RESEARCH ARTICLE

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Filled prescriptions for opioids among children and adolescents – A nationwide study from 2010 to 2018

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Abstract

Background: Prescribing opioids for children and adolescents should be reserved for advanced life-limiting diseases and moderate-to-severe acute pain. Pediatric codeine use is discouraged by several authorities, but the effects of these recommendations are not fully known. We investigated opioid utilization trends among 0–18-year-olds and characterized those who filled ≥1 opioid prescriptions, with emphasis on those who did so >3 times within a year.

Methods: The prevalence of filled opioid prescriptions among 0–18-year-old Norwegians in 2010–2018 (N = 77,942) was measured from nationwide healthcare registries. Characteristics, healthcare utilization, and other drug use of those who newly filled 1, 2–3, or >3 opioid prescriptions in 2011–2014 were compared to 2015–2018, excluding persons with cancer.

Results: From 2010 to 2018, the prevalence of opioid use decreased from 9.0 to 7.0 per 1000 persons. The largest decrease was among children <12 years, from 4.1 to 0.4 per 1000 persons, mainly due to decreasing codeine use. The proportion of those who filled >3 opioid prescriptions was 2.1% in 2011–2014 and 3.1% in 2015–2018. Those with >3 dispensations had a median of 4 contacts/year with secondary healthcare (interquartile range 2–7); the most frequent diagnoses indicated post-surgery follow-up. Most commonly dispensed other drugs were non-steroidal anti-inflammatory drugs.

Conclusions: Opioid dispensations for the young have declined in recent years. Multiple opioid dispensations were rare and associated with frequent healthcare utilization. Reducing codeine is in line with recommendations, but the effects of decreased opioid use on the quality of pain management remain unknown.

KEYWORDS
adolescents, children, opioids, pharmacoepidemiology

1 | INTRODUCTION

Opioid analgesics are indicated for use in children and adolescents in advanced life-limiting diseases, such as cancer, as well as in moderate-to-severe acute pain conditions when non-pharmacological treatment and non-opioid analgesics fail to provide adequate pain control.[1,2] However, there are major concerns related to persistent treatment with opioids in children and adolescents. There is currently very little evidence to support the use of opioids for chronic non-cancer pain in this population[3] and the long-term adverse effects of opioids, e.g., the risk of endocrine and immunological deficiency, and the risk for developing an addiction, are still not well-known. Moreover, there are concerns over the use of the weak opioid codeine among children, as it has the potential to cause severe adverse effects including respiratory depression in rapid metabolizers.[4] In the United States (US), there were dramatic increases in hospitalizations of children and adolescents for opioid poisonings from 1997 to 2012, and this raised the question of whether opioid prescribing for this population had changed.[5]

In 2006–2012, the prevalence of filled opioid prescriptions among Norwegian children increased by 25%, to 13.4 per 1000 persons in 2012.[6] This prevalence was approximately four times as high as in Sweden and twice as high as in Denmark, but the reasons underpinning the discrepancy are unclear.[7] Moreover, approximately 95% of children who filled a prescription for opioids, received codeine. In 2013, the Norwegian Medicines Agency strongly discouraged the use of codeine in children below 12 years of age.[8] This recommendation resulted in an 80% reduction in the prevalence of filled codeine prescriptions from 2011 to 2015 in this age group.[9] The decline in codeine dispensations was accompanied by only a minor increase in filled prescriptions of other opioids, implying a significant reduction in opioid use among Norwegian children during these years. However, the latent effects of this recommendation, its effects on the characteristics of opioid utilization, and its impact on the use of prescription opioids in older children and adolescents are currently unknown. Similarly, despite potential risks, there is little research into persistent opioid use and its determinants in this population.[10]

Current literature of population-based studies on the outpatient use of opioids among children and adolescents is still scarce.[7,11] Previous large-scale studies have focused on drug dispensation patterns but have lacked data either on morbidity, co-medication, or the use of healthcare services.[6,7,10-13] Given the high annual prevalence of opioid use in Norwegian children compared to neighboring countries between 2006 and 2012 and the changes in prescribing recommendations to younger children, further investigations on the development of these trends, characteristics of opioid users, and on the persistence of opioid use in these populations are needed.

