A systematic review of medication non-adherence in persons with dementia or cognitive impairment

Daisy Smith1,*, Janaka Lovell1,*, Carolina Weller2, Bronwyn Kennedy1, Margaret Winbolt1, Carmel Young1, Joseph Ibrahim1

1 Department of Forensic Medicine, Monash University, Southbank, Victoria, Australia, 2 Ballarat Health Services, Ballarat, Victoria, Australia, 3 Department of Epidemiology and Preventive Medicine, Monash University, Victoria, Australia, 4 Australian Centre for Evidence Based Aged Care, College of Science, Health and Engineering, La Trobe University, Victoria, Australia

* These authors contributed equally to this work.
† These authors also contributed equally to this work.
* daisy.smith@monash.edu

Abstract

Background

Adherence to medication is vital for disease management while simultaneously reducing healthcare expenditure. Older persons with cognitive impairment (CI) are at risk for non-adherence as cognitive processes are needed to manage medications. This systematic review focuses on the relationship between medication non-adherence and specific cognitive domains in persons with CI, and explores determinants of medication non-adherence. When available, relationships and factors are compared with cognitively intact populations.

Methods

A seven database systematic search of studies published between 1 January 1949–31 December 2015 examining medication non-adherence in community dwelling persons with CI or dementia was conducted. Articles reporting medication non-adherence in people with CI or dementia in the community, with or without caregiver supports were eligible for inclusion. Papers reporting adherence to treatments in cognitively intact populations, populations from hospital or institutional settings, for non-prescribed medication or those describing dementia as a factor predicting medication non-adherence were excluded. Data on study and population characteristics, research design, data sources and analysis, specific cognitive domains, non-adherence prevalence, measurement of adherence, salient findings, factors associated with adherence and strategies to improve medication adherence were extracted. Study limitations included inconsistencies between data sources and definitions, resulting in a loss of fidelity in the value and comprehensiveness of data, as well as exclusion of non-pharmacological treatments and regimens.

Findings

Fifteen studies met inclusion criteria. Adherence among CI subjects ranged from 10.7%–38% with better rates of adherence in non-CI individuals. Medication non-adherence
Table 1. DSM V Criteria for Diagnosing Major & Minor Neurocognitive Disorder (NCD)*.

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex attention</td>
<td>Includes sustained attention, divided attention, selective attention and information processing speed.</td>
</tr>
<tr>
<td>Executive function</td>
<td>Includes planning, decision making, and working memory, responding to feedback, inhibition and mental flexibility.</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>Includes free recall, cued recall, recognition memory, semantic and autobiographical long term memory, and implicit learning.</td>
</tr>
<tr>
<td>Language</td>
<td>Includes object naming, word finding, fluency, grammar and syntax, and receptive language.</td>
</tr>
<tr>
<td>Perceptual-motor function</td>
<td>Includes visual perception, visuoconstructional reasoning and perceptual-motor coordination.</td>
</tr>
<tr>
<td>Social cognition</td>
<td>Includes recognition of emotions, theory of mind and insight.</td>
</tr>
</tbody>
</table>

*Dementia newly defined as Major NCD; CI newly defined as Minor NCD in DSM-V. 

doi:10.1371/journal.pone.0170651.t001

Aims

The aim of this systematic review is to elucidate the relationship between medication non-adherence and specific cognitive domains in persons with dementia/CI. The secondary aim is to determine factors related to medication non-adherence in persons with dementia/CI who take medication for treatment of comorbid chronic disease(s).

Methods

Definitions

This review has adopted the clinical diagnostic criteria of the Diagnostic Statistical Manual version 5 (DSM-V) to define dementia and cognitive impairment and outline the specific cognitive domains (Table 1) [22].

Study selection

Eligibility criteria encompassed articles reporting medication non-adherence in people with CI or dementia in the community, with or without caregiver support.

