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Sleep medicines are often prescribed for older adults (≥75 years) without appropriate dosing instructions: A nationwide retrospective register study in Finland

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Abstract

Background: Sleep medicines should be prescribed cautiously, accompanied by instructions that ensure appropriate use and reduce risks. This is especially important for older adults, for whom many of these medicines are classified as potentially inappropriate medicines.

Methods: We investigated the use and appropriateness of dosing instructions for sleep medicines (described in the Finnish National Current Care Guideline for Insomnia) prescribed for older adults (≥75 years) and dispensed with instruction label in pharmacies. The retrospective reimbursement register data for year 2020 by the Social Insurance Institution of Finland was used as the data source (1,080,843 purchases by 143,886 individuals of which 565,228 purchases were pharmacy dispenses). The appropriateness of the pharmacy dosing instructions containing keyword(s) referring to insomnia treatment was examined according to the prescribed dose, time of intake, frequency of use, and warnings/remarks. A random sample of 1000 instructions was used to manually analyze the phrasing and appropriateness.

Outcomes: We focused our analysis on 58.1% (328,285 purchases by 87,396 individuals) of the pharmacy dispenses, which contained dosing instructions referring insomnia treatment. Of these, zopiclone and mirtazapine were the most prescribed drugs (134,631 and 112,463 purchases, respectively). Dose and time of intake were specified in most of the instructions (98.4% and 83.4%, respectively), whereas frequency of use was specified in 57.3%. A small percentage of the instructions included warnings/remarks (2.8%). Overall, only 2.1% of the instructions contained information about a single dose, time of intake, temporary use, and warnings/remarks and were thus defined as sufficient. Notably, 47.7% ($n = 515,615$) of all the purchases in our dataset were

Sini-Tuulia Eronen and Terhi Kurko: equal contribution.

dispensed via automated multi-dose dispensing systems, which is aimed for long-term treatment.

Interpretation: It is common to prescribe sleep medicines for older adults without appropriate dosing instructions, particularly excluding warnings against long-term, regular use. Actions to change the current prescribing practices are warranted.

KEYWORDS

automated multi-dose dispensing systems, dosing instructions, hypnotic, insomnia, medication safety, older adults, prescribing

1 | INTRODUCTION

Sleep disorders, especially insomnia, are highly prevalent and often follow a chronic course.[1] Cognitive behavioral therapy for insomnia (CBT-I) is the primary choice of treatment for insomnia, regardless of the underlying etiology, or the patient's age or sex.[1,2] Yet, in practice the treatment is often initiated with pharmacological treatments and CBT-I remain rarely routinely implemented. GABAergic hypnotic-sedative drugs, such as benzodiazepines (e.g., diazepam) and benzodiazepine-like drugs (Z-drugs; e.g., zolpidem), facilitate sleep onset, and may be suitable for early management of insomnia.[1–3] However, these drugs alter sleep structure and reduce the amount of deep, non-rapid eye movement (NREM) sleep and rapid-eye movement (REM) sleep.[1,4] Potential adverse effects and other clinical problems include dizziness, problems in motor functions and coordination (e.g., impaired walking), and drug dependency.[5] In general, long-term use of sedatives is associated with impaired cognitive and physical performance.[5–9] Medicines that promote sleep primarily through their ability to block the central histaminergic systems (including sedative antidepressants and some antipsychotics at lower doses) are often considered safer for long-term treatment of insomnia, although their long-term efficacy remains unclear.[1–3,10] Notably, the *European Guidelines for the Treatment and Diagnosis of Insomnia*[1] do not recommend treatment of insomnia with sedative antihistamines or antipsychotics due to lack of evidence and the risk of developing tolerance (see Reference [11]). In general, pharmacological intervention—mainly benzodiazepines, benzodiazepine-like drugs, or orexin receptor antagonists—is recommended only for short-term (≤4 weeks) treatment of insomnia.[1] Long-term pharmacotherapy is warranted but should be restricted to specific circumstances on an individual basis, for example, when insomnia may aggravate psychiatric symptoms (e.g., schizophrenia and bipolar disorder).

