

Use of sedating medications around nursing home admission in Denmark

Anton Pottegård^{1,2,3}  | Carina Lundby^{1,2,3,4} | Dorte Ejg Jarbøl⁴ |
Søren Post Larsen⁵ | Bettina Clauber Hoppe⁵ | Helene Hoffmann⁵ |
Wade Thompson^{2,3,4}

¹Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

²Hospital Pharmacy Funen, Odense University Hospital, Odense, Denmark

³Odense Deprescribing Initiative (ODIN), Odense, Denmark

⁴Research Unit of General Practice, Department of Public Health, University of Southern Denmark, Odense, Denmark

⁵TYPE2DIALOG, Kongens Lyngby, Denmark

Correspondence

Wade Thompson, Research Unit of General Practice, University of Southern Denmark, JB Winsløvsvej 9, DK-5000, Odense, Denmark.
Email: wthompson@health.sdu.dk

Abstract

Purpose: To examine use of sedating medications around the time of nursing home admission in Denmark.

Methods: We conducted a register-based drug utilization study, describing patterns of commonly used medications with sedative effects leading up to and after nursing home admission using data from 94 Danish nursing homes between 2015 and 2017.

Results: We identified 5179 residents (median age 84 years, 63% female) and described monthly incidence and total use of benzodiazepines (BZDs), Z drugs, mirtazapine/mianserin, quetiapine, promethazine, and melatonin. The proportion of unique users of sedating medications was similar before and after admission (42% before vs. 40% after) despite an increase in total use after admission. The overall incidence of sedating medications peaked in the 6 months before and 6 months after admission (peaking at 4.6 per 100 person-months 1 month after admission). The most commonly initiated medications were mirtazapine/mianserin, followed by BZDs and Z drugs. Total use of sedating medications increased leading up to admission (peaking at 1001 defined daily doses per 100 residents per month 1 month after admission) and decreased gradually after admission.

Conclusions: Sedative medication initiation increases sharply leading up to admission in Danish nursing homes. Mirtazapine/mianserin is a commonly used agent in nursing homes, despite limited evidence on benefits and harms. Efforts to promote rational use of these medications in nursing homes remain warranted.

KEYWORDS

drug utilization, hypnotics and sedatives, nursing homes, polypharmacy

Key points

- There are harms associated with sedating medications, such as benzodiazepines, and concerns with their use in older people; however, limited alternatives exist.
- Sedating medication use is common in newly admitted nursing home residents in Denmark, and increases leading up to and shortly after admission.
- Mirtazapine/mianserin is commonly used agents in Danish nursing home residents despite limited evidence on their use in this context.

1 | INTRODUCTION

Sleep disturbances, depression, anxiety, and behavioral and psychological symptoms of dementia (BPSD) are common conditions among nursing home residents. These multifactorial and often co-existing conditions are associated with negative consequences such as decreased function and increased risk of falls.^{1,2} Sleep problems can be caused by environmental factors (e.g., noise, lighting, and room sharing), age-related changes in sleep architecture, other medical problems (e.g., anxiety, pain, and dementia), and behavioral factors.² Non-pharmacological approaches to treatment are generally preferred,^{2,3} however, these approaches may be difficult to implement due to lack of training/knowledge or organizational factors (e.g., lack of access or time from healthcare providers).⁴ Therefore, sleep and psychiatric conditions are often managed with medications such as benzodiazepines (BZDs), Z drugs (zopiclone, zolpidem), antipsychotics such as quetiapine, or antidepressants (including sedating antidepressants, e.g., mirtazapine or trazodone).^{2,5} These sedating medications carry potential harms (e.g., confusion, dizziness) and have been associated with adverse health outcomes such as falls and impaired cognition.^{6–8} Several studies have reported decreasing rates of BZD use in the 2000s and 2010s.^{5,9,10} One concern, however, is that avoiding BZDs may prompt switching to, or use of, alternative medications (e.g., Z drugs, quetiapine, mirtazapine), which have their own safety concerns.^{5,11–13} Indeed, prescribing of low dose quetiapine appears to be increasing among older persons as reported in Scandinavia, Canada, and Australia.^{5,14–17} Detailed data on the use of these sedating drugs are necessary to guide initiatives to ensure their appropriate use. The time around nursing home admission is of particular interest. This transition may precipitate mood or sleep problems, leading to pharmacological management, while mood problems leading to pharmacological management may itself precipitate admission. Further, use of unsafe medications among community dwelling adults may contribute to adverse health outcomes, necessitating nursing home admission. The aim of this study was to describe patterns of sedating medication use around nursing home admission in Denmark.

