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Original Study

The Association of Anticholinergic Drugs and Delirium in Nursing Home Patients With Dementia: Results From the SHELTER Study

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ABSTRACT

Objectives: Drugs with anticholinergic properties are associated with an increased prevalence of delirium, especially in older persons. The aim of this study was to evaluate the association between the use of this class of drugs in nursing home (NH) patients and prevalence of delirium, particularly in people with dementia.
Design: Cross-sectional multicenter study.
Setting and participants: 3924 nursing home patients of 57 nursing homes in 7 European countries participating in the Services and Health for Elderly in Long TERmcare (SHELTER) project.
Methods: Descriptive statistics, calculation of percentage, and multivariable logistic analysis were applied to describe the relationship between anticholinergic drug use and prevalence of delirium in NH patients. The Anticholinergic Risk Scale (ARS) and the Anticholinergic Burden Scale (ACB) were used to calculate the anticholinergic load.
Results: 54% of patients with dementia and 60% without dementia received at least 1 anticholinergic drug according to the ACB. The prevalence of delirium was higher in the dementia group (21%) compared with the nondementia group (11%). Overall, anticholinergic burden according to the ACB and ARS was associated with delirium both in patients with and without dementia, with odds ratios ranging from 1.07 [95% confidence interval (CI) 0.94-1.21] to 1.26 (95% CI 1.11-1.44). These associations reached statistical significance only in the group of patients with dementia. Among patients with dementia, delirium prevalence increased only modestly with increasing anticholinergic burden according to the ACB, from 20% (with none or minimal anticholinergic burden) to 25% (with moderate burden) and 27% delirium (with strong burden scores).
Conclusions and Implications: The ACB scale is relatively capable to detect anticholinergic side effects, which are positively associated with prevalence of delirium in NH patients. Given the modest nature of this association, strong recommendations are currently not warranted, and more longitudinal studies are needed.

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Delirium in older patients is common and associated with poor outcomes, such as functional impairments, institutionalization, and increased mortality.[1,2] Delirium is severely distressing both for patients and for relatives and caregivers.[3,4] Pre-existing cognitive decline and dementia are among the most important risk factors for delirium.[5] The prevalence of delirium superimposed on dementia (DSD) ranges between 22% and 70%, depending on diagnostic criteria and on the severity of the dementia.[6]

Drugs are a major precipitating, but also treatable, factor for delirium in older persons.[7,8] In particular, drugs with anticholinergic properties are associated with an increased incidence and severity of delirium.[9,10] Nevertheless, 20%-50% of older patients are reported to use at least 1 drug with anticholinergic properties.[11]

Based on strong evidence for cholinergic deficiency in people with dementia[12] and the evidence that the cholinergic system is likely to be involved in delirium,[13] it is plausible to assume that the use of drugs with anticholinergic properties increases the risk of delirium in patients with pre-existing dementia. However, several studies do not support a specific relationship between these medicines and DSD.[14,15] These studies were performed in patients admitted to general hospitals, whereas the most frail older persons with dementia live in nursing homes (NHs). These patients particularly may be at increased risk of anticholinergic side effects because of higher rates of multimorbidity, associated polypharmacy, and age-related changes of pharmacokinetics and pharmacodynamics.[16]

Study results from NH populations are inconsistent, reporting an increased incidence of DSD or no effect of use of drugs with anticholinergic properties.[17,18] Different methods used to assess anticholinergic use and variation in diagnostic tools for delirium may have contributed to these diverging study findings.[19]

The availability of a database with patient characteristics from different European countries provides a unique opportunity to investigate the effect of anticholinergic drugs on delirium prevalence in a large NH population. The aim of this study is to investigate to what extent the use of drugs with anticholinergic properties in NH patients is associated with prevalence of delirium, particularly in people with dementia and to explore whether such an association would allow for clear recommendations with respect to clinical diagnosis and management of delirium in NH patients.