Inclusion criteria comprised original research in peer-reviewed journals available in English language between 1 January 1949–31 December 2015. Studies with participants who had dementia as described by authors and comorbid chronic diseases were included. Articles reporting dementia of different severities were also included. Article definitions and methods of diagnosing dementia were not restricted to the DSM-V clinical diagnostic criteria used to structure this review.

Excluded were studies on medication non-adherence in hospital or institutional setting (e.g. nursing home). Papers reporting adherence to treatments other than prescribed medication and those that described dementia as a factor predicting medication non-adherence were excluded. We also excluded study populations consisting of cognitively intact persons only.

Reporting guidelines

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (PRISMA-P checklist)[23] (S1 Table).
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Aim</th>
<th>Country</th>
<th>Design</th>
<th>Methodology</th>
<th>Setting</th>
<th>Population</th>
<th>No. of persons with CI/Dementia (%)</th>
<th>Quality of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foebel, 2012</td>
<td>Role of caregivers and caregiver stress in medication adherence in older home care clients with MCI</td>
<td>CAN</td>
<td>R, Co</td>
<td>HD, Sur, MR, St, Fam/C,</td>
<td>State/County</td>
<td>Persons with heart failure, MCI &amp; caregivers</td>
<td>59,662 (42%)</td>
<td>G</td>
</tr>
<tr>
<td>Mackin, 2006</td>
<td>Determine the relative contribution of measures of cognitive functioning and mood status on treatment adherence</td>
<td>USA</td>
<td>R, Co</td>
<td>HD, HC, Sur, Int</td>
<td>State/County</td>
<td>Older adults at primary care clinics</td>
<td>29%</td>
<td>F</td>
</tr>
<tr>
<td>Poon, 2009</td>
<td>Evaluate the utilization of and adherence to antihypertensive and dementia medications in a cohort of veterans across different racial/ethnic groups</td>
<td>USA</td>
<td>R, Co</td>
<td>HD, MR, Sur</td>
<td>National</td>
<td>Veteran with a diagnosis of both hypertension and dementia</td>
<td>56,561 (100%)</td>
<td>G</td>
</tr>
<tr>
<td>Hawkins, 2012</td>
<td>Describe the cognitive domains affected in patients with CI, examine clinical and demographic variables potentially associated with CI, and to determine the relationship between CI and MA</td>
<td>USA</td>
<td>P, Co</td>
<td>HD, MR, Int, St</td>
<td>State/County</td>
<td>English speaking veterans. No subjects had known CI before study enrollment (N = 251)</td>
<td>144 (68%)</td>
<td>F</td>
</tr>
<tr>
<td>Thiruchselvam, 2012</td>
<td>Examine the influence of cognitive, medical, behavioural, and social risk factors on medication NAD in community-dwelling older adults with CI</td>
<td>CAN</td>
<td>P, Co</td>
<td>Sur, MR, HC, Int, Fam/C,</td>
<td>National</td>
<td>Older adults with CI whom lived alone and took at least one medication</td>
<td>339 (100%)</td>
<td>F</td>
</tr>
<tr>
<td>Smith, 2007</td>
<td>Assess telehealth home monitoring system.</td>
<td>USA</td>
<td>P,Co</td>
<td>Sur, Fam/C, Int, MRD</td>
<td>National</td>
<td>People with mild dementia who live alone and took &gt;1 medications daily. Three groups: video, phone, control.</td>
<td>14 (100%)</td>
<td>F</td>
</tr>
<tr>
<td>Kamimura, 2012</td>
<td>Test efficacy of medication reminder device in medication management for elderly patients with MCI</td>
<td>USA</td>
<td>P, Co</td>
<td>Fam/C, MRD, Int</td>
<td>National</td>
<td>Elderly with MCI</td>
<td>18 (100%)</td>
<td>G</td>
</tr>
<tr>
<td>Conn, 1994</td>
<td>Assess patients taking drugs for co-morbid disease to determine whether this had a role in slowing further cognitive decline.</td>
<td>USA</td>
<td>P, Co</td>
<td>MR, Int</td>
<td>State/County</td>
<td>Persons with CI (&lt;23 MMSE score) and non-impaired controls (N = 178)</td>
<td>35 (20%)</td>
<td>F</td>
</tr>
<tr>
<td>Insel, 2006</td>
<td>Examine the relationship between adherence and measures of executive functioning or working memory and memory.</td>
<td>USA</td>
<td>P, Co</td>
<td>Sur</td>
<td>National</td>
<td>Community-based older adults taking daily prescribed medications.</td>
<td>95</td>
<td>G</td>
</tr>
<tr>
<td>Boucher, 1996</td>
<td>Describe problems of dementia patients with CI spousal caregivers.</td>
<td>USA</td>
<td>CC</td>
<td>HC, Int, Sur, Fam/C</td>
<td>National</td>
<td>Dementia patients</td>
<td>AD: 56 (86%); Other: 9 (14%)</td>
<td>G</td>
</tr>
</tbody>
</table>