2 | METHODS

2.1 | Design and data sources

This was a register-based descriptive drug utilization study. We leveraged a cohort of persons moving into 94 nursing homes across Denmark from 2015 to 2017. This cohort has previously been described in terms of morbidity and mortality¹⁸ as well as overall medication use.¹⁹ The cohort was established after 18 Danish municipalities were invited to participate in an initial study,¹⁸ of which 11 municipalities agreed to participate and provided personal registration numbers of people moving into their nursing homes between 2015 and 2017.²⁰ We linked the cohort to the National Patient Register²⁰ and Danish National Prescription Registry²¹ to obtain information about hospital diagnoses and prescription drug use. Data were linked using the

personal identification number, which is a unique identifier assigned to all Danish residents. We examined specific medications that have sedating properties: BZDs, Z drugs (zopiclone, zolpidem), mirtazapine/mianserin, low dose quetiapine (<100 mg), promethazine, and melatonin (see Table S1). These medications were judged to be commonly used in the nursing home setting and therefore of particular interest for our research question. Medications were selected based on discussion with clinicians practicing in nursing homes and researchers with experience in the Danish nursing home context. Trazodone is not used in Denmark.

2.2 | Research questions

The analyses followed four pre-specified research questions:

1. Incident use: we calculated the monthly rate of new (incident; first fill in 2 years) use of BZDs, Z drugs, mirtazapine/mianserin, low dose quetiapine, promethazine, and melatonin in the 2 years leading up to and following nursing home admission.
2. Total use: we described the total monthly use of each medication class above in defined daily doses (DDDs)²² per resident per month in the 2 years leading up to and following nursing home admission.
3. Resident characteristics: we identified those who used no medication in the year leading up to nursing home admission, and in the year following admission, respectively. This formed four cohorts (non-use both before and after; use both before and after; non-use/use; and use/non-use), for which we reported age, sex, comorbidities (any history of diagnosis leading up to index date of nursing home admission), concomitant medication use (use in the 180 days leading up to nursing home admission), and Charlson comorbidity index.
4. Before and after admission: we described the number of nursing home residents who filled prescriptions for 0, 1, or 2+ different sedating medications in the year before admission compared to the year after admission. Residents were classified as using 2+ medications if they filled at least one prescription for each medication during the year. We also examined which specific sedating medications were used in the year before and after admission.

2.3 | Analysis

Stata 16 was used for data analysis. For research questions 1 and 2, we censored residents upon death. As sensitivity analyses for question 1 and 2, we censored people 30 days before dying to limit the impact from palliative prescribing. Further, for question 3, we excluded the 30 days before and 30 days after nursing home admission, in order to account for medication changes made around nursing home admission. Finally, for question 4, we included a sensitivity analysis where individuals had to fill at least two prescriptions for a medication during the year to be classified as a user.

2.4 | Ethics

This study was based solely on register data and thus did not require approval from an ethics board, as stipulated by Danish law.

3 | RESULTS

We identified 5179 persons who were admitted to the 94 nursing homes during the study period. The median age was 84 years (interquartile range 77–89) and 63% were female. Around 42% had a heart failure diagnosis, 32% had a dementia diagnosis, and 25% had a cancer diagnosis (Table S1). In the year leading up to nursing home admission, there were 2157 users (42%) of at least one sedating medication, while in the year after admission there were 2086 (40%) users. In both periods, the most commonly used medications were mirtazapine/mianserin (18.9% before and 20.7% after), BZDs (14.7% and 12.9%), and Z drugs (16.0% and 12.3%). Mirtazapine/mianserin use was made up predominantly of mirtazapine users (87% of total users). There were 249 quetiapine users (5%) before admission, and 299 (6%) after admission (Table S2).

With respect to incident use, the overall monthly initiation rate of sedating medications increased from 1.5 per 100 person-months 6 months before nursing home admission to 4.2 per 100 person-months 2 months before admission (Figure S1). The initiation rate peaked at 4.6 per 100 person-months 1 month after admission, then decreased to about 1 per 100 person-months around 9 months after admission. The most commonly initiated individual medication class was mirtazapine/mianserin, followed by BZDs and Z drugs (Figure 1). The supplementary analysis censoring at 30 days before death yielded a slight drop in BZD incidence in the month after admission (Figure S2).

