Minor Increase in Risk of Road Traffic Accidents After Prescriptions of Antidepressants: A Study of Population Registry Data in Norway

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Objectives: Experimental studies have shown that both depression and the use of antidepressants may impair the ability to drive a motor vehicle. Population-based studies have been inconclusive. Differences in results have been shown for cyclic, sedating antidepressants and newer, nonsedating antidepressants. The objective of the present study was to examine whether the use of antidepressants by drivers increased the risk of being involved in traffic accidents.

Method: From April 2004 to September 2006, information on prescriptions, road accidents, and emigrations/deaths was obtained from 3 Norwegian population-based registries. Data on people between the ages 18–69 (N = 3.1 million) were linked. Exposure consisted of receiving prescriptions for any antidepressants. Standardized incidence ratios (SIRs) were calculated by comparing the incidence of accidents during time exposed with the incidence over the time not exposed. Sedating antidepressants (tricyclic antidepressants, mianserin, and mirtazapine) were studied together as one group, and newer, nonsedating antidepressants (selective serotonin reuptake inhibitors, moclobemide, venlafaxine, and reboxetine) as another.

Results: During the study period, 20,494 road accidents with personal injuries occurred, including 204 and 884 in which the driver was exposed to sedating antidepressants or newer, nonsedating antidepressants, respectively. The traffic accident risk increased slightly for drivers who had received prescriptions for sedating antidepressants (SIR = 1.4, 95% CI = 1.2 to 1.6) or nonsedating antidepressants (SIR = 1.6, 95% CI = 1.5 to 1.7). The SIR estimates were similar for male and female drivers and slightly higher for young drivers (18–34 years of age) using older sedative antidepressants. SIR estimates did not change substantially for different time periods after dispensing of the prescription, for concomitant use of other impairing drugs, or for new users.

***Conclusion*:** There was a slightly increased risk of being involved in a traffic accident after having received a prescription for any antidepressants. In the present study, it was not possible to determine whether this increase was due to the antidepressant, the effect of the depression, or characteristics of the patients being prescribed these drugs.

(J Clin Psychiatry 2008;69:1099–1103)

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The authors thank the staff of the Road Accident Registry at Statistics Norway for providing accident data.

The authors report no financial affiliations or other relationships relevant to the subject of this article.

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Antidepressant drugs are commonly used.[1] In Norway, as many as 5% to 10% of the adult population will receive a prescription for an antidepressant drug during the course of 1 year.[2] It would be important to study adverse events of such commonly used drugs. Drugs that impair psychomotor ability and those that may impose a traffic accident risk are issued with a warning label in Norway; this is not the case for any of the antidepressants on the market. Because of the widespread use of antidepressants, it is important to investigate whether the use of antidepressants imposes an increased traffic accident risk. Both cyclic, sedating antidepressants and newer, nonsedating antidepressants have shown to decrease psychomotor performance in a laboratory setting,[3,4] while other studies have had problems establishing this.[5] Similarly, antidepressants have been shown to impair ability to drive in an on-the-road setting.[6] The impairment seems to be more pronounced for cyclic, sedating antidepressants[7] than for newer, nonsedating antidepressants.[8] There seems to be a tolerance for the impairing effects of the cyclic, sedating antidepressants, except for mianserin.[9] Responsibility studies are hampered by the fact that few persons will drive while using antidepressants.[10–12] Some responsibility studies have, however, found an increased risk of traffic accidents while using sedative antidepressants,[13,14] but others have not.[15]

The research into antidepressants and driving ability is complicated by the fact that both antidepressants and depression itself may impair ability to drive.[16] There is little literature on the psychomotor impairment following depression.[4] Some literature points to the fact that depressed patients both with and without antidepressant treatment will be impaired drivers.[17] Any improvement in driving ability after initiation of antidepressant treatment may have different explanations. Patients may develop a tolerance to the sedating effects of the drugs.[6] The patients may learn to compensate for impairing effects of the drug, a process that might come easier in healthy volunteers than in depressed patients.[18] But treatment might both cure the affective symptoms and improve the patient's ability to drive.[17] It must also be taken into consideration that antidepressants are given for a variety of maladies, of which depression is only one. All these complicating factors point to the importance of studying the use of antidepressants and traffic accident risk in a real life setting.

