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ORIGINAL RESEARCH ARTICLE

Short-Term Risk of Unintentional Poisoning After New Initiation of Central Nervous System Medications in Swedish Older Adults: A Register-Based Case-Crossover Study

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Abstract

Introduction Medications acting on the central nervous system (CNS) are common causes of medication-related unintentional poisoning. Little is known about the short-term effects of CNS medications on unintentional poisoning.

Objective This study aims to determine the short-term association between newly prescribed CNS drugs and unintentional poisoning.

Methods We conducted a register-based case-crossover study of 9354 patients (age ≥ 50 years) with first-time hospitalization for unintentional poisoning in Sweden between 1 July, 2006 and 30 September, 2018. Newly initiated CNS medication was identified based on dispensations from the Swedish Prescribed Drug Register during 28 days prior to the unintentional poisoning event and compared with dispensations during an equally long control period. Conditional logistic regression was used to estimate the odds ratio and 95% confidence intervals.

Results After a newly initiated CNS treatment, we found an increased risk of unintentional poisoning during the following 2 weeks with an odds ratio (95%) being 2.52 (1.98–3.21) and 1.47 (1.08–2.00) for the first and second week, respectively. The risk was elevated in all sub-groups but to a different degree with odds ratio ranges of 1.73–2.47 by age, 1.91–2.21 by sex, 1.40–2.30 by Charlson Comorbidity Index, 2.00–2.07 by neuropsychiatric comorbidity, and 1.63–2.82 by number of other medications.

Conclusions The risk of unintentional poisoning doubles in 2 weeks following a new initiation of CNS drugs and the risk is increased across a range of population groups. Clinicians should carefully monitor signs of poisoning after such initiation among not only multimorbid older adults but also those with less comorbidity and polypharmacy.

Key Points

The risk of unintentional poisoning doubles in 2 weeks following a new initiation of central nervous system drugs.

The risk is increased across a range of population groups by age, sex, underlying comorbidities, and use of other medications.

Clinicians should carefully monitor signs of poisoning after the initiation of central nervous system drugs.

1 Introduction

Older adults experience age-related changes in the distribution of body fat and renal and hepatic function, which alter the pharmacodynamics and pharmacokinetics of medications [1]. These changes occur already at the age of 50 years [2, 3]. In addition, a higher prevalence of chronic diseases and multimorbidity, which require treatment with multiple medications, make older adults particularly vulnerable to adverse drug events such as poisoning [2]. Considering the global increase in the prevalence of unintentional poisonings (from 0.04% in 2005 to 0.05% in 2019) [4] and the high morbidity and mortality from poisoning

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[5, 6], there is a need to identify the high-risk groups and determine the risk factors of unintentional poisoning.

It has been shown that the risk factors of unintentional poisoning include age-related impairments, sex, medication use, alcohol consumption, and mental disorders [2, 6]. A growing body of epidemiological studies has identified that medication intake is a primary cause of unintentional poisoning for all age groups [5, 7, 8]. The pathways between medication and accidental poisoning are complex and remain to be explored. Possible mechanisms might include acute drug–drug or drug–disease interactions, accidental overdosing, or medication errors [2, 9]. Most of the unintentional poisoning events are acute (86.8%) while a much smaller proportion seem to be due to chronic exposure (9.55%) [10]. Regarding the vulnerability to adverse drug events due to age-related changes, multimorbidity, or polypharmacy, older adults may be more vulnerable (e.g., a high risk of fall injuries and injurious road traffic crashes) at the start of a newly prescribed drug [11, 12], and it is hence important to pay more attention to the short-term effects of medications.