The total use of sedating medications increased leading up to admission from 596 DDD/100- person-months at 24 months before

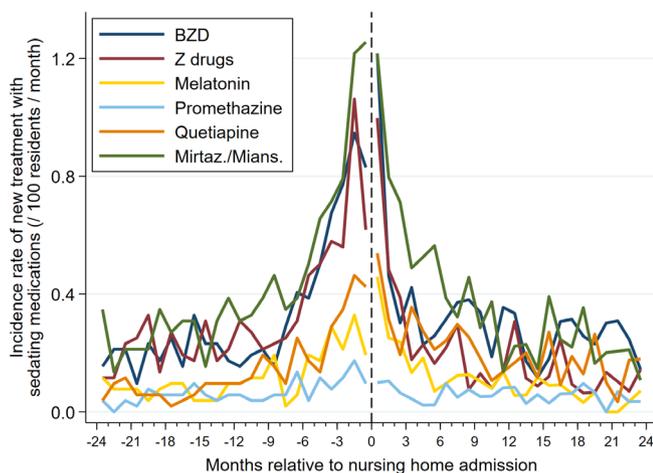


FIGURE 1 Incidence of sedating medications before and after nursing home admission [Colour figure can be viewed at wileyonlinelibrary.com]

admission to 1001 DDD/100-person-months at one month after admission, then gradually decreased to 765 DDD/100-person-months at 24 months after admission (Figure 2). The increase was most pronounced for mirtazapine/mianserin, peaking at 428 DDD/100-person-months 1 month after admission. The supplementary analysis censoring at 30 days before death produced a small drop in total BZD use in the month after admission but otherwise had no impact (Figure S3).

With respect to resident characteristics, non-users of sedating medications both before and after admission were slightly older than those using sedating medications (median age 85 years, compared to a median age 82–83 years; Table S2). Further, there were fewer concomitant opioid users in the group who did not use sedating medications in both periods (28%) or who did not use sedating medications before admission but did use sleep medications after (30%), compared to other groups (40%–43%).

With respect to sedating medication use before and after admission, Figure 3 displays the trajectories of sedating medication users 1 year before and after nursing home admission. The number of people not using a sedating medication before admission but using one after admission (7%; $n = 344$; non-use/use) was similar to the number using one sedating medication before admission but not after (8%; $n = 412$; use/non-use). Our sensitivity analysis requiring at least two fills of each medication per year resulted in more people being classified as non-users (as expected given a more restrictive definition), but with a similar distribution (Figure S4).

Single use of BZDs (346 to 298 users) and Z drugs (401 to 311 users) decreased, while single use increased for mirtazapine/mianserin (552 to 640 users) and quetiapine (89 to 112 users) (Table S3).

In a post hoc analysis, we identified new users of mirtazapine/mianserin within 1 year before or after nursing home admission ($n = 911$) of which 38% ($n = 346$) had filled a prescription for another antidepressant in the year before mirtazapine/mianserin initiation.

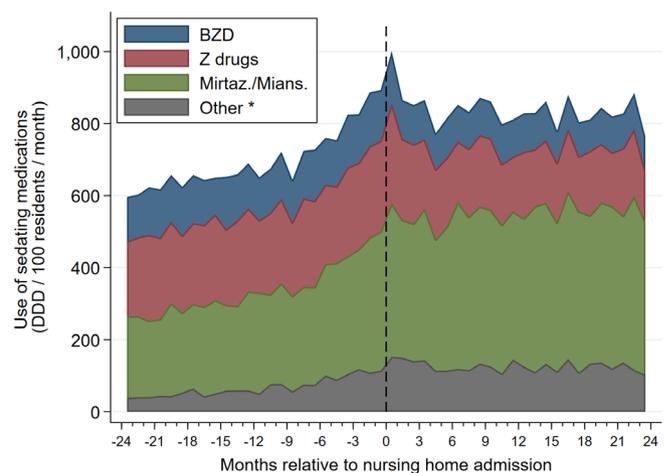


FIGURE 2 Total use of sedating medications before and after nursing home admission. *other = melatonin, promethazine, and low dose quetiapine [Colour figure can be viewed at wileyonlinelibrary.com]