The aim of this study was to investigate by population-based registries if receiving a prescription for antidepressants was related to any increase in the risk of traffic accidents. Both cyclic, sedating antidepressants (tricyclic antidepressants, mianserin, and mirtazapine) and newer, nonsedating antidepressants (monoamine reuptake inhibitors, reversible monoamine oxidase A inhibitors, and others) were studied.

METHOD

Databases

Data were retrieved from 3 Norwegian population-based registries: the Prescription Database (NorPD), the Road Accident Registry (NRAR), and the Central Population Registry (NCPR). Coupling these data enabled us to investigate if newly dispensed prescriptions on antidepressants increased the risk of being involved in road traffic accidents.[19,20]

The NorPD covers the entire Norwegian population (4.6 million inhabitants). From January 1, 2004, all pharmacies in Norway were required by law to submit electronic data on all dispensed prescriptions to the Norwegian Institute of Public Health. The NorPD contains information on all prescription drugs dispensed to individual patients who live outside institutions.[21,22] The following data were collected for this study: patients' unique identifiers, gender, and age; the date of dispensing; and drug information (e.g., package size, number of packages, anatomical therapeutic chemical code, and defined daily dose [DDD]).[23]

The NorPD includes no information on if or when the dispensed medicines are used. We therefore used the number of days corresponding to the number of DDDs dispensed of these drugs as a proxy for exposure to antidepressants. Even if patients generally will use drugs both for a longer time or a shorter period depending on doses and degree of adherence, we considered this time frame as the best proxy for actually exposed time. Nonadherence or using less than a DDD per day may have yielded conservative estimates for risk. In previous published articles,[19,20] we used different exposure times as proxy for use, and these were also tested in the present work, without changing our estimates substantially.

We studied the number of accidents in the time exposed to 2 different groups of antidepressants: first, cyclic, sedating antidepressants, including tricyclic antidepressants (clomipramine, trimipramine, amitriptyline, nortriptyline, and doxepin), and, second, the tetracyclic antidepressants mianserin and mirtazapine. We also studied exposure to newer, nonsedating antidepressants, including serotonin reuptake inhibitors (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram), reversible monoamine oxidase A inhibitors (moclobemide), and other newer antidepressants (venlafaxine and reboxetine). We studied exposure in patients aged 18 to 69 and compared them with nonexposure subjects during the 30 months of the NorPD from April 1, 2004, to September 30, 2006. We studied both prevalent and incident use:

(1) Prevalent use: any exposure to drug within study.
(2) Incident (new) use: first time exposure to the drug after a 180-day wash-out period.

The NRAR at Statistics Norway provided information about motor vehicle accidents involving personal injuries on Norwegian roads.[24] There is an obligation to report all these accidents to the police. The NRAR uses the police's database of accidents but does not provide information on the driver's responsibility. We extracted drivers 18 to 69 years old involved in accidents as drivers from April 1, 2004, through September 30, 2006 (N = 20,494). The study period was chosen to start 3 months after upstart of NorPD, as most prescriptions for antidepressants are filled for 3 months at the time. We also had information on the time of day when the accidents occurred.

The NCPR contains demographical information on all residents in Norway since 1960, including date of birth, place of residence, and date of eventual emigration or death.[25] All Norwegians born April 1934 through September 1988, and living in Norway from 2004 to 2006, were included (N = 3.1 million). The persons were followed up from the age of 18 or from April 1, 2004, until date of involvement in an accident with personal injury as driver, emigration, reaching the age of 70 years, or death or until September 30, 2006, whichever occurred first.

Data from the 3 registries were linked based on the unique 11-digit identification number assigned to all individuals living in Norway after 1960. These unique person identifiers were entered manually, but always controlled

Table 1. Number of Total and Exposed Person-Years for Cyclic, Sedating Antidepressants and Newer, Nonsedating Antidepressants[a]

	Person-Years		
Age Group	Total Number	Exposed to Cyclic, Sedating Antidepressants	Exposed to Newer, Nonsedating Antidepressants
All subjects			
Male	3,764,477	27,631	87,806
Female	3,684,906	40,474	171,637
Age 18–34 y			
Male	1,263,082	4385	19,741
Female	1,229,609	4227	34,237
Age 35–54 y			
Male	1,637,810	13,333	43,286
Female	1,585,416	18,473	84,565
Age 55–69 y			
Male	863,585	9913	24,778
Female	869,881	17,774	52,836

[a]The number of days corresponding to the number of defined daily doses dispensed was taken as exposure time.

