a controlled substance in several countries.[4,5,7,8]

In Scandinavia, tramadol is among the most commonly used opioid for chronic non-cancer pain (CNCP).[9] During last decade,

Norway and Denmark have experienced an increase in tramadol use while the consumption has decreased in Sweden and Iceland and has been stable in Finland.[9] The 1-year periodic prevalence of tramadol users in the adult Norwegian population increased more than 3-fold from 1.7% in 2004 to 4.7% in 2014.[10] Simultaneously, the prevalence of codeine use decreased from 10.6% to 9.1%.[10] Thus, the increase in tramadol outweighs the decrease in codeine use, and most of the increase in tramadol use represents increasing opioid use overall. Because the same concerns regarding problematic opioid use and overdoses apply for tramadol as for other opioids, the increasing tramadol use is concerning and needs to be investigated further.[11-16]

The Norwegian guidelines for opioid use for CNCP have always been relatively strict, emphasizing that opioids should only be prescribed to a small minority of patients after a thorough evaluation and close monitoring.[12,17,18] The Norwegian Directorate of Health recommends opioid treatment with one single opioid drug/formulation and avoidance of co-medication with benzodiazepines (BZDs).[19]

Based on four years of follow-up, the aim was to investigate, prospectively, the drug use pattern among tramadol users in a national cohort who received tramadol in 2012, stratified according to their prior opioid exposure.

KEY POINTS

- The study examined the drug use pattern in a national cohort of tramadol users stratified according to previous use of opioids.
- A significant minority of opioid naïve tramadol users (5.8%) developed a recurrent opioid use with a doubled increase in mean consumption and one-quarter proceeded to strong opioid use.
- Strong opioid users with chronic non-cancer pain developed a prescription pattern like the pattern of patients in palliative care with a high, consistent, and increasing mean consumption of strong opioids.
- Among recurrent opioid users, a high proportion was co-medicated with benzodiazepines which conflicts with guideline recommendations

2 | METHODS

2.1 | Study design

A prospective cohort study based on data from the complete national Norwegian Prescription Database (NorPD). The study population was stratified into four groups based on previous opioid use (2 years a priori) and followed for four years.

2.2 | Data source

Since January 2004, Norwegian pharmacies have been obliged to submit electronic information on all dispensed prescription drugs (reimbursed or non-reimbursed) to the Norwegian Institute of Public Health for inclusion in the NorPD, covering the entire Norwegian population of 5.2 million. The prescription database does not contain information on drugs received by patients in hospitals/other institutions (as part of the institutional prescription, rather than individual prescriptions) such as nursing homes or drugs sold over the counter without prescriptions at an individual level. Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification.[20] It is possible to follow patients over time anonymously, as a unique encrypted personal identity number identifies the patients. Our study was based on the following variables: unique personal identity number, sex, age, dispensing date, and drug information including ATC code, drug quantity measured in defined daily doses (DDD) and the reimbursement code for opioids.[21]

Data were retrieved for the period of 2010 to 2016 on all dispensed analgesic opioids (ATC code N02A) including tramadol (N02AX02, N02AX52) used in Norway. The research period is chosen since the use of tramadol began to increase considerably from the year of 2010 after a moderate increase of consumption during the last decade. Codeine (in combination with paracetamol N02AA59) and tramadolwere categorized as weak opioids, whereas ketobemidone (N02AB01), morphine (N02AA01), fentanyl (N02AB03), buprenorphine (N02AE01), hydromorphone (N02AA03), oxycodone (N02AA05, N02AA55), pethidine (N02AB02), and fentanyl (N02AB03) were categorized as strong opioids.[22] As an integrated study of co-prescription with BZDs, we studied the following BZDs: N05BA (diazepam, oxazepam, alprazolam, lorazepam), N05CD (nitrazepam, flunitrazepam, midazolam), and N03AE01 (clonazepam). Furthermore, we studied the following Z-hypnotics N05CF01 (zopiclone) and N05CF02 (zolpidem).

We recorded the reimbursement code for opioids used by terminal patients in palliative care to obtain financial reimbursement of opioid cost. The code was then used as a proxy for receiving palliative care when stratifying drugs used as a palliative treatment of malignant pain or treatment of acute or CNCP.

