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Possible opioid-saving effect of cannabis-based medicine using individual-based data from the Norwegian Prescription Database

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Abstract

Some ecological studies have shown that areas with higher use of cannabis may have lower opioid use and fewer opioid-related problems. Newer studies are questioning this finding. Few individually based studies have been performed. Using data from the Norwegian Prescription Database, this study investigated the individual level effect of prescribed cannabis extract (Sativex®) in prescription opioid users on their opioid use in the following year. Looking at all those filling a prescription for Sativex®, opioid use was only marginally lowered in the follow-up period. Some Sativex® users, however, filled more prescriptions for Sativex® and were able to reduce their opioid use substantially. Further studies are needed to elucidate more details on these patients, so as to know who can benefit from such cannabis-based extracts in reducing their opioid use.

KEYWORDS
cannabis-based medicine, pharmacoepidemiology, prescription opioids

1 | INTRODUCTION

Opioids are effective for treating acute pain, but caution should be observed when using these drugs for chronic conditions because of the problem of tolerance development,[1,2] prescription drug abuse and opioid dependence.[3] The United States have seen a sharp increase in the use of prescription opioids during recent decades followed by a dramatic increase in the use of heroin,[4] a high number of overdose deaths[5] and even in the number of suicides.[6]

Cannabis is used for recreational purposes throughout the world and is the most commonly used illegal drug.[7] Although regulated by international treaties on narcotics trade, it has been legalized in several states in the United States and in some other countries.[8] We have also seen extensive use of medical cannabis drug, with easy access for many groups.[9]

We have seen increasing research on the medical use of cannabis for several different maladies.[10] Many of the suggested indications are currently speculative, but a modest effect on neuropathic pain seems to be a well-documented indication.[11–14] However, these reviews have been criticized for their quality, and more rigorous reviews have been requested.[15–17]

It has been debated whether the use of cannabis could have an opioid-reducing effect.[18–20] Reports show a beneficial effect of cannabis used together with opioids in cancer pain relief[21] and other chronic pain.[18] Early US ecological studies indicated that medical cannabis prescribing was associated with significant reductions in opioid prescribing,[22–25] opening a discussion on the possible role of medical cannabis in curbing the current US opioid epidemic.[26–28] A more recent ecological study, however, questions these results and whether there is any benefit for the opioid crises in the use of medical cannabis.[29] Studies on individual level are rarer but have shown that people who inject drugs and use cannabis use less opioids[30] and that pain patients can reduce their use of opioids when they use medical cannabis.[31,32] Other studies find no positive effect,[33] and some even suggest that cannabis use is a risk factor for developing problematic opioid use.[34,35] The latest review of the literature concluded that there was low quality evidence for a modest effect of adding cannabis concerning reduction or stopping opioids.[36] The need for further research is evident.

Medicinal cannabis products exist in several different forms and formulations. In Europe, the most common products are produced by Bedrocan®, who markets a series of different products such as standardized cannabis cigarettes or extracts, for example, in oils, and Sativex®, an oro-mucosal spray containing standardized amounts of Δ9-tetrahydrocannabinol (THC) and cannabinol (CBD).[37]

One prescription for Sativex® will in Norway provide up to 4 weeks of Sativex® use, giving up to 12 doses of 2.5 mg of THC and CBD, respectively, every day.[38]

Even if there are some studies of a possible opioid-saving effect of cannabis on an individual level, these are scarce and most of them are from the United States, where there is high use of both opioids and cannabis. The situation might be different in countries with lower use of both.[39] In the current study, we investigated whether the introduction of the cannabis extract Sativex® had any impact on the use of opioids on an individual level in Norway. Such an investigation could shed light on a possible opioid-reducing effect of cannabis.

1.1 | Aim

The study aimed to investigate the use of a cannabis extract (Sativex®) among opioid users and to see whether their use had any effect on use of opioids. More specifically, we wanted to investigate the following:

1. How many opioid users filled at least one prescription for Sativex® during the observation period?
2. Compared to opioid users not using Sativex®, how did their opioid use evolve from one year to the next?
3. Were there any differences between frequent and occasional users of Sativex® concerning opioid use in the follow-up year?