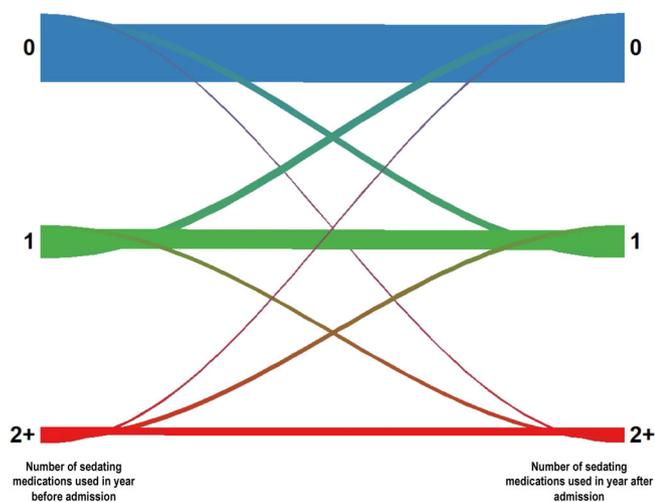


FIGURE 3 Trajectories of sedating medication use before and after nursing home admission [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

We found that initiation of BZDs, Z drugs, and mirtazapine/mianserin increased sharply leading up to nursing home admission and that use of these agents was high both before and after nursing home admission. Although use of BZD and Z drugs decreased after admission, this was partially offset by increases in quetiapine and mirtazapine/mianserin use, the latter being the most commonly used and initiated. This suggests that BZD and Z drug use may to some extent be replaced by other sedative medications in the time after nursing home admission.

The finding that initiation of sedating medication peaks leading up to nursing home admission may be partly explained by worsening sleep or mental health problems increasing the risk of long-term care placement as shown in previous studies.² It is also possible that people have been admitted to nursing homes following hospitalization, during which a sedating medication was initiated. In a previous study involving this cohort, around one half of patients had been admitted to hospital at least once in the 6 months prior to nursing home admission.¹⁸ Increased prescribing of sedating medications around this time may therefore be a general sign of worsening sleep, mental health, and/or generally declining functional level. However, sedating medications themselves have adverse effects (e.g., falls, impaired cognition) that may precipitate nursing home placement. This interplay suggests that careful attention should be paid to prescribing of sedating medications in older persons at increased risk of nursing home placement.

We found that mirtazapine was commonly used and initiated in nursing home residents, consistent with studies in the United States²³ and Finland.²⁴ While prescribers may look for safer alternatives to BZDs and Z drugs, the safety and efficacy of mirtazapine or mianserin for sleep, and even for depression, agitation, or anxiety,^{25–27} is not well-established among nursing home residents. Existing evidence for mirtazapine for sleep disorders points to unclear benefit, and potential

for adverse effects (such as somnolence, falls, and daytime sleepiness), while there is limited evidence for mianserin.^{25,27,28}

Use of sedating medications before and after nursing home admission has previously been examined in Canada.²⁹ BZDs were common at admission and many residents were initiated on these medications following admission, which is similar to our study. However, we found an overall reduction in the number of BZD and Z drug users after admission. While encouraging, this reduction was accompanied by increases in mirtazapine and quetiapine use. Another Canadian study⁵ similarly found that a reduction in BZD use in older persons was accompanied by increases in alternatives (quetiapine, trazodone). Increasing medication initiation leading up to admission is consistent with a previous study in Danish nursing homes.¹⁹

The principle strength of our study is the large sample of nursing home residents, with unambiguous linkage to highly valid Danish registry data.²¹ A possible limitation is that we do not know the indication for the medications. Observed mirtazapine/mianserin use likely represents a mixture of use for depression, insomnia, and/or BPSD. Of note, only 38% of mirtazapine/mianserin initiators had filled prescriptions for other antidepressants in the year before initiation. These drugs are not first-line treatment for depression in Denmark, which suggests a substantial portion of initiation may be for sleep (off-label) or at least mood disorders when sleep is a concern.³⁰ Even if used for depression or BPSD, there is only limited evidence on the benefits/harm balance of mirtazapine among nursing home residents.^{25–27} We attempted to reduce misclassification by excluding BZDs not used for insomnia (e.g., midazolam). We restricted to low doses of quetiapine (<100 mg), however, these doses of quetiapine may also be used for behavioral symptoms of dementia. We did not include other antipsychotics (e.g., risperidone) that may also be used to manage sleep or psychiatric problems nor did we investigate dose reductions or increases of any of the medications.