2.3 | Study population

The analyses are based on 154 042 individuals (≥18 years), who had at least one prescription of tramadol in 2012. We stratified patients into four study population groups according to their pre-exposure level of opioid use (2 years before their first prescription of tramadol in 2012) (Table 1):

Group 1: Opioid naïve tramadol users; individuals, who did not receive any prescription of opioids, during the previous 2 years

Group 2: Former weak opioid users; individuals, who received prescriptions of only weak opioids including tramadol, during the previous 2 years

Group 3: Former strong opioid users; individuals, who received prescriptions of strong opioids, during the previous 2 years. This group includes patients who had received both strong and weak opioids.

Group 4: Users in palliative care; individuals who received reimbursement of opioids for palliative treatment, during the previous 2 years.

TABLE 1 Study population characteristics of tramadol users at baseline in 2012, stratified into four different groups according to their opioid use in a 2-year period (770 days before the first prescription of tramadol in 2012) (*N* = 154 042). The table represents the opioid use (amount, the number of prescriptions, and prevalence of different type of opioid users)

	Group 1: Opioid Naïve Tramadol Users *N* = 64 792	Group 2: Former Weak Opioid Users *N* = 76 712	Group 3: Former Strong Opioid Users *N* = 9313	Group 4: Users in Palliative Care *N* = 3225
	Individuals, who did not receive any prescription of opioids in 2010-2011	Individuals, who received prescriptions of only weak opioids in 2010-2011	Individuals, who received prescriptions of strong opioids in 2010-2011	Individuals, who received palliative care and opioid prescriptions in 2010-2011
Female *N* (%)	35 182 (54.3)	46 692 (60.9)	6052 (65.0)	2006 (62.2)
Mean age (SD)	54.1 (18.2)	56.6 (17.6)	62.3 (18.0)	66.6 (15.4)
DDD mean, median,®IQR	-	140, 30, 10-133	353, 145, 36-450	484, 220, 52-652
Prescriptions mean, median	-	8,3	21,12	20,13
Type of opioid users during a 2-year period before baseline, *N* (%)				
Codeine		52 263 (68.1)	5824 (62.5)	1753 (58.0)
Tramadol		44 113 (42.5)	6012 (64.6)	1995 (66.0)
Oxycodone			4141 (44.5)	878 (29.1)
Buprenorphine			3534 (38.2)	638 (21.1)
Ketobemidone			1247 (13.4)	108 (3.6)
Pethidine			373 (4.0)	20 (0.7)
Fentanyl			708 (7.6)	356 (11.8)
Morphine			621 (6.7)	255 (8.4)
Others			811 (.7)	100 (3.3)

Abbreviations: DDD, defined daily doses; IQR, interquartile range.

If users from groups 1 to 3, during the follow-up period, received reimbursement of opioids for palliative treatment, they remained in their original study population group.

The follow-up periods of recurrent use of opioids, BZDs, and Z-hypnotics were divided into four 365-day (1st to 4th year) periods during the years 2012 to 2016: 1 to 365, 366 to 730, 731 to 1095, and 1096 to 1490 days after the first prescription in 2012, respectively.

2.4 | Analyses strategy and statistical analyses

In the analyses, the following case definitions were applied:

- *Recurrent opioid users* received opioids at least once during each of the four 365 day's periods.
- *Consistent recurrent users* met the criteria of recurrent opioid use and received six or more prescriptions of opioids during the fourth 1-year period.
- *Possible concurrent drug users* met the criteria for recurrent opioid use and within the fourth 365 day's period received one or more prescriptions of BZDs or Z-hypnotics.
- *Possible problematic drug users* met the criteria for recurrent opioid use and received, during the fourth 365 day's period, prescriptions of ≥365 DDD opioids, ≥100 DDD BZDs, and ≥100 DDD Z-hypnotics.

First, we identified tramadol users in 2012, resulting in a cohort of 154 042 individuals for further analyses (Figure 1). Second, the date of their first prescription of tramadol in 2012 was used to calculate the exact 2-year period (770 days) before baseline and the individual and combined 4-year follow-up period (1490 days). Third, we stratified the study population into four different groups according to their use of opioids 2 years before baseline. Fourth, in a 2-year period before baseline, we analyzed study population characteristics, the use of opioids (amount, type, and the number of prescriptions) in four different study population groups (Table 1). Fifth, we excluded individuals, who had died/stopped using opioids, in each follow-up year (Figure 1). Sixth, among recurrent opioid users, during each year of the 4-year follow-up period, we studied opioid consumption and the possible concurrent use of BZDs or Z-hypnotics (Table 2). Seventh, among recurrent opioid users, at the fourth year of follow-up, we studied: (1) the prevalence of possible concurrent users of BZDs and Z-hypnotics (Table 3), (B) the prevalence of consistent recurrent opioid users, and (C) the prevalence of possible problematic drug users.