2 | METHODS

2.1 | Data source

All data for this study were drawn from the Norwegian Prescription Database (NorPD). From 1 January 2004, all pharmacies are obliged to submit data for all dispensed drugs electronically to NorPD administered by the Norwegian Institute of Public Health (www.norpd.no). NorPD contains information on all drugs dispensed from pharmacies, except for drugs administered at hospitals, in nursing homes or outpatient clinics. In NorPD, drugs are classified by the anatomic-therapeutic-chemical (ATC) system of WHO.[40]

2.2 | Study population

All patients above 18 years of age who had filled at least one prescription for an opioid (ATC codes N02A*) during the 10 years from 1 January 2010 to 31 December 2019 were eligible for the study. The study population among

these were those who received at least one prescription for the cannabis-based medicine Sativex® (N02BG10).

2.3 | Data and analysis strategy

In the study, the parameters collected were patients' unique identifiers (encrypted), gender, year of birth, year of death, and date of dispensing, drug name, Nordic Article Number, and defined daily dose (DDD). On the basis of DDD, we calculated milligrams (mg) of oral morphine equivalents (OMEQ).[41] Sativex® has no defined DDD,[42] but we studied those with any use of the drug and defined those who filled zero to one prescription of Sativex® within 364 days after the index prescription as "occasional users," and those filling two or more prescriptions for Sativex® within 364 days after the index prescription to "frequent users."

2.4 | Pharmacoepidemiological analysis

We restricted our analysis to opioid users who had received at least one prescription for opioids in the year prior to filling their first prescription for Sativex® from 2011 to 2018, leaving 1 year to observe changes in opioid use after the first prescription.

We compared the Sativex® users to a matched control group of opioid users who did not receive any prescriptions for Sativex® concerning their use of opioids in the follow-up year. The control group of nonusers of Sativex® was constructed as follows: For each Sativex® user, same-sex nonusers born the same year, with roughly the same opioid consumption, were eligible as controls. The amount of OMEQ (mg) for the Sativex® user during the 365 days before the index date was compared with the amount OMEQ for the control during the calendar year of the Sativex® user's index date. The control was chosen randomly among those with an OMEQ amount within ±1% of the Sativex® user's OMEQ amount. If there were no eligible controls within the calliper window of ±1%, the window was broadened in steps of 1% until it contained at least one eligible control. For the control group, we used the calendar year as the period for calculating opioid use (index year), and the year after as follow-up year. This was different from the dynamic years used for the Sativex® users, where we looked at the 365 days before and 0–364 days after their first prescription for Sativex® as index- and follow-up year, respectively. Exact date of dispensing was not available, only number of days since an individual-specific, but unknown date in the past, and hence we could not start the controls' opioid use period at the index date of the Sativex® users' first prescription. After the matching, we excluded individuals who died within the calendar year after the index date. For the controls, the time for possible death was exactly 1 year, but for the Sativex® users, it was on average 1.5 years because the "index date" could be anywhere between 1 January and 31 December in the index year.

We compared the matched nonusers of Sativex® with occasional users and frequent users on age, gender and opioid use in the index year to check the matching, but also to investigate differences between occasional and frequent users. We compared the three groups on number (share) of those stopping opioid use ("stoppers"), average amount of opioids (in OMEQs) in the follow-up year, and average change in the amount of opioid used from the index year to the follow-up year (excluding the stoppers).

In a final linear regression analysis, we investigated predictors of increase in OMEQ from the index year to the follow-up year including both users of Sativex® and nonusers (the control group). As explanatory variables, we included age, gender, amount of opioid use in the index year and the number of Sativex® prescriptions. For the latter, we compared occasional and frequent Sativex® users with nonusers. We also performed a sensitivity analysis by investigating separately in a regression analysis the effect of only one prescription for Sativex® and five or more prescriptions for Sativex®.

2.5 | Statistical analyses

For age, we reported means and standard deviation (SD), but for all other continuous variables (e.g., OMEQ), we reported 25 and 75 percentiles as we know that drug use among those receiving prescriptions is heavily skewed.[43] For all categorical variables with less than 5 in the group, values are given as "<5" due to regulations on anonymity given by NorPD. For categorical variables, χ^2 test was used to investigate significance; for age, Student's t-test was used, but for other continuous variables, Mann–Whitney U-test or Kruskal–Wallis test were used. We calculated the relative risk (RR) of stopping opioid use from the index year to the follow-up year taking into account gender, age, Sativex® use and amount of opioid used in the index year. Lastly, we performed a regression analysis with relative increase in opioid use from the index year to the follow-up year in continuers as outcome. Due to the asymmetric nature of this relative increase, we used

$$Y = \begin{cases} X, & X < 1 \\ 2 - 1/X, & X \geq 1 \end{cases} \text{ where}$$
$$= \frac{\text{mg OMEQ in follow-up year}}{\text{mg OMEQ in index year}}.$$

as dependent variable in the linear regression analysis. The regression coefficients (β) with 95% confidence intervals (95% CI) were reported. The analyses were performed using the statistical program "R" version 4.0.3.