Older adults are especially vulnerable to several adverse effects associated with the use of benzodiazepines and Z-drugs. These adverse effects include increased risk of falls,[12] cognitive decline, and dementia,[1,5,13,14] perhaps through a reduction in NREM sleep and glymphatic clearance of amyloid beta.[15] Older adults are also at higher risk for long-term use of benzodiazepines and Z-drugs than younger individuals.[16,17] Therefore, many international criteria consider sedative sleep medicines as

Significant Outcomes

- Nearly half of the medicine purchases were dispensed via automated dose dispensing, which is a practice that can maintain regular, long-term treatment.
- Dosing instructions for prescribed sleep medicines are often insufficient.
- Only a minority of dosing instructions contained warnings/remarks concerning long-term use.

Limitations

- The data included only medicine purchases covered by the national public reimbursement scheme.
- The analysis included only prescriptions with the written dosing instructions with keyword(s) indicating the treatment of insomnia.
- Dosing instructions of sleep medicines dispensed through automated multi-dose dispensing were excluded although they made almost half of all purchases.

potentially inappropriate medications (PIMs) for geriatric care.[18,19] PIMs are medications that pose a higher risk of adverse effects or inefficacy when prescribed for older adults.[18] PIMs are usually best avoided or used with caution in geriatric patients. There is also a wide consensus that the benzodiazepines and Z-drugs should be restricted to only short-term use,[1,2] and most prescribing guidelines recommend limiting the treatment duration to a maximum of 2 weeks.[1,18,20] However, according to a systematic review, the use and long-term use of benzodiazepines and Z-drugs is common in older age groups.[21] In Finland, the overall prevalence of benzodiazepine and Z-drug use was 21.0% still in 2014, long-term use among older adults (aged ≥75 years) being 6.5%.[22]

Good prescribing practices support the rational and safe use of medicines. Medicine users should be provided with instructions to ensure appropriate use and to avoid risks and unnecessary (long-term) use. In Finland, each time a medicine is prescribed, the prescriber is obliged to write dosing instructions for the patient, which are transferred to the label attached to the medicinal product package when the medicine is dispensed from the community pharmacy.[23] According to the regulations in Finland, every prescription should contain written dosing instructions that cover information about single and daily *dose(s)*, time of intake, indication of the medicine, and regularity or duration of use (i.e., length of drug therapy).[23] The dosing instructions should be written in plain language.[24] The written instructions are especially important for older patients, as they often use multiple medicines concomitantly and may mix their medicines. It is also important for them to understand how their medicines work. However, in real-life practice, older adults are only rarely aware of the potential risks of benzodiazepines that they use on a long-term basis.[25]

The aim of this nationwide retrospective register study was to investigate the use and appropriateness of the dosing instructions for sedative sleep medicines prescribed to older adults in Finland. We focused on ≥75-year-old individuals because this age group typically starts experiencing more age-related health issues (incl. polypharmacy), and impaired functional changes owing to the cumulative effects of aging.

2 | MATERIALS AND METHODS

2.1 | Utilized register-based data

The data for this nationwide retrospective study were derived from the electronic "Dispensations reimbursable under the National Health Insurance Scheme" register (later Prescription Register)[26] maintained by KELA (the Finnish Social Insurance Institution, SII) to investigate the extent of use and content of dosing instructions for sleep medicines among Finnish residents aged ≥75 years. The Prescription Register contains the records of all prescription medicine purchases reimbursed by the public National Health Insurance covering all permanent Finnish residents living in noninstitutional settings.[26,27] The study was based on the dosing instructions of medicine purchases potentially used for the treatment of insomnia by persons aged ≥75 years during a 1-year period from January 1, 2020, to December 31, 2020. We focused on purchases of pharmacologically sedative drugs and defined sleep medicines as the following medicines included in the Finnish National Current Care Guideline of Insomnia[20]: zolpidem, oxazepam, quetiapine, lorazepam, trimipramine, diazepam, alprazolam, doxepin, mirtazapine, pregabalin, zopiclone, and trazodone. Thus, purchases of sleep medicines not included in the Finnish reimbursement scheme (e.g., temazepam products) were excluded. Moreover, melatonin was also excluded from the analysis. Data about the date of dispensation, Anatomical Therapeutic Chemical (ATC) classification, the pharmaceutical form of the medicine dispensed, its strength, package size, and the number of packages dispensed during the study period were collected. All available strengths of medicines were included in the data. The dosing instructions for each medicine are recorded in the Prescription Register in their original format. Of the background variable data of the patients, sex and age data were used.