(Continued)
Medication non-adherence and adherence

The definition of medication non-adherence and adherence varied widely (Table 3) with studies describing under and overtaking (n = 2), omission of a single dose (n = 7), deviation from a prescribed time (n = 2) and deviation from dose intervals (n = 3).

Six studies described the frequency of medication non-adherence [14, 18, 20, 21, 27, 28]. The frequencies of non-adherence varied considerably across studies. The smallest rate was 10.7% among CI older adults aged 65 or more years using surveys in a cohort study [21]. The greatest rate was 38% of participants “falling below the adherence threshold of taking medication correctly 85% of the time” in one prospective cohort study using electronic monitoring [14]. Adherence frequencies using ‘pill counts’ ranged from 17%-100% among older adults with Alzheimer’s Disease (AD) from one case control study [27].

Under and overtaking medications. Two prospective cohort studies reported under and overtaking medications were common [18, 20]. In one study, 17.4% of participants reported at least one incident of medication non-adherence during the 12-month prospective follow up period [20]. These comprised one incident (14.7%), two incidents (2.4%) and three incidents (0.3%) [20]. The other study, examined all domains (excluding abstract reasoning) in participants with heart failure who screened positive for CI [18]. Through pill counts of all prescribed medication, this found that MCI and severe CI persons were 30% and 27% non-adherent (pills were not taken, over taken or a combination of both) respectively within a 30 day period [18].

