

# The Older Brain on Drugs: Substances That May Cause Cognitive Impairment

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*Alcohol, recreational drugs, over-the-counter, and prescription medications may cause a range of cognitive impairments from confusion to delirium, and may even mimic dementia. Moderate to high alcohol consumption is one of the often overlooked risk factors for development of dementia and cognitive impairment among older adults. Substances such as opioids, benzodiazepines, and anticholinergics pose a particular risk of cognitive impairment and the risk increases when these are combined with multiple medications, as polypharmacy is common in patients over 65. A substance-induced dementia may have a better prognosis compared to other types of dementia, as once the instigating factor is gone, the cognition often improves.*

**Key words:** Alcohol related dementia, geriatric substance abuse and dependence, polypharmacy, anticholinergic adverse effects, cognitive impairment

## Introduction

When assessing cognition in older adults, it is important to consider that a variety of substances may cause both permanent and reversible cognitive impairment. Alcohol abuse may cause dementia or dementia-like syndromes. Recreational drugs, as well as over-the-counter (OTC) and prescription medications, may cause a range of cognitive impairments from confusion to delirium, and may even mimic dementia. Polypharmacy (defined as use of more than five drugs), which is common among older adults, increases the risk of adverse interactions that may interfere with cognition.<sup>1-3</sup> A careful assessment of drug, alcohol, prescription,

and nonprescription substance use can therefore allow for modifiable risk factors for cognitive impairment to be identified and addressed.

## Alcohol Use and Cognitive Impairment Among Older Adults

Alcohol is the most commonly used recreational drug in older adults. Among 40,556 U.S. adults age 60 years and older, 52.8% of men and 37.2% of women were current drinkers.<sup>4</sup> Drinking guidelines suggest that a safe amount of alcohol intake for individuals over age 65 would be no more than seven drinks per week and no more than four at one sitting for

both men and women (see Table 1).<sup>5</sup>

Cognitive function in adults has been shown to have a J-shaped relationship with level of alcohol intake (see Figure 1). Several studies have shown that light to moderate drinkers have generally superior cognitive function than abstainers and heavy drinkers.<sup>6-9</sup> Particularly, the cardiovascular benefits of flavonoids in red wine have been hypothesized to preserve cognitive function, although protective socioeconomic factors may also be of importance in the wine-drinking population groups studied.<sup>10,11</sup> In contrast, moderate to heavy drinking has been shown to increase risk of cognitive impairment, particularly in older adults.<sup>12</sup>

Alcohol use poses an additional risk to older adults with illness in terms of adverse interactions between alcohol and both prescribed and OTC medications, especially psychoactive medications such as benzodiazepines, anticonvulsants, and antidepressants.<sup>13</sup> In a survey of 83,321 older outpatients, 19% of those taking prescription medications known to adversely interact with alcohol reported concomitant alcohol use.<sup>14</sup>

The acute cognitive effects of alcohol use are well known, but less well studied are the long-term effects of chronic alcohol use on brain function, particularly among older individuals.<sup>13</sup> Alcohol intoxication can cause cognitive effects such as disinhibition, ataxia, and short-term memory impairment.<sup>15</sup> Historically, the Wernicke-Korsakoff syndrome was considered to entirely explain the dangers of chronic alcohol overuse, but current data indicate that alcohol-induced dementia may be linked to other causes as well.<sup>16</sup>

## Wernicke-Korsakoff Syndrome

Clinically, the term *Wernicke-Korsakoff syndrome* is best conceptualized as two distinct syndromes, one associated with the confusional state and often reversible findings of Wernicke encephalopathy, the other the persistent and irreversible learning and memory deficits of Korsakoff dementia. The term *Wernicke encephalopathy* is used to describe the clinical triad of

**Table 1:** Alcohol Use Categories

	Drinks per week*	Grams of alcohol per week	Ounces of alcohol per week
Abstinence	0	0	0
Light drinking	7	0–70	0–10.5
Moderate drinking	7–14	70–140	10.5–21
Heavy drinking	>14	>140	>21

\*One drink =43 mls (1.5 oz) liquor, 142mls (5 oz) wine, 341mls (12 oz) beer. Abstinence = no drinking in the past 1 year.

