International Journal of Preventive Medicine Research
Vol. 4, No. 2, 2018, pp. 18-24
http://www.aiscience.org/journal/ijpmr
ISSN: 2381-7038 (Print); ISSN: 2381-7046 (Online)

Potentially Inappropriate Medication in Patients Admitted with Diagnosis of Delirium Superimposed on Dementia

Gudrun Hefner[1, *], Martina Hahn[2], Sibylle Christine Roll[2], Ansgar Klimke[1], Christoph Hiemke[3], Joachim Röschke[4]

[1]Psychiatric Hospital, Vitos Klinik Hochtaunus, Friedrichsdorf, Germany
[2]Psychiatric Hospital, Vitos Klinik Eichberg, Eltville, Germany
[3]Department of Psychiatry and Psychotherapy, University Medical Center, Mainz, Germany
[4]SCIVIAS Psychiatric Hospital, Bad Soden, Germany

Abstract

Drugs may enhance the incidence of delirium in predisposed patients with dementia. This study analyzed prescription of potentially inappropriate medications (PIMs) of the Priscus list and the delirigenic burden of drugs and their role as precipitating factors for the development of delirium in patients with dementia. Patients with the diagnosis of dementia who had been hospitalized because of a delirium were screened retrospectively for number and sort of PIMs, as defined by the Priscus list. The delirogenic drug burden was assessed by a risk-scale ranging from 0 (not existing) to 4 (high) per drug and calculation of a sum score per patient. Overall, 79 patients (57.0% female) with a mean (Mean±SD) age of 81.1±6.6 years were included. They received by mean 6.0±3.3 drugs at admission and 6.9±2.8 at discharge. At admission 15 patients (19.0%) received at least one Priscus-PIM and 57 (72.9%) at least one drug with delirogenic properties. Prescription of PIMs slightly decreased by 20% at discharge. The mean delirogenic burden sum score was 2.0±2.1 (range 0-11) at admission and decreased by 40% to 1.2±1.2 (range 0-5) at discharge. Drugs were diagnosed as precipitating factors for delirium in 13 patients (16.5%). Besides amitriptyline, drugs with a strong delirogenic activity, as promethazine or levomepromazine, have not been considered as a possible reason for delirium. Although physicians try to avoid inappropriate drug-prescribing to demented patients, delirogenic drugs are frequently given to patients with dementia and in a significant number of patients they were associated with the occurrence of delirium. Preliminary evidence indicated that reduction of the delirogenic burden score of the medication is more appropriate to dimish this risk than reduction of PIM prescriptions. More cautious prescribing by the physician is indicated and future interventions may need to focus on polypharmacy to optimize pharmacological treatment in vulnerable demented patients.

Keywords

Dementia, Delirium, Potentially Inappropriate Medication, Priscus-List, Adverse Drug Reactions, Risk-Scale

Received: April 21, 2018 / Accepted: May 14, 2018 / Published online: June 7, 2018

1. Introduction

The health-care system is confronted with a growing number of elderly patients suffering from dementia, being among the most frequent mental disorders in Europe in the old age population [1, 2]. In the European Union (EU), about 6.3 million people were affected by dementia in 2011, the overall prevalence rate was 0.5% in individuals aged 60-64 years,

* Corresponding author
E-mail address: Gudrun.Hefner@vitos-rheingau.de (G. Hefner)

5.4% at the age of ≥60 years and 23.7% at the age of ≥85 years [1].

Dementia can be complicated by delirium, an acutely disturbed state of mind with fluctuating symptoms [3] that is present in nearly 20% of demented outpatients [4].

Predisposing factors make individuals vulnerable for the development of delirium and precipitating factors may trigger pathophysiological mechanisms resulting in delirium by a complex interplay [5-7]. Dementia is the most important predisposing factor [3] and multiple drugs have the potential to induce delirium [8].

Because of comorbid diseases [9], demented patients are often treated by polypharmacy [10] and therefore high-risk patients for the development of adverse drug reactions (ADRs) [11]. ADRs are often the result of cumulative drug effects, especially due to anticholinergic properties [12-14].