All analyses were done in SPSS version 24.

2.5 | Ethical considerations

According to Norwegian legislation, the use of the anonymous population data from NorPD does not require an application to the Regional Committee for Medical Research Ethics nor informed consent.

3 | RESULTS

3.1 | Study population

In 2012, 3.9% of the adult population (≥18 years) in Norway received at least one prescription of tramadol (154 042 out of 3 932 250

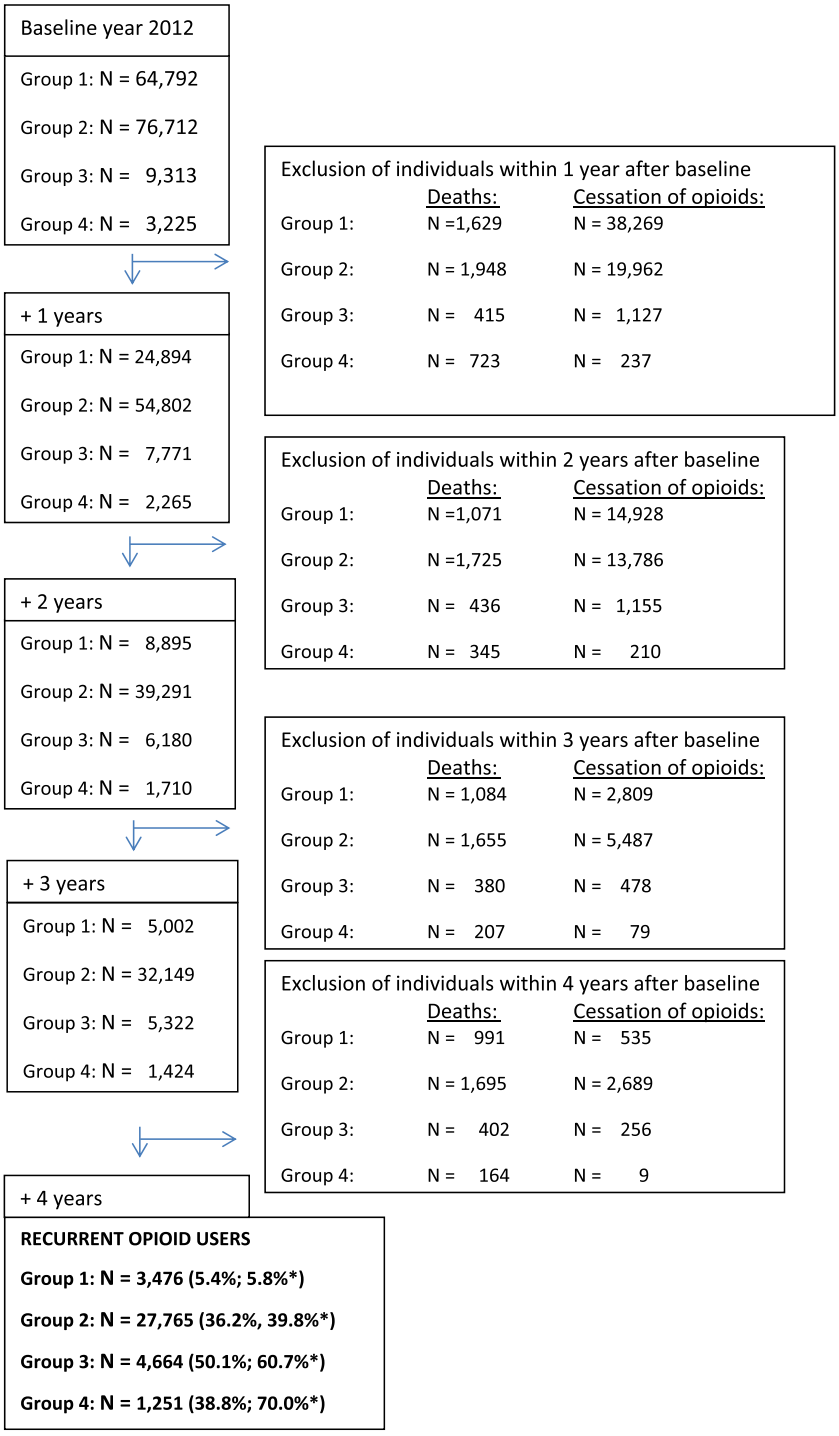

FIGURE 1 Flow chart over persistent opioid users according to four different study populations [Colour figure can be viewed at wileyonlinelibrary.com]