Methods

Population

The population for this cross-sectional multicenter study was derived from the Services and Health for Elderly in Long TERmcare (SHELTER) project. Details of this study design are described elsewhere.[20] This study included a total of 4156 patients from 57 participating NHs in 7 European countries (the Czech Republic, England, Finland, France, Germany, Italy, and the Netherlands) and 1 non-EU country (Israel). All short- and long-stay patients without any exclusion admitted to the participating nursing homes and those admitted within the following 3 months from the beginning of the study were assessed using the interRAI long-term care facilities (interRAI LTCF) assessment instrument.[21] The interRAI LTCF instrument is a comprehensive geriatric assessment instrument and composed of more than 300 items including, for example, sociodemographic variables, clinical characteristics, medical diagnoses, and drug use. The interRAI LTCF has been proved to reliably assess health status and care needs of NH patients.[22] Assessors responsible for data collection were trained in 2-day course to use a variety of information sources, such as direct observation, interviews with the person under care, family, friends, or formal service providers, and review clinical records, both medical and nursing. Most assessors were nurses, but other professionals participated also. In line with interRAI's standard approach to coding, all assessors were instructed to exercise their best clinical judgment in order to record observations based on their evaluation of the most accurate information source.[20]

Setting

Between May 2009 and July 2010, study partners in each country identified NHs willing to participate. All patients were assessed on baseline, 6 months, and 1 year, if still in the facility, using the interRAI LTCF. If no longer in the facility, reason (death, hospitalization, discharge to home or another institution) and date of death or discharge were recorded. The study ended in July 2011. Medical ethical approval was obtained following local regulations for all facilities in all participating countries according to local ethical regulations. Residents were invited to take part in the study and were free to decline participation. Consent was obtained with assurance of data confidentiality.[20] For the present study, we used data from the baseline assessments only.

Dementia Diagnosis

For identification of patients with dementia, all records on baseline with Alzheimer's disease or dementia other than Alzheimer's disease were used. The validity of such diagnostic information in LTCF patients has been verified using comparisons to administrative records.[23]

Delirium Model

On baseline, a diagnosis of delirium was approximated based on the following model using criteria recorded in the SHELTER database: an acute change in mental status deviating from usual functioning (ie, restlessness, lethargy, difficult to arouse, altered environmental perception) within the 3 days before the assessment or a new onset or worsening of 1 or more of the following symptoms: easily distracted (ie, episodes of difficulty paying attention; person gets sidetracked), episodes of disorganized speech (ie, speech is nonsensical, irrelevant, or rambling from subject to subject, person loses train of thought), and mental function variation over the course of the day.[24]

Measuring Anticholinergic Use

As part of the interRAI LTCF assessment, researchers collected information about all drugs that patients were using in the 3-day period before the baseline assessment. Drugs were coded according to the Anatomical Therapeutic and Chemical (ATC) codes of the World Health Organization Collaborating Centre for Drug Statistics Methodology (www.whocc.no).

Both the Anticholinergic Risk Scale (ARS)[25] and Anticholinergic Cognitive Burden Scale (ACB)[26] are validated tools for estimating the extent to which an individual patient may be at risk of anticholinergic adverse effects.[19,27] Both scales rank drugs for anticholinergic potential on a 3-point scale (0 = limited or none, 1 = moderate, 2 = strong, and 3 = very strong); the score is the sum of points of number of drugs with anticholinergic effect. For characterizing anticholinergic use and to increase the power of our analyses, we also applied a trichotomy comparing the categories none or minimal (scores 0 and 1), moderate (score 2), and strong (scores 3-10) anticholinergic drug burden on an ordinal scale for both the ARS and ACB.

Other Measures

Cognitive impairment on baseline was measured using the Cognitive Performance Scale (CPS), which incorporates memory impairment, level of consciousness, and executive function, like

activity of daily life into a score ranging from 0 (intact) to 6 (very severe impairment).[28] For measuring comorbidity on baseline, an adapted comorbidity index according to the Charlson Comorbidity Index was used.[29]

