mhc MENTAL HEALTH CLINICIAN

LITERATURE REVIEW Open Access

# Drug-induced cognitive impairment: Effect of cardiovascular agents

**Marketa Marvanova, PharmD, PhD, CGP, BCPP[1]**

**How to cite:** Marvanova M. Drug-induced cognitive impairment: Effect of cardiovascular agents. Ment Health Clin [Internet]. 2016;6(4):201-6. DOI: 10.9740/mhc.2016.07.201.

## Abstract

**Introduction:** Cardiovascular agents can be associated with a negative effect on cognition, especially in older adults, critically ill people, and those with baseline cognitive impairment. Negative effect on cognition is commonly reported as uncomplicated acute confusion and delirium and, less commonly, chronic cognitive changes due to drug-induced depression and/or dementia.

**Methods:** A literature review of case reports, case series, prospective cohort studies, clinical trials, and literature reviews were included in this study. Articles were located using online databases PubMed and Medline using the following keywords: antiarrhythmic agents, anticholinergic burden, antihypertensive agents, beta-blockers, cardiovascular agents, cognitive impairment, delirium, cognition, dementia, depression, digoxin, diuretics, and drug-induced cognitive impairment.

**Results:** In general, use of all antihypertensives, especially in the case of polypharmacy or inappropriate dosing, can lead to hypotension and/or bradycardia, and thus lead to mental/cognitive status change due to decreased cerebral perfusion. Use of diuretics can be associated with fluid/electrolyte and/or acid-base imbalance, resulting in the onset of confusion and delirium. In addition, cardiovascular agents with central bioavailability, such digoxin and select antiarrhythmics, and antihypertensives may carry a risk for cognitive impairment due to various mechanisms proposed, such as antagonism of central muscarinic acetylcholine receptors, neurotransmission imbalance in the brain, and disruption of physiologic function of sodium/potassium ATPase in the neuronal cells.

**Discussion:** When dealing with an individual who presents with acute, subacute, and chronic changes in cognitive function, one should perform a thorough medication history as the first step in order to aid in the identification of drug-induced cognitive impairment.

**Keywords:** cognitive impairment, dementia, digoxin, delirium, antihypertensive agents, antiarrhythmic agents, diuretics, anticholinergic burden

[1] (Corresponding author) Chair and Associate Professor, Department of Pharmacy Practice, School of Pharmacy, College of Health Professions, North Dakota State University, Fargo, North Dakota; Adjunct Associate Professor of Neurology, Feinberg School of Pharmacy, Northwestern University, Chicago, Illinois, marketa.marvanova@ndsu.edu

## Introduction

Drug-induced cognitive impairment is one of the most common reversible and preventable complications associated with acute and chronic changes in cognition. Treatment with most medications can be associated with some level of cognitive impairment or complications in vulnerable patients; however, certain medication classes are more commonly implicated.[1-5]

Specific populations are more prone to drug-induced cognitive impairment.[1,6-8] Advanced age, cognitive impairment, and dementia are strong risk factors for the development of confusion, delirium, and dementia.[1,2,9] The etiology of drug-altered cognitive function is usually multifactorial. Age- and/or pathophysiology-related changes in pharmacokinetics, pharmacodynamics, brain homeostasis, blood-brain barrier permeability, and neurochemistry are known factors.[1,2,10,11] Additionally, an increased number of comorbidities, as well as frailty, coexisting cognitive impairment, high pill burden, and

supratherapeutic drug serum concentrations, such as digoxin, have also been identified as important factors predisposing an individual to increased risk for drug-induced cognitive impairment.[1,2,12,13] Because medication-induced cognitive impairment is often reversible, it is important to conduct comprehensive medication reconciliation in order to provide for early identification and withdrawal of the offending agent(s). In addition, preventative strategies directed at avoiding high-risk medications when possible, especially in the most susceptible, and/or appropriately adjusting doses based on age- or pathophysiology-related changes and close follow-up and monitoring, may prevent complications.

The use of cardiovascular agents, especially those with central nervous system (CNS) bioavailability, such as antiarrhythmics (eg, disopyramide, quinidine), cardiac glycosides (eg, digoxin), and sympathetic antihypertensives (eg, clonidine, methyldopa propranolol, reserpine), has been associated with reports of cognitive impairment. Impairment ranges from simple acute confusion and delirium to more chronic changes in cognition.[1-6] Cardiovascular agents can cause cognitive impairments via several potential mechanisms that are discussed in the text below. The data are limited to case reports and case series as well as a few prospective cohort studies and fewer randomized controlled trials.

