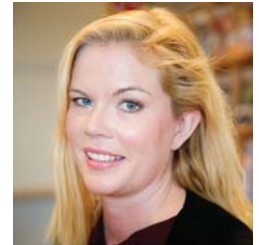


# Inappropriate Drug Use in People with Cognitive Impairment and Dementia: A Systematic Review

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**Abstract:** The aim of this systematic review was to identify, assess and summarize studies about potentially inappropriate drug use (IDU) in cognitive impairment and dementia and to present findings about whether cognitive impairment and dementia are associated with IDU. The search was made in Medline/PubMed using free terms in the title or abstract. The inclusion criteria were: English language, published until 1 March 2014, original quantitative study and assessment of overall IDU with a consensus based summarized measure. Exclusion criteria were: focus on specific patient group (other than cognitive impairment or dementia), focus on specific drug class and failure to present a prevalence measure of IDU or an effect estimate (i.e. odds ratio). Of the initial 182 studies found in Medline, 22 articles fulfilled the criteria. Most studies used the Beers criteria for assessment of IDU. Prevalence of IDU among individuals with cognitive impairment or dementia ranged from 10.2% to 56.4% and was higher in nursing home settings than in community-dwelling samples. Most studies reported a lower likelihood of IDU in case of cognitive impairment or dementia. To conclude, IDU is highly prevalent among persons with cognitive impairment and dementia, although these conditions seem to be associated with a lower probability of IDU. This might reflect an awareness among clinicians of cautious prescribing to this vulnerable group of patients. More studies on large cohorts of persons with cognitive impairment and dementia are needed to draw conclusions about optimal drug prescribing to this frail group of older persons.

**Keywords:** Cognitive impairment, dementia, inappropriate drug use, systematic review.

## BACKGROUND

The worldwide aging of the population imposes great demands on the society and health care systems, where the increased use of pharmaceutical drugs is an important challenge. At the individual level, the challenge is to balance problems related to drug use without denying older people potentially valuable drug therapy. At the societal level, the challenge is to minimize drug-related illness, hospitalizations and associated costs [1, 2].

Older people often have multiple diseases and impairments and aging also leads to changes in both the turnover of drugs in the body (pharmacokinetics) and their actions (pharmacodynamics), which result in prolonged action and stronger effects of many drugs [3]. At the same time, drug use extensively among older people and polypharmacy (i.e. concurrent use of many drugs) is common. In Sweden, 39% of community-dwelling and 76% of institutionalized persons aged  $\geq 65$  years are exposed to polypharmacy ( $\geq 5$  drugs) [4]. There is a lack of evidence for this kind of drug therapy because clinical drug trials often exclude older patients with polypharmacy and multiple comorbidities [5]. Hence, this lack of evidence leaves the clinician with difficult decisions about risks and benefits of drug treatment

in advanced ages. Taken together, older people have the greatest risks of adverse drug reactions [6].

Particularly vulnerable are dementia patients who are especially sensitive to adverse effects of CNS-acting drugs [7]. Dementia causes specific disease-related brain-changes that lead to increased sensitivity to centrally acting drugs and cognitive deficits further complicates drug treatment [3]. There is a high risk of both under- and over treatment due to communication problems and psychiatric and behavioral changes. This might lead to inappropriate treatment with psychotropic drugs [8] and a neglect of somatic conditions [9]. However, relatively few studies have assessed the quality of prescription in people with dementia.

An important concept of quality of drug therapy in old age is potentially inappropriate drug use (IDU), which is defined as drug therapy that poses potential risks that outweigh potential benefits [10]. There are many measures of IDU in older people and these are explicit measures generally based on consensus panels [11]. Some of the most common measures of IDU include the Beers criteria (originally from 1991) [10] and the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria developed in 2008 [12]. Holmes has also developed a specific tool for assessment of inappropriate drug prescribing in advanced dementia for patients where the primary goal is palliation of symptoms [13].

IDU is common in older people (ranging from about 12% to 63%) [11], particularly in institutions where the frailest

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older persons reside [14], and have been associated with adverse outcomes such as hospitalization and mortality [15, 16]. However, there is tentative support for prevention of the majority of these problems through educational outreach and improved knowledge about drug prescribing for older people [17]. Nonetheless, IDU in persons with cognitive impairment or dementia is an understudied area. The present review may be the first systematic review on this topic.

The objective of this systematic review was to identify, assess and summarize available studies about potential IDU in cognitive impairment and dementia and to present findings about whether cognitive impairment and dementia are associated with IDU.