The primary aim of this study was to investigate the prevalence of filled prescriptions among children and adolescents in Norway and to describe changes over time from 2010 to 2018. Secondary aims were to assess the characteristics, underlying diagnoses, other prescription drug use, and secondary healthcare utilization of those who newly filled prescriptions for opioids for non-cancer pain in

Editorial Comment

Opioid prescription practices have become more cautious and considered in recent years, with good reason.

In this analysis of national registry data for drug prescriptions and healthcare contacts for children, there was comparison of opioid prescription practice for two time periods, the second after new governmental policies discouraging liberal prescription of codeine to children. The findings showed that particularly codeine prescriptions decreased for children under 12 years of age. Further findings show that opioids are still important and prescribed for longer periods in a small minority in some advanced healthcare situations.

2011–2014 comparing to those who did so in 2015–2018, with emphasis on those filling more than three opioid prescriptions within a year.

2 | MATERIAL AND METHODS

2.1 | Data sources

This study utilized data from 2010 to 2018 from two nationwide administrative registries – the Norwegian Prescription Database (NorPD) and the Norwegian Patient Registry (NPR). The NorPD is an electronic registry which has obtained data on all prescriptions to individuals dispensed from all community pharmacies in Norway since 2004.[14] Each filled prescription has been registered with patient identifiers and drug information, including the date of dispensing and an Anatomical Therapeutic Chemical (ATC) code, identifying the specific drug.[15] The NorPD includes information on all filled prescriptions for opioids in Norway, where analgesic opioids are available only through prescription.

The NPR is an administrative database containing data from all public specialist healthcare services since 2008.[16] It includes data on hospitalizations and outpatient visits in hospitals, as well as consultations with specialists in private practice with public reimbursement. All Norwegian residents are covered by the public healthcare system through a national insurance scheme and healthcare is free of charge for children under 16 years. Healthcare providers must report patients' healthcare service use to the NPR, which then links to a governmental reimbursement system for funding of health services. Every admission to a hospital or an appointment with a specialist or an outpatient clinic has been registered with information such as date, diagnosis, and patient data. All diagnoses are reported according to the International Classification of Diseases, 10th Revision (ICD-10).

A unique person identifier, held by all Norwegian inhabitants, enabled the linkage of individual data from these two data sources.

Pseudonymization of the person identifier before linkage of registry data ensured that the study population remained unidentifiable to the research group.

2.2 | Study population

All Norwegian inhabitants below 18 years of age (1.1 million) with a valid personal identification number were eligible for this study. Children and adolescents who filled at least one prescription for analgesic opioids (ATC code N02A) and were aged less than 18 years on the date of the first opioid dispensation during the study period (2010–2018) were identified as target study population (i.e., "opioid users") and enrolled in the analyses.

2.3 | Analysis of opioid utilization over time

For the target study population, annual (i.e., 1-year periodic) prevalence of opioid use during the study period was calculated after stratification into age groups (0–11, 12–14, and 15–18 years). The numerator, number of children and adolescents who filled at least one prescription of opioids, was calculated each calendar year from 2010 to 2018. The denominator, the total number of inhabitants in each age group in Norway on 1st of July in each year from 2010 to 2018, was retrieved from the Norwegian statistics bureau, Statistics Norway.[17]

2.4 | Characteristics of opioid users in two 4-year cohorts

To define characteristics of opioid users and changes over time, we only included new users of opioids. These users were stratified into two cohorts according to the first filled prescription: the first cohort from 2011 to 2014 and the second cohort from 2015 to 2018. The cohort years were chosen to roughly reflect the time before and after the recommendation of the Norwegian Medicines Agency to avoid codeine in younger children, allowing time for uptake. New opioid use was defined as a filled opioid prescription after 365 days' washout, that is, no filled opioid prescriptions within a year. Subsequently, new use could only begin after 2010 for the first cohort and after 2014 for the second cohort. Users in the first cohort were allowed to become users in the second cohort if they filled the criteria for the washout. Those with cancer diagnoses within the study period (ICD-10 codes C00–99) were excluded from these analyses (N = 784).