Omission of a single dose. Omission of a single dose was specified in seven studies [14, 18, 21, 25, 26, 32, 34]. When reported, adherence frequencies fell to 42%-71%. The majority used pill counts to determine medication adherence (n = 4) whilst the remaining used self-reports (n = 1), survey (n = 1) and a medication-monitoring device (n = 1). Most studies did
<table>
<thead>
<tr>
<th>Author, year</th>
<th>CI associated with NAD</th>
<th>Method of ascertaining CI</th>
<th>Severity of CI</th>
<th>Domain (s) affected</th>
<th>Definition of non-adherence</th>
<th>Method of determining non-adherence</th>
<th>Adherence rates (n)</th>
<th>Other risk factors for non-adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiruchselvam, 2012</td>
<td>Y</td>
<td>DRS: Dementia &amp; CI score &lt; 130</td>
<td>M / S: 339 (100%)</td>
<td>A, AB, VC, LM, E</td>
<td>2 or more incidents of over/under dosing of medication</td>
<td>Independent rater review</td>
<td>17.4% had at least one incident of medication NAD reported</td>
<td>Previous occurrence of NAD; ≥ 4 medications; increase in certain DRS subset scores</td>
</tr>
<tr>
<td>Okuno, 2001</td>
<td>Y</td>
<td>MMSE: CI score &lt; 24</td>
<td>S: 56 (26.4%)</td>
<td>-</td>
<td>ADH rate &lt; 80%</td>
<td>Pill count</td>
<td>Poor ADH rates (&lt;80%): 75 (34.6%)</td>
<td>CL: medication concern; educational; initially self-selected prescribed drugs; no medication calendar; poor relationship with physician</td>
</tr>
<tr>
<td>Cameron, 2010</td>
<td>Y</td>
<td>MMSE: CI score &lt; 26 &amp; MoCA: score &lt; 26</td>
<td>M / S: 68 (73%)</td>
<td>-</td>
<td>-</td>
<td>Interview (6 +/- 5 days after hospitalization)</td>
<td>Inadequate self-care maintenance: 43 (47%)</td>
<td>Experience with CHF &lt; 2 months; MCI; Comorbidity Index</td>
</tr>
<tr>
<td>Conn, 1994</td>
<td>N</td>
<td>MMSE: CI score &lt; 23</td>
<td>M / S: 35 (20%)</td>
<td>-</td>
<td>Pills usually missed per week</td>
<td>Pill count and self-report</td>
<td>Relation between CI and ADH/NAD recorded not MA</td>
<td>-</td>
</tr>
<tr>
<td>Kamimura, 2012</td>
<td>-</td>
<td>MMSE &amp; CDR</td>
<td>MMSE— M: 13 (72.2%); S: 5 (27.8%); CDR— M: 10 (55.6%); S: 8 (44.4%)</td>
<td>-</td>
<td>Elderly with MCI</td>
<td>SAMR prior to device use &amp; at 1 and 3 months after use</td>
<td>Ability to use medication reminder device not MA recorded</td>
<td>-</td>
</tr>
<tr>
<td>Smith, 2007</td>
<td>-</td>
<td>MMSE: MCI score 24–27; Dementia score &lt; 24</td>
<td>M / S: 14 (100%)</td>
<td>-</td>
<td>-</td>
<td>Pill count</td>
<td>ADH rates in the video-monitored group remained stable whereas phone group and control group declined</td>
<td>Phone intervention and no telehealth home monitoring</td>
</tr>
</tbody>
</table>

**General:** () Not stated/specified.

**CI associated with non-adherence:** Y = Yes; N = No.

**Severity of CI:** M = Mild Cognitive Impairment; S = Severe Cognitive Impairment; NGM/R = No global Measurement/Reporting of Cognitive Impairment.

**Methods of ascertaining CI:** CPS = Cognitive Performance Scale; DRS = Dementia Rating Scale; MMSE = Mini-Mental State Examination; SLUMS = Saint Louis University Mental Status (SLUMS) examination; BRIDS = Blessed-Roth (functional) Dementia Scale; KOMCT = Katzman Orientation-Memory-Concentration Test; CMSQ = Comprehensive Mental Status Questionnaire.

**Domains affected:** A = Attention; AB = Abstract Reasoning; VC = Visual and Constructional; LM = Learning and Memory; E = Executive Function; I = Information Processing; L = Language.

**Definition of non-adherence:** MPR = Medication Possession Ratio.

**Method of determining non-adherence:** MMTR = Medication Management Test; SAMR = Self-administration Medication Rate.

**Dementia type:** MCI = Mild cognitive impairment; AD = Alzheimer’s Disease; CI = Cognitive impairment.

**Adherence:** NAD = non-adherence; ADH = adherence.

doi:10.1371/journal.pone.0170651.003
recruited participants showing signs of CI (e.g. MMSE scores <25) [21] or deficits in domains indicative of impairment [14]. The remaining studies, using CI population samples, reported poorer executive performance increased the likelihood of non-adherence (n = 1) [20] or was not statistically significant (n = 2) [18, 30]. Interestingly, two used the DRS initiation/preservation subscale [20, 20].

**Abstract reasoning.** One prospective cohort study reported better performance on the DRS conceptualization subscale increased the likelihood of non-adherence [20].

**Receptive and expressive language.** There was not a significant association between language domain tested and medication adherence in one prospective cohort study [18].