Prescribed medications acting on the central nervous system (CNS), such as opioids, antidepressants, benzodiazepines, antipsychotics, and antiepileptics are among the leading causes of unintentional poisoning for adults aged 25 years and above [5, 9]. It has also been found that poisonings associated with CNS medications were more than twice higher compared with those due to non-psychoactive medications in older adults [9]. The use of CNS drugs is widespread, especially among older adults [13]. A systematic review and meta-analysis of 89 study populations indicated that the overall pooled proportion of CNS medicine use was 35.0% (95% confidence interval [CI] 33.1–36.8%) among aged care home residents [14]. In Sweden, the prevalence of CNS medication use was 6.7–14.6% among community-dwelling old adults [15]. Some CNS drugs cause side effects such as anxiety, confusion, and fainting. In addition, CNS drugs may interact with other health disorders and medicines with drug–disease or drug–drug interactions resulting in an increased risk of unintentional poisoning [16, 17]. In general, side effects from medications are more common in the initiation phase, and it is especially common for CNS drug side effects at initiation before the patient gets used to them [18–20]. However, whether the risk of unintentional poisoning is particularly high during the initial phase of drug therapy is still unknown. Thus, more evidence is needed on the short-term effects of CNS medications for the prevention of medication-related unintentional poisoning. Based on Swedish health registers, this study aims to determine the short-term association between newly prescribed CNS drugs and unintentional poisoning in older adults as well as to explore the modifying factors of the associations.

2 Methods

2.1 Study Design

A case-crossover design was employed to evaluate the association between newly initiated CNS drug treatment and unintentional poisoning [21, 22]. By using patients as self-controls, the design inherently adjusts for confounding due to time-in-varying factors, such as habitual health behaviors, long-term diet, and the tendency to seek professional care, which are not recorded in healthcare databases [21, 23]. We compared the occurrence of dispensed CNS medications during the period prior to the poisoning event (the case period) with the occurrence during an earlier period when no poisoning event had occurred (the control period) within the same patient.

2.2 Data Source

This study was based on Swedish register data: the National Patient Register and the Swedish Prescribed Drug Register. The National Patient Register has national coverage of all hospital care in Sweden since 1987 and includes information on hospital admission date and primary and secondary diagnoses coded according to the International Classification of Diseases. The overall positive predictive value of diagnoses in the register is about 85–95% [24]. The Swedish Prescribed Drug Register contains information regarding all pharmacy-dispensed prescribed drugs to the whole population since July 2005 [25]. Drug information is classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

2.3 Study Population

At the time of extraction of the data, registers had only been updated until September 2018. All individuals aged 50 years and older who had been hospitalized because of unintentional poisoning from 1 July, 2006 to 30 September, 2018 were identified from the National Patient Register based on the International Classification of Diseases, 10th Revision external cause classification codes X40–49 (Unintentional poisoning), i.e., regardless of the mechanism. The majority of the events (71.7%) were coded as X44 (Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances). Only the first event of unintentional poisoning during the study period was considered. As such, patients having a prior history of unintentional poisoning before 1 July, 2006 were excluded (n = 163). The onset of unintentional poisoning was defined as the date of hospital admission. The inclusion procedure

of study patients is shown in Fig. S1 of the Electronic Supplementary Material (ESM). A total of 9354 patients were included in the analysis.

2.4 Definitions of Newly Prescribed Medications

In Sweden, CNS medications are only available through prescriptions, not over the counter. Using the Swedish Prescribed Drug Register, all dispensed CNS medications (ATC code N02-06) during the 32 weeks prior to the unintentional poisoning event were identified and analyzed including both therapeutic and pharmacological subgroups. As illustrated in the case-crossover design (Fig. S2 of the ESM), newly initiated CNS medication use was defined as dispensation of CNS medications within the case period (1–28 days prior to the onset of unintentional poisoning) but none within the wash-out period (29–112 days prior to the onset of unintentional poisoning). The same definition was applied to the control period (113–140 days prior to the onset of unintentional poisoning) and the wash-out period (141–224 days prior to the onset of unintentional poisoning).