According to the total number of filled opioid prescriptions within one year, users in these two four-year cohorts were further grouped into three categories: only one prescription of opioids filled, two to three, and more than three prescriptions filled. We defined those who filled an opioid prescription more than three times during a year as recurrent users of opioids, as there are no gold standard definitions to describe this phenomenon. We measured the

characteristics of these populations within 365 days from the first filled opioid prescription. We analysed the number of opioid users, age at first dispensation, the number of female opioid users, the numbers of which opioid agent was dispensed first, and the amount of opioids dispensed (measured as Defined Daily doses, DDDs[15] and oral morphine equivalent milligrams, OMEQ, per day). To estimate the amounts of OMEQ per day, we converted the doses of opioids to oral morphine taking into account the opioid agent, dose, and the route of administration.[18]

2.5 | Healthcare utilization, secondary healthcare diagnoses, and other drug use

We measured secondary healthcare utilization as the number of secondary care diagnoses and as the number of contacts with specialists. To increase relevance for opioid use, we analysed the diagnoses around the first filled opioid prescription, that is, three months before and three months after the dispensation. The number of different diagnoses among youth who filled opioid prescriptions and the number of contacts with specialists were retrieved from the NPR. One patient could have had multiple diagnoses or contacts during the six months.

For recurrent opioid users in both 4-year cohorts, we also studied the most frequent diagnoses they received. Similar to the full-cohort analysis, only diagnoses three months before and three months after the dispensation we analysed. Due to ethical concerns, only the most prevalent diagnoses, that is, diagnoses found in 20 or more children or adolescents in both cohorts, are presented in this study.

Furthermore, we studied the most frequently filled prescriptions of other drugs during 365 days from the first opioid prescription among all opioid users. After stratifying the population by the number of filled prescriptions per year (1, 2 to 3 and 4 or more), the analysis was conducted at the fourth ATC level. In addition to this, we calculated the prevalence of hypnotics: benzodiazepines and related drugs (BZDRs) (ATC codes N05CD, N05BA, and N05CF), melatonin (N05CH01), and alimemazine (R06AD01).

Descriptive statistics were used to present the above results in numbers of observations, proportions with 95% confidence intervals, means with standard deviation (SD), and medians with interquartile ranges (IQR). Kruskal-Wallis non-parametric test and Pearson's chi-squared test were used to detect differences between the cohorts and subgroups. We considered p-values of <0.05 as statistically significant.

2.6 | Research ethics

The register linkage was approved by The Regional Committee for Medical Research Ethics and by the Norwegian Data Protection Authority (decision numbers 2010/131 and 10/00447-5, respectively). Data collection for the NorPD and NPR is mandatory and

anonymous data are, according to Norwegian legislation, available for research without obtaining consent from each person in the study population.

3 | RESULTS

3.1 | Opioid utilization in children and adolescents from 2010 to 2018

Overall, 77,942 children and adolescents filled a prescription for opioids between 2010 and 2018. The annual prevalence of opioid use decreased from 9.0/1000 persons in 2010 to 7.0/1000 persons in 2018 (Table 1). Among those aged 15–18, opioid use increased from 22.2/1000 persons in 2010 to 25.3/1000 persons in 2012 and then remained stable until 2018 (Figure 1). Among those aged 12–14, the prevalence decreased from 9.1/1000 persons in 2010 to 7.2/1000 persons in 2018. The largest decrease was observed in children aged 0–11, among whom opioid use decreased from 4.1/1000 persons in 2010 to 0.4/1000 persons in 2018. Among all children and adolescents, the proportion of codeine as the first opioid of the year declined from 89.7% in 2010 to 65.2% in 2018 (data not shown). At the same time, the proportion of tramadol increased from 9.6% in 2010 to 30.4% in 2018.