### Factors associated with non-adherence

**Individual factors.** Eleven studies documented individual factors associated with medication adherence and non-adherence in cognitively intact and cognitively impaired individuals [14, 18, 20, 21, 26, 27, 30, 31, 33–35] (Table 4).

Individual hazardous factors reported: African American and Hispanic ethnicity [31]; forgetting [21, 26]; lower scores in cognitive domain test indicative of deficits [14, 20, 21, 30]; dementia/CI [18, 27, 33, 35]; depression [30]; inadequate self-care confidence [33]; lower level of education, concern about taking prescribed drugs and intentional noncompliance [35].

Of note, global dementia/CI scores using MMSE [14, 26] were not associated with adherence in two prospective cohort studies and when reported, total MMSE score ranged from 14–23 (M = 20.72) [26]. Presence of dementia was associated with not knowing the name and purpose of medications, having others assisting and preparing medications and an adult child assisting with medications [26].

**Dyad/Career.** The likelihood of participants with CI having a caregiver to assist with medications was reported in six studies [25–29, 34]. Presence of caregiver established self-administration dependence and low capacity of self-medication [26, 28] as well as improved adherence [27, 34]. Informants were able to accurately predict the care recipient’s adherence rates and performance on medication management tasks in one case-control study [27].

Participants with CI were more likely to have someone prepare medication [26, 27, 29]. Hazardous factors affecting medication adherence for CI persons included caregiver distress, not living with a caregiver [34], absence of assistance (e.g. reminders, pill box check and setting-up lists) [27] and spouses as primary caregivers who were also cognitively impaired [25].

**Medication.** Three studies reported medication factors in relation to non-adherence [20, 21, 35]. Taking fewer drugs was associated with improved adherence in one study using self-reports [21] and CI persons taking four or more daily medications had a 2.5 fold increase in non-adherence compared to those taking less than four medications according to independent rater-reviews [20]. Conversely, a cross-sectional study reported a non significant association between medication adherence and: the number of drugs or frequency of drug administration; or with/without one dose package; or use of medication calendar or written drug information using pill counts [35].

**Medication aids.** A memory assistive device was used more often by CI participants (32/35) than non-CI participants (132/143) [28]. The lack of such device was associated with non-adherence [35]. Better scores on memory subscales were also associated with participants setting up their own medication schedules [21]. Additionally, environmental cues associated with the repetitive task of taking medication were reported to have contributed to increased adherence [14].

**Healthcare system factors.** Health system factors were reported in three studies [21, 30, 35]. There was a negative correlation between physician rating and patient’s ratings of
Telecommunication technology [32] and a medication reminder device [29] were used to assess medication self-administration in participants with dementia. These suggested that participants could become proficient users of such interventions [29, 32]. Video monitoring intervention stabilized adherence even as global mental status declined over time, while adherence for the control group (no monitoring) declined as global mental status declined [32]. End-of-study adherence was statistically significant for the video monitored group (81%) compared to controls (62%) [32].

One study reported 89% (n = 231/257) participants with an assistive system to track medication were fully adherent. This proportion was similar to those not using assistive methods (87% (n = 74/86) [21]. The most common assistive system was specific placement of medications to trigger memory (34.2%, n = 92). These findings were discordant with another study, whereby CI participants’ MMSE scores were not associated with reported use of memory focused assistive methods [26].

Discussion

Statement of key findings

Poor adherence to medication regimens in people with CI ranged from 10.7% [21] to 38% [14] while adherence levels ranged from 17% to 100% among older adults with Alzheimer’s Dementia [27].

Frequencies of adherence in these CI populations were worse when compared to cognitively intact populations [14, 21].

Interestingly, when an informal caregiver was ensuring adherence, the objective adherence rates were similar in cognitively intact and impaired populations [27].

Aggregate analysis and direct comparison was limited because of inconsistencies and variations in definitions of adherence and non-adherence. Also the methods of ascertaining adherence were disparate [26].

To our knowledge, this is one of very few systematic reviews to deconstruct cognitive functioning and identify specific domains associated with medication adherence [21].