Statistical Analysis

Patients' baseline characteristics, dementia diagnosis, prevalence of delirium, and use of anticholinergic drugs characterized according to the ARS and ACB were assessed using frequency analyses. Logistic regression analyses were performed to calculate the odds ratio (OR) and corresponding 95% confidence interval (CI) for prevalence of delirium in patients with and without dementia according to different measures of anticholinergic drug exposure (total number of anticholinergic drugs and categories of anticholinergic burden with the ARS and ACB). The number of anticholinergic drugs was treated as a continuous variable, and the anticholinergic burden divided into 3 categories: none or minimal, 0-1; moderate, 2; and strong, 3-10. For the SHELTER database, 10 was the highest score for both ACB and ARS. All analyses were adjusted for age, cognitive function according to the CPS and comorbidity using the Charlson Comorbidity Index. For distribution of the prevalence of delirium in relation to anticholinergic drug burden according to ACB, we calculated the percentage of those with delirium within the ACB drug burden categories in patients with and without dementia, with corresponding 95% CIs. For stratification of the anticholinergic risk score according to the cognitive impairment severity levels, we calculated the percentage of patients with delirium within the ACB drug burden for categories of patients with a specific CPS score (1 = borderline intact, 2 = mild impairment, 3 = moderate impairment, 4 = moderate or severe impairment, 5 = severe impairment, 6 = very severe impairment). All analyses were conducted using IBM SPSS Statistics 26 for Windows (IBM Corp, Armonk, NY).

Results

The study group was composed of 4156 NH patients. A total of 228 participants without drug information at baseline and 4 participants with missing dementia diagnosis at baseline were excluded, resulting in a final sample size of 3924 participants. No imputations were used for the small number of missing values, 1.9% or less (Table 1).

The sociodemographic, clinical characteristics and use of anticholinergic drugs according to dementia status are summarized in Table 1.

The study population was composed of 73% women and 27% men with an average age of, respectively, 84 and 80 years and with a diagnosis of dementia in 53.7% of all cases. The prevalence of delirium was higher in the dementia group (21.1%) than in participants without dementia (10.9%).

Overall, 2216 of all 3924 patients (56.1%) received at least 1 anticholinergic drug according to the ACB list and 1101 (28.1%) according the ARS. The 10 most commonly used somatic medications with anticholinergic properties according to the ACB list were (in descending order) furosemide, metoprolol, digoxin, atenolol, warfarin, morphine, fentanyl, prednisone, diazepam, and venlafaxine. The most frequently used antipsychotics were quetiapine, risperidone, and haloperidol.

Overall, the ACB was more capable in documenting anticholinergic effects, with classifying anticholinergic burden as "strong" in 16.6% in both the dementia group and the nondementia group vs a similar classification according to the ARS in 5.0% in the dementia group and 7.1% in the nondementia group. The Charlson Comorbidity Index indicated, as expected, more morbidity in the dementia group as well as more frequent cognitive impairment as rated by CPS (Table 1).

All analyses showed an increased OR for the association of delirium with anticholinergic burden, in all models adjusted for age, Charlson Comorbidity Index, and cognitive function (Table 2). The ORs in patients with dementia were higher than in those without dementia. The odds of having a delirium diagnosis increased significantly by 17% with each 1-point increase on the ARS, reflecting an increased anticholinergic burden (OR 1.17, 95% CI 1.04-1.31), contrasting with a nonsignificant increase by 7% for each ARS point in the nondementia group (OR 1.07, 95% CI 0.94-1.31). The anticholinergic burden, as reflected in ACB scores, was also significantly associated with delirium in the dementia group (OR 1.14, 95% CI 1.06-1.23), whereas this association was not significant in the nondementia group (OR 1.07, 95% CI 0.97-1.18). Recoding of the ARS and ACB scores on an ordinal scale gave essentially the same results, with slightly higher ORs, whereas the association between delirium and the ordinal ARS now failed to reach significance in the dementia group (Table 2).

Figure 1 presents the distribution of the prevalence of delirium in relation to anticholinergic drug burden according to the ACB in patients with and without dementia. Distribution of delirium prevalence is expressed as a percentage of patients with delirium within the anticholinergic burden category. The nondementia group showed almost no difference according to the ordinal increasing anticholinergic burden. In the dementia group, delirium prevalence was higher, and the distribution in the anticholinergic burden categories increased from 20% (with none or minimal anticholinergic burden), to 25% (with moderate burden) and 27% delirium (with strong burden scores). A stratification of the anticholinergic burden and delirium according to the severity of cognitive impairment following CPS is presented in Figure 2. As reported by Hartmaier et al,[30] a CPS score of ≥4 corresponds to a dementia diagnosis.