3 | RESULTS

Of the 2 210 149 patients who filled at least one prescription for opioids during the 10-year period, only 1424 (0.06%) filled at least one prescription for Sativex®. Of these Sativex® users, 882 (49.7%) received at least one prescription for opioids in the year prior to starting Sativex®. The number of incident users of Sativex® who also received opioids the year before their prescription rose from <5 in 2011 to 275 in 2019 (Figure 1). When regarding any opioid use in the whole observation period, the number receiving a prescription for Sativex® rose from <5 in 2011 to 462 in 2019. For both measures, there were peaks in 2013 and 2019.

The 607 opioid users who received a prescription for Sativex® before 1 January 2019 (and were available for 1 year of follow-up) used a median of 2000-mg OMEQ (IQ range 370–10 039 mg) not different from the matched controls ($p = 0.822$) (Table 1). The number of deaths were more than six times higher in Sativex® users than in controls ($p < 0.001$). It should, however, be noted that the controls had 365 days of follow-up with respect to death, whereas the Sativex® users had between 365 and 730 days of follow-up, dependent on the date of the first Sativex® prescription.
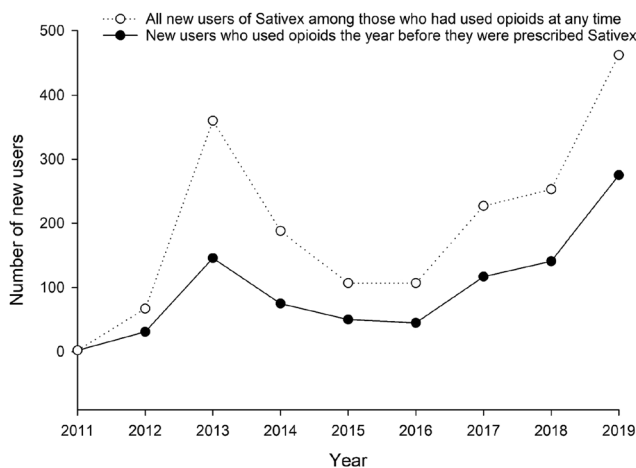

FIGURE 1 Number of incident users of Sativex® per year from 2011 to 2019 in Norway among users of opioids. Dotted line indicates all users of opioids, while continuous line represents those who received at least one prescription for opioids during the 365 days before their first prescription of Sativex®. Data from NorPD

There was a trend that opioid users who became frequent users of Sativex® more often stopped their opioid use compared with controls and occasional users, but this was not statistically significant (Table 2A). In the multivariate analysis, we found no significant predictors of stopping opioid use, except that those who used the least opioids more often stopped ($p < 0.001$).

In those who continued use of opioids, the use in the follow-up year did not differ among all users of Sativex® and the controls ($p = 0.792$; Table 1) nor did the median change in opioid use differ ($p = 0.813$), but we found a difference between occasional users and frequent users of Sativex® (Table 1). The frequent users of Sativex® used less opioids in the follow-up year compared with the occasional users ($p = 0.002$; Table 1), and while the median opioid use increased among the occasional users, it decreased among the frequent user ($p < 0.001$).

To a large extent, the regression analysis confirmed these results (Table 2B). Occasional users of Sativex® who continued using opioids in the follow-up year, increased their use of opioids ($p < 0.001$). This was opposite among the frequent users of Sativex® who decreased their use of opioids in the follow-up year compared with nonusers of Sativex® ($p = 0.008$). In a sensitivity analysis (data not shown in table), we also looked at those filling only one prescription for Sativex® showing that these individuals increased their use of opioids substantially ($p < 0.001$), whereas those who filled five prescriptions or more for Sativex® in the follow-up year, decreased their opioid use substantially ($p < 0.001$). Those opioid users who used more opioids in the index year decreased their opioid use in the follow-up year.