2.5 Potentially Modifying Factors

Factors that could potentially modify the effect of CNS medications on the risk of unintentional poisoning were identified based on previous literature [2, 6, 9]. The modifying factors in this study included sex, age, comorbidity, neuropsychiatric disease, and concurrent use of other medications. Age was categorized into three groups: 50–64, 65–79, and ≥ 80 years. Comorbid disease status was assessed using the Charlson Comorbidity Index [26]. The Charlson Comorbidity Index scores were calculated based on diagnoses 1 year prior to the unintentional poisoning event and categorized as 0, 1–2, 3–4, and ≥ 5. Furthermore, we identified neuropsychiatric diseases during 1 year before poisoning according to the categorization to evaluate neuropsychiatric diseases [27]. In addition, we calculated the total number of different medications (excluding the CNS medications) dispensed within the 180 days prior to the onset of unintentional poisoning based on the ATC codes. The number of medications was grouped into 0, 1–4, and ≥ 5.

2.6 Statistical Analysis

Descriptive statistics were used to present categorical variables as frequencies/percentages, and continuous variables as means (standard deviation). Conditional logistic regression was used to estimate the associations between newly prescribed CNS medications and unintentional poisoning based on the ATC Classification System. Effect estimates were odds ratio (OR) and 95% CIs. We performed an induction time analysis using a 2-day window period within the case and control periods to determine the risk peak. Modification of the risk by age, sex, comorbidity, neuropsychiatric disease, and number of medications was assessed in subgroups by levels of the potential effect modifiers. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 Results

We identified 9354 patients who had a first-ever diagnosis of unintentional poisoning from July 2006 to September 2018 in Sweden. Table 1 summarizes the patients' demographic and clinical characteristics. Participants were predominantly aged older than 65 years (67.31%), and 53.87% of them were female (Table 1). More than half of the patients did not experience any severe comorbidity (Charlson Comorbidity Index scores <1) or neuropsychiatric diseases in the previous year prior to the event (Table 1). The majority of patients (78.64%) were dispensed fewer than five medications during the 6 months prior to the poisoning event (Table 1). Among the 9354 patients, 730 were exposed to newly initiated CNS medication treatment either in the case or control period. Detailed information is given in Table 1.

In general, an increased overall risk of unintentional poisoning was found in the first 2 weeks after initiation (1–7 days: OR 2.52, 95% CI 1.98–3.21; 8–14 days: OR 1.47, 95% CI 1.08–2.00). Figure 1 shows the association with a 2-day case period, suggesting that the risk of unintentional poisoning risk was highest 2 days after initiation and decreased afterwards. The increase in risk remained statistically significant up until 10 days after initiation.

The overall effects of newly initiated CNS medications (ATC code N02-06) on unintentional poisoning were highest during the first 2 weeks after initiation (Table 2). As shown in Table 2, four (antiepileptic drugs, antiparkinson drugs, psycholeptic drugs, and psychoanaleptics) out of five therapeutic subgroups of CNS medications were associated with an increased risk of unintentional poisoning. An increased risk was observed for seven (opioid drugs, other analgesics and antipyretics, antipsychotic drugs, anxiolytic drugs, hypnotics and sedatives, antidepressant drugs, antidementia drugs) out of 12 pharmacological subtypes of CNS medications.

In subgroup analyses, newly prescribed CNS drugs were associated with an unintentional poisoning risk for all subgroups of sex, age, and neuropsychiatric chronic disease (Table 3). The OR ranged from 1.73 to 2.47 by age group, from 1.91 to 2.21 by sex, from 1.40 to 2.30 by comorbidity, from 2.00 to 2.07 by neuropsychiatric disease, and from 1.63 to 2.82 by use of other medications.

Table 1 Demographic and clinical characteristics of patients with unintentional poisoning, *n* (%)

Characteristics	Total (*n* = 9354)	Exposed to newly initiated CNS medications[a] (*n* = 730)
Age group (years)		
50–64	3058 (32.69)	189 (25.89)
65–79	3202 (34.23)	257 (35.21)
≥ 80	3094 (33.08)	284 (38.90)
Sex		
Male	4315 (46.13)	364 (49.86)
Female	5039 (53.87)	366 (50.14)
Charlson Comorbidity Index score		
0	5895 (63.02)	441 (60.41)
1–2	1946 (20.80)	180 (24.66)
3–4	869 (9.29)	64 (8.77)
≥ 5	644 (6.88)	45 (6.16)
Neuropsychiatric comorbidity		
No	7164 (76.59)	614 (84.11)
Yes	2190 (23.41)	116 (15.89)
Number of different medications		
0	3414 (36.50)	332 (45.48)
1–4	3942 (42.14)	338 (46.30)
≥ 5	1998 (21.36)	60 (8.22)