**METHODS**

**Search Strategy**

The search for studies was made by one researcher (KJ) in the Medline electronic database, using the PubMed interface. The following free terms were used: “inappropriate”, “dementia”, “cognitive impairment”, “Alzheimer”, “drug”, “drugs”, “medication” and “medications” in the title or abstract.

**INCLUSION CRITERIA**

The articles had to be published in English up until 1 March 2014. Only indexed original research papers were included. They also had to have a quantitative design,

analyze overall IDU (i.e. not specific drug classes such as psychotropics) with an explicit consensus based summarized measure of IDU.

**EXCLUSION CRITERIA**

Articles were excluded if they focused on specific patient groups (e.g. fallers, cardiovascular patients) or specific drug classes. They were also excluded if they failed to present a prevalence measure for IDU or an effect estimate (i.e. odds ratio [OR] with 95% confidence intervals [CIs]) for the association between cognitive impairment or dementia and IDU.

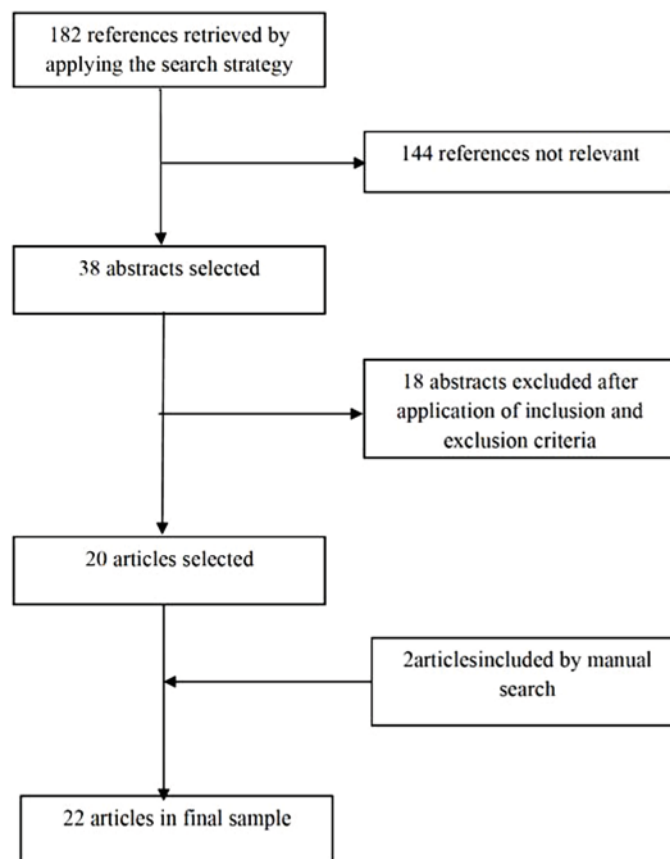
**SELECTION OF STUDIES**

After the initial search, abstracts of the papers that included the topic of IDU in cognitive impairment or dementia were retrieved. Thereafter, the inclusion and exclusion criteria were applied. Finally, the articles that fulfilled these criteria were retrieved in full-text.

Papers identified through manual search of reference lists of selected papers also underwent assessment according to the established inclusion and exclusion criteria.

**DATA EXTRACTION**

The following data were extracted from the papers that fulfilled the above mentioned criteria: country, population characteristics (including assessment of dementia and