4 | DISCUSSION

This study showed that very few opioid-using patients filled a prescription for Sativex® during the observation period. The few who did did not differ overall in their use of opioids in the 1-year follow-up period starting on the day of the first Sativex® prescription compared with controls. However, when considering the number of Sativex® prescriptions filled by the patients during the follow-up year, another pattern occurred. Those filling one to two prescriptions (occasional users) increased their use of opioids in the follow-up year, whereas those who filled more prescriptions (frequent users) reduced their opioid use significantly, even to the point where we saw a dose–response effect.

Many European countries have allowed the use of cannabis-based medicine,[37] including standardized cannabis extracts like Sativex®.[44] Few studies have investigated the prevalence of use in Europe, but European

TABLE 1 Background variables and the use of opioids in those receiving 1–2 ("occasional users") and 3 or more prescriptions ("frequent users") for Sativex® the first year following the first Sativex® prescription, compared with a control group (matched on opioid use, gender, and age)

		Not receiving prescriptions for Sativex® (control)	Receiving at least one prescription for Sativex® during a year				
			All Sativex® users	P values[a]	Occasional users	Frequent users	P values[b]
		N = 607 (50.0%)	N = 607 (50.0%)		N = 351 (28.9%)	N = 256 (21.1%)	
Gender women	N (%)	343 (56.5)	343 (56.5)	1.000[c]	194 (55.3)	149 (58.2)	.524[c]
Age at first prescription of Sativex®	mean (SD)	52.9 (13.5)	52.9 (13.5)	1.000[d]	54.3 (13.9)	50.9 (12.6)	.002[d]
Deaths following year[e]	N (%)	15 (2.5)	98 (16.1)	<.001[c]	68 (19.4)	30 (11.7)	.016[c]
Opioid use							
OMEQ[f] index year	Median (IQ range)	2006 (370; 10 103)	2000 (370; 10 039)	.822[g]	2280 (420; 11 395)	1653 (251; 8496)	.385[g]
Alive stoppers following year[h]	N (%)	140 (23.6)	136 (26.7)	.270[c]	70 (24.7)	66 (29.2)	.302[c]
OMEQ[f] following year among continuing survivors	Median (IQ range)	4000 (1000; 17 092)	4000 (975; 17 174)	.792[g]	4080 (1000; 17 174)	3826 (956; 17 062)	.002[g]
Increase in OMEQ[f] following year among continuing survivors	Median (IQ range)	0 (−1000; 768)	−15 (−1551; 1675)	.813[g]	75 (−878; 3220)	−315 (−3589; 314)	<.001[g]

Note: The table includes the Sativex® users that had received at least one prescription for opioids in the year before they received a prescription for Sativex®.

[a]For differences between all Sativex® users and controls.

[b]For differences between occasional and frequent Sativex® users.

[c]χ^2-test.

[d]Student's t-test.

[e]Within calendar year after the index year.

[f]OMEQ: oral morphine equivalents in mg.[41]

[g]Mann–Whitney U-test.

[h]Sativex® users: no opioid prescriptions 0–364 days after the first Sativex® prescription; controls: no opioid prescriptions the calendar year after the index year.

TABLE 2A Relative risk (RR) for stopping opioid use in the follow-up year for occasional and frequent users of Sativex® compared with nonusers (unadjusted and adjusted estimates)

	Ref	Unadjusted		Adjusted	
		RR (95% CI)	*P* value	RR (95% CI)	*P* value
Gender	Male	0.98 (0.80; 1.20)	.852	0.98 (0.82; 1.17)	.811[a]
Age (per 10 years)	Continuous	0.91 (0.84; 0.98)		1.00 (0.94; 1.07)	.95[a]
Sativex® group					
Occasional users	Nonusers	0.98 (0.77; 1.25)	.883	1.07 (0.87; 1.33)	.510[a]
Frequent users	Nonusers	1.14 (0.89; 1.47)	.288	1.10 (0.88; 1.37)	.401[a]
Amount of opioids ($\log_2$ of OMEQ) year before first prescription of Sativex®	Continuous	0.76 (0.74; 0.78)	**<.001**	0.76 (0.74; 0.78)	**<.001**[a]

Note: Significant values are presented in bold.
[a]Adjusted for the other variables in the leftmost column.