Because of age-related pharmacokinetic and pharmacodynamic changes [15, 16] patients with the diagnosis of dementia are highly susceptible to anticholinergic drugs [12, 14]. Physicians should therefore minimize the prescription of drugs with delirogenic, especially anticholinergic potential in this population [9, 13, 17].

The first step to prevent ADRs and optimize complex pharmacotherapy is to identify inappropriate or high-risk drugs or drug-combinations for demented patients [18, 19].

Lists of potentially inappropriate medication (PIM) in the elderly, such as the Beers or the Priscus list [20, 21], have been developed to improve safety and tolerability of pharmacotherapy in the elderly. The German Priscus list has been published in 2010. It contains 83 drugs, including a lot of drugs with delirogenic potential [21]. In a study of Wuchera and colleagues [22], 22% of patients with dementia received at least one Priscus-PIM, mostly antidepressants, benzodiazepines, and analgetics.

Anticholinergic risk-scales were developed which list drugs according to their anticholinergic potential, reviewed by Duran and colleagues [23]. In 2015, a new risk scale was established by Hefner and colleagues that refered not only to anticholinergic but also to other mechanisms of central nervous depression that may cause delirum by grading 106 drugs from 1 (minimal delirogenic activity) to 4 (high delirogenic activity) [19]. The scale enables quantification of the delirogenic burden in elderly patients with multiple drug intake. An increased risk was detected for a sum score of the listed drugs of at least 5 [19].

In general, the prescription of PIMs and delirogenic drugs among people with dementia is frequent and associated with advanced morbidity and adverse outcomes [24, 25].

Aim of this study was to analyze the frequency of PIM or delirogenic medication use in demented patients and their role as possible precipitating factors for the development of delirium.

2. Study Design and Methods

This retrospective analysis was conducted at the department of Psychiatry and Psychotherapy, St. Valentinus hospital, Bad Soden, Germany. All patients admitted with the diagnosis of delirium and dementia (April 2009 – June 2012) were included for analysis. Overall, 79 patients could be included.

Medical records of the patients were screened retrospectively for clinical data at admission and discharge. No limitation was made with respect to the severity of illness, psychiatric secondary diagnosis according to International classification of Mental and Behavioural Disorders, 10th Revision (ICD-10), treatment-time or dosage of the administered drugs and comedication. Non-adherence to medication or drug serum concentration could not be retrospectively evaluated.

Patient-characteristics like age, gender, diagnosis (ICD-10), comorbidities and medication were collected for analysis. The total number of administered drugs per day was calculated, excluding topical, ophthalmic, inhaled and otologic medications. Dietary supplements and medical devices were also excluded from the calculations.

The number and sort of Priscus-PIMs [21] were checked by analyzing medication profile of the patients. All drugs that fulfilled the criteria (dosage, galenic formulations that are not recommended) of a potentially inappropriate Priscus-PIM [21] were included.

The delirogenic burden of a patient was assessed by the risk-scale of Hefner and colleagues [19]. Medication of the patients was analyzed for drugs which were listed in the risk-scale. Afterwards, risk-points of all drugs were summarized to a sum score (delirogenic burden). Drugs which were administered non-systemic, e.g. topical, ophthalmic, inhaled, and otologic preparations were excluded from the calculation.

Descriptive statistics of patient data were presented as mean values ± standard deviations (Mean±SD). Frequencies of various data were presented, reflecting the total number and the percent of cases (%). Using Spearman´s correlation analysis, a possible correlation between various factors was determined. Statistical analysis was carried out by using IBM® SPSS® Statistics version 21.0 (IBM GmbH, Ehningen, Germany). A P-value of $p<0.05$ was considered as statistically significant.

3. Results

In total, 79 patients (57.0% female) with a mean age of 81.1±6.6 years could be included in the study (Table 1). Main diagnosis (ICD-10) in all patients (100.0%) was a delirium superimposed on dementia (F05.1). Most frequent secondary diagnosis was a dementia in Alzheimer disease with late onset (F00.1, 34.2%), a mixed cortical and subcortical vascular dementia (F01.3, 27.8%), and an organic mood affective disorder (F06.3, 22.8%).