Source: Blow FC, et al., 2002.<sup>5</sup>

confusion, ataxia, and nystagmus.<sup>17,18</sup> Thiamine deficiency resulting from moderate to heavy alcohol use through subsequent malnutrition and malabsorption damages regions of the hypothalamus, diencephalon, and brain stem.<sup>16</sup> This damage is reversible with thiamine replacement therapy early in the course

of illness but becomes irreversible over time.<sup>19</sup> There is a range of susceptibility to thiamine deficiency and subsequent risk of brain damage among heavy alcohol users that may be partly related to abnormalities in the transketolase protein found in susceptible individuals.<sup>20</sup>

### Alcohol-Related Dementia

Moderate to high alcohol consumption is one of the risk factors for development of dementia prior to age 65.<sup>12</sup> Saunders, *et al.*,<sup>21</sup> found a 4.6 times greater risk of dementia for community-dwelling men over 65 who had a history of heavy drinking. Oslin, *et al.*,<sup>22</sup> developed criteria for probable alcohol-related dementia (ARD) (Table 2). Typical impairments seen in ARD include deficits in abstracting abilities and short-term memory, and in executive control. These cognitive patterns contrast to those seen in Alzheimer’s dementia (AD), where the memory impairment is profound and involves both recognition and recall, and individuals frequently present with word-finding deficits. Among abstinent individuals with ARD neither cognitive nor physical functioning deteriorate, unlike among those with a progressive dementia such as AD. Not all older drinkers with dementia meet criteria for

**Table 2:** Classification of Probable Alcohol-Related Dementia

- A. The criteria for the clinical diagnosis of Probable Alcohol-Related Dementia include the following:
  1. A clinical diagnosis of dementia at least 60 days after the last exposure to alcohol.
  2. Significant alcohol use as defined by a minimum average of 35 standard drinks per week for men (28 for women) for greater than a period of 5 years. The period of significant alcohol use must occur within 3 years of the initial onset of dementia.
- B. The diagnosis of Alcohol-Related Dementia is supported by the presence of any of the following:
  1. Alcohol-related hepatic, pancreatic, gastrointestinal, cardiovascular, or renal disease, i.e., other end-organ damage.
  2. Ataxia or peripheral sensory polyneuropathy (not attributable to other specific causes).
  3. Beyond 60 days of abstinence, the cognitive impairment stabilizes or improves.
  4. After 60 days of abstinence, any neuroimaging evidence of ventricular or sulcal dilatation improves.
  5. Neuroimaging evidence of cerebellar atrophy, especially of the vermis.
- C. The following clinical features cast doubt on the diagnosis of Alcohol-Related Dementia.
  1. The presence of language impairment, especially dysnomia or anomia.
  2. The presence of focal neurologic signs or symptoms (except ataxia or peripheral sensory polyneuropathy).
  3. Neuroimaging evidence for cortical or subcortical infarction, subdural hematoma, or other focal brain pathology.
  4. Elevated Hachinski Ischemia Scale score.
- D. Clinical features that are neither supportive nor cast doubt on the diagnosis of Alcohol-Related Dementia include:
  1. Neuroimaging evidence of cortical atrophy.
  2. The presence of periventricular or deep white matter lesions on neuroimaging in the absence of focal infarct(s).
  3. The presence of the Apolipoprotein e4 allele.

Source: Oslin DW, et al., 2003.<sup>23</sup>

**Table 3:** Common Drugs Potentially Worsening Cognition

Type of drug	Example
Antihistamine	Hydroxyzine, diphenhydramine, OTC cold/allergy remedies
Antispasmodic	Alverine, hyoscyamine
Antidepressants	Fluoxetine, paroxetine, amitriptyline
Benzodiazepines	Lorazepam, diazepam, alprazolam
Opioids	Codeine, morphine, meperidine
Antiarrhythmic	Digoxin
Diuretic	Furosemide, hydrochlorothiazide
Antiparkinsonian	Carbidopa-Levodopa (Sinemet®), bztropine
Antibiotics	Ciprofloxacin, metronidazole, cephalexin
Bladder stabilizer	Oxybutynin, tolterodine
H2 receptor Antagonists	Cimetidine, ranitidine
Anti-inflammatories	Ibuprofen, naproxen, prednisone
Antiemetics	Diphenhydrinate, meclizine
Anticonvulsants	Dilantin, tegretol, valproic acid
Alpha 1 Blockers	Tamsulosin, terazosin
Antihypertensives	Beta-blockers, alpha-antagonists, calcium channel blockers
Brochodilator	Theophylline

Adapted from: Young J, et al., 2007;<sup>41</sup> AHCPR Clinical Practice Guidelines, 1996.<sup>42</sup>

