

# The Risk of Motor Vehicle Accidents Involving Drivers With Prescriptions for Codeine or Tramadol

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Previous studies have only partially characterized the road-accident risks linked to driving while taking opioid analgesics used for moderate pain.<sup>1–4</sup> A prospective cohort design with data from national population-based registries—the Norwegian Prescription Database and the Norwegian Road Accident Registry—and observation of >8 million person-years were used in order to examine whether a driver who has filled a prescription for codeine or tramadol is at increased risk of being involved in a road accident resulting in injury to persons.

## RESULTS

### Exposure

During the study period (33 months), 181 accidents that resulted in injury and involved drivers with codeine exposure (defined as within 7 days after the date of dispensation) were registered; 20 involved drivers exposed to tramadol. The risk of being involved in an accident was significant for drivers using codeine (standardized incidence ratio (SIR) for both sexes and all age groups combined: 1.9; 95% confidence interval: 1.6–2.2). The SIR for tramadol (1.5; 95% confidence interval: 0.9–2.3) was not significant but showed an upward trend.

**Table 1**, left column, shows the SIR for accidents involving injury to persons, for male and female drivers of different age groups after exposure to codeine. The relatively few accidents in the tramadol group did not allow further stratification into age groups.

### Coprescription

A further study of the codeine group showed that, when data from those who were simultaneously exposed to other impairing drugs (other opioids, benzodiazepines, hypnotics, carisoprodol, and sodium oxybate) were excluded, the SIR for accidents in the codeine-exposed drivers no longer showed an increase (**Table 1**, right column).

### Nonregular use

We studied the impact of nonregular use by examining data from accidents resulting in injury and involving users who filled their first prescription for codeine after a washout period of 180 days. The SIR for nonregular users of codeine was not increased, as shown in **Table 2**.

### Low vs. high drug consumption

**Table 3** shows the SIR data relating to traffic accidents involving exposure to codeine in drivers who had filled prescriptions for fewer than 60 defined daily doses (DDD) of codeine (low-consuming group) and those who had filled prescriptions for 60 or more DDDs (high-consuming group) in the 6-month period prior to the cohort observation time, which was 27 months. The SIR was markedly increased in the high-consuming group and not increased in the low-consuming group. When data from those who had been exposed to other impairing drugs during the relevant time period were excluded from consideration, the SIR for accidents among the high-codeine-consuming group no longer showed any increase.

## DISCUSSION

Codeine/acetaminophen combinations (30 mg codeine and 400 or 500 mg acetaminophen) and, to a much lesser extent, tramadol are the preferred analgesics with opioid effects used in Norway for moderate pain. In Norway, prescriptions are required for all compounds containing codeine or tramadol. Like other central nervous depressants, opioids may reduce psychomotor performance or other functions that are potentially relevant to the ability to drive safely. Existing studies have only partially characterized the road-accident risks linked to opioid analgesics prescribed for moderate pain. Some controlled studies have indicated that codeine and tramadol, especially in high doses, might impair driver performance.<sup>1,5,6</sup> Other studies have failed to demonstrate such effects.<sup>7–10</sup> We have previously

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**Table 1 Exposure to codeine**

	(A) Codeine				(B) Codeine, person-time with coprescription excluded			
	Observed accidents	Expected accidents	SIR	95% CI	Observed accidents	Expected accidents	SIR	95% CI
Total	181	95.9	1.9	1.6–2.2	83	65.6	1.3	1.0–1.6
Male	107	54.7	2.0	1.6–2.4	49	38.8	1.3	0.9–1.7
Female	74	41.2	1.8	1.4–2.3	34	26.8	1.3	0.9–1.8
Male (18–34 years)	25	12.8	2.0	1.3–2.9	12	10.6	1.1	0.6–2.0
Female (18–34 years)	17	9.2	1.8	1.1–2.9	8	7.4	1.1	0.5–2.1
Male (35–54 years)	70	27.6	2.5	1.9–3.2	28	18.5	1.5	1.0–2.1
Female (35–54 years)	45	22.5	2.0	1.4–2.6	23	13.7	1.7	1.0–2.4
Male (55–69 years)	12	14.4	0.8	0.4–1.4	9	9.7	0.9	0.4–1.6
Female (55–69 years)	12	9.5	1.3	0.7–2.2	3	5.7	0.5	0.0–1.3

(A) Standardized incidence ratios (SIRs) for traffic accidents after exposure to codeine. The table shows the number of observed accidents, the number of expected accidents, and the SIR for 7 days starting on the day after dispensation of the drugs, stratified by gender and age group. (B) SIR for traffic accidents after exposure to codeine excluding person-time exposure to other impairing drugs (other opioids, benzodiazepines, hypnotics, carisoprodol, and sodium oxybate) and stratified by gender and age. Individuals who filled a prescription for other impairing drugs the same day as they were dispensed the opioid studied, or on any of the 6 prior days, were excluded. The observation duration was 33 months for both groups A and B.

CI, confidence interval.