3.2 | Characteristics of opioid users

A total of 37,624 children and adolescents filled a new prescription for opioids in 2011–2014. Their mean age at first opioid dispensation was 13 (SD 4.7), and 51.6% were female (Table 1). In 2015–2018, a total of 27,569 filled a prescription for opioids. The mean age was to 16 (SD 2.1, p for the difference between cohorts <0.001) and

the proportion of females increased slightly to 54.5% ($p < 0.001$). In 2011–2014, the median amount of opioids dispensed per person in OMEQ was 30 mg (IQR: 15, 75), increasing to 60 mg in 2015–2018 (IQR: 30, 99). Similarly, the number of diagnoses increased slightly, although the median number stayed at 2 (IQR: 1, 3) ($p = 0.002$). The median number of contacts with specialists increased from 2 (IQR: 1, 4) in 2011–2014 to 3 (IQR: 1, 5) in 2015–2018 ($p < 0.001$). As the proportion of codeine as the first opioid dispensed decreased from 86.7% in 2011–2014 to 70.6% in 2015–2018 ($p < 0.001$), the proportion of tramadol increased from 12.9% to 27.2% The proportions of morphine and oxycodone increased from 0.1% to 0.4% and from 0.3% to 1.6%, respectively, in the same time frame ($p < 0.001$).

In 2011–2014, 2.1% of the persons filling prescriptions for opioids were categorized as recurrent users of opioids, increasing to 3.1% in 2015–2018 (Table 2). In the first cohort, the mean age of recurrent users at first dispensation was older (16 years) in comparison to those who filled one (13 years) or 2–3 prescriptions for opioids (14 years, p for all differences <0.001), while the mean age was 16 for all groups in the second cohort. Recurrent opioid users were more likely to be female ($p < 0.001$ in both cohorts). In 2011–2014, the recurrent users filled prescriptions for a median of OMEQ 265 mg (IQR: 135, 615) and 365 mg in 2015–2018 (IQR: 180, 705). Among the recurrent users, the proportion of codeine as the first dispensed opioid decreased from 76.3% in the first cohort to 65.7% in the second cohort.

In both 4-year cohorts, chronic tonsillitis was the most frequent diagnosis from secondary healthcare among the recurrent users of opioids (13.9% of the first cohort, 95% CI: 11.5–16.3 and 14.4%, 95% CI: 12.0–16.7, in the second cohort) (Table 3). Other diagnoses frequently indicated follow-up from treatment and/or surgery (e.g., Z09.4, Z09.0, Z47.8, and Z09.8) or pain in specific locations (e.g., R10.4, abdominal pain; M25.5; pain in joint; M79.6, pain in limb).

TABLE 1 Children and adolescents (0–18 years) without cancer diagnosis and with new filled prescription for opioids in 2011–2014 (N = 37,624) compared with 2015–2018 (N = 27,569)

	Cohort 2011 to 2014	Cohort 2015 to 2018	p-value
Number of opioid users (%)	37,624	27,569	
Age at first dispensation, mean (SD)	13 (4.7)	16 (2.1)	<0.001
Number of girls (%)	19 399 (51.6)	15 020 (54.5)	<0.001
Amount dispensed as OMEQ (milligrams), median (IQR)	30 (15, 75)	60 (30, 99)	<0.001
Number (%) of the first opioid dispensed			
Codeine[a]	32 611 (86.7)	19 459 (70.6)	<0.001
Tramadol[b]	4840 (12.9)	7492 (27.2)	<0.001
Oxycodone[c]	108 (0.3)	453 (1.6)	<0.001
Morphine	21 (0.1)	112 (0.4)	<0.001
Other opioids	41 (0.1)	53 (0.2)	0.006

DDD =Defined Daily Dose; IQR =Interquartile Range; OMEQ =Oral Morphine Equivalents; SD =Standard Deviation.