By mean, patients had 4.7±3.3 comorbid conditions and received 6.0±3.3 drugs at admission and 6.9±2.8 drugs at discharge (Table 1). At admission, 19.0% of the patients (n=15) received at least one Priscus-PIM (Table 2) and 15.2% (n=12) at discharge. The most frequently prescribed Priscus-PIMs at admission (Table 3) were diazepam (n=3), digoxin and derivatives (n=3) as well as zopiclone>3.75mg/d (n=3), and haloperidol>2mg/d (n=4), diazepam (n=2) and digoxin and derivatives (n=2) at discharge. Detailed information is presented in tables 1-3.

Table 1. Sample characteristics of patients (n=79) with diagnosis of delirium and dementia.

		Min-Max	Mean (±SD)
Number of patients [n]		N/A	
Age [n]		70-95	81.1±6.6
Female [n, %]	45 (57.0)	N/A	
Male [n, %]	34 (43.0)		
Number of medications	admission	0-16	6.0±3.3
	discharge	2-18	6.9±2.8
Number of Priscus-PIMs [21]	admission	0-4	0.2±0.6
	discharge	0-1	0.2±0.4
Delirogenic burden score [19]	admission	0-11	2.0±2.1
	discharge	0-5	1.2±1.2
Number of comorbidities		0-19	4.7±3.3
Duration of hospitalization [days]		1-84	14.8±11.1

PIM=potentially inappropriate medication

Mean calculated delirogenic burden was 2.0±2.1 (range 0-11) at admission and 1.2±1.2 (range 0-5) at discharge (Table 1, 2).

Table 2. Delirogenic burden scores and Priscus-PIMs, detected in patients (n=79) admitted to hospital with the diagnosis of delirium superimposed on dementia.

Delirogenic burden score [19]	Number of patients		Number of Priscus-PIMs [21]	Number of patients	
	admission	discharge		admission	discharge
0	22 (27.8%)	26 (32.9%)	0	64 (81.0%)	67 (84.8%)
1	13 (16.5%)	25 (31.6%)	1	14 (17.7%)	12 (15.2%)
2	21 (26.6%)	17 (21.5%)	2	0	0
3	9 (11.4%)	7 (8.9%)	3	0	0
4	10 (12.7%)	3 (3.8%)	4	1 (1.3%)	0
5	1 (1.3%)	1 (1.3%)	Total	79 (100.0%)	
7	1 (1.3%)				
10	1 (1.3%)				
11	1 (1.3%)				
Total	79 (100.0%)				

PIM=potentially inappropriate medication

Drugs with a high and moderate delirogen potential (3 or 4 risk-points) [19] that were prescribed at admission and discharge were listed in table 3. At discharge, no drug with high delirogenic potential of 4 risk-points [19] was prescribed anymore.

Table 3. Prescription of drugs with an at least moderate delirogenic burden score (3 risk-points) and of Priscus PIMs. Overall, 12 drugs with moderate or high delirogenic potential were prescribed at admission and 6 at discharge. 18 Priscus-PIMs were identified in patients at admission and 12 at discharge.

Delirogenic medication with 3 or 4 risk-points [19]		Priscus-PIMs [21]	
(Number of patients at admission, risk-points)	(Number of patients at discharge, risk-points)	(Number of patients at admission)	(Number of patients at discharge)
Olanzapine (n=4, 3)	Olanzapine (n=2, 3)	Diazepam (n=3)	Haloperidol>2mg/d (n=4)
Amitriptyline (n=2, 4)	Oxybutynin (n=1, 3)	Digoxin and derivatives (n=3)	Diazepam (n=2)
Promethazine (n=2, 4)		Zopiclone>3.75mg/d (n=3)	Digoxin and derivatives (n=2)
Levomepromazine (n=1, 4)		Amitriptyline (n=2)	Clonidine (n=1)
Opipramol (n=1, 4)		Bromazepam (n=1)	Etoricoxib (n=1)

Delirogenic medication with 3 or 4 risk-points [19]	Priscus-PIMs [21]	
Oxybutynin (n=1, 3)	Fluoxetine (n=1)	Nifedipine (non retarded) (n=1)
Trimipramine (n=1, 4)	Haloperidol>2mg/d (n=1)	Olanzapine>10mg/d (n=1)
	Levomepromazine (n=1)	
	Oxazepam>60mg/d (n=1)	
	Triazolam (n=1)	
	Trimipramine (n=1)	

PIM=potentially inappropriate medication

Overall, 4 patients had a sum score of at least 5 risk-points at admission and 1 patient at discharge (n=1) (Table 2, 4).