**Fig. (1).** Flowchart of systematic article search.

**Table 1. Prevalence of inappropriate drug use (IDU) in persons with cognitive impairment or dementia.**

Reference, Year	Country	Population Characteristics, Sample Size and Assessment of Dementia or Cognitive Impairment	Assessment of Drug Use	Criteria for IDU	Prevalence (at Least one IDU)
Montastruc <i>et al.</i> , 2013 [23]	France	Community-dwelling Alzheimer patients assessed by DSM-IV and NINCDS-ADRDA criteria for Alzheimer-type dementia at mild to moderate stage (n=684)	Caregiver reports	Laroche list	46.8%
Fiss <i>et al.</i> , 2013 [20]	Germany	Community-dwelling persons with cognitive impairment assessed by DemTect screening (n=111)	In-home interviews	PRISCUS list	19.8%
Koyama <i>et al.</i> , 2013 [21]	USA	Community-dwelling women with dementia based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (n=260)	Self-reported drug use within the past 30 days	Beers list	33.1%
Parsons <i>et al.</i> , 2012 [32]	UK	Older people with dementia (derived from medical records) in care homes (n=119)	Medical records	STOPP criteria	46.2%
Bosboom <i>et al.</i> , 2012 [29]	Australia	Dementia patients (in medical records) in residential aged care facilities (n=226)	Medical records	Modified Beers list	56.4%
Colloca <i>et al.</i> , 2012 [30]	SHELTER (8 European countries)	Nursing home residents with severe cognitive impairment assessed by the cognitive performance scale (CPS) (n=1 449)	Medical records	Holmes list	44.9%
Lau <i>et al.</i> , 2011 [27]	USA	Community-dwelling older adults with dementia assessed by the Clinical Dementia Rating (CDR) scale (n=1 994)	Self-reported drug use within the last 2 weeks	Beers list	16.2%
Tjia <i>et al.</i> , 2010 [34]	USA	Nursing home residents with advanced dementia assessed by the Cognitive Performance Scale (n=323)	Medical records	Holmes list	37.5%
Weston <i>et al.</i> , 2010 [28]	USA	Patients clinically diagnosed with mild cognitive impairment (n=689)	Self-report and caregiver report	Beers list	20.8%
Lau <i>et al.</i> , 2010 [26]	USA	Community-dwelling persons with dementia assessed by the Clinical Dementia Rating (CDR) scale (n=2 665)	Self-report	Beers list	15.0%
Holmes <i>et al.</i> , 2008 [13]	USA	Patients with advanced dementia assessed by the Functional Assessment Stages (FAST) in long-term care (n=34)	Nursing home records and proxy interviews	Holmes list	29.4%
Wawruch <i>et al.</i> , 2008 [36]	Slovakia	Hospitalized dementia patients (dementia diagnosis from medical records) (n=89)	Medical records	Beers list	22.4%
Raivio <i>et al.</i> , 2006 [33]	Finland	Hospitalized patients and nursing home residents with dementia based on the Diagnostic and Statistical Manual of Mental Disorders (4th edition) [DSM-IV] criteria (n=255)	Medical records	Beers list	36.9%
Fialova <i>et al.</i> , 2005 [25]	Eight European countries	Home care patients with cognitive impairment assessed by the Cognitive Performance Scale (CPS) (n=773)	Self-reported, caregiver reported and medical records	Beers and McLeod list	20.7%
Zuckerman <i>et al.</i> , 2005 [35]	USA	Dementia patients admitted to nursing home (n=334). Dementia diagnosis based on Diagnostic and Statistical Manual of Mental Disorders (3rd edition)	Prescription claims	Beers list	20%
Ay <i>et al.</i> , 2005 [24]	Turkey	Community-dwelling persons with dementia assessed by the Mini Mental State Examination (MMSE) (n=322)	Self-reported drug use in the previous three weeks	Beers list	10.2%
Nygaard <i>et al.</i> , 2003 [31]	Norway	Cognitively impaired (assessed by the Clinical Dementia Rating (CDR)) nursing home residents (n=870)	Medical records	Modified Beers list	21.6%

cognitive impairment), assessment of drug use, criteria for IDU, prevalence of IDU and effect estimate (i.e. OR with 95% CI) for the association between cognitive impairment or

dementia and IDU. In some instances, the prevalence of IDU was not available and then had to be calculated. Adjusted ORs were extracted where possible.

**Table 2. Association between cognitive impairment or dementia and inappropriate drug use (IDU).**

Reference, Year	Country	Population Characteristics, Sample Size and Assessment of Dementia or Cognitive Impairment	Assessment of Drug Use	Criteria for IDU	ORs (95% CIs) for IDU
Dosa <i>et al.</i> , 2013 [19]	USA	Veterans Affairs nursing homes (n=27 133). Dementia assessed by the Cognitive Performance Scale (CPS).	Pharmacy data	Health PlanEmployer Data and Information Set (HEDIS) list	Moderate dementia: OR: 0.72 (0.64-0.82) Severe dementia: OR: 0.72 (0.61-0.85)
Mann <i>et al.</i> , 2013 [22]	Austria	Nursing home residents (n=1 844). Cognitive impairment assessed by the Dementia Screening Scale	Medical records	Austrian list	Cognitive impairment: OR: 0.71 (0.55-0.92)
Zuckerman <i>et al.</i> , 2005 [35]	USA	Patients admitted to nursing home (n=546). Dementia diagnosis based on Diagnostic and Statistical Manual of Mental Disorders (3rd edition)	Prescription claims	Beers list	Dementia: OR: 0.97 (0.58-1.62)
Ay <i>et al.</i> , 2005 [24]	Turkey	Community-dwelling persons (n=1 019). Dementia assessed by the Mini Mental State Examination (MMSE)	Self-reported drug use in the previous three weeks	Beers list	Dementia: OR: 1.07 (0.69-1.67)
Perri <i>et al.</i> , 2005 [38]	USA	Nursing home residents (n=1 117). Dementia diagnosis collected from medical records	Medical records	Beers list	Dementia: OR: 0.748 (0.565-0.991)
Nygaard <i>et al.</i> , 2003 [31]	Norway	Nursing home residents (n=1 042). Cognitive impairment assessed by the Clinical Dementia Rating (CDR)	Medical records	Modified Beers list	Cognitive impairment: OR: 0.64 (0.41-0.99)
Onder <i>et al.</i> , 2003 [37]	Italy	Hospitalized older persons (n=5 734). Cognitive impairment assessed by the Hodkinson abbreviated mental test (AMT)	Questionnaire data by study physician	Beers list	Cognitive impairment: OR: 0.77 (0.64-0.94)
Sloane <i>et al.</i> , 2002 [18]	USA	Residential care/assisted living facilities (n=2 078). Dementia assessed by the Mini-Mental State Examination (MMSE).	Medical records	Modified Beers list	Moderate or severe dementia: OR: 0.655 (0.463-0.926)