Table 1
Sociodemographic and Clinical Characteristics and Use of Anticholinergic Drugs of the Total Study Population According to Dementia Status

	Dementia (n = 2108)		No Dementia (n = 1816)	
	n	%	n	%
Gender				
Male	516	24.5	534	29.4
Female	1592	75.5	1282	70.6
Age, y				
<75	287	13.6	417	23.0
75-84	718	34.1	548	30.2
85+	1103	52.3	851	46.9
Delirium				
No	1626	77.1	1605	88.4
Yes	444	21.1	198	10.9
Missing	38	1.8	13	0.7
ACB				
No (0)	974	46.2	734	40.4
Yes (≥1)	1134	53.8	1082	59.6
ACB				
None or minimal (0-1)	1563	74.1	1276	70.3
Moderate (2)	196	9.3	238	13.1
Strong (3-10)	349	16.6	302	16.6
ARS				
No (0)	1489	70.6	1334	73.5
Yes (≥1)	619	29.4	482	26.5
ARS				
None or minimal (0-1)	1874	88.9	1567	86.3
Moderate (2)	129	6.1	112	6.2
Strong (3-10)	105	5.0	137	7.5
Charlson Comorbidity Index				
0-3	1128	53.5	1279	70.4
4-5	837	39.7	450	24.8
6-11	134	6.4	55	3.0
Missing	9	0.4	32	1.8
CPS				
Mild (0-1)	180	8.5	1007	55.5
Moderate (2-4)	921	43.7	564	31.1
Severe (5-6)	968	45.9	235	12.9
Missing	39	1.9	10	0.6

Table 2
Prevalence of Delirium Associated With Anticholinergic Drugs According to ACB and ARS in Nursing Home Patients With and Without Dementia

	Delirium in Patients With Dementia (n = 444)		Delirium in Patients Without Dementia (n = 198)	
	Odds Ratio (95% CI)*	*P* Value	Odds Ratio (95% CI)*	*P* Value
ARS raw score (0 through 10)	1.17 (1.04-1.31)	.007	1.07 (0.94-1.21)	.305
ARS ordinal (none or minimal, moderate, strong)	1.26 (0.99-1.49)	.062	1.10 (0.86-1.43)	.435
ACB raw score (0 through 10)	1.14 (1.06-1.23)	.001	1.07 (0.97-1.18)	.175
ACB ordinal (none or minimal, moderate, strong)	1.26 (1.11-1.44)	.001	1.14 (0.94-1.38)	.195

*Adjusted for age, cognitive level (CPS), and Charlson Comorbidity Index *P* value < .05.

Discussion

In the present study, we explored the relationship between the prevalence of delirium and the use of drugs with anticholinergic activity in 3924 patients in European long-term care facilities. We found that the use of anticholinergic drugs, as characterized by the ARS and ACB, is associated with delirium both in patients with and without dementia. The risk for delirium in the dementia group was approximately twice as high. These results are in agreement with previous studies. Egberts et al. found a positive association between delirium prevalence and use of anticholinergic drugs among acutely ill older patients admitted to a hospital.[31] A higher risk for delirium in nursing home patients with dementia and use of anticholinergic drugs was described by Landi et al.[17] Foebel et al[32] found in the SHELTER study a positive relationship for delirium and the specific use of antipsychotic drugs with anticholinergic properties among patients with dementia in European NHs. However, Kolanowski et al[15] found no effect of anticholinergic drugs, according to ACB, on delirium severity among patients with delirium superimposed on dementia admitted to a post-acute care facility. Lackner et al[33] described that short-term treatment with an anticholinergic drug for urge incontinence in female NH patients was not associated with delirium. Pasina et al[34] reported a dose-effect relationship between ACB score and delirium in older patients admitted to an acute geriatric ward. However, after adjustment for dementia status, the association was not statistically significant anymore, thus highlighting the overriding effect of dementia as a strong risk factor for delirium.[34]

In our study, after adjustment for age, comorbidity, and degree of cognitive function, overall, the odds for the association of anticholinergic effects with delirium was greater than 1, irrespective of dementia status, although not significant in patients free from dementia. The latter may be explained by the lower prevalence of delirium in this group, making this analysis prone to a type I statistical error, or it may also reflect a lower sensitivity to anticholinergic effects, because of a better preserved central cholinergic system in patients free from dementia.

Taken together with the higher percentages of patients with anticholinergic burden according to the ACB, this can possibly be taken as a reflection of the overall greater capability of the ACB for characterizing anticholinergic properties.