## Reduction in Cerebral Blood Flow Due to Decreased Cardiac Output

Low-cerebral perfusion states associated with hypotension, bradycardia, and advanced or complete heart block due to inhibition of atrioventricular node can lead to reduced cognitive performance, particularly in domains of orientation, attention, and memory, due to cardiac low-output states associated with reduced cerebral blood flow.[14-16] Although an important consideration, one must keep in mind that arterial hypertension increases the risk for cerebrovascular diseases and is one of the major risk factors for the development of vascular dementia.[17,18] Hypertension also seems to be associated with an increased prevalence of idiopathic Alzheimer disease.[18-20]

Use of all antihypertensives, including diuretics, can be associated with specific drug-induced cardiovascular events, such as bradycardia, hypotension, and orthostatic hypotension. This is especially true when specific comorbidities are present or when polypharmacy or inappropriate dosing/prescribing is present. A cross-sectional analysis of the Irish Longitudinal Study on Ageing of 5936 individuals (mean age, 63 ± 9 years; female, 54.0%) identified that significant negative impacts on global cognitive function ($P = .01$) and memory ($P = .002$) in elderly women were associated with orthostatic hypotension, whereas other cognitive domains (executive function, processing speed, and attention) were unaffected.[21] In addition, aggressive lowering of blood pressure, especially in elderly individuals or those with coexisting cognitive impairment, may have a negative effect on cognition.[22,23] Recent data from Mossello et al[22] demonstrated that strict control of daytime systolic blood pressure in older community-dwelling adults with mild cognitive impairment or dementia was not associated with better health-related outcomes, and in fact could result in a greater progression of cognitive decline. These findings are consistent with those from the Leiden 85-plus Study,[23] which demonstrated an association between lower systolic blood pressure and poorer cognitive outcomes in older patients with mild cognitive impairment or dementia.[23]

Beta blockers, nondihydropyridine calcium channel blockers, alpha$_2$-receptor agonists, class IA and class III antiarrhythmics, and digoxin can be associated with a risk of bradycardia and advanced or complete heart block.[24] This risk increases especially when there is a coexisting cardiac abnormality, such as left ventricular dysfunction, or during coadministration of various cardiovascular or noncardiovascular medications with negative chronotropic effect, such as cholinesterase inhibitors used for treatment of myasthenia gravis and Alzheimer disease, leading to additive inhibition of atrioventricular node conduction.[24]

## Fluid/Electrolyte and/or Acid-Base Imbalance

Diuretics, when used as polytherapy or in the presence of severe nausea/vomiting or renal impairment, can be associated with dehydration, and electrolyte and/or acid-base imbalances.[25,26] This can result in confusion and increased risk for delirium.[8,26,27] Additionally, hypokalemia and hypomagnesemia due to the use of thiazide and loop diuretics[24] may increase digoxin toxicity, such as confusion and delirium, despite serum digoxin concentration within the recommended therapeutic concentration (<2.0 ng/mL).[28]

## Antagonism of Central Muscarinic Acetylcholine Receptors

Impaired cholinergic neurotransmission has been implicated in the pathogenesis of delirium, mild cognitive impairment, Alzheimer disease, and dementia with Lewy bodies.[29] Individuals with already reduced central cholinergic activity, such as elderly people or those with baseline dementia, are at increased risk for cognitive complications due to the use of anticholinergic medications.[2,4,6,30,31] Antagonism of the central muscarinic receptors can result

in problems with attention and delirium[2] as well as chronic cognitive deficits.[6,32] A longitudinal cohort study of individuals (n = 372) 60 years and older without senile dementia at recruitment who were followed for 2 years reported that consistent use of anticholinergic medications was associated with poorer cognitive performance in a variety of cognitive performance domains: attention ($P < .001$), simple reaction speed ($P < .001$), primary and secondary visuospatial memory ($P < .01$), narrative recall ($P < .01$), and language tasks ($P < .001$). Implicit memory and logical reasoning were unaffected. Pursuant to these findings, it was suggested that consistent use of anticholinergic drugs was a strong predictor of mild cognitive impairment (odds ratio, 5.12; $P = 0.001$) compared with nonusers.[6] Medications in this study with various anticholinergic effects included drugs used in psychiatry (eg, amitriptyline, clomipramine, amoxapine, hydroxyzine), cardiology (eg, digoxin, furosemide), neurology (eg, trihexyphenidyl), pneumology (eg, theophylline), and urology (eg, oxybutynin), and also those medications with analgesic and anti-inflammatory effects (eg, codeine, chlorpheniramine, belladonna alkaloids).