CNS central nervous system

[a]Exposed to newly dispensed CNS medications either in a 4-week case period or control period but not in both or neither

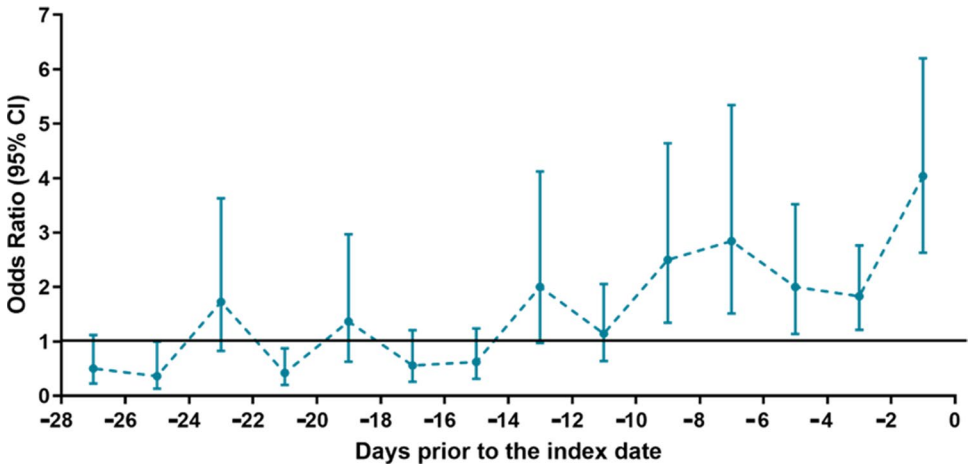

Fig. 1 Risk of unintentional poisoning in 2-day periods during 4 weeks after newly initiated central nervous system medications (*n* = 9354). *CI* confidence interval

4 Discussion

Our study provides evidence that the risk of unintentional poisoning is increased during the first 2 weeks after initiation of CNS medication therapy for older adults. The risk is increased across a range of population groups, and it does not vary significantly by age, sex, underlying comorbidity, psychiatric disease, or use of other medications.

Our study provides novel information about the short-term effects of newly initiated CNS drugs on unintentional poisoning. It showed that the risk of unintentional poisoning is increased within 2 weeks after the initiation of CNS medications. In general, the time course from the start of treatment is one of the important characteristics of an adverse drug reaction, to which a three-dimensional approach is proposed based on dose, time, and susceptibility of the newly initiated medication [28]. Our study was in line with

Table 2 Risk of unintentional poisoning in the 2-week period following newly initiated CNS medications ($n = 730$)

CNS medications (ATC code)	Newly initiated CNS medication treatment in case period but not control period[a]	Newly initiated CNS medication treatment in control period but not case period[b]	Odds ratio	95% confidence interval
All CNS medications (N02-06)	329	120	2.06	1.70–2.48
Therapeutic subgroups				
Analgesic drugs (N02)	391	174	2.25	1.88–2.69
Antiepileptic drugs (N03)	132	54	2.44	1.78–3.35
Antiparkinson drugs (N04)	23	13	1.77	0.90–3.49
Psycholeptics drugs (N05)	259	161	1.61	1.32–1.96
Psychoanaleptics (N06)	210	133	1.58	1.27–1.96
Pharmacological subgroups[c]				
Opioid drugs (N02A)	384	134	2.87	2.35–3.49
Other analgesics and antipyretics (N02B)	342	179	1.91	1.59–2.29
Antiepileptic drugs (N03A)	132	54	2.44	1.78–3.35
Dopaminergic agents (N04B)	21	12	1.75	0.86–3.56
Antipsychotic drugs (N05A)	91	43	2.12	1.47–3.04
Anxiolytic drugs (N05B)	202	96	2.10	1.65–2.68
Hypnotics and sedatives drugs (N05C)	225	142	1.58	1.28–1.96
Antidepressant drugs (N06A)	191	128	1.49	1.19–1.87
Antidementia drugs (N06D)	32	13	2.46	1.29–4.69