[a]in combination with paracetamol

[b]alone or in combination with paracetamol
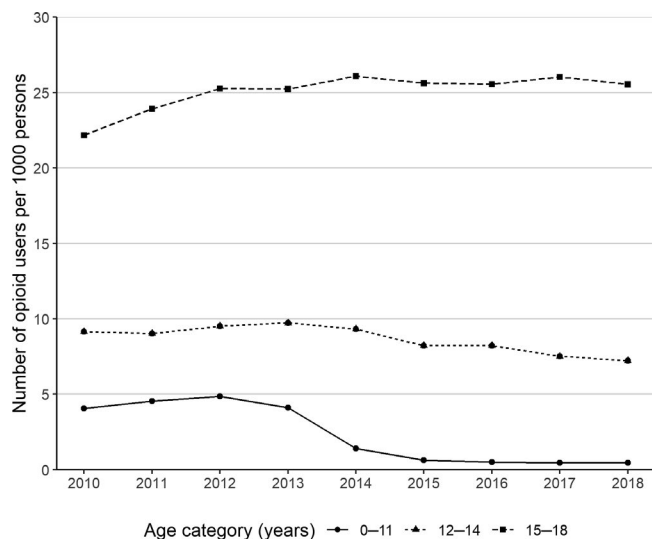
[c]alone or in combination with naloxone.

FIGURE 1 Prevalence of filled opioid prescriptions per 1000 persons in 2010–2018 by age group

In both 4-year cohorts, the most frequently used category of other drugs was non-steroidal anti-inflammatory drugs (NSAIDs), ranging from 36.1% (95% CI: 35.5–36.8) among those who filled one prescription for opioids in the second cohort to 67.5% (95% CI: 64.2–70.8) among recurrent opioid users in the first cohort (Figure 2). Compared to those with only one prescription for opioids filled, recurrent opioid users filled a prescription for most other drug categories more frequently in both cohorts, with the exceptions of antiallergics for eyes, psychostimulants, and in the first cohort for corticosteroids. Compared with those with 2–3 filled prescriptions for opioids, in both cohorts filled prescriptions of alimemazine, beta-lactam antibacterials, antidepressants, BZDRs, drugs for constipation and for peptic ulcer, and NSAIDs were more frequent among the recurrent opioid users.

4 | DISCUSSION

To our knowledge, this is the first population-wide study on prescription opioid use among children and adolescents with analyses of other drug use and healthcare utilization. We found a persistent decreasing trend of filled opioid prescriptions annually between 2010 and 2018, but only among those aged less than 15 years. Simultaneously, there was a slight increase in opioid utilization among those aged 15–18 years. Filling multiple opioid prescriptions per year was generally rare and commonly accompanied by an increasing number of diagnoses, frequent contacts with secondary care, and also frequent use of other prescription drugs. The common use of BZDRs among recurrent opioid users calls for special attention due to an increased risk for CNS depression and the development of addiction.

Our findings on the declining use of opioids among children and adolescents in most recent years are in line with the results from several previous studies conducted in the USA and

Australia.[10-13,19-21] However, the prevalence of opioid use has been remarkably higher in studies conducted in the United States, but also somewhat so in Australia.[10,11,19,20] The decreasing trends have also previously been attributed to decreased codeine use in some of these populations. In our study, although the increased proportion of tramadol users may be attributed to the substitution of codeine, the absolute numbers of filled prescriptions still suggest that most codeine was not replaced with other opioids. Codeine is a weak opioid agonist, which has genetic variability in its conversion to an effective analgesic via the hepatic enzyme CYP2D6, resulting in varying efficacy and increased risk of severe adverse effects among ultra-rapid metabolizers.[4] In addition to the Norwegian Medicines Agency, its use among children has also been discouraged by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the American Academy of Pediatrics (AAP).[4,22,23] Its decreasing use can thus be considered a positive finding. However, the fact that codeine continues to be the most common opioid used indicates that several patients are put at risk of serious adverse events.