The delirogenic burden [19] correlated significantly with the total number of prescribed drugs (r=0.462, p<0.01, CI 95%). No significant correlation (p>0.05) was found between the number of Priscus-PIMs [21] and the number of prescribed drugs.

Overall, relating to the 79 patients, 184 reasons for the development of delirium were documented by the physicians. Besides the predisposing factor of dementia (100.0%), most common diagnosed precipitating factors were exsiccosis/dehydration (62.0%) and acute urinary tract infection (25.3%). Drugs were diagnosed as precipitating factor for delirium in 13 patients (16.5%), including amitriptyline (n=3), multiple analgesics consumption (n=3), levetiracetam (n=2), levodopa (n=2), carbamazepine (n=1), the combination memantine and theophylline (n=1) and phenytoin (n=1).

Besides amitriptyline, drugs with a strong anticholinergic/delirogenic activity (4 risk-points [19]) as promethazine, levomepromazine, trimipramine or opipramol (Table 3) were not considered as reason for the development of delirium. More detailed information is given in table 4.

Table 4. Diagnosed reasons for delirium and prescribed drugs of demented patients admitted with a delirogenic burden score ≥5 (n=4). Diagnosed reasons for delirium of 10 patients admitted with a delirogenic burden score of 4 were also prescribed. Overall, 184 reasons for the development of delirium have been diagnosed by the physician in 79 patients.

Delirogenic drug combination Drug (risk-points [19])	Delirogenic burden score [19] (number of patients)	Diagnosed reason for delirium (number of patients)
amitriptyline (4), citalopram (2), metformin (1), olanzapine (3), tramadol (1)	11 (n=1)	Dementia and amitriptyline (n=1)
amitriptyline (4), diazepam (1), levomepromazine (4), zopiclone (1)	10 (n=1)	Dementia and amitriptyline (n=1)
clonazepam (1), promethazine (4), quetiapine (2)	7 (n=1)	Dementia, exsiccosis and an acute urinary tract infection (n=1)
amitriptyline-administration has been stopped before the admission due to amitriptyline-intoxication, metformin (1), opipramol (4)	5 (n=1)	Dementia and amitriptyline (n=1)
N/A	4 (n=10)	Dementia (n=10), exsiccosis (n=6), acute urinary tract infection (n=4), analgesics (n=1), cerebral hypoxia (n=1), decompensated cardiac insufficiency (n=1), Levodopa (n=1)

4. Discussion

This study analyzed the use of Priscus-PIMs [21] and the delirogenic burden of drugs [19] prescribed to patients with delirium superimposed on dementia and their role as possible precipitating factor for the development of delirium causing hospital admission.

Overall, 19.0% of the included patients (n=15) received at least one Priscus-PIM (Table 2) [21] at admission and 15.2% (n=12) at discharge. This prevalence rate was similar to other studies that analyzed the use of Pricus-PIMs in demented patients. Wucherer and colleagues [22] detected a Priscus-PIM prevalence rate of 22% in community-dwelling people with dementia, and Fiss and colleagues [26] identified for a German healthcare sector Priscus-PIM-use in 19.8% of demented patients.

In this study, the most frequently prescribed PIMs were anxiolytic, hypnotic, cardiac and antidepressant drugs, which was similar as in the studies by Wucherer et al. [22] and Fiss et al. [26].

More PIMs were found by Siebert and coworkers [27], in a clinic of geriatric rehabilitation. In the elderly patients, 35% received Priscus-PIMs at admission and 29% at discharge.