## RESULTS

The search strategy resulted in 182 papers in Medline. Fig. 1 displays the selection process in a flow chart diagram.

After initial screening of title and/or abstract, 38 abstracts about IDU and cognitive impairment or dementia were collected. These abstracts were then assessed according to the inclusion and exclusion criteria and resulted in inclusion of 20 papers that were retrieved in full-text. Two more papers were also added after manual search of reference lists of the selected papers after fulfillment of inclusion and exclusion criteria.

The publication of studies increased over time; there was one paper published in 2002 (earliest included paper) [18] and five in 2013 [19-23] (Tables 1 and 2).

Table 1 shows the 17 included articles that reported prevalence of IDU in persons with cognitive impairment or dementia. The studies were conducted in Europe, Asia, USA and Australia. The population characteristics varied considerably in setting and sample size. Eight studies were based on community-dwelling samples [20, 21, 23-28], 8 conducted in nursing homes [13, 29-35] and 2 in the hospital setting [33, 36]. The assessment of drug use was made through medical records in the nursing home and hospital settings, whereas self-reported drug use was collected in the community-dwelling setting. Sample size of individuals with cognitive impairment or dementia ranged

from 34 [13] to 2 665 [26]. Five studies were based on people with cognitive impairment (mild to severe) and 12 on dementia patients. Most studies used the Beers criteria (64.7%; 11/17) [21, 24-29, 31, 33, 35, 36]. Three studies used the Holmes criteria for prescribing in advanced dementia [13, 30, 34].

Prevalence of IDU among individuals with cognitive impairment or dementia ranged from 10.2% to 56.4% (Table 1). Most studies, however, reported a prevalence of IDU between 20 to 50 % (76.5%; 13/17). The lowest prevalence was reported from Turkey [24] and the highest from Australia [29]. Yet, the limited number of studies prohibited comparisons between countries. Prevalence was higher in nursing home settings than in community-dwelling samples. Also, the three studies that used the Holmes criteria for prescribing in advanced dementia [13, 30, 34] were among those that reported the highest prevalence of IDU (29.4%-44.9%). Common IDU in advanced dementia were lipid-lowering agents, antiplatelet agents (excluding acetylsalicylic acid), anti-dementia drugs and antispasmodics [13, 30, 34].

Table 2 shows the 8 included articles that investigated the association between cognitive impairment or dementia and IDU. Three of these studies [24, 31, 35] were also included in Table 1.

The studies included in Table 2 were based on people both with and without cognitive impairment or dementia and had, thus, larger sample sizes than the prevalence studies in

Table 1. The represented countries and settings were, however, similar to the prevalence studies. Also here were the Beers criteria the most commonly used measure of IDU (75%; 6/8) [18, 24, 31, 35, 37, 38].

Six [18, 19, 22, 31, 37, 38] of the 8 articles reported a lower likelihood of IDU in case of cognitive impairment or dementia (Table 2). The remaining 2 papers [24, 35] showed no statistically significant association (with wide confidence intervals) between cognitive impairment or dementia and IDU. Hence, no study reported a positive association.

## DISCUSSION

This review endeavored to compile and contribute to the knowledge about IDU in people with cognitive impairment and dementia by systematically identifying, assessing and summarizing available studies on the topic. The findings of this review suggest that the prevalence of IDU in people with cognitive impairment and dementia is high. Nevertheless, these conditions seem to be associated with a lower likelihood of IDU.