TABLE 2B Linear regression for relative increase in opioid (in oral morphine equivalents; OMEQ) use from index year to follow-up year in occasional and frequent users of Sativex® compared with nonusers (unadjusted and adjusted analysis)

	Ref	Unadjusted		Adjusted	
		Beta (95% CI)	*P* value	Beta (95% CI)	*P* value
Gender	Male	.01 (−0.06; 0.07)	.874	.01 (−0.05; 0.08)	.678[a]
Age (per 10 years)	Continuous	.02 (0.00; 0.05)	.086	.02 (−0.01; 0.04)	.232[a]
Sativex® group					
Occasional users	Nonusers	.16 (0.08; 0.24)	**<.001**	.16 (0.09; 0.24)	**<.001**[a]
Frequent users	Nonusers	−.09 (−0.18; 0.00)	**.039**	−.09 (−0.17; 0.00)	**.046**[a]
Amount of opioids ($\log_2$ of OMEQ) year before first prescription of Sativex®	Continuous	−.02 (−0.03; −0.01)	**<.001**	−.02 (−0.04; −0.01)	**<.001**[a]

Note: Higher relative increase than in non-users gives a beta-coefficient above 0, while lower relative increase gives a beta-coefficient below 0. The dependent variable in the regression is $Y = \begin{cases} X, & X < 1 \\ 2 - 1/X, & X \geq 1 \end{cases}$ where $X = \frac{\text{OMEQ follow-up year}}{\text{OMEQ index year}}$. Significant values are presented in bold.
[a]Adjusted for the other variables in the leftmost column.

levels of use are still thought to be quite low.[45] Our study confirms that the prevalence of use of the cannabis extract Sativex® was very low in Norway in the observation period. This may have several explanations. There could be scepticism concerning the effect of cannabis-based medicines or little knowledge among health professionals.[46] Another reason could be the high costs of Sativex® not reimbursed in the Norwegian health care system. After a peak in 2013, two years after its introduction to the Norwegian market, there was a drop in the number of new Sativex® users. This early peak may reflect a high expectation of the effect of the drug,[47] maybe followed by a more realistic attitude. Since 2013, there has been a steady increase in the number of users to approximately 230 new users each year, a number that spiked again in 2019, for unknown reasons.

In the present study, there was no general opioid-saving effect of Sativex® in all those who tried the drug.

Our findings could thus be interpreted as contrary to other researchers looking into cannabis-based medicine.[22–25,32,48,49] However, looking more closely at different patterns of Sativex® use after the initial prescription, we found that those filling only one or two prescriptions in the follow-up year (occasional users) increased their opioids use substantially, whereas there was a decrease in those filling three or more prescriptions (frequent users). The decrease was even more evident among those filling five or more prescriptions. This strongly indicates that *some* patients experience a beneficial effect from their Sativex® use and continue this use, while reducing their opioid use. Earlier research has not been able to point to specific patients having a greater benefit of medicinal cannabis.[50] Our study was limited to pointing out that some patients may experience an opioid-saving effect of Sativex®, but the study cannot provide more detail on *who* these patients were.

It is also noteworthy that the findings do not suggest that cannabis-based medicines drives opioid use,[34,35] an effect we have previously observed for benzodiazepines.[51] It must be noted that Norway is a country with moderate use of opioids[52] in addition to the very low use of cannabis as medicinal drug.

4.1 | Limitations

This study on whether starting to use the cannabis-based medicine Sativex® resulted in a change in the use of opioids has some limitations. The study covered only the use of Sativex®, and not medical cannabis prescribed as standard joints, or "self-prescribed" medical cannabis. As it was a prescription database study, we have no information on other use of cannabis in the patients included, like the use of medicinal cannabis imported by individuals from abroad. Thus, many of the measures included in previous studies on medical cannabis are not captured by this study. Furthermore, the study only looked at opioid consumption for the first year after starting treatment with Sativex®. In chronic conditions, longer follow-up times could be necessary, because of the long duration of the condition. Also, we do not have information about the indication for Sativex® use in the individual patient. Thus, we cannot evaluate the effect in pain patients separately, only study opioid usage in general. Lastly, even if people filled prescriptions for drugs, we do not know if the drugs were in fact taken (secondary noncompliance).

4.2 | Conclusion

This is one of a few studies investigating the impact of medicinal cannabis use on individual level opioid use. Very few opioid users used the cannabis extract Sativex®. For opioid users in general, we found little evidence that the use of a cannabis-based medicine reduced their use of opioids. Some individuals, however, seemed to benefit from continued use of Sativex® and were able to reduce their use of opioids after having started with the drug. Further studies should be performed to identify the characteristics of individuals who may experience such beneficial effects.

CONFLICT OF INTEREST
None of the authors have any conflicts of interest to report.

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