The steps used for data selection are shown in Figure 1. The sleep medicine purchases, and dose instructions related to these medicines were collected from the Prescription Register (1,080,843 purchases). Data of purchases from automated multi-dose dispensing systems were separated from the data. The dosing instructions for the remaining medicines purchased were divided into separate datasets according to their ATC codes. These dosing instructions for each individual medicine were separately searched by using predetermined keywords or their parts referring to the treatment of insomnia or insomnia symptoms (Tables S1 and S2). For this study, only dosing instructions written in Finnish language were included for further analysis as they constituted 95.5% of the instructions related to sleep medicine purchases (Figure 1). Each of the dosing instruction was analyzed separately. We validated the keywords with dosing instructions related to purchases of zolpidem and trazodone. As a result, the keywords or parts of the keywords were found in 99.5% of the zolpidem data and 99.3% of the trazodone data. With these keywords, we identified the dosing instructions for each of the medicine purchases included in the further analyses ($n = 328,285$ dosing instructions).

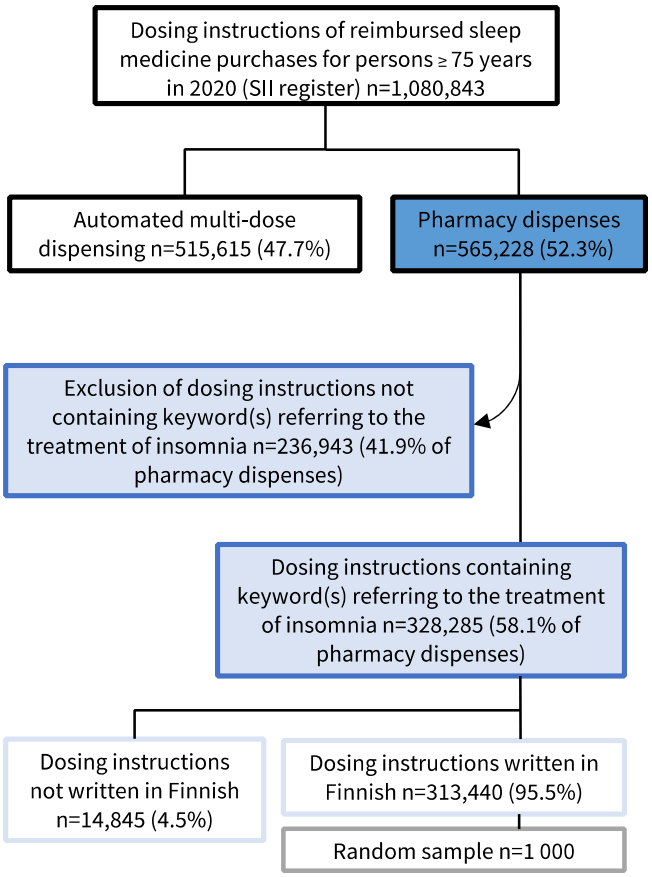

FIGURE 1 (A) Flowchart for analyzing dosing instructions of sleep medicine purchases and their characteristics. SII, the Finnish Social Insurance Institution.

2.2 | Analysis of the instruction labels

Every prescription medicine package dispensed from the community pharmacy must contain an instruction label for the medicine user. It must contain instructions for use (single and daily dose(s)), and may contain the purpose of the use, if indicated by the prescriber in the prescription. In this study, the *instruction labels* refer to the instructions for use provided to the medicine user on the dispensing label attached to the medicine package when it is dispensed. The dosing instructions are required to be written exactly as specified in the prescription. We examined the appropriateness of dosing instructions according to four pre-determined criteria shown in Table 1 (criteria 1–4). The criteria were self-specified but based on national legislation[23,24] and Finnish National Current Care Guideline for Insomnia.[20] It was assessed whether each dosing instruction fulfilled the criteria 1–4. The number of fulfilled criteria, including the information, was summed for each medicine.

A random sample of 1000 dosing instructions was used to assess the validity of the analysis. Dosing instructions for all drugs except clobazam were included in the analysis. These dosing instructions were read individually, and the aforementioned criteria (1–4, Table 1) were used for the analysis. In addition, instructions for dose reduction or planned discontinuation (deprescribing) and explicit instructions for the duration of use were assessed (criterion 5, Table 1). This extra criterion was based on the recommendation of the Finnish National Current Care Guideline for Insomnia.[18]

Descriptive data analyzes were performed using IBM SPSS Statistics (version 28.0). Microsoft Excel was used for data handling and processing.