ARD, but alcohol may still contribute to a mixed dementia.<sup>23</sup>

Direct neurotoxicity is a proposed mechanism by which heavy alcohol consumption causes shrinkage detectable by imaging studies in total cortical and sub-cortical volume.<sup>16</sup> Antilla, *et al.*,<sup>24</sup> found that APOE $\epsilon$ -4 allele (a gene that predisposes to AD) carriers who drink any alcohol are three times more likely to develop dementia than APOE $\epsilon$ -4 carriers who are nondrinkers. APOE $\epsilon$ -4 carriers do not show benefit from light to moderate drinking as do noncarriers.<sup>25</sup>

### Reversability of Alcohol-Induced Dementia

There is demonstrated gradual improvement of cognitive ability with prolonged abstinence.<sup>22</sup> However, in an apparently clinically healthy population of abstinent

alcohol-dependent subjects, deficient verbal and nonverbal abstraction, along with altered visuo-motor coordination, learning, and memory have been reported to persist despite prolonged periods of abstinence.<sup>26</sup> Such deficits in executive functioning, learning, and concentration may lead to poor treatment outcomes even in alcohol-dependent individuals who appear to be healthy and wish to limit their drinking.

### Marijuana

While cannabis use has been shown to be associated with acute neuropsychological effects including deficits in attention, short term memory, and executive functioning as seen in intoxication, impairments in the former two areas have more recently been shown to continue after years of nonuse.<sup>27,28</sup>

### Opiates

Opiates are commonly prescribed medications that have high abuse potential with tolerance developing. Although no geriatric population data is currently available, in a 2002 U.S. survey, of 6.2 million persons over the age of 12, 4.4 million had used narcotic pain relievers nonmedically.<sup>29</sup> Both acute and chronic opioid use is associated with neuropsychological deficits in executive functions, attention, concentration, recall, visuospatial skills, and psychomotor speed.<sup>30</sup>

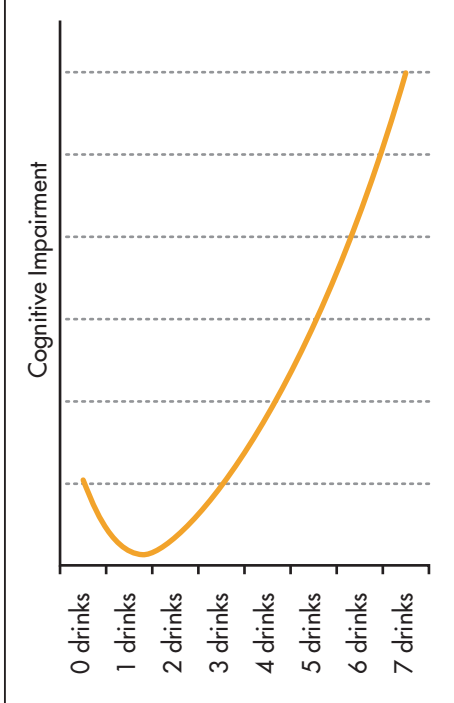
### Benzodiazepines

Benzodiazepines are commonly used as anxiolytics and for insomnia (clonazepam [Klonopin®], lorazepam [Ativan®], triazolam [Halcion®]). Benzodiazepine use is associated with a host of cognitive and psychomotor side effects including episodic memory problems, poor concentration, disinhibition, drowsiness, dysarthria, motor incoordination, and falls.<sup>31-34</sup> Benzodiazepines slow reaction time, lead to visuospatial deficits, impair driving skills, and increase the risk of motor vehicle crashes, especially among older adults.<sup>35,36</sup> Memory impairment may be reversed when benzodiazepines are stopped.<sup>37</sup> Despite benzodiazepines being on the list of Beers criteria of inappropriate medications for older adults<sup>1</sup> and a trend towards decreased prescribing,<sup>38</sup> tranquilizers as a class comprised 5.3% of all prescriptions given to Canadian women over 60 in 2006.<sup>39</sup>

### Anticholinergics and Other Drugs to Avoid

A number of medications should generally be avoided by older adults as well as by individuals who have dementia, as they are thought to potentially worsen cognitive impairment (Table 3).<sup>1,40</sup> These effects can be especially severe. Chronic use of anticholinergic medications may cause a cognitively intact individual to seem demented. In a geriatric community study (n=201), those who had serum anticholinergic activity greater than 2.8 pmol/ml were 13 times more likely to