Table 2. Standardized Incidence Ratios (SIRs) for Traffic Accidents After Exposure to Cyclic, Sedating Antidepressants and Newer, Nonsedating Antidepressants[a]

	Cyclic, Sedating Antidepressants			Newer, Nonsedating Antidepressants		
Age Group	N	SIR	95% CI	N	SIR	95% CI
All drug users	204	1.4	1.2 to 1.6	884	1.6	1.5 to 1.7
Male	113	1.4	1.2 to 1.7	427	1.6	1.4 to 1.7
Female	91	1.5	1.2 to 1.8	457	1.6	1.5 to 1.8
Age 18–34 y						
Male	35	1.7	1.2 to 2.4	152	1.7	1.4 to 2.0
Female	22	2.2	1.3 to 3.3	143	1.7	1.5 to 2.0
Age 35–54 y						
Male	50	1.3	1.0 to 1.7	195	1.6	1.4 to 1.8
Female	46	1.4	1.1 to 1.9	230	1.6	1.4 to 1.8
Age 55–69 y						
Male	28	1.2	0.8 to 1.7	80	1.4	1.1 to 1.7
Female	23	1.2	0.7 to 1.7	84	1.5	1.2 to 1.8

[a]The table shows number of accidents and SIRs using as exposure time the number of days corresponding to the defined daily doses dispensed for all exposed time and stratified according to gender and age groups.

against the NCPR. Both the employees at the pharmacies dispensing the medicines and employees at police stations registering traffic accidents had online access to an electronic updated version of the NCPR. The identifiers were also checked during the linking process. Hence, when 2 records were linked, these stemmed from the same person. Between 2% and 3% of prescriptions in the NorPD were not included in this study because they were lacking a unique person identifier. For the NRAR, only a negligible number of cases were excluded due to the driver being a foreigner without a Norwegian unique person identifier.

Statistical Methods

The incidence of accidents among the exposed person-time was compared with the incidence of accidents among the unexposed person-time by calculating the standardized incidence ratio (SIR). SIRs above unity indicate an increased risk of being involved in an accident with personal injury as driver. The study period, April 2004 to September 2006, was divided into thirty 1-month periods to adjust for possible seasonal variations. Numbers were further calculated in both sexes and in 10 age groups (18–24, 25–29, …, 65–69 years). The age grouping was based on the ages of the subjects on May 1, 2005. Results are presented for 3 broader age groups (18–34, 35–54, and 55–69 years).

For the SIR values based on fewer than 100 observed accidents among exposed patients, exact 95% confidence intervals were calculated on the assumption of a Poisson distribution of the observed number of accidents among exposed patients, with the mean estimated by the expected number of accidents among exposed patients.

The numbers of total and exposed person-years for cyclic and newer antidepressants are given in Table 1.

Table 3. Standardized Incidence Ratios (SIRs) for Traffic Accidents for Incident (de novo) Users of Cyclic, Sedating Antidepressants and Newer, Nonsedating Antidepressants[a]

	Cyclic, Sedating Antidepressants			Newer, Nonsedating Antidepressants		
Group	N	SIR	95% CI	N	SIR	95% CI
All drug users	34	1.0	0.7 to 1.4	119	1.6	1.3 to 1.9
Male	26	1.3	0.8 to 1.9	62	1.6	1.2 to 2.0
Female	8	0.6	0.3 to 1.3	57	1.6	1.2 to 2.0

[a]The table shows number of accidents and SIRs using as exposure time the number of days corresponding to the defined daily doses dispensed after a wash-out period of 180 days for all exposed time and stratified according to gender.

RESULTS

Using the number of days corresponding to the number of DDDs as exposure time, 204 accidents involving person injury were registered after exposure to sedating antidepressants versus 884 for nonsedating antidepressants. Mean age was 44 years for drivers involved in accidents after exposure to sedating antidepressants, with a similar age of 41 years for drivers exposed to newer, nonsedating antidepressants.

Table 2 shows the SIRs for accidents involving person injury after exposure to sedating antidepressants or nonsedating antidepressants for the whole exposed population, for male and female drivers, and for 3 different age strata. Exposure to both the sedating and the nonsedating antidepressants led to significant but only slightly increased SIRs.

The impact of de novo use was studied by looking at accidents involving person injury in incident users. Table 3 gives these data and shows that the SIR was similar in the de novo users of newer, nonsedating antidepressants as in prevalent users of these drugs.

