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REVIEW

Anticholinergic drug use and risk for dementia: target for dementia prevention

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Abstract An increasing number of longitudinal cohort studies have identified a risk increase for dementia by the chronic use of drugs with anticholinergic properties. The respective data from the German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe) also showing risk increase (hazard ratio = 2.081) are reported here. The mechanisms by which the risk increase is transported are still unknown. Irritation of compensated alterations of cholinergic transmission at the pre-dementia stage of Alzheimer's disease (AD) or acceleration of neuroinflammation by disturbance of the anti-inflammatory effect of cholinergic innervation are discussed. In terms of dementia prevention, centrally acting anticholinergic drugs should be strictly avoided, because of long-term dementia risk increase in addition to acute negative effects on cognition.

Keywords Dementia · Risk · Anticholinergic drugs

Epidemiological studies have identified several factors that modify the risk for dementia and that may serve as target for dementia prevention. These include lifestyle factors such as physical activity and nutrition, as well as medical conditions like diabetes and hypertension. Also, the use of specific drugs has been associated with dementia risk. The most prominent finding is the dementia risk reduction by the chronic intake of non-steroidal anti-inflammatory agents (