Our finding that sedating medication use increases leading up to nursing home admission, suggests that prescribers should be particularly vigilant with prescribing sedating medication in older people at increased risk of long-term care placement. Close to nursing home admission, people may be at increased risk of BPSD, sleep problems, or mood problems which may be treated with sedating medications, potentially increasing the risk of falls or worsening cognition around this transition phase. We acknowledge that a major problem in clinical practice, is the lack of safe and effective treatment options to manage sleep and mood problems in this population. Thus, our findings also underscore the need for increased access to, and training in non-pharmacological interventions for sleep and psychiatric disorders, as well as implementation of multi-faceted interventions addressing different components of sleep and psychiatric problems in nursing home residents (e.g., addressing environmental and behavioral triggers).² Finally, the high use of mirtazapine in our population highlights the urgent need for evidence on the benefits and harms of this agent for sleep and depression in nursing home residents.

In conclusion, use of sedating medications is common among Danish nursing home residents and increases sharply leading up to and shortly after admission. Given the known risks of these

medications, efforts to encourage appropriate use and deprescribing of BZDs and Z drugs continue to be needed. Further, the common use and initiation of mirtazapine/mianserin in Danish nursing home residents despite unclear benefit and potential for harm, warrants efforts to promote rational use of these medications and further examination of their safety and efficacy among nursing home residents.

ACKNOWLEDGMENTS

The authors would like to thank the following municipalities for their participation in the study: Bornholm, Brøndby, Esbjerg, Fåborg-Midtfyn, Gladsaxe, Næstved, Odder, Randers, Ringsted, Rødovre and Syddjurs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Carina Lundby, Anton Pottegård, and Wade Thompson conceived the study; all authors designed the study; Anton Pottegård conducted data analysis; all authors interpreted results; Anton Pottegård and Wade Thompson drafted the manuscript; all authors provided critical revisions and approved submission.

ORCID

Anton Pottegård  <https://orcid.org/0000-0001-9314-5679>

REFERENCES

- Gindin J, Shochat T, Chetrit A, et al. Insomnia in long-term care facilities: a comparison of seven European countries and Israel: the services and health for elderly in long TERM care study. *J Am Geriatr Soc*. 2014;62(11):2033-2039. <https://doi.org/10.1111/jgs.13099>
- Ye L, Richards KC. Sleep and long-term care. *Sleep Med Clin*. 2018;13(1):117-125. <https://doi.org/10.1016/j.jsmc.2017.09.011>
- Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;165(2):125-133. <https://doi.org/10.7326/M15-2175>
- Green AR, Lee P, Reeve E, et al. Clinicians' perspectives on barriers and enablers of optimal prescribing in patients with dementia and coexisting conditions. *J Am Board Fam Med*. 2019;32(3):383-391. <https://doi.org/10.3122/jabfm.2019.03.180335>
- Iaboni A, Bronskill SE, Reynolds KB, et al. Changing pattern of sedative use in older adults: a population-based cohort study. *Drugs Aging*. 2016;33(7):523-533. <https://doi.org/10.1007/s40266-016-0380-3>
- Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med*. 2009;169(21):1952-1960. <https://doi.org/10.1001/archinternmed.2009.357>
- By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS beers criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674-694. <https://doi.org/10.1111/jgs.15767>
- The Society for Post-Acute and Long-Term Care Medicine. *Ten Things Physicians and Patients Should Question. Choosing Wisely*. 2013. <http://www.choosingwisely.org/societies/amda-the-society-for-post-acute-and-long-term-care-medicine/>
- Eriksen SI, Bjerrum L. Reducing prescriptions of long-acting benzodiazepine drugs in Denmark: a descriptive analysis of nationwide prescriptions during a 10-year period. *Basic Clin Pharmacol Toxicol*. 2015;116(6):499-502. <https://doi.org/10.1111/bcpt.12347>
- Brett J, Maust DT, Bouck Z, et al. Benzodiazepine use in older adults in the United States, Ontario, and Australia from 2010 to 2016. *J Am Geriatr Soc*. 2018;66(6):1180-1185. <https://doi.org/10.1111/jgs.15292>
- McKean A, Monasterio E. Off-label use of atypical antipsychotics. *CNS Drugs*. 2012;26(5):383-390. <https://doi.org/10.2165/11632030-000000000-00000>
- Brandt J, Leong C. Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. *Drugs R D*. 2017;17(4):493-507. <https://doi.org/10.1007/s40268-017-0207-7>
- McCall C, McCall WV. What is the role of sedating antidepressants, antipsychotics, and anticonvulsants in the management of insomnia? *Curr Psychiatry Rep*. 2012;14(5):494-502. <https://doi.org/10.1007/s11920-012-0302-y>
- Højlund M, Pottegård A, Johnsen E, et al. Trends in utilization and dosing of antipsychotic drugs in Scandinavia: comparison of 2006 and 2016. *Br J Clin Pharmacol*. 2019;85(7):1598-1606. <https://doi.org/10.1111/bcp.13945>
- Gjerden P, Bramness JG, Tvete IF, Slørdal L. The antipsychotic agent quetiapine is increasingly not used as such: dispensed prescriptions in Norway 2004-2015. *Eur J Clin Pharmacol*. 2017;73(9):1173-1179. <https://doi.org/10.1007/s00228-017-2281-8>
- Stephenson CP, Karanges E, McGregor IS. Trends in the utilisation of psychotropic medications in Australia from 2000 to 2011. *Aust New Zeal J Psychiatry*. 2013;47(1):74-87. <https://doi.org/10.1177/0004867412466595>
- Pringsheim T, Gardner DM. Dispensed prescriptions for quetiapine and other second-generation antipsychotics in Canada from 2005 to 2012: a descriptive study. *C Open*. 2014;2(4):E225-E232. <https://doi.org/10.9778/cmajo.20140009>
- Reilev M, Lundby C, Jensen J, Larsen SP, Hoffmann H, Pottegård A. Morbidity and mortality among older people admitted to nursing home. *Age Ageing*. 2019;49(1):67-73. <https://doi.org/10.1093/ageing/afz136>
- Lundby C, Jensen J, Larsen SP, Hoffmann H, Pottegård A, Reilev M. Use of medication among nursing home residents: a Danish drug utilisation study. *Age Ageing*. 2020;7:814-820. <https://doi.org/10.1093/ageing/afaa029>
- Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. <https://doi.org/10.2147/CLEP.S91125>
- Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798-798f. <https://doi.org/10.1093/ije/dyw213>
- World Health Organization. Defined daily dose (DDD). https://www.who.int/medicines/regulation/medicines-safety/toolkit_ddd/en/
- Shah S, Schoenbachler B, Streim J, Meeks S. Antidepressant prescribing patterns in the nursing home: second-generation issues revisited. *J Am Med Dir Assoc*. 2012;13(4):406.e13-8. <https://doi.org/10.1016/j.jamda.2011.09.004>
- Aalto UL, Raito H-M, Finne-Soveri H, Kautiainen H, Pitkälä KH. Temporal trends in the use of anticholinergic drugs among older people living in long-term care facilities in Helsinki. *Drugs Aging*. 2020;37(1):27-34. <https://doi.org/10.1007/s40266-019-00720-6>
- Roose SP, Nelson JC, Salzman C, Hollander SB, Rodrigues H. Mirtazapine in the Nursing Home Study Group. Open-label study of mirtazapine orally disintegrating tablets in depressed patients in the