ATC Anatomical Therapeutic Chemical, *CNS* central nervous system

[a]Exposed during 1–14 days but not during 29–112 days, 113–126 days, and 141–224 days prior to the onset of unintentional poisoning

[b]Exposed during 113–126 days but not during 1–14 days, 29–112 days, and 141–224 days prior to the onset of unintentional poisoning

[c]ATC codes including N02C (Migraine medication), N04A (Anticholinergic agents for Parkinson), N06B (Psychostimulants, agents used for ADHD and nootropic), and N06C (Psycholeptics and psychoanaleptics in combination) are not listed because of very few exposed cases ($n < 10$)

previous studies that showed that an increased risk of acute adverse medical events (e.g., hip fractures, acute respiratory failure among patients with chronic obstructive pulmonary disease, upper gastrointestinal bleeding) in the first 2 weeks of drug therapy such as nonbenzodiazepine sleep medication, antipsychotics, and serotonin reuptake inhibitors [18–20, 29]. However, previous studies might fail to disentangle the effect among new users from the long-term users.

In addition, the underlying comorbidity and concurrent use of other medications may increase the probability of either an acute drug–disease interaction or a drug–drug interaction, and then increase the risk of unintentional poisoning [16, 17, 30, 31]. Many substances that may interact with CNS medications or decrease drug elimination, such as nonsteroidal anti-inflammatory drugs and muscle relaxants, are found to be related to poisoning when taken simultaneously with CNS drugs [30, 31]. However, we found that the short-term risk of unintentional poisoning after the initiation of CNS medication does not vary significantly by age, sex, underlying comorbidity, psychiatric comorbidity, or using other medications, although the effect size differs a bit between the subgroups. In our study, patients with less comorbidity or prescribed medications showed an increased risk of unintentional poisoning after new initiation of CNS drugs. However, the effect size does not vary greatly between people with and without multimorbidity or polypharmacy. One potential explanation could be that the effect among multimorbid individuals is underestimated because of exposure-dependent under-reporting of poisoning events, for example, owing to the difficulty for clinicians to differentiate multiple symptoms. Another explanation could be that older adults with polypharmacy and multiple diseases are already a risk group visible to the clinicians and therefore caution is applied when initiating new medications [32]. Our findings indicate that monitoring is needed in the first 2 weeks after the initiation of CNS drugs not only among already established risk groups of older adults but also among those with none or less comorbidity and polypharmacy.

Possible mechanisms for medication-related poisonings can be summarized as either direct side effects of CNS medications or indirect effects due to drug–drug interactions and disease–drug interactions [2, 9]. In addition, accidental overdosing and medication errors are other common reasons in clinical practice of poisoning. People are more vulnerable in the early phase of therapy after the initiation owing to the handling problems of new drugs, confusion states of

Table 3 Risk of unintentional poisoning in the 2-week period following newly initiated CNS medications (N02-06), stratified by patient characteristics ($n = 730$)

Characteristics	Newly initiated CNS medication treatment in case period but not control period[a]	Newly initiated CNS medication treatment in control period but not control period[b]	Odds ratio	95% confidence interval
Age group (years)				
50–64	79	32	2.47	1.64–3.72
65–79	111	64	1.73	1.28–2.36
≥ 80	139	64	2.17	1.62–2.92
Sex				
Male	172	78	2.21	1.69–2.88
Female	157	82	1.91	1.47–2.50
Charlson Comorbidity Index score[c]				
0	193	84	2.30	1.78–2.97
1–2	85	45	1.89	1.32–2.71
3–4	28	20	1.40	0.79–2.49
≥ 5	23	11	2.09	1.02–4.29
Number of neuropsychiatric diseases[c]				
0	279	135	2.07	1.68–2.54
≥ 1	50	25	2.00	1.24–3.23
Number of different medications dispensed[d]				
0	158	56	2.82	2.08–3.83
1–4	145	89	1.63	1.25–2.12
≥ 5	26	15	1.73	0.92–3.27