In addition to exploring the SIRs in different age strata, in women and men, for different drug groups, we performed an analysis using different time periods after dispensing of the drugs as exposed time (e.g., 7 days and 14 days after dispensing). These different exposure times did not change the SIR estimates significantly. We also looked at the importance of co-prescriptions of benzodiazepines and opioids, but including these restrictions did not change the estimates. We also looked at time of day when the accidents had occurred. The time of day for accidents in exposed persons did not differ from that of none exposed. These data are not shown.

DISCUSSION

In this study, we found a moderate increase in the risk of being involved in traffic accidents with person injury after having filled a prescription for an antidepressant. This was true for both prevalent and incident use, for both genders, for all age strata, and for the different antidepressant drugs. The increase was not higher than what has been seen for receiving any drug (SIR = 1.4, 95% CI = 1.3 to 1.5).[20]

Our findings resemble those of 3 other epidemiologic studies.[13–15] Two of them addressed cyclic, sedating antidepressants.[13,14] One found an increased relative risk of being involved in a traffic accident involving person injury for older people[14]; the other claimed an increased culpability with the use of cyclic, sedating antidepressants[13] but did not perform formal testing of the findings. Doing so post hoc, the findings were not statistically significant. A third study addressed both cyclic, sedating antidepressants and newer, nonsedating antidepressants, but failed to detect an increased risk for traffic accidents for any of these.[15]

These studies were smaller than the present, which may explain their difficulty in reaching statistical significance.[13,15] Looking at the use of benzodiazepines and traffic accident risk, it has similarly been difficult to establish an increased risk in older people because of a high background incidence rate.[15,26] We found a small, but similar age effect in the present study on antidepressants. Others have found an increased risk only for older people.[14,15] Possibly due to a cohort effect, elderly people will use relatively more cyclic, sedating antidepressants than younger users.[2]

In the present study, we had no opportunity to distinguish between effects of the drug or if the increased SIR indicated some characteristic of the persons receiving the drugs or was a product of the disease (confounding by indication). Antidepressant users may represent a different population with a higher susceptibility for traffic accidents, or depression itself may reduce ability to drive.[4,16] The NorPD does not include diagnosis, and thus we could not control for this confounding by indication.[27] Others have tried to solve the problem by comparing patients who receive more than 1 prescription with those receiving 1 prescription,[28] but could not escape this issue of confounding. We tried to address this via other strategies. First, we compared prevalent users with incident users, finding no major differences. Second, we compared exposure to cyclic, sedating antidepressants with exposure to newer, nonsedating antidepressants. If exposure to cyclic, sedating antidepressants had given a higher risk for traffic accidents than exposure to newer, nonsedating antidepressants, and if we assumed that both groups had the same indication for use, this could have solved the problem of confounding by indication and pointed to an effect of the drug. In the present study, however, we did not find a difference between the drug groups, thus leaving the question of confounding by indication open.

In the present study, we used number of days corresponding to DDDs prescribed as proxy for exposure time. Because we do not know if a potential change in traffic accident risk would be related to antidepressant use in a dose-response related fashion or if there is a threshold for effects, it is difficult to predict how higher or lower dosing or nonadherence to therapy might influence our estimates on SIRs.

Additionally, we had no opportunity to control for the use of alcohol or narcotics. We know that users of antidepressants will use more benzodiazepines and this could be responsible for the increased SIRs. We know from other studies that alcohol, narcotics, and impairing prescription drugs give an increased accident risk.[15,20,29] Using 7 days as exposure time and excluding from our analysis those who received benzodiazepines in the 2 weeks adjacent to the filling of antidepressant prescription, we found no major change in our SIR estimates. This still may not have been sufficient to correct for this confounding, thus it is important to keep it in mind.

This investigation had total capture of the whole of Norway, producing a large sample without the problem of selection or recall bias. We believe that the quality of the linkage using the unique 11-digit person identifier was high. We had full knowledge of the types and amount of drugs that the patients had received. We did not know, however, how the drugs were intended to be used or if the drugs in fact were taken. To compensate for this, we also calculated the SIRs assuming a longer exposure period after filling a prescription. The SIRs did not drop assuming this prolonged exposure period.

We did not distinguish between different kinds of accidents (e.g., accident severity) like others have done,[15,26] and we had no information on driver culpability.[30–33] In pharmacology, dose-response relationships are important when trying to establish causal relationships. With the present research design, we were unable to investigate a dose-response relationship.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), doxepin (Sinequan, Zonalon, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

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