The delirogenic burden of the patients was by mean 2.0±2.1 (range 0-11) at admission and 1.2±1.2 (range 0-5) at discharge (Table 1, 2). In a previous study on non-demented patients, a risk score of at least 5 points was observed that is associated with an increased risk for ADRs [19]. This score was observed for only 4 patients at admission (5.2%) and 1 patient at discharge (1.3%). This may indicate that a lower risk score could be sufficient to induce delirium in patients with dementia.

A significant correlation was found between the delirogenic

burden score [19] and the number of Priscus-PIMs ($p<0.01$). This was not surprising, since many Priscus-PIMs [21] are also in the delirgenic burden scale of Hefner and colleagues [19]. This insinuates that both, reduction of PIM prescriptions and of the delirogenic burden score will lead to risk reduction. This suggestion, however, was not supported by findings in this study.

The observation that drugs like amitriptyline, promethazine or levomepromazine with a high delirogenic burden score of 4 risk-points [19] were all discontinued after admission indicates that the delirogenic potential was considered by the treating physicians as relvant risk factor. On the other hand, little changes were observed during hospitalization with regard to discontinuation of PIMs. The prescription rate was changed from 19.0 to 15.2%. This indicates that the delirogenic burden score is a more appropriate indicator for the risk of delirium than number of PIMs.

Awareness among physicians to be cautious about the prescribing of potentially inappropriate and delirogenic drugs to demented patients were present which is in line with Johnell et al. [28]. Nevertheless, inappropriate drug use among people with dementia is frequent and associated amongst others with advanced morbidity [24, 29]. Therefore, more cautious prescribing especially of benzodiazepines and anticholinergic drugs or combination of psychotropic drugs in demented patients is indicated to avoid ADRs, such as delirium, in these vulnerable patients [29].

Most patients of this study were polymedicated, they received by mean 6.0±3.3 drugs at admission and 6.9±2.8 drugs at discharge (Table 1). In a study by Barry and colleagues, polypharmacy was observed in 81.5% of demented patients [10]. It is an important predisposing risk factor for delirium [30] and a risk factor for prescription of potentially inappropriate drugs [10, 31, 32]. This was confirmed by the significant correlation between delirogenic burden score and the total number of drugs per day ($p<0.05$).

Parsons et al. [32] emphasized the need of new tools to assess medication appropriateness in vulnerable demented people, including misprescribing, overprescribing or underprescribing of certain medications. The findings of this pilot study indicate that the delirogenic burden risk scale used by us for retrospective analysis in patients with delirium superimposed on dementia could be a useful tool for risk reduction for these patients.

The interpretation of the study-results is restricted by the retrospective nature of the study design. Therefore, results are only explorative and do not prove any causal relationship.

Data for this study were assessed in 2009-2012, so a trend towards a more rational drug therapy could be expected to date [33]. On the other hand, the study by Wucherer and colleagues [22], conducted in 2016, detected similar PIM prevalence rates, so medication management seemed to have not changed remarkably.

5. Conclusions

Priscus-PIMs and the delirogenic burden score of drugs were established for risk reduction of medications given to old aged patients.

PIMs and delirogenic drugs are frequently given to patients with dementia. In a significant number of patients they were found to be associated with the occurrence of delirium. Therefore, medication has to be checked more intensively for delirogenic drugs and drug combinations in clinical routine. Although physicians seem to be cautious with the prescribing of Priscus-PIMs and overall delirogenic medication, medication management in often polypharmaceuted demented patients is still improvable to increase the tolerability of medication and to avoid adverse drug reactions, such as delirium. More cautious prescribing by the physician is indicated and future interventions may need to focus on polypharmacy to optimize pharmacological treatment in vulnerable demented patients.

Most important, patient´s risk profile should be evaluated before the occurrence of delirium. The avoidance of reversible precipitating factors, such as of high-risk drugs and drug combinations, may be a fast and successful intervention to prevent delirium. The findings in this study indicated that reduction of the delirogenic burden score of the medication is more appropriate to dimish the risk of delirium than reduction of number of PIM prescriptions. Prospective studies in a larger sample of patients with dementia or of multimorbid old aged patients have to clarify if assessment of the delirogenic burden and reduction of the score during decision making of medications can reduce the occurrence of delirium or other ADRs like orthostatic disturbances, falls or disorientation.