Our findings indicate that the effect of dementia status on delirium prevalence is larger than the effect of anticholinergic burden (Figure 1). Delirium prevalence was clearly higher among patients with dementia than in those without cognitive decline. Within these groups, the effect of anticholinergic burden was also different. Delirium prevalence did not increase with increasing anticholinergic burden in patients without dementia. However, delirium prevalence increased slightly with increasing anticholinergic burden in patients with dementia. In accordance with the present study findings, Landi et al[17] reported a higher probability of delirium incidence on taking drugs with higher anticholinergic properties among NH patients. The findings of Lagarto et al[35] are also consistent with the present results, reporting an association between increased anticholinergic drug exposure and delirium prevalence, especially in patients with brain disease, in their study mostly of cerebrovascular origin.

The apparent inconsistencies between the results of the present analysis and those in literature can be explained in many ways. Methodological differences such as the methods used to characterize anticholinergic burden, characteristics and size of the study population, and the nature and severity of comorbidity all do play a potential

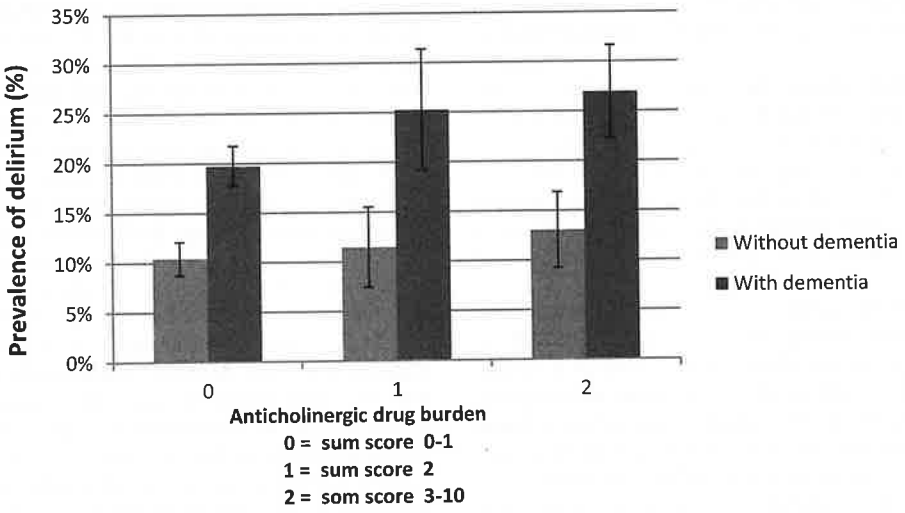

Fig. 1. Distribution of the prevalence of delirium in relation to anticholinergic drug burden according to ACB in patients with and without dementia, within 95% confidence intervals.

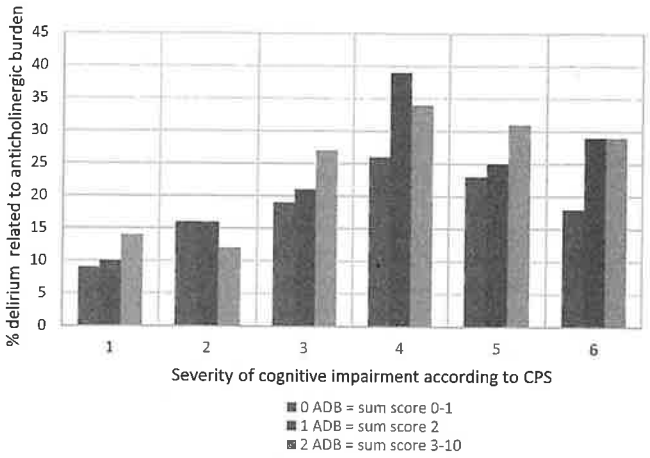

Fig. 2. Distribution of the prevalence of delirium according to cognitive impairment severity levels measured with CPS in relation to anticholinergic drug burden in ACB. Cognitive Performance Scale: 1 = borderline intact, 2 = mild impairment, 3 = moderate impairment, 4 = moderate severe impairment, 5 = severe impairment, 6 = very severe impairment. ADB, anticholinergic drug burden.