Class IA antiarrhythmics, such as disopyramide and quinidine, exhibit antagonistic properties on peripheral and central muscarinic receptors.[24,33] The anticholinergic effect of disopyramide appears to be more pronounced than that of quinidine. It was estimated that the usual recommended therapeutic dosage of 600 mg of disopyramide daily in divided doses (150 mg orally every 6 hours) in adults compares with a 0.4- to 0.6-mg dose of atropine. Commonly reported adverse effects, such as blurred vision, constipation, xerostomia, xerophthalmia, and urinary retention or hesitancy, were those associated with the anticholinergic properties of the drug.[33] It is also postulated that disopyramide-associated risk for delirium is due to its strong central anticholinergic effect.[8] Use of anticholinergic medications, especially those with strong central anticholinergic activity, can induce or contribute to development of delirium and chronic cognitive deficit, especially in critically ill individuals, elderly individuals, or when used in high cumulative doses.[4,31,34] Delirium secondary to anticholinergic toxicity may present with or without peripheral anticholinergic adverse effects.[34]

It was suggested that special attention should be paid to the total anticholinergic burden of all medications taken by the patient, characterized as a cumulative exposure to multiple medications with anticholinergic activity, rather than just the single-agent effect. Higher anticholinergic burden was associated with greater risk for cognitive impairment.[30,35,36] There are a variety of scales that have been developed to assess drug-induced anticholinergic burden, such as the Anticholinergic Cognitive Burden (ACB) scale,[4] the Anticholinergic Drug Scale,[37] and the Anticholinergic Risk Scale.[38] It was suggested that the ACB scale (0, no anticholinergic activity; 1, possible anticholinergic activity; 2, moderate anticholinergic activity; and 3, strong anticholinergic activity) might more accurately measure the negative effect of anticholinergic medications on cognition compared with the two other listed scales.[4,39] Pasina et al[39] demonstrated the ACB scale to be a useful tool permitting the identification of drugs potentially associated with cognitive impairment related to cumulative anticholinergic dose. Cumulative risk of cognitive impairment was demonstrated as a decline in Mini-Mental State Examination score of 0.33 points during a 2 year-period associated with each point increase in the ACB total score.[32] Interestingly, select diuretics (eg, furosemide, chlorthalidone, and hydrochlorothiazide), select antiarrhythmics (eg, disopyramide and quinidine), and select antihypertensives (eg, atenolol, captopril, hydralazine, metoprolol, nifedipine, and timolol maleate) are rated as an ACB score of 1.[4] It was suggested that taking a single medication with ACB score $>2$ or having a total ACB score of all anticholinergic medications $\geq 3$ can have a clinical impact on an older patient's cognition. Thus, medications even with an ACB score of 1 can contribute to cognitive impairment. When the total ACB score is $\geq 3$, the clinician should consider modifying the regimen in order to decrease the score to $<3$.[4]

## Neurotransmission Imbalance in the CNS

Centrally available antihypertensives with sympathetic nervous system blocking properties, such as beta blockers, have been linked in a variety of reports to cognitive changes. Reports have described deficits in cognitive function,[40,41] including memory.[42,43] Solomon and colleagues[42] studied the effect of two centrally available antihypertensives, propranolol and methyldopa, on memory function in a small group of outpatients with hypertension (n = 41; mean age, 54.5 ± 12.3 years). Participants were assigned to 4 groups: (1) hypertensive group (HTG) receiving methyldopa plus diuretics (n = 10); (2) HTG receiving propranolol plus diuretic (n = 11); (3) HTG receiving diuretic alone (n = 12); and (4) normotensive group receiving propranolol only (n = 8). Compared with the controlled HTG receiving diuretic alone, both the methyldopa- and propranolol-treated groups (HTG as well as normotensive group) had significant impairment in verbal memory functioning ($P = .01$) as assessed before by the Wechsler-Russell Memory Scale. Visual memory was unaffected. In addition, no difference in any memory testing was observed among the methyldopa- and propranolol-treated HTG.[42] Because there is some evidence of association of beta blockers (eg, lipophilic propranolol) with cognitive dysfunction, it is important to note that overall research yielded very contradictory conclusions.[44-46] Beta blockers have been historically associated with risk for drug-induced depression. It was

hypothesized that chronic blockage of beta receptors in the brain can lead to decreased beta receptor density and bindings.[47] Based on findings from randomized trials, it seems that the class of beta blockers might not be associated with drug-induced depression as previously believed, because results from clinical trials are very heterogeneous.[48,49]