- nursing home. *Curr Med Res Opin.* 2003;19(8):737-746. <https://doi.org/10.1185/030079903125002441>
26. Cakir S. The efficacy of mirtazapine in agitated patients with Alzheimer's disease: a 12-week open-label pilot study. *Neuropsychiatr Dis Treat.* 2008;4(5):963-966. <https://doi.org/10.2147/NDT.S3201>
27. Nelson JC, Hollander SB, Betzel J, Smolen P, Mirtazapine Nursing Home Study Group. Mirtazapine orally disintegrating tablets in depressed nursing home residents 85 years of age and older. *Int J Geriatr Psychiatry.* 2006;21(9):898-901. <https://doi.org/10.1002/gps.1589>
28. Scoralick FM, Louzada LL, Quintas JL, Naves JOS, Camargos EF, Nóbrega OT. Mirtazapine does not improve sleep disorders in Alzheimer's disease: results from a double-blind, placebo-controlled pilot study. *Psychogeriatrics.* 2016;17(2):89-96. <https://doi.org/10.1111/psyg.12191>
29. Maclagan LC, Maxwell CJ, Gandhi S, et al. Frailty and potentially inappropriate medication use at nursing home transition. *J Am Geriatr Soc.* 2017;65(10):2205-2212. <https://doi.org/10.1111/jgs.15016>
30. Rådet for Anvendelse af Dyr Sygehusmedicin. Behandlingsvejledning inklusiv lægemiddelrekommandation for medicinsk behandling af unipolar depression. 2015. <https://rads.dk/media/1910/unipolar-depression-beh-og-rek-april-2015-193678.pdf>

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Pottegård A, Lundby C, Jarbøl DE, et al. Use of sedating medications around nursing home admission in Denmark. *Pharmacoepidemiol Drug Saf.* 2021;1-6. doi:10.1002/pds.5341