The reported prevalence of IDU varied greatly between studies, ranging from 10.2% to 56.4%, although most studies reported a prevalence between 20 to 50%. This is in line with a recent review of IDU in general populations of older people that reported a range of 11.5% to 62.5% [11]. The variation in occurrence of IDU may be explained by differences in assessment of IDU, study design, setting and population characteristics. Indeed, drugs included in explicit criteria for IDU (e.g. Beers list) may have limited availability in other countries outside of where they were originally established [39]. Also, IDU was more common in the institutional than in the community-dwelling setting. This finding is consistent with a previous investigation of older people in which institutionalization was identified as a potential risk factor for IDU [14]. Further, most studies used the Beers criteria for assessment of IDU [10]. These studies reported a variation in prevalence of IDU between 10% and 56%. The second most commonly used assessment tool was the Holmes list, which is intended for use in patients with advanced dementia where the primary goal is palliation of symptoms [13]. The prevalence of IDU in these studies was high and ranged between 29% and 45%. Hence, the population characteristics and the actual assessment method of IDU have a great impact on the reported prevalence.

Persons with cognitive impairment or dementia are particularly susceptible to adverse effects of drugs and communication problems further complicates drug treatment [7]. Hence, drug prescribing to this vulnerable group of patients should be made very cautiously and ideally be adjusted and reconsidered as the disease progresses. In the early stages of disease, life prolonging treatments are indicated, where as drugs that reduce suffering is of highest priority in the advanced stages [34]. The clinician is faced with many difficult decisions and little evidence to rely on. Thus, more research is needed on how to best treat patients with cognitive impairment and dementia across the different stages of disease [40].

Despite the high exposure to IDU, cognitive impairment and dementia were associated with a lower probability of

IDU in most studies. No study reported a positive association between cognitive impairment or dementia and IDU. However, the same criteria for IDU were used for patients with and without cognitive impairment or dementia, although there may be a difference in which medications that should be regarded as appropriate or inappropriate in these two groups [13]. In particular, studies have reported higher prevalence of anticholinergic and sedative drugs in persons with cognitive impairment and dementia [41, 42], although these drugs are of particular concern in this population [7].

This consistent finding of an inverse or no effect of cognitive impairment or dementia on IDU is difficult to explain and probably multifactorial. Mann *et al.* found in their study that it was neuropsychiatric symptoms rather than cognitive impairment that provoked IDU [22]. Many of the psychotropic drugs that are used for treatment of neuropsychiatric symptoms are indeed considered as inappropriate prescribing [43]. Sloane *et al.* argue that their finding of an independent relationship between dementia and absence of IDU may be because conditions or symptoms that are treated with IDU are rarely voiced by persons with dementia and give the example of pain medications [18]. This might also hold true for cardiovascular drugs, as persons with dementia have been found to have less potential drug-disease interactions involving cardiovascular agents than those without dementia [44]. Perri *et al.* suggest that possible explanations include physicians' vigilance in prescribing to patients with reduced cognitive capacity in fear of further cognitive impairment from adverse drug effects [38]. In this sense, the consistent finding of an inverse or no effect of cognitive impairment or dementia on IDU may reflect appropriate prescription to frail older patients and may be a sign of good clinical practice [37].

This review has some limitations. First, the search strategy, application of inclusion and exclusion criteria and selection of studies might have resulted in missed articles that were not identified or incorrectly excluded. The search was made in one database (Medline/PubMed), only included articles published in English and with an explicit consensus based summarized measure of IDU (i.e. not on other dimensions of suboptimal drug use, such as drug-drug interactions). However, 22 articles in the final sample may be regarded as a fairly large number in comparison with other reviews on related topics [11].

Second, the systematic search and assessment of inclusion and exclusion criteria were made by one person, which may increase the risk of bias.

Third, this review focused on prevalence of IDU and on the possible association between cognitive impairment or dementia and IDU. Hence, neither interventions for reduction of IDU [17] nor outcomes of IDU were considered [2]. Reviews about these topics in cognitive impairment and dementia are needed, although they might be difficult to complete due to limited number of published studies.

Finally, potentially IDU is not equal to actual IDU given that a drug judged to be inappropriate by definition may sometimes be justified and indicated for the individual patient [45].

## CONCLUSIONS

IDU is highly prevalent among persons with cognitive impairment and dementia. This is of concern given that these persons are highly susceptible to adverse drug reactions and may have problems with communicating adverse effects.

Still, cognitive impairment and dementia were associated with a lower risk of IDU. This might reflect an awareness among clinicians of cautious prescription to this vulnerable group of patients. More studies on large cohorts of persons with cognitive impairment and dementia are needed to draw conclusions about optimal drug prescription to this frail group of older persons.

## CONFLICT OF INTEREST

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