TABLE 1 Criteria for sufficient information content in sleep medicine dosing instructions (based on national legislation (References [23, 24]) and National Current Care Guideline for Insomnia (Reference [20]).

Criteria	Rationale for the assessment
(1) Single dose	Medicine user must know how much to take the medicine at a time
(2) Time of intake	The exact time of dosing for sleep medicines is important to ensure optimal efficacy, align with desired sleep schedules, minimize side effects and risks, and avoid potential interactions.
(3) Temporary use	Sleep medicines are only meant for irregular short-term use
(4) Warnings and/or remarks	Sleep medicines are potentially inappropriate medicines for older adults
(5) Instructions for deprescribing[a]	Sleep medicine use should last for maximum 2 weeks including the gradual discontinuation

[a]Based on the assessment of the random sample of 1,000 dosing instructions.

3 | RESULTS

This register study resulted in a dataset of 1,080,843 sedative sleep medicine purchases by 143,886 individuals aged ≥75 years in year 2020 (Figure 1). The three most dispensed medicines in the whole dataset were mirtazapine, quetiapine, and zopiclone (Table 2). Most purchases were subsequent partial deliveries of prescriptions, and the average number of annual dispensations was 3.8 per person, indicating long-term use. Almost half (47.7) of the medicine purchases were made through automated multi-dose dispensing systems, and were thus likely intended for regular, long-term use. Of the remaining purchases, 328,285 purchases by 87,396 different individuals contained keyword(s) potentially referring to the

TABLE 2 Comparison of sleep medicine dispenses included in the original material.

			Community pharmacy dispenses (not containing multi-dose dispenses), $N = 565228$				Automated multi-dose dispenses, $N = 515615$		All dispenses, $N = 1080843$	
	Suitability for older persons		Indicated[a] for the treatment of insomnia		Other					
Medicine	Beers criteria	CCG	*n*	%	*n*	%	*n*	%	*n*	%
Zopiclone (N05CF01)	NA	Short term only	134,631	41.0	13,279	5.6	33,839	6.6	181,749	16.8
Mirtazapine (N06AX11)	With caution (C)	With depression	112,463	34.3	38,144	16.1	211,959	41.1	362,566	33.5
Zolpidem (N05CF02)	Avoid (D)	Short term only	37,860	11.5	4185	1.8	4997	1.0	47,042	4.4
Quetiapine (N05AH04)	Avoid (D)	Special occations	23,756	7.2	33,327	14.1	132,434	25.7	189,517	17.5
Oxazepam (N05BA04)	Avoid (D)	Short term only	15,564	4.7	65,230	27.5	48,560	9.4	129,354	12.0
Trazodone (N06AX05)	NA	With depression	940	0.3	466	0.2	2494	0.5	3900	0.4
Lorazepam (N05BA06)	Avoid (D)	Avoid	771	0.2	10,703	4.5	22,711	4.4	34,185	3.2
Trimipramine (N06AA06)	Avoid (D)	With depression	620	0.2	374	0.2	163	<0.1	1157	0.1
Pregabalin (N03AX16)	With caution (C)	NA	584	0.2	56,273	23.7	53,957	10.5	110,814	10.3
Diazepam (N05BA01)	Avoid (D)	Avoid	559	0.2	4961	2.1	1061	0.2	6581	0.6
Alprazolam (N05BA12)	Avoid (D)	Avoid	507	0.2	9309	3.9	2947	0.6	12,763	1.2
Doxepine (N06AA12)	Avoid (D)	Low dosage	24	<0.1	17	0.0	8	<0.1	49	<0.1
Midazolam (N05CD08)	NA	Avoid	5	<0.1	350	0.1	0	0	355	<0.1
Clobazam (N05BA09)	NA	NA	1	<0.1	325	0.1	485	<0.1	811	0.1
Total			328,285	100.0	236,943	100.0	515,615	100.0	1,080,843	100.0
Type of prescription										
Original prescription			157,093	47.9	109,372	46.4	28,761	5.6	295,226	27.3
Subsequent partial delivery by prescription			170,706	52.0	126,592	53.6	486,688	94.4	783,986	72.5
Other			486	0.1	979	0.4	166	<0.1	1631	0.2
Total			328,285	100.0	236,943	100.0	515,615	100.0	1,080,843	100.0
Sex										
Women			59,299	67.9	43,446	65.0	18,015	71.6	97,706	67.9
Men			28,097	32.1	20,994	35.0	7142	28.4	46,180	32.1
Total[b]			87,396	100.0	64,440	100.0	25,157	100.0	143,886	100.0
Age group										
75–79 years			30,386	34.8	21,462	39.0	4186	16.6	46,833	32.5
80–84 years			26,390	30.2	18,432	29.0	6342	25.2	41,866	29.1
85–89 years			18,744	21.4	14,196	19.0	7389	29.4	32,128	22.3
90–94 years			9414	10.8	7,958	10.0	5387	21.4	17,826	12.4
95–years			2462	2.8	2,392	3.0	1853	7.4	5233	3.6
Total			87,396	100.0	64,440	100.0	25,157	100.0	143,886	100.0