Similarly to codeine, tramadol has genetic variation in its activation by CYP2D6, and its use among children can thus be considered problematic.[24-26] These results suggest that clinicians may need further guidance on safer alternatives to both codeine and tramadol in these populations, or on how to dose according to CYP2D6 genotype.[26] Nevertheless, our results suggest that the 2013 recommendations by the Norwegian Medicines Agency, as an addition to international prescribing guidelines, can be considered as an example of a successful health policy intervention with long-term consequences.

Conversely, the reduced use of opioid analgesics also raises concern about the unmet needs of pain management in the youngest population. As we cannot determine the appropriateness of opioid use in this study due to the lack of data on opioid dose, pain, or the specific indications to which the opioids were prescribed, future clinical research should carefully investigate how moderate-to-severe pain is currently treated, especially among children aged below 12. Our results on the increasing OMEQ doses in 2011–2014 compared to 2015–2018 suggest that the reduction in the number of users has mainly happened among those with less intense or shorter term opioid treatment. Nonetheless, the questions of whether the current pain management is satisfactory in children and whether the recommendation to avoid codeine in this age-group could have contributed in suboptimal pain management in children is an issue of concern which deserves further research. Similarly, the slightly increasing trends of opioid use among those aged 15–18 calls for follow-up investigation in the near future.

Our findings on the rarity of recurrent opioid use in the young population can be considered reassuring. The healthcare utilization and most frequent diagnoses in this population suggest that this is a small group of patients with complex health issues. Generally, opioid use for chronic pain among children is of unknown efficacy with largely unknown risks[3] and prescription opioid use in adolescence may also be a risk factor for substance use disorder in later

TABLE 2 Children and adolescents (0–18 years) without cancer diagnosis and with filled prescriptions for opioids in 2011–2014 (N = 37,624) compared with 2015–2018 (N = 27,569)

Number of filled prescriptions within a year	Cohort with filled prescriptions in 2011–2014				Cohort with filled prescriptions in 2015–2018			
	1	2 to 3	4 or more	p-value	1	2 to 3	4 or more	p-value
Number of opioid users (%)	29748 (79.1%)	7069 (18.8%)	807 (2.1%)		20 961 (76.0%)	5765 (20.9%)	843 (3.1%)	
Age first dispensation, mean (SD)	13 (4.5)	14 (4.5)	16 (3.4)	<0.001	16 (2.2)	16 (2.0)	16 (2.0)	<0.001
Number of girls (%)	14975 (50.3%)	3924 (55.5%)	500 (62.0%)	<0.001	10 988 (52.4%)	3497 (60.7%)	535 (63.5%)	<0.001
Amount dispensed as DDDs, median (IQR)	5 (3,7)	10 (7–17)	29 (20–44)	<0.001	5 (3–7)	10 (8–17)	27 (18–43)	<0.001
Amount dispensed as OMEQ (milligrams), median (IQR)	30 (15–30)	60 (45–130)	265 (135–615)	<0.001	30 (30–100)	115 (60–200)	365 (180–705)	<0.001
Median (IQR) of different diagnoses	2 (1–3)	2 (1–4)	3 (1–5)	<0.001	2 (1–3)	2 (1–4)	3 (1–5)	0.002
Median (IQR) number of contacts with specialist healthcare	2 (1–4)	3 (1–5)	4 (2–7)	<0.001	2 (1–4)	3 (2–5)	4 (2–7)	<0.001
Number (%) of the first opioid dispensed								
Codeine[a]	25879 (87.0%)	6116 (86.5%)	616 (76.3%)	<0.001	14 849 (71.0%)	4056 (70.6%)	554 (65.7%)	0.005
Tramadol[b]	3802 (12.8%)	873 (12.4%)	165 (20.4%)	<0.001	5862 (28.0%)	1402 (24.3%)	228 (27.0%)	<0.001
Oxycodone[c]	31 (0.1%)	58 (0.8%)	19 (2.4%)	<0.001	139 (0.7%)	269 (4.7%)	45 (5.3%)	<0.001
Morphine	12 (0.0%)	5 (0.1%)	4 (0.0%)	<0.001	79 (0.4v)	22 (0.3%)	11 (1.3%)	<0.001
Other opioids	24 (0.1%)	17 (2.4%)	0 (0.0%)	<0.001	32 (0.2) %	16 (0.3%)	5 (0.6%)	0.004

DDD =Defined Daily Dose; IQR =Interquartile Range; OMEQ =Oral Morphine Equivalents; SD =Standard Deviation.