Acknowledgements

The research study did not receive funds or support from any source.

Compliance with Ethical Standards

The study was accordance with the formal regulations of the ethics committee of the Landesärztkammer Mainz which do not require an explicit ethic vote for retrospective analysis of anonymized clinical data.

Conflict of Interest Statement

Christoph Hiemke has received speaker's and consultancy fees from Janssen, Stada and Servier. All the authors do not have any possible conflicts of interest.

References

[1] Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 21: 655-679. doi: 10.1016/j.euroneuro.2011.07.018

[2] Cova I, Markova A, Campini I, Grande G, Mariani C, Pomati S (2017) Worldwide trends in the prevalence of dementia. J Neurol Sci 379: 259-260. doi: 10.1016/j.jns.2017.06.030

[3] Roden M, Simmons BB (2014) Delirium superimposed on dementia and mild cognitive impairment. Postgrad Med 126: 129-137. doi: 10.3810/pgm.2014.10.2827

[4] Hasegawa N, Hashimoto M, Yuuki S, Honda K, Yatabe Y, Araki K, Ikeda M (2013) Prevalence of delirium among outpatients with dementia. Int Psychogeriatr 25: 1877-1883. doi: 10.1017/S1041610213001191

[5] Singler K, Thomas C (2017) [HELP - Hospital Elder Life Program - multimodal delirium prevention in elderly patients]. Internist (Berl) 58: 125-131. doi: 10.1007/s00108-016-0181-0

[6] Inouye SK (1999) Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord 10: 393-400.

[7] Mittal V, Muralee S, Williamson D, McEnerney N, Thomas J, Cash M, Tampi RR (2011) Review: delirium in the elderly: a comprehensive review. Am J Alzheimers Dis Other Demen 26: 97-109. doi: 10.1177/1533317510397331

[8] Meyer S, Meyer O, Kressig RW (2010) [Drug-induced delirium]. Ther Umsch 67: 79-83. doi: 10.1024/0040-5930/a000015

[9] Hofmann W (2017) [Dementia and comorbid conditions]. Internist (Berl) 58: 105-116. doi: 10.1007/s00108-016-0182-z

[10] Barry HE, Cooper JA, Ryan C, Passmore AP, Robinson AL, Molloy GJ, Darcy CM, Buchanan H, Hughes CM (2016) Potentially Inappropriate Prescribing Among People with Dementia in Primary Care: A Retrospective Cross-Sectional Study Using the Enhanced Prescribing Database. J Alzheimers Dis 52: 1503-1513. doi: 10.3233/JAD-151177

[11] Goldberg RM, Mabee J, Chan L, Wong S (1996) Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. Am J Emerg Med 14: 447-450.

[12] Mintzer J, Burns A (2000) Anticholinergic side-effects of drugs in elderly people. J R Soc Med 93: 457-462.

[13] Gray SL, Hanlon JT (2016) Anticholinergic medication use and dementia: latest evidence and clinical implications. Ther Adv Drug Saf 7: 217-224.

[14] Shinohara M, Yamada M (2016) [Drug-induced Cognitive Impairment]. Brain Nerve 68: 421-428. doi: 10.11477/mf.1416200415

[15] Klotz U (2009) Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev 41: 67-76. doi: 10.1080/03602530902722679

[16] McLean AJ, Le Couteur DG (2004) Aging biology and geriatric clinical pharmacology. Pharmacol Rev 56: 163-184.

[17] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA (2001) Cardiovascular Health Study Collaborative Research G. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56: M146-156.

[18] Chang CB, Chen JH, Wen CJ, Kuo HK, Lu IS, Chiu LS, Wu SC, Chan DC (2011) Potentially inappropriate medications in geriatric outpatients with polypharmacy: application of six sets of published explicit criteria. Br J Clin Pharmacol 72: 482-489. doi: 10.1111/j.1365-2125.2011.04010.x

[19] Hefner G, Shams ME, Wenzel-Seifert K, Fellgiebel A, Falter T, Haen E, Hiemke C (2015) Rating the delirogenic potential of drugs for prediction of side effects in elderly psychiatric inpatients. J J Pharma Pharmacovigilance 1: 003.