individuals).[10] Out of those, 64 792 were opioid naïve tramadol users (group 1), 76 712 were previous users of weak opioids (group 2), 9313 were previous users of strong opioids (group 3), and 3225 received opioids with reimbursement for palliative treatment (group 4) (Table 1). The proportion of women was higher in all groups, and users in palliative care had the highest mean age (66.6 years) and opioid naïve tramadol users (54.1 years) the lowest (Table 1). In the 2-year period before baseline, the mean consumption of opioids was highest in users in palliative care compared with other former users of strong and weak opioids (484 DDD, 353 DDD, and 140 DDD, respectively) (Table 1).

3.2 | Recurrent opioid users

The proportions of recurrent opioid users (defined by use in 2016) were, 5.8% (n = 3476) in opioid naïve tramadol users, 39.8% (n = 27 765) in former weak opioid users, 60.7% (n = 4664) in former strong opioid users, and 70.0% (n = 1251) in users in palliative care (Figure 1).

When the recurrent users, within each of the four groups, were followed for 4 years the opioid naïve tramadol users almost doubled their mean opioid consumption from 66 DDD to 108 DDD, and former weak opioid users increased their mean opioid consumption from 173 to 191 DDD (Table 2). Throughout the study period, former

TABLE 2 Use of opioids, benzodiazepines, and Z-hypnotics among the four different study population groups, who has used opioids in each of all 4 years of follow-up from 2012 to 2016 (recurrent opioid users) in a 2-year period before baseline and in a 4-year follow-up period