Interpretation

Cognitive domains. Specific cognitive domains receiving the most attention were memory and executive functioning. Studies with CI populations found intact memory was a significant predictor of medication adherence [18, 20]. Any associations with executive functioning remain unclear due to discordant study results. Persons with CI may not be able to understand, retain or follow instructions, implying that interventions focusing on traditional models of patient education may fall short in this population [18].

The impacts of a better level of executive performance in persons with CI on medication adherence were discordant, one reported improvement [20] and another did not [18].

In contrast, studies with populations considered cognitively intact reported better executive function to be a significant factor for adherence [14, 21]. These discordant results may be due to differing methods utilized to test this domain. Executive functions correlate with instrumental activities of daily living requiring goal directed activities [37] suggesting executive abilities involving mental flexibility, including implementing, planning and maintaining intentions, may be important for medication adherence [20].

Interestingly, better performance on the subscale of abstract reasoning increased the likelihood of medication non-adherence in a sample of CI older adults. This may be explained by intentional non-adherence due to individuals’ concerns about the medication [35] as this requires the ability to abstract and form fundamental connections between medication and
and satisfying the basic principles of optimal medication use. Therefore, future research should focus on a subpopulation of persons with dementia or CI with co-morbid diseases [49].

**Interventions.** Unfortunately, interventions were investigated by only two studies [29, 32] which had small sample sizes.

A recurring theme is the importance of caregivers for the success of interventions [29]. This, however, reinforces the dependency of older people with dementia and is inconsistent with the philosophy of promoting self-determination and independence critical to a person's quality of life [47]. Individual strategies (e.g., medication regimens or setting up schedules) used in two studies [21, 26], led to recruitment of willing participants with caregivers, hence may not represent the general older population.

Several interventions (such as medication and disease education, medication reviews and packaging/dispensing of medications) for the general older adult population have been documented. Despite moderate success, few studies have attempted to translate these findings to older adults with dementia or CI. This study updates and extends the knowledge of a previously published systematic review [9]. This study included a more comprehensive search to retrieve a broader scope of articles and focuses on the impact of specific cognitive domains on medication adherence.

Research into the effect of a memory-promoting device designed for participants with HIV-associated memory impairment demonstrated improvements in adherence to highly active-antiretroviral therapy (HAART) for these participants but not for memory-intact participants [48]. These results suggest different approaches are necessary for each population.

**Medical consequences.** Medication non-adherence, particularly overdose, may result in toxicity due to altered pharmacodynamics in the older population [49]. Well-known consequences: poor disease control, increased hospitalizations, disability and early death [20] were rarely examined in the appraised studies. Research in this field tends to exclude persons with dementia/CI, limiting the ability to extrapolate results to the growing cognitively impaired population [8, 9].

**Strengths and limitations**

This is an extensive review with a comprehensive search strategy and was not limited to quantitative research. Studies were scored using recognized reporting standards, determining that only one [26] of the 15 reviewed met less than half of the specified criteria. Limitations were the inconsistencies between data sources and definitions, resulting in a loss of fidelity in the value and comprehensiveness of data gathered by each method. Finally, non-pharmacological treatments and regimens were excluded. Articles that were written or translated into English were only able to be included in this review.

**Implications**

Clinical practice must take into account the accumulating research for the prevention of medication non-adherence and the management strategies available for this population. Medication reminder devices are suggested to combat this issue, however, the degree of efficacy of these devices and the appropriate support for using such a device amongst this population are yet to be determined [29].

Given the paucity of data available, future research could explore a realist review approach to combine theoretical understanding and empirical evidence. A realist review focuses on explaining contextual relationships between how interventions are applied and produce outcomes [30]. This may enable a deeper understanding of potential effectiveness of interventions while waiting for empirical clinical study evidence.
Visualization: JJ DS JL CW BK MW.

Writing - original draft: JJ DS JL CW BK MW.

Writing - review & editing: JJ DS JL CW BK MW.

References