[20] Simonson W (2016) The 2015 updated Beers Criteria: The evolution continues. Geriatr Nurs 37: 61-62. doi: 10.1016/j.gerinurse.2015.12.006

[21] Holt S, Schmiedl S, Thurmann PA (2010) Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int 107: 543-551. doi: 10.3238/arztebl.2010.0543

[22] Wucherer D, Eichler T, Hertel J, Kilimann I, Richter S, Michalowsky B, Thyrian JR, Teipel S, Hoffmann W (2017) Potentially Inappropriate Medication in Community-Dwelling Primary Care Patients who were Screened Positive for Dementia. J Alzheimers Dis 55: 691-701.

[23] Duran CE, Azermai M, Vander Stichele RH (2013) Systematic review of anticholinergic risk scales in older adults. Eur J Clin Pharmacol 69: 1485-1496. doi: 10.1007/s00228-013-1499-3

[24] Renom-Guiteras A, Thürmann PA, Miralles R, Klaaßen-Mielke R, Thiem U, Stephan A, Bleijlevens MH, Jolley D, Leino-Kilpi H, Rahm Hallberg I, Saks K, Soto-Martin M, Zabalegui A, Meyer G (2017) RightTimePlaceCare Consortium. Potentially inappropriate medication among people with dementia in eight European countries. Age Ageing: 1-7. doi: 10.1093/ageing/afx147

[25] Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Wolfe R, Connors MH, Elliott RA (2017) Potentially Inappropriate Medication, Anticholinergic Burden, and Mortality in People Attending Memory Clinics. J Alzheimers Dis 60: 349-358. doi: 10.3233/JAD-170265

[26] Fiss T, Thyrian JR, Fendrich K, van den Berg N, Hoffmann W (2013) Cognitive impairment in primary ambulatory health care: pharmacotherapy and the use of potentially inappropriate medicine. Int J Geriatr Psychiatry 28: 173-181. doi: 10.1002/gps.3806

[27] Siebert S, Elkeles B, Hempel G, Kruse J, Smollich M (2013) [The PRISCUS list in clinical routine. Practicability and comparison to international PIM lists]. Z Gerontol Geriatr 46: 35-47. doi: 10.1007/s00391-012-0324-4

[28] Johnell K (2015) Inappropriate Drug Use in People with Cognitive Impairment and Dementia: A Systematic Review. Curr Clin Pharmacol 10: 178-184.

[29] Sköldunger A, Fastbom J, Wimo A, Fratiglioni L, Johnell K (2015) Impact of Inappropriate Drug Use on Hospitalizations, Mortality, and Costs in Older Persons and Persons with Dementia: Findings from the SNAC Study. Drugs Aging 32: 671-678. doi: 10.1007/s40266-015-0287-4

[30] Hein C, Forgues A, Piau A, Sommet A, Vellas B, Nourhashémi F (2014) Impact of polypharmacy on occurrence of delirium in elderly emergency patients. J Am Med Dir Assoc 15: 850.e11-15. doi: 10.1016/j.jamda.2014.08.012

[31] Tommelein E, Mehuys E, Petrovic M, Somers A, Colin P, Boussery K (2015) Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. Eur J Clin Pharmacol 71: 1415-1427. doi: 10.1007/s00228-015-1954-4

[32] Parsons C (2017) Polypharmacy and inappropriate medication use in patients with dementia: an underresearched problem. Ther Adv Drug Saf 8: 31-46. doi: 10.1177/2042098616670798

[33] Zimmermann T, Kaduszkiewicz H, van den Bussche H, Schon G, Brettschneider C, Konig HH, Wiese B, Bickel H, Mosch E, Luppa M, Riedel-Heller S, Werle J, Weyerer S, Fuchs A, Pentzek M, Hanisch B, Maier W, Scherer M, Jessen F, AgeCoDe-Study G (2013) [Potentially inappropriate medication in elderly primary care patients: A retrospective, longitudinal analysis]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 56: 941-949. doi: 10.1007/s00103-013-1767-5