[a]in combination with paracetamol.

[b]alone or in combination with paracetamol.

[c]alone or in combination with naloxone.

TABLE 3 Most frequent secondary care diagnoses among children and adolescents with >3 filled prescriptions for opioids within a year (recurrent users) in 2011–2014 or 2015–2018

Diagnosis	ICD–10 codes	Cohort of 2011–2014 (N = 807)		Cohort of 2015–2018 (N = 843)	
		N	% (95% CI)	N	% (95% CI)
Chronic tonsillitis	J35.0	112	13.9 (11.5–16.3)	121	14.4 (12.0–16.7)
Follow-up examination after treatment of fracture	Z09.4	74	9.2 (7.2–11.2)	103	12.2 (10.0–14.4)
Other and unspecified abdominal pain	R10.4	51	6.3 (4.6–8.0)	60	7.1 (5.4–8.9)
Follow-up examination after surgery for other conditions [than malignant neoplasms]	Z09.0	48	5.9 (4.3–7.6)	84	10.0 (7.9–12.0)
General psychiatric examination, not elsewhere classified	Z00.4	39	4.8 (3.4–6.3)	5.5	46 (3.9–7.0)
Other specified orthopedic follow-up care	Z47.8	38	4.7 (3.2–6.2)	39	4.6 (3.2–6.0)
Pain in joint	M25.5	36	4.5 (3.0–5.9)	32	3.8 (2.5–5.1)
Observation for suspected mental and behavioral disorders	Z03.2	26	3.2 (2.0–4.4)	26	3.1 (1.9–4.3)
Follow-up examination after other treatment for other conditions [than malignant neoplasms]	Z09.8	26	3.2 (2.0–4.4)	32	3.8 (2.5–5.1)
Other physical therapy	Z50.1	25	3.1 (1.9–4.3)	26	3.1 (1.9–4.3)
Pain in limb	M79.6	20	2.5 (1.4–3.6)	27	3.2 (2.0–4.4)

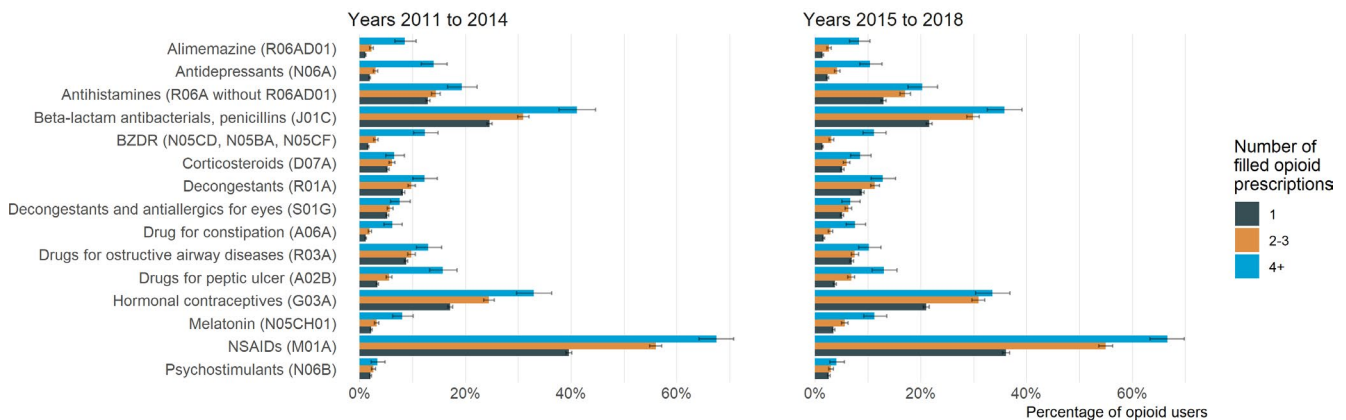ICD-10, International Classification of Diseases, 10th revision.