**Table 2 Nonregular use of codeine**

	Codeine, nonregular use			
	Observed accidents	Expected accidents	SIR	95% CI
Total	27	25.5	1.1	0.7–1.5
Male	20	15.9	1.3	0.8–1.9
Female	7	9.6	0.7	0.3–1.5

Standardized incidence ratios (SIRs) for traffic accidents after exposure to codeine alone. Exposure times only for individuals who received their first prescription for codeine after a washout period of 180 days. Stratified by gender. Observation duration 27 months.

CI, confidence interval.

reported that there is a relationship between blood codeine levels and driving-related impairment in those suspected of driving under the influence of codeine.<sup>11</sup>

Analytical epidemiological studies of the risks of being involved in traffic accidents while using drugs with limited opioid effects, or all opioids as a group, have shown low relative risks, often not statistically significant.<sup>12–15</sup> An earlier study, using the same methodology as in this one, has shown that drivers using natural opium alkaloids face an increased risk of being involved in an accident, the SIR being 2.0 (95% confidence interval: 1.7–2.4).<sup>16</sup>

In this study, we found an increased SIR of motor vehicle accidents that resulted in injury and involved drivers exposed to codeine. The SIR was not increased when data involving simultaneous exposure to other impairing drugs were excluded from the relevant codeine-exposure period or when codeine nonregular use was analyzed alone. The SIR was markedly increased in the codeine “high-consuming group” but not in the “low-consuming group.” Again, the SIR dropped when data involving exposure to other impairing drugs were excluded from the codeine-exposure time in the high-consuming group. The SIR showed an upward trend, not statistically significant, for tramadol exposure. Data from 2005 show that ~60% of codeine users in Norway were given only one prescription of codeine that year.<sup>17</sup> At the other

end of the scale, the 1% of codeine users who were prescribed the greatest amount of codeine accounted for 16% of the total codeine prescribed.<sup>18</sup> This prescription pattern is also seen for other drugs with potential for abuse.<sup>19</sup> The fact that most of the subjects consume small amounts of the drug while relatively few have very high consumption is a determining factor in our interpretation of the results. Furthermore, we showed that coprescription of benzodiazepines is highly prevalent and increases in parallel with the amount of codeine prescribed.<sup>18</sup> This is an important confounding factor for evaluating accident risk. Of the 181 codeine-exposed patients involved in accidents, 98 had been prescribed other impairing drugs within 7 days prior to filling the prescription for codeine.

The SIR relating to nonregular use of codeine did not show an increase. The finding that the SIR was not increased in nonregular codeine use may seem the very opposite of what would be expected for an opioid. Tolerance is a prominent feature of opioids as a group, although the development of tolerance for the effects of codeine in the context of driving is not well characterized. The fact that nonregular codeine users did not have elevated SIRs may reflect the fact that the road-accident risk associated with low-dose, sporadic consumption of the drug is low.

In order to find out more about the subgroup of high consumers, we analyzed our material according to the dose of codeine prescribed. The population’s use of codeine compounds was observed over a period of 6 months prior to the start of the cohort observation. We knew from a previous work that the amount of codeine used over a period of time is a strong predictor of future patterns of use.<sup>20</sup> The definition of “high consumers”—prescribed 60 or more DDDs in 6 months—had been set on the basis of previous work and applies to approximately 10% of all codeine users.<sup>18</sup> In the same study, we showed that 50% of high consumers of codeine are also prescribed high amounts of benzodiazepines. One DDD of the codeine combinations represents 120 and 90 mg codeine,

**Table 3 Low vs. high consumers of codeine**

	(A) Codeine low consumers				(B) Codeine high consumers				(C) Codeine high consumers, person-time with coprescription excluded			
	Observed accidents	Expected accidents	SIR	95% CI	Observed accidents	Expected accidents	SIR	95% CI	Observed accidents	Expected accidents	SIR	95% CI
Total	63	50.1	1.3	1.0–1.6	83	28.4	2.9	2.3–3.6	18	20.9	0.9	0.5–1.3
Male	39	30.1	1.3	0.9–1.8	45	14.9	3.0	2.2–4.0	11	14.2	0.8	0.3–1.3
Female	24	20.0	1.2	0.8–1.8	38	13.5	2.8	1.9–3.8	7	6.8	1.0	0.3–1.9

(A) Standardized incidence ratios (SIRs) for traffic accidents after exposure to codeine for subjects filling prescriptions for fewer than 60 defined daily doses (DDDs) of codeine in the 6-month period prior to the cohort observation period. The table shows the number of observed accidents, the number of expected accidents, and the SIR for 7 days starting the day after dispensation of the drug, stratified by gender of the driver. (B) SIR for traffic accidents after exposure to codeine for subjects filling prescriptions for 60 or more DDDs of codeine in the 6-month period prior to the cohort observation period. (C) SIR for high-consuming group excluding person-time exposure to other impairing drugs (other opioids, benzodiazepines, hypnotics, carisoprodol, and sodium oxybate). Individuals who filled a prescription for other impairing drugs on the same day that they were dispensed the opioid being studied, or on any of the 6 previous days, were excluded. The observation duration was 27 months for groups A, B, and C.