role.[15,31,33,36] Specifically, the influence of assessment of anticholinergic burden may be important: the ACB list includes more drugs (97) compared with ARS (44) that contribute to the anticholinergic burden score. Especially in ACB level 1, 44 frequently prescribed drugs in older people are represented.[37] This may affect the amount of drugs used when applying a linear or ordinal scale in a large study population. For clinical practice, our modest discriminatory findings in anticholinergic burden levels give little guidance for identification of those at risk of delirium or for drugs management in nursing home patients suffering from delirium. Only a modest dose-response relationship was found, and therefore these findings do not support the association of increased anticholinergic burden as a robust explanation for increased delirium risk in individual cases. However, in addition to increased risks of delirium, anticholinergic agents are also associated with a wide spectrum of other adverse effects than delirium, including dizziness, blurred vision, urinary retention, and constipation,[38] leading to geriatric syndromes with negative outcome on mortality and a poor quality of life.[39,40] Findings by Ah et al[41] suggest that especially the combination of anticholinergic drugs with cholinesterase inhibitors may be problematic as this was associated with a reduced treatment response or symptom exacerbation and an increased risk of delirium. Combined with the present findings, these insights from the literature concerning anticholinergic side effects should warrant reservations concerning the use of this class of drugs in geriatric populations. Possibly the ACB scale may be helpful in identifying and characterizing specific drugs, and as such this scale may perhaps play a role in more general guidelines, in addition to other guidelines like the AGS Beers Criteria[42] that advise to stop unnecessary medication as a component of a prescribing cascade,[43] to switch to alternative medication[44] or to stimulate nonpharmacologic interventions to manage clinical problems.[45]

The present study has several limitations. First, it was a cross-sectional study, which allowed us only the description of prevalence of delirium in relation to the use of drugs with anticholinergic activity. The data available did not allow to establish a follow-up for incidence of delirium in relation to drug prescription. Further, it was not known how long drugs were taken, as drug use was recorded for only 3 days prior to the assessment. Similarly, the SHLETER database did not allow to characterize the exact temporal relation between drug prescription and any mental changes during this period or even before. Another limitation concerning the anticholinergic burden is the fact that both the ACB and ARS list are based only on dichotomous (yes/no) information on use of drugs with or without anticholinergic properties but both do not incorporate dosing information to further characterize in detail the anticholinergic burden.

The diagnosis of delirium, especially in people with dementia, is challenging and concerns a clinical diagnosis supported by a diagnostic tool like the confusion assessment method (CAM).[46] Based on the SHELTER data, which are accurate and allow access to adequate numbers of participants we had to apply a relatively simple diagnostics algorithm. Thus, in a strict sense our analysis is not based on a formal clinical diagnosis of delirium, but on the presence of the most important symptoms of delirium. This approach has been successfully applied before, using the SHELTER data, and it serves to preserve consistency between various analyses based on these data.[24,32] The algorithm that we applied led to a prevalence of 21% delirium in dementia. This percentage can be considered low according to some of the various percentages from the current literature; however, it is important to note that it is not likely that any diagnostic uncertainty would affect participants using or not using drugs with anticholinergic properties differently. The overrepresentation of mental changes with an acute onset in users of anticholinergic drugs remains, whether this is labeled as "delirium" or as "symptoms of delirium."

A strong point of the present study is the inclusion of a large sample of NH patients, representing to a large degree the everyday clinical reality in this specific institutional setting. Second, the diagnosis of dementia is well established because dementia is often a reason for admission to a nursing home. Third, because the study population consists of NH patients, a wide range of dementia severity is taken into account, which also included the severely cognitive impaired patients who are often excluded from studies.

Conclusions and Implications

In conclusion, we found a positive association between prevalence of delirium and use of drugs with anticholinergic activity in patients with and without dementia in European nursing homes. This association was statistically significant only in NH patients suffering from dementia. Differences in delirium prevalence were modest with increasing cholinergic burden in NH patients with dementia. According to these findings, caution is warranted in prescribing drugs with anticholinergic side effects, whereas the modest strength of the present associations does not allow strong recommendations with respect to the use of these kinds of drugs as a highly sensitive indicator of delirium superimposed on dementia in diagnostic terms. The ACB scale seems to be most capable to detect unwarranted anticholinergic side effects in nursing home patients. Future studies, preferably of a prospective nature, may further characterize the role of drugs with anticholinergic properties in relation to delirium in NH patients.

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