Note: Drugs are listed according to the number of pharmacy purchases of dispenses with dosing instructions containing keywords referring to the treatment of insomnia.
Abbreviations: CCG, National Current Care Guideline for Insomnia (Reference [20]), NA, not available.
[a]Dosing instructions contain keyword(s) referring to the treatment of insomnia.
[b]The total person number does not sum to persons with all dispenses as individual may have bought studied medicines via dose-dispensing or as sleep medicines or other indications during the study period.

treatment of insomnia. Of these, the three most dispensed drugs were zopiclone (41.0%), mirtazapine (34.3%), and zolpidem (11.5%) (Table 2). Notably, of all the 12 drugs included in the study, only zopiclone and zolpidem have insomnia as their primary and only indication. Despite this, approximately one-tenth of the dosing instructions for zopiclone (9.0%) and zolpidem (10.0%) did not contain words referring to the treatment of insomnia.

Most (98.4%) of the dosing instructions that indicated the treatment of insomnia included the dose of the medication and time of intake (83.4%) (Table 3). Temporary short-term use was mentioned in 57.3% of the dosing instructions, whereas only 2.8% included warnings, such as "not suitable for long-term use" ($n = 8895$) (Table 3). Overall, only 2.1% of the dosing instructions fulfilled all the four criteria for sufficient instructions, as we defined based on the national legislation[23,24] and the Finnish Current Care Guideline for Insomnia.[20] None of the dosing instructions for five drugs (doxepin, midazolam, trimipramine, alprazolam, and lorazepam) fulfilled all the criteria for sufficient instructions. The dosing instructions fulfilling all four criteria were most often, although very rarely, found for zopiclone (4.0%), zolpidem (3.3%), and oxazepam (1.3%).

The dosing instructions for different medicines differed most significantly in the frequency of expressing the time of intake. This parameter was most frequently present in the instructions for doxepin (95.5%), trimipramine (91.8%) and quetiapine (86.4%) and less frequent in those for lorazepam (57.7%), diazepam (60.9%,) and oxazepam (63.9%). In addition, a mention of temporary use was most frequently observed in the instructions for zolpidem (86.0%) and zopiclone (85.8%) and least frequently observed in those for trazodone (15.6%), pregabalin (16.8%), and mirtazapine (19.0%). Other remarks and warnings concerning appropriate use were more rarely included in the dosing instructions, most commonly for zopiclone (5.0%) and zolpidem (4.4%). For other medicines, remarks or warnings were included in 0%–2.7% of the dispensed prescriptions.

In a randomized sample of 1000 dosing instructions, the dose was included in almost all instructions (98.8%, $n = 988$). The time of drug intake was specified in 82.5% ($n = 825$) of the instructions, and warnings or remarks were included in 5.5% ($n = 55$). The instruction for gradual discontinuation/deprescribing of the medicine was clearly mentioned in 5.2% of the dosing instructions ($n = 52$). Only three drugs had these instructions: zopiclone ($n = 35$), zolpidem ($n = 15$), and oxazepam ($n = 2$). Original examples of sufficient and inadequate dosing instructions are given in Table 4.