FIGURE 2 Most frequently filled prescriptions for drugs other than opioids among opioid users in 2011–2014 (N = 37,624) and 2015–2018 (N = 27,569). Prevalence of persons with at least one filled prescription within one year of the first opioid dispensation, with 95% confidence intervals, stratified by the number of prescriptions filled for opioids. BZDR, benzodiazepines and related drugs; NSAIDs, Non-steroidal anti-inflammatory drugs

life.[27] In our study, the secondary care diagnoses of recurrent opioid users frequently indicate follow-up after surgical operations. Postoperative pain management can often be finding a balance between appropriate management of postoperative pain while minimizing the risks related to opioid prescribing.[28] Surgery has been previously suggested as a pathway to persistent opioid use among adolescents which may be related to both unresolved postsurgical pain and addiction-related behavior.[28,29,30] Utilizing multimodal pain management strategies and risk assessment are thus important to reduce inappropriate opioid use and other risks of opioid use among young patients.

The frequency of filled prescriptions for NSAIDs among all opioid users in this study indicates the needs of managing acute or inflammatory pain or both. Despite the high prevalence of NSAID dispensations, their use is likely still underestimated, as data for drugs purchased over-the-counter (OTC) are not available at an individual level. In addition, the use of BZDRs was common in this study, especially among recurrent users of opioids. This is potentially a cause for concern, as the use of multiple CNS depressants may increase the risk of adverse effects of these drugs, especially at high doses,[31] but concomitant use also increases their misuse potential. The high prevalence of other hypnotics, that is, melatonin and alimemazine,

could suggest that sleep-related problems are frequent in this population, but future studies are needed to increase knowledge on the subject.

4.1 | Strengths and limitations

A major strength of this study is the comprehensiveness of the used registries. We analyzed all filled opioid prescriptions among all Norwegian children and adolescents during multiple years. Nordic administrative registries have been used for pharmacoepidemiological research for decades and have overall good coverage and validity.[14] It should be noted that analyses on the use of opioids during hospitalizations or OTC drugs were not included as these data are not attainable at an individual level. Similarly, although filled prescriptions are a better measure of actual drug use than prescriptions,[32] we cannot ascertain the dispensed drugs truly were used. This is especially important, as one-time purchases were frequent in our study.

As discussed previously, we had no data on the indication of the opioid therapy or on pain severity, which are limitations to this study. Similarly, although we analyzed the secondary healthcare diagnoses for recurrent opioid users, we were not able to ascertain whether these diagnoses were related to opioid therapy or not. Moreover, although the opioids were also prescribed by primary care physicians, we had no data on primary care diagnoses. As to the use of drugs other than opioids, we analyzed the filled prescriptions during the year opioids were also dispensed: whether these drugs were used concomitantly with opioids is not known.

5 | CONCLUSIONS

Similarly to the utilization trends in the USA and Australia, opioid use and especially codeine use among Norwegian children appears to be decreasing, following pediatric treatment guidelines. Our results indicate that official guidelines from medicinal agencies have the potential to rapidly reduce harmful prescription practices in the population, underlining the importance of monitoring prescription practices and changes over time. Moreover, our results suggest that recurrent opioid use was rare and in most frequent in a subgroup of adolescents with complex health issues. Future studies should research how well pediatric pain, especially among those under 12 years, is currently treated. Similarly, the increased use of tramadol and frequent hypnotic and anxiolytic use in opioid using children and adolescents can be causes of concern and warrant further research.

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