CI, confidence interval.

respectively, for the two compounds that are currently on the market in Norway. When we divided the available data into “low” and “high” consumer categories, it became apparent that it was the high-consuming group that was at increased risk for motor vehicle accidents.

Of the 83 codeine-exposed subjects in the high consuming group who had been involved in accidents, 65 had been prescribed other impairing drugs in the days prior to filling a prescription for codeine compounds. When the other 18 patients in the high-consuming group, who had not been exposed to other impairing drugs in the accident period, were analyzed separately, the SIR was no longer elevated. The low number of accidents in this group is not sufficient to reliably exclude the possibility that a high dose of codeine alone can increase accident risk, even without other factors. On the other hand, this study does not provide evidence that codeine use by itself increases accident risk.

**METHODS**

Materials and methods are described in detail elsewhere<sup>16</sup> and are further described in the **Supplementary Data** online. Data were retrieved from three Norwegian population-based registries: the Norwegian Prescription Database (NorPD), the Norwegian Road Accident Registry, and the Norwegian Central Population Registry.

**Study cohort.** All inhabitants of Norway born from January 1934 through September 1988, and living in Norway in 2004–2006, were included (3.1 million).

The individuals were followed up from the age of 18 or from 7 January 2004 until the date of their involvement (as a driver) in an accident resulting in injury, or their emigration, or their reaching the age of 70 years, or their death, or until 30 September 2006, whichever occurred first (i.e., the study period was from 7 January 2004 until 30 September 2006).

To analyze the role of the consumption levels of codeine (low vs. high), we observed the amount of prescribed codeine compounds in the whole population from 1 January 2004 to 30 June 2004. After this 6-month observation period, data from individuals who were prescribed 60 or more DDDs of codeine during the observation period were analyzed separately from data from those who were prescribed fewer than 60 DDDs (as two different cohorts). The observation time for these two groups was from 1 July 2004 to 30 September 2006.

**Registries**

**Norwegian Road Accident Registry.** The Norwegian Road Accident Registry, based on the police’s database of accidents and maintained by

Statistics Norway, provides information about accidents on Norwegian roads resulting in injuries.<sup>21</sup> There is a legal obligation to report such accidents to the police.

**NorPD.** The NorPD<sup>16,22</sup> is a research database that captures all prescriptions at pharmacies dispensed to individual patients treated in ambulatory care in Norway since 1 January 2004. All pharmacies are obliged to report data on all prescribed drugs to NorPD.

**Exposure period.** We studied those who used codeine and tramadol during the study period and compared them with nonusers of the same age range.

In the analysis of accident incidence rates in the low- and high consumption cohorts, the observation time was 6 months less, i.e., 27 months.

The NorPD includes no information on when or whether the dispensed medicines were actually used. We therefore used an assumed period of usage of 7 days, starting the day after the date of dispensing. In this study, the date of dispensation is the date of delivery to the patient through the pharmacy.

**Statistical methods.** The incidence of accidents in the group comprising exposed persons-time was compared with the incidence of accidents among the group comprising unexposed persons-time, by calculating the SIR. Individuals who were not exposed to any of the study opioids but filled a prescription for other impairing drugs were excluded from the unexposed persons-time group at 7 days starting the day after they filled the prescription. These “exclusion drugs” included all other opioids, benzodiazepines, and other hypnotics registered in Norway, as well as carisoprodol and sodium oxybate.

The study period was divided into 1-month periods so as to adjust for possible seasonal variations. Findings were calculated for both sexes and in 10 age groups (18–24, 25–29, ..., and 65–69 years). The age grouping was based on age as of 1 May 2005. SIRs above unity indicate an increased risk of being involved as a driver in an accident that results in injury. Results are presented for three broader age groups (18–34, 35–54, and 55–69 years). SIRs and confidence intervals were calculated in accordance with the method described by Andersen *et al.*<sup>23</sup>

**Supplementary Table S1** online shows the total observation time and the exposed persons-time data for each drug.

We performed four calculations:

1. *Exposure:* “Exposed” and “unexposed” were taken as relating only to codeine or tramadol.
2. *Coprescription:* Individuals exposed to study opioids were excluded if they filled a prescription for other impairing drugs the same day as the opiate, or on any of the 6 previous days. These “exclusion drugs” included all other opioids, benzodiazepines, and hypnotics registered in Norway, as well as carisoprodol and sodium oxybate.

3. *Nonregular use*: Exposure time related only to individuals who received their first prescription for weak opiates after a washout period of 180 days.
4. *High consumption*: Individuals who filled prescriptions for 60 or more DDDs in the observation period of 6 months were analyzed as a separate cohort.

The strengths and shortcomings of our study as well as materials and methods are discussed in more detail in the **Supplementary Data** online.

**SUPPLEMENTARY MATERIAL** is linked to the online version of the paper at <http://www.nature.com/cpt>

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#### CONFLICT OF INTEREST

The authors declared no conflict of interest.

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