	Group 1: Opioid Naïve Tramadol Users *N* = 3476	Group 2: Former Weak Opioid Users *N* = 27 765	Group 3: Former Strong Opioid Users *N* = 4664	Group 4: Users in Palliative Care *N* = 1251
Opioid use	DDD mean, median (IQR)			
- 2 years	-	157, 83 (27-205)	275, 160 (55–378)	420, 288 (120-549)
- 1 years	-	156, 83 (29-200)	277, 168 (61-365)	405, 267 (125-523)
+ 1 year	66, 33 (13-81)	173, 103 (40-225)	301, 191 (80-393)	413, 279 (133-520)
+ 2 years	81, 40 (13-100)	183, 113 (43-238)	311, 200 (81-401)	413, 230 (130-533)
+ 3 years	95, 47 (17-116)	190, 117 (48-250)	318, 203 (83-417)	415, 283 (127-542)
+ 4 years	108, 50 (17-175)	191, 117 (42-251)	318, 200 (77-407)	430, 280 (119-535)
Strong opioids	N (%), DDD mean, median, (IQR)			
- 2 years	-	-	2917 (62.5%), 80, 16 (5-65)	499 (39.9%), 274, 109 (30-270)
- 1 years	-	-	3419 (73.3%), 77, 17 (5-65)	554 (44.3%), 255, 90 (28-255)
+ 1 year	494 (14.2%), 50, 15 (15.5-53)	2660 (9.6%), 45, 12 (12.4-45)	2452 (52.6%), 125, 47 (10-140)	528 (42.2%), 283, 134 (47-301)
+ 2 years	598 (17.2%), 81, 28 (28.7-79)	3393 (12.2%), 77, 23 (73.6-78)	2368 (50.8%), 173, 68 (16-182)	579 (46.3%), 302, 134 (36-360)
+ 3 years	745 (21.4%), 99, 34 (34.9-90)	4375 (15.8%), 98, 30 (30.8-97)	2520 (54.0%), 197, 78 (17-223)	595 (47.6%), 334, 163 (48-413)
+ 4 years	809 (23.3%), 140, 36 (36.8-114)	5183 (18.7%), 114, 36 (36.8-118)	2551 (54.7%), 222, 92 (22-242)	633 (50.6%), 379, 157 (49-403)
Benzodiazepines	*N* (%), DDD mean, median, IQR			
- 2 years	667 (19.2%), 131, 48 (15-150)	9286 (33.4%), 227, 100 (25-278)	2222 (47.6%), 304, 139 (38-400)	600 (48.0%), 298, 150 (50-397)
- 1 years	738 (21.2%), 116,50 (15-135)	9549 (34.4%), 221, 95 (25-270)	2287 (49.0%). 293, 143 (40-375)	613 (49.0%), 314, 150 (50-390)
+ 1 year	827 (23.8%), 130, 50 (15-150)	9648 (34.8%), 212, 98 (25-263)	2230 (47.8%), 278, 140 (40-350)	585 (46.8%), 296, 150 (50-355)
+ 2 years	853 (24.5%), 144, 56 (18-150)	9628 (34.7%), 215, 100 (25-272)	2188 (46.9%), 279, 140 (45-360)	569 (45.5%), 285, 150 (45-346)
+ 3 years	884 (25.4%), 152, 60 (20-175)	9626 (34.7%), 211, 100 (25-262)	2144 (46.0%), 278, 150 (40-351)	581 (46.4%), 269, 140 (38-350)
+ 4 years	881 (25.3%), 150, 60 (15-177)	9563 (34.4%), 204, 98 (25-250)	2170 (46.5%), 264, 129 (33-330)	569 (45.5%), 261, 130 (38-341)
Z-hypnotics	N (%), DDD mean, median, IQR			
- 2 years	807 (23.2%), 209, 160 (40-300)	9792 (35.3%), 280, 210 (60-400)	2187 (46.9%), 319, 267 (90-420)	584 (46.7%), 340, 300 (100-433)
- 1 years	951 (27.4%), 213 127 (35-300)	10, 381 (37.4%), 285, 210 (60-400)	2293 (49.2%), 334, 290 (100-430)	610 (48.8%), 349, 300 (110-456)
+ 1 year	1122 (32.3%), 213, 150 (50-300)	10 963 (39.5%), 282, 215 (70-400)	2407 (51.6%), 329, 280 (100-400)	604 (48.3%), 347, 300 (108-418)
+ 2 years	1123 (32.3%), 233, 190 (60-360)	10 924 (39.3%), 301, 250 (90-400)	2323 (49.8%), 344, 300 (110-430)	588 (47.0%), 369, 300 (136-430)
+ 3 years	1165 (33.5%), 243, 200 (60-362)	11 010 (39.7%), 303, 261 (90-400)	2324 (49.8%), 349, 300 (131-430)	587 (46.9%), 367, 300 (170-442)
+ 4 years	1182 (34.0%), 247, 200 (60-364)	11 065 (39.9%), 300, 260 (96-400)	2325 (49.9%), 337, 300 (173-420)	582 (46.5%), 370, 300 (150-450)

Abbreviations: DDD, defined daily doses; IQR, interquartile range.

Group 1: Individuals, who did not receive any prescription of opioids in 2010 to 2012 (opioid naïve tramadol users).

Group 2: Individuals, who received prescriptions of only weak opioids in 2010 to 2012 (former weak opioid user group).

Group 3: Individuals, who received prescriptions of strong and/or weak opioids in 2010 to 2012 (former strong opioid user group).

Group 4: Individuals, who received palliative care and prescriptions of opioids in 2010 to 2012 (users in palliative care group).

TABLE 3 The possible concurrent drug use of opioids, benzodiazepines, and Z-hypnotics, at the fourth year of follow-up, in recurrent opioid users (who have used opioids in each of all four years from 2012 to 2016), stratified into four different study population groups

n (%)	Group 1: Opioid Naïve Tramadol Users *n* = 413 (11.9)	Group 2: Former Weak Opioid Users *n* = 5070 (18.3)	Group 3: Former Strong Opioid Users *n* = 1239 (26.6)	Group 4: Users in Palliative Care *n* = 319 (25.5)
	DDD mean, median (IQR)			
Opioids, in total	175, 67 (75-164)	246, 163 (65-328)	400, 254 (103-493)	453, 309 (143-588)
Benzodiazepines	150, 65 (20-192)	188, 99 (25-239)	238, 120 (40-300)	241, 122 (40-275)
Z-hypnotics	284, 241 (90-400)	352, 300 (125-432)	379, 330 (150-500)	411, 357 (200-500)

Abbreviations: DDD, defined daily doses; IQR, interquartile range.

strong opioid users and users in palliative care had stable mean consumptions of 300 DDD and 410 DDD (Table 2). In opioid naïve tramadol users, the periodic prevalence of strong opioid use increased from 14.2% in 2012 to 23.3% in 2016. Furthermore, an increasing periodic prevalence of strong opioid use from 9.6% to 18.7% was seen among former weak opioid users (Table 2).