4 | DISCUSSION

This nationwide study indicates significant shortcomings in the dosing instructions accompanying the prescriptions of sleep medicines for older adults in Finland. Although nearly all screened dosing instructions included the information about a single dose and the time of intake, only a minority (2%) of the instructions contained sufficient information to ensure appropriate use of the medicines that are classified as potentially inappropriate medicines (PIMs) for older adults.[18,19] Therefore, the dosing instructions frequently missed information that is required to be provided in a prescription according to the Finnish legislation. Most worrying finding was that the missing information often concerned warnings or notes regarding regular and long-term use of sleep medicines. Notably, the pitfalls in dosing instructions were similar across all assessed medicines. This suboptimal prescribing practice may be one of the contributing factors to the regular long-term use of sleep medicines, and contrary to guidelines.[20] Thus, our study implies that sufficient, readily available dosing instructions could be a feasible, but currently undervalued method to support appropriate and safe medication use in outpatient care. Further research is needed to evaluate the impact of improved dosing instructions on appropriateness and prevalence of sleep medicine use for insomnia in older adults.

Our findings indicate that automated multi-dose dispensing may be another contributing factor to regular, long-term use of sleep medicines in older adults. Most strikingly, nearly a half of the reimbursed medicine purchases in our study were multi-dose dispensations, meaning that sedative medicines were regularly administered as part of the standard daily medication regimen. In our dataset, mirtazapine and quetiapine were the most commonly dispensed medicines through automated multi-dose dispensing. Importantly, these medicines are widely used also for other indications than insomnia (mirtazapine as an antidepressant and quetiapine as an antipsychotic drug). However, regardless of indication, most drugs in our dataset are considered as PIMs for older adults. The finding that these drugs are so commonly dispensed via automated multi-dose dispensing systems raises concerns that should be examined in future studies. Automated multi-dose dispensing systems should be assessed to determine whether the practices, believed to promote rational pharmacotherapy and medication safety, maintains long-term use of PIMs, and exposes older outpatients to preventable harm. Regular medication reviews have been recommended to be integrated into the automated dose dispensing process to prospectively manage medication-related risks.[29,28] Notably, automated multidose dispensing is expected to become more common practice in geriatric outpatient care as the population is aging.

More research is needed to assess the potential association between long-term use of sleep medicines

TABLE 3 Analyzed purchase data for medicines indicated for the treatment of insomnia ($n = 328,285$), their suitability for older adults, and the content of the dosing instructions by active substance.

Medicine ATC code Suitability for older persons (Beers Criteria) Suitability for older persons (CCG)		Zopiclone[a] N05CF01 NA Short term only	Zolpidem[a] N05CF02 Avoid (D) Short term only	Mirtazapine N06AX11 With caution (C) Can be used if also depression	Trazodone N06AX05 NA Can be used if also depression	Trimipramine N06AA06 Avoid (D) Can be used if also depression	Doxepine N06AA12 Avoid (D)[b] Can be used with a very low dosage	Quetiapine N05AH04 Avoid (D)[c] Only for special occations	Oxazepam N05BA04 Avoid (D) Short term only	Diazepam N05BA01 Avoid (D) Avoid	Lorazepam N05BA06 Avoid (D) Avoid	Alprazolam N05BA12 Avoid (D) Avoid	Pregabalin N03AX16 With caution (C[d]) NA	Total
All community pharmacy dispenses	*n*	147,910	42,045	150,607	1406	994	41	57,083	80,794	5520	11,474	9816	56,857	565,228
Label include keyword(s) referring treatment of insomnia	%	**91.0**	**90.0**	**74.7**	**66.9**	**62.4**	**58.5**	**41.6**	**19.3**	**10.1**	**6.7**	**5.2**	**1.0**	**58.1**
	n	134,631	37,860	112,463	940	620	24	23,756	15,564	559	771	507	584	328,285
Label include information about daily dose	%	**98.4**	**98.4**	**98.4**	**96.4**	**98.8**	**100.0**	**98.2**	**97.9**	**98.0**	**97.0**	**99.6**	**98.3**	**98.4**
	n	124,941	35,759	106,519	890	591	22	22,629	14,710	531	706	457	572	308,332
Label include information about time of intake	%	**83.1**	**82.4**	**86.3**	**86.0**	**91.8**	**95.5**	**86.4**	**63.9**	**60.9**	**57.7**	**71.2**	**82.3**	**83.4**
	n	105,548	29,949	93,346	794	549	21	19,896	9607	330	420	327	479	261,266
Label include information about frequency of use	%	**85.8**	**86.0**	**19.0**	**15.6**	**19.1**	**27.3**	**27.4**	**73.1**	**65.5**	**56.9**	**63.0**	**16.8**	**57.3**
	n	108,958	31,275	20,544	144	114	6	6324	10,983	355	414	289	98	179,509
Label include warnings and/or remarks	%	**5.0**	**4.4**	**0.4**	**0.3**	**1.0**	**0.0**	**0.7**	**2.2**	**0.7**	**2.6**	**1.7**	**2.7**	**2.8**
	n	6336	1599	400	3	6	0	166	338	4	19	8	16	8895
Label containing sufficient information[e]	%	**4.0**	**3.3**	**0.2**	**0.1**	**0.0**	**0.0**	**0.2**	**1.3**	**0.6**	**0.0**	**0.0**	**0.2**	**2.1**
	n	5018	1202	166	1	0	0	48	200	3	0	0	1	6639
Deficient instruction[f]	%	**1.7**	**1.8**	**1.8**	**5.1**	**2.2**	**0.0**	**2.4**	**2.2**	**2.8**	**3.0**	**0.7**	**2.7**	**1.8**
	n	2204	643	1910	47	13	0	544	335	15	22	3	16	5752