Reserpine, methyldopa, and clonidine can cause disruption in the release of various catecholamines and/or serotonin (5-HT) in cortical and subcortical regions. This may lead to neuropsychiatric complications, such as confusion, delirium, depression, and cognitive impairment, such as lapses in memory and poor concentration.[50-55] Risk is increased when medications are used in high or toxic doses; thus, careful adjustment of medication dosing for each patient should be done. Reserpine depletes stores of 5-HT, dopamine, and norepinephrine in the CNS. Both cardiovascular and CNS effects may persist for a period of time following withdrawal of reserpine. The synthesis of new vesicles can restore sympathetic function; however, this process takes several weeks.[56] Methyldopa is converted to alpha-methyl-noradrenaline, a false neurotransmitter, and can deplete norepinephrine stores.[24] Clonidine as agonist at presynaptic alpha$_2$-receptors in the brain inhibits the release of norepinephrine into neuronal synapse, leading to CNS depression due to enhanced inhibitory neurotransmission.[24] It is approximately 50% metabolized hepatically to inactive metabolites, whereas about 50% of the parental drug is excreted in urine unchanged.[24] Supratherapeutic/toxic serum concentrations due to clonidine overdose, compounding error, intrathecal pump malfunction, and significant decrease in metabolism and elimination, are associated with increased risk for CNS depression, miosis with pronounced hypotension, and bradycardia.[34]

## Disruption of Physiologic Function of $Na^+/K^+$ ATPase in the Neuronal Cells

Digoxin is a narrow therapeutic index drug that inhibits sodium/potassium ($Na^+/K^+$) ATPase enzyme.[28] Neurotoxic effect of digoxin has been associated with a variety of neuropsychiatric complications, such as visual aberration, anxiety, depression, confusion, hallucinations, and delirium.[2,13,28,57-59] Risk increases with accumulation and consequently leads to digitalis cardiotoxicity and neurotoxicity.[8] Digoxin is primarily eliminated through glomerular filtration in unchanged form; thus, it has a tendency to accumulate in older adults or individuals with impaired renal function.[28] Digoxin is also a substrate for the P-glycoprotein transport system located in the gastrointestinal system and kidneys. Inhibition of this cellular drug efflux pump leads to increased oral absorption of digoxin (increased bioavailability) and/or decreased renal elimination.[24,60] Digoxin concentrations are significantly increased by interaction with agents that are potent inhibitors of the P-glycoprotein transport system, such as verapamil, amiodarone, and quinidine.[28,61] When oral digoxin is administered with amiodarone, the digoxin serum concentration is increased by 70%.[24,28] Coadministration of quinidine with oral or intravenous digoxin leads to a 100% or a 54% to 83% increase in the digoxin serum concentrations, respectively.[28] It is postulated that increased digoxin serum concentrations above therapeutic range can be associated with profound disruption of neuronal activity due to disruption of physiologic function of $Na^+/K^+$ ATPase. This causes an increase in intracellular calcium and displaces magnesium from its binding sites. This disruption ultimately leads to decreased mitochondrial ATP production and further inhibition of $Na^+/K^+$ ATPase.[61,62] In order to reduce the risk for delirium and other neuropsychiatric/neurocognitive complications, it is recommended to adjust the dose based on renal function, and to empirically reduce oral digoxin dose by approximately 50% when amiodarone, verapamil, or quinidine therapy is added.[24,28]

## Summary

Cardiovascular agents carry a risk for cognitive impairment via several potential mechanisms, leading to acute, subacute, and chronic changes in cognitive function. Older adults, individuals with preexisting cognitive impairment, those with frailty, and critically ill individuals are at increased risk. Clinicians should be aware of these risks and complications. In clinical situations, when caring for an individual with changes in cognitive function, one should always perform a thorough medication history as the first step in order to aid in the identification of drug-induced cognitive impairment as a result or contribution of the use of cardiovascular medications.

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