3.3 | Possible concurrent drug use among recurrent opioid users

3.3.1 | Opioids and benzodiazepines

We found a stable and high proportion of BZD users in all groups during follow-up (Table 2). In the first 1-year follow-up period, the proportion of possible concurrent users of BZDs was 23.8% of opioid naïve tramadol users, 34.8% of former weak opioid users, 47.8% of former strong opioid users, and 46.8% of users in palliative care. During follow-up, both the 1-year periodic prevalence and doses of BZDs were stable in all groups, but highest among former strong opioid users and users in palliative care (Table 2).

3.3.2 | Opioids and Z-hypnotics

The proportion of possible concurrent Z-hypnotics users was even higher than the possible concurrent use of BZDs and remained stable during follow-up (Table 2). In all groups, more than 30% had a recurrent use of Z-hypnotics, receiving at least one prescription of Z-hypnotics during each of the four 1-year periods. Doses and 1-year periodic prevalence were high and stable during follow-up with a slight increase among opioid naïve tramadol users (Table 2).

3.3.3 | Opioids, benzodiazepines, and Z-hypnotics

In the fourth year of follow-up, among recurrent users, 11.9% of opioid naïve tramadol users had a possible concurrent use of opioids, BZDs, and Z-hypnotics, compared with 18.3% of former weak opioid users, 26.6% of former strong opioid users, and 25.5% of users in palliative care (Table 3). In patients receiving all three drugs, the opioid doses were higher than the average in each group (Table 3).

3.3.4 | Consistent recurrent opioid users

In the fourth year of follow-up, among those who became recurrent opioid users: 40.3% of opioid naïve tramadol users, 58.6% of weak opioid users, 76.1% of strong opioid users, and 78.6% of users in palliative care were defined as consistent recurrent opioid users (Data not shown).

3.3.5 | Possible problematic drug users

The criteria of possible problematic drug use (during the fourth 365 day's period: ≥365 DDD opioids, ≥100 DDD BZDs, and ≥100 DDD Z-hypnotics) were met by 0.5% of opioid naïve tramadol users, 2.2% of former weak opioid users, and 5.5% of strong opioid users. In the group of patients receiving reimbursement for palliative treatment, 6.8% met the same criteria.

4 | DISCUSSION

The main finding was that although only 5.8% of opioid naïve tramadol users became recurrent users, these patients doubled the annual opioid dose during the 4-year follow-up, one-fifth proceeded to strong opioids, more than one-third had a consistent recurrent use, one-quarter was co-medicated with BZDs, one-third was co-medicated with Z-hypnotics, and one-tenth was co-medicated with both drugs. Thus, in a significant minority (about 1/20) of patients using tramadol, their first opioid prescription may be the first step towards a long-term opioid use that in many patients is combined with using other drugs with addiction potential. In the two non-palliative care patient's groups, who had been former users of weak or strong opioids before receiving tramadol, the rates of recurrent use (39.8%, 60.7%), consistent recurrent use (58.6%, 76.1%), and possible problematic drug use (2.2%, 5.5%) were higher. This prescription pattern indicates that these patients have developed or are at risk of developing problematic opioid use.

Another concern is that the group of former strong opioids users had a prescription pattern quite similar to the users in palliative care, even though guidelines and treatment principles for opioids in these two patient populations differ substantially.[23] Acute pain conditions tend to follow a predictable and linear trajectory and usually respond well to opioids. In contrast, opioid treatment for chronic pain with no predictable or linear trajectory often only initially provides pain relief. In addition, many bio-psycho-social factors influence the experience, perception, and report of chronic pain, which can explain why long-term opioid treatment for chronic pain does not deliver expected outcomes including lowering pain scores. Because of chronic pain conditions' complexity, it is inappropriate to offer the simple stepladder approach which is more suitable for cancer-related pain conditions.[23,24]

New opioid users' drug use pattern has previously been investigated in studies based on the NorPD.[25,26] One study found that 7% of new weak opioid users had a repeated opioid use (received an opioid prescription at least once during each of 4 years) and only 0.08% developed a prescription pattern indicating problematic opioid use (>365 DDD of opioids during each of 4 years, opioid prescriptions

from >3 doctors, and >100 DDDs of BZDs concurrently).[25] This result corresponds to our findings except that we found higher proportions of recurrent users (0.5%-6.8%) with a possible problematic drug use. However, an accurate comparison between these pharmaco-epidemiological studies can be difficult due to different study designs and different criteria for problematic opioid use such as symptoms of physiological and psychological dependence, dose escalations, and prolonged treatment periods.[27] Notably, our design enables us to explore the dose progress, shift to strong opioids, and co-medication in both opioid naïve tramadol user and former opioid users.