Note: Drugs are listed according to the proportion (%) of labels that included an indication (keyword(s)) for insomnia treatment.

Abbreviations: CCG, National Current Care Guideline for Insomnia (Ref. 20); NA, not available.

[a]Insomnia is the only official indication.

[b]Dose >6 mg per day.

[c]Dose reduction in renal impairment.

[d]Parkinson's disease.

[e]The dosing instruction included the dose, time of intake, warnings or remarks, and mention of irregular use.

[f]The dosing instructions did not contain critical information (e.g., dose).

TABLE 4 Examples of original dosing instructions (sufficient or inadequate) selected from a random sample of 1000 dosing instructions.

Medicine (ATC-code)	Examples of sufficient dosing instructions	Examples of inadequate dosing instructions
Zopiclone (N05CF01)	"1/2–1 tablet in the evening just before sleeping. Maximum 5 times a week. INCREASES RISK FOR FALLS! Next dispensing earliest 27 days since previous one. Short term use of insomnia."	"To give sleep"
	"1/2–1 tablets for the night, only when needed. In long term use can weaken memory. Sleep medicine."	"1 × 1 insomnia"
	"1/2 tablet in the evening, recommend to use only on 4 nights a week, because can cause dependence and efficacy can weaken when used often. It is not allowed to take every night. To help sleeping."	"As guided for sleeping"
Mirtazapine (N06AX11)	"As needed 1 tablet for a night. Medicine can weaken the efficacy of Moxonidis blood pressure lowering efficacy. To help to sleep during night."	"To help sleeping 1/2 a day"
	"0.25 tablets in the evening 1–2 hours before going to bed. Use the lowest effective dose. There is no need to use Imovane at the same time. Treatment of insomnia."	"1 × 1 medicine helping to sleep"
	"1/4–1/2 tablets in the evening as needed to help to get sleep. Melatonin is the first choice. The lower the dose the more effective is the effect on sleep and insomnia."	"according to a separate instruction to support sleep"
Zolpidem (N05CF02)	"0.5–1 tablets as needed for night. Weakens the quality of sleep. Continuous use worsens insomnia. Worsens memory and other cognitive function. Increases falls. Total weekly use must be decreased by 0.5 tablets during 1 week"	"Sleep medicine"
	"1/2–1 tablets as needed in the evening just before going to bed. Maximum three nights a week. Long term use can weaken memory and balance. It is recommended to slip the dose in to half and quitting the use. Treatment of insomnia."	"1–2 a day. Sleep medicine"
	"1/2–1 tablets as needed for night, not over 2 weeks regular use. May cause dependence. Sleeping medicine"	"1/2 × 1–2/day for disturbed sleep"
Quetiapine (N05AH04)	"1/2–1 tablets in the evening as needed. May increase risk for falls. Sleep enhancing, anxiolytic medicine."	"0 + 0 + 1 sleep and anxiolytic medicine"
	"1 tablet in evening, as needed. Not together with Opamox. Insomnia, anxiety"	"2–3 night sleep medicine"
	"0.5–2 tablets in the evening as needed or regularly. May cause dizziness. Insomnia and anxiety"	"night for insomnia"
Oxazepam (N05BA04)	"1/2–1 tablets in the evening when going to bed 3–4 nights a week. May cause aiheuttaa dependence, memory disturbance in long term regular use. sleep medicine"	"0.5 × 1–2 for insomnia"
	"1/2–1 tablets a night as needed. Not for daily use. May cause dependence! Next dispense is earliest after 1.5 months. For insomnia"	"1 day sleep medicine"