CNS central nervous system

[a]Exposed during 1–14 days but not during 29–112 days, 113–126 days, and 141–224 days prior to the onset of unintentional poisoning

[b]Exposed during 113–126 days but not during 1–14 days, 29–112 days, and 141–224 days prior to the onset of unintentional poisoning

[c]Within 1 year before the onset of unintentional poisoning

[d]Within 6 months prior to the onset excluding the CNS medications included in analyses

patients, mixing up of drugs in polypharmacy, and dosing errors on prescription (e.g., the doctor chooses a start dose that is too high). Central nervous system drugs act on specific receptors that modulate synaptic transmission, which in turn either suppress or stimulate the CNS. Side effects on the CNS, including drowsiness, dizziness, and depression, may occur at the early stage of therapy for some CNS medications such as barbiturates and benzodiazepines [33]. Moreover, the therapeutic windows of some CNS medications, such as phenytoin and lithium, are relatively narrow, which means that their therapeutic doses are close to the toxic doses. Hence, there can be a risk of being poisoned by these drugs when taking as prescribed [34, 35]. Thus, the adverse drug reactions may occur especially when there is an impairment in the pharmacodynamics and pharmacokinetics of a newly prescribed CNS medication.

A strength of this study is that it is a register-based study that covers all the hospitalizations related to unintentional poisoning. Furthermore, we conducted a self-matching case-crossover study design that could eliminate the time-invariant confounders (e.g., genetics, lifestyle, functional status). However, this study has several limitations. First, our study only included unintentional poisoning that led to hospital admission, thus mild cases and directly fatal cases may have been missed. If those exposed to recent new CNS medications directly die more often because of poisoning, we would underestimate the risk. Second, we used prescription as a proxy for intake, and the nonadherence would underestimate the actual poisoning risk. Third, the course of the disease stage (e.g., psychosis in the case period but not in the control period) might affect the association. However, we did not have the information regarding indication for prescription in this study. Fourth, there might be time-varying confounding that we could not adjust for using this study design, such as acute illness or confounding by indication. Finally, little is known about the validity of the unintentional poisoning diagnosis. A study in 2015 in three Scandinavian countries validated the diagnoses of intent of injuries with expert assessments and showed that few intentional injuries (3%) were reclassified, whereas the corresponding number for unintentional injuries was somewhat higher (> 9%) [36]. Although the study is based on fatalities and we cannot directly generalize to diagnoses in hospital, it indicates that

we cannot rule out the diagnostic coding errors made by physicians with regard to intent in our material.

Although there are quite high ORs for the immediate days after initiation, it is important to consider the quite low absolute risk of unintentional poisoning. Based on the official statistical database held by the Swedish National Board of Health and Welfare, the yearly incidence of unintentional poisoning was 23.30 per 100,000 inhabitants (aged 50 years and older) in 2006 (start of our study period) [37]. Giving that the OR is 2.06 for 2 weeks following the new initiation of any CNS drug, the estimated yearly incidence would be 24.24 per 100,000 inhabitants among exposed people. This corresponds to a yearly risk ratio of 1.04.

5 Conclusions

Our study found an increased risk of unintentional poisoning following newly initiated CNS drug therapy among older adults, and especially so within the first 2 weeks. Given the widespread use of CNS medications, clinicians should monitor signs of poisoning after such initiation not only among multimorbid older adults but also among those with less comorbidity and polypharmacy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-022-01197-w.

Declarations

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Conflict of interest The authors declare no conflicts of interest.

Ethics approval This study was approved by the Swedish Ethical Review Authority (case number: 2021-01863).

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The data used in this study are available upon reasonable request to the corresponding author.

Code availability Not applicable.

Authors' contributions Study concept and design: YL, JM, LL, and CR; data analysis: YZ; drafting the manuscript: YZ and YL; interpretation of results: all authors; reviewing the manuscript: YL, JM, LL, CR, and KJ; approval of the submission: all authors.

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