In 2015, 17% of the Norwegian population received opioid treatment and the rate of high-risk opioid users was 2.7/1.000 in 2013.[28] A current Norwegian drug report stated an increase in the number of drug-induced deaths, in which opioids were the most frequent drug involved. In 2014, among adults (aged 15-64 years), the Norwegian average of drug-induced mortality rate was 75.6 deaths/million, compared with the European average of 20.3 deaths/million.[28] Measurements of mortality rates may, however, vary considerably between the European countries.[29]

It is well-known that opioid users, especially long-term high dose opioid users, have increased risks for co-medication with BZDs or Z-hypnotics compared with non-opioid users.[26,30-34] Likewise, in our study, high-dose opioid users were also high-dose users of sedative. Among former strong opioid users and users in palliative care, who became recurrent users, almost half used BZDs or Z-hypnotics, and one-quarter used both drugs concurrently. Among recurrent users, in the two other study population groups, 34.0% to 39.9% used Z-hypnotics, 25.3% to 34.4% used BZDs, and 11.9% to 18.3% used both drugs. Regarding individuals with CNCP, a high prevalence of sleep difficulties and anxiety may contribute to the high prevalence of concurrent use of sedative-hypnotics.[35,36] Nevertheless, this concurrent drug use is not recommended for individuals with CNCP since BZDs or Z-hypnotics act as central nervous system depressants and increases the risk of addictive behavior, drug toxicity, mortality, and overdose-related deaths.[37-39] In contrast, for users in palliative care, the opioid use pattern may continue despite severe side-effects if crucial to relieve pain, distress, and anxiety.

4.1 | Strengths and limitations

This study's strength is that it is based on a complete national database covering the entire Norwegian population, which minimizes the risk of selection and information bias. Furthermore, the use of NorPD enables to follow cohorts over time.

It is a limiting factor that NorPD does not provide information about drug use during hospitalization/other institutions, which can cause a minor underestimation of the actual drug use. As hospitalization increases with age, underestimation is most likely in the elderly,[40] among sick hospitalized patients and consequently in users of palliative care. Another limitation is unavailable information about whether the dispensed drugs were used as prescribed.

Using reimbursement code to stratify the study population between palliative care treatment and acute pain/CNCP could have caused a potential inaccurate stratification. Furthermore, inaccurate use of the code can have occurred when separating cancer patients' palliative care from those in curatively intended treatment or in complete remission. It is also important to recognize that patients were stratified according to baseline status in 2012. Some of the patients, who were stratified as non-palliative at baseline, may have developed a life-limiting disease and become palliative care patients during follow-up. This may explain some cases of dose-escalation and co-medication in the three non-palliative groups in our study.

Because problematic opioid use by definition is described in terms of behavioral patterns, not drug consumption, it is not possible to accurately identify persons with problematic opioid use based on prescription register data alone. Some of the recurrent users may not have received tramadol for CNCP but for separate acute pain episodes, and some of the possible concurrent drug users may not have used BZDs and/or z-hypnotics simultaneously with opioids.

Nevertheless, our findings highlight that even though a minority of patients receiving tramadol become recurrent users, those patients receive prescriptions which conflict with existing guidelines and might lead to problematic opioid use. This underlines the importance of careful selection and monitoring of patients who initiate opioid therapy and particularly those who proceed to recurrent use. Additionally, current studies have investigated the risk of opioid misuse and pain relief among opioid naïve CNCP patients, and their conclusions do not support initiating of opioid therapy for CNCP. Association between each refill and week of opioid use with large increases in opioid misuse was found, as well as a less effective pain-related function over 12 months using opioids compared with non-opioid medication.[41,42] It is relevant to question whether it is the appropriate patient population, who receive long-term opioid treatment for CNCP[26] since a substantial number of patients' pharmacological treatment conflicts with guideline recommendations.[18,19,43]

ETHICS STATEMENT

The authors state that no ethical approval was needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have contributed substantially to the study. They have discussed the results and commented on the manuscript.

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