Figure 1:  
**Cognitive Impairment and Chronic Daily Alcohol Use Patterns**



have a MMSE <24, which might be easily mistaken for a dementing process.<sup>43</sup> Anticholinergic effects are found in a wide range of both prescription and over-the-counter medications (see Figure 2). Some of the anticholinergic OTC medications (such as diphenhydramine [Benedryl®] and dimenhydrinate [Gravol®]) are com-

monly taken by older adults as sleep aids owing to their sedating effects.<sup>46</sup>

### Polypharmacy

It is important to draw attention to polypharmacy, which increases the risk for the development of substance-induced impairment and for other adverse drug reactions. Multiple drug usage is common in all developed countries. In the U.S., polypharmacy is found in 40% of those older than 65 years.<sup>47</sup> Residents of long-term care facilities are a small but important group of patients who ingest many daily medications, taking an average of six to eight drugs daily.<sup>48,49</sup> Use of multiple medications with anticholinergic effects can increase patients' total anticholinergic burden as evidenced by clinical signs such as dry mouth, sedation, confusion and even hallucinations and delirium.<sup>50</sup> Use of medications that interfere with drug metabolism at the same cytochrome also elevates risk of cognitive adverse effects (e.g. CYP3A inhibitor, fluoxetine with alprazolam can increase risk of oversedation).<sup>51</sup> With a larger number of medications, it is understandable that there will be more drug reactions and interactions, and concomitant potential mental confusion or cognitive symptoms.

### Conclusion

There are a range of substances that can contribute to the development of cogni-

tive impairment, some of which may mimic a more serious cognitive disorder and others that might progress to a full-blown dementia, while the majority of cases may likely fall somewhere in between. Together this behooves the clinician to undertake a thorough assessment, keep an open mind, and remember to ask the questions. Prognostically, a substance-induced dementia may also have a better outcome compared to other types of dementia, as once the instigating factor is gone, the cognition often improves.

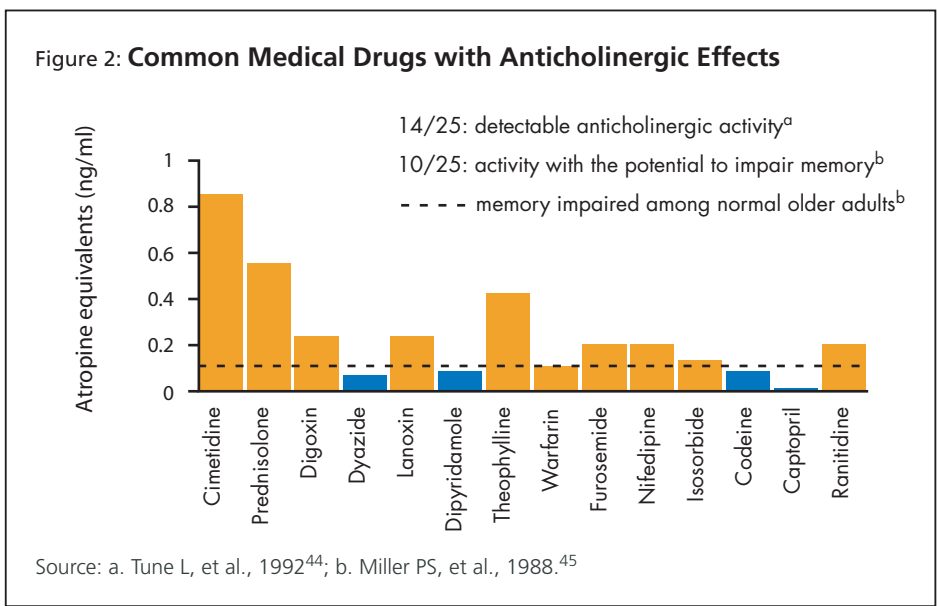


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Figure 2: **Common Medical Drugs with Anticholinergic Effects**



Source: a. Tune L, et al., 1992<sup>44</sup>; b. Miller PS, et al., 1988.<sup>45</sup>



**Key Points**

Moderate to high alcohol consumption is one of the risk factors for development of dementia prior to age 65.

Acute and chronic opioid use is associated with neuropsychological deficits in executive functions, attention, concentration, recall, visuospatial skills, and psychomotor speed.

Despite benzodiazepines being on the list of Beers criteria of inappropriate medications for older adults and a trend towards decreased prescribing, tranquilizer use among older adults persists at a significant rate.

Anticholinergic effects are associated with use of a wide range of both prescription and over-the-counter medications.

Polypharmacy (defined as use of five or more drugs) is found in as many as 40% of those older than 65 years.

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