and the content of dosing instructions. It is also important to investigate whether the content of dosing instructions differs according to the age of patients. Furthermore, clear, explicit content of dosing instructions and instructions for gradual discontinuation/deprescribing may reduce the long-term use of sleep medicines and promote safer pharmacotherapy among older adults. Our findings indicate that it is important to take action regarding to the common pitfalls in prescribing practices and to enhance the use of dosing instructions in guiding patients in appropriate medicine-taking behaviors. This is especially important when prescribing high-risk medicines such as sleep medicines to older adults.

4.1 | Policy, practice implications, and future research

- This study identified two factors that potentially expose older adults to preventable harm of sedative sleep medicine use: automated multi-dose dispensing (potentially leading or maintaining long-term, regular use) and poor quality of dosing instructions. It is important to take action on both contributing factors.
- It is important to make prescribers adhere to prescribing instructions and treatment guidelines so that the dosing instructions contain the necessary information for the medicine user to use the medicine safely and appropriately. The minimum dosing instructions

should include indication, dose, time of intake, length of treatment, and warnings/remarks most relevant for given medicine user, and if needed, instructions for gradual discontinuation/deprescribing.
- It is also important to investigate the potential treatment outcomes and consequences of poorly instructed prescriptions of benzodiazepines and Z-drugs in older adults.
- Future studies should identify subgroups of older adults who are more vulnerable to the side effects of (long-term) use of sleep medicines, such as nocturnal confusion and falls.

4.2 | Strengths and limitations

Although dosing instructions are a vital source of customized information for medicine users, to our knowledge, this is the first study assessing the content of the dosing instructions. The present study is based on all the purchases of reimbursed sedative sleep medicines, including their dosing instructions, in Finns aged ≥75 years in 2020. Therefore, it offers a relatively comprehensive and timely overview of the quality of sleep medicine prescribing practice in Finland, with a special focus on appropriateness of dosing instructions. However, this study has limitations. First, our approach may give an overly positive impression of the content of use instructions, as it only includes those dosing instructions that were, based on keyword(s) in the labels, indicated for the treatment of insomnia or insomnia symptoms. For example, nearly 20,000 purchases of the hypnotics zopiclone and zolpidem were prescribed and dispensed with dosing instructions without clear indication for insomnia. Second, the data consisted only of medicines reimbursed according to the Finnish Health Insurance Act in 2020. Therefore, purchases of non-reimbursable but widely used sleep medicines such as melatonin or temazepam are not included in the data. Third, the indication (or its severity) to which the medicine was prescribed is not possible to specify in our study. Relatedly, owing to potential typographical errors in the dosing instructions, some instructions might have been excluded from the actual analysis. However, the qualification of the research material was done carefully and validated. Moreover, the study was conducted during the pandemic, which may have also produced mixed effects on the prescribing and use of sleep medicines, and prevalence of insomnia and insomnia symptoms. However, the data describe the first year of the COVID-19 pandemic, with radically diminished contacts between patients and health care professionals. Finally, we only considered prescription labels as a source of dosing instructions. Dosing instructions and other critical information could have been passed on verbally, or medications could have been dispensed by caregivers with sufficient knowledge about dosing and potential harms.

To conclude our findings indicate that appropriate instructions, particularly warnings about long-term regular use, are neglected in routine practice in prescribing sedative sleep medicines for older adults (≥75 years). Urgent actions to change current clinical prescribing practices are warranted.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests. No specific funding has been obtained to carry out this research. T.R. and M.A. are employed by the University of Helsinki. T.K. is employed by the Social Insurance Institution of Finland. S.T-E. was working as a master's student for this work. This study has been partially funded by the Social Insurance Institution (Kela).

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13661.

DATA AVAILABILITY STATEMENT

Due to data protection regulations of the secondary use of administrative, individual-level register data in Finland, the authors do not have the permission to make the data supporting the current findings available. Interested parties may however apply for permission to access the data from the Social Insurance Institution of Finland (Kela), https://www.kela.fi/web/en/data-permits-and-data-requests; email: tietoaineistot@kela.fi.

ETHICS STATEMENT

This solely register-based study does not require ethical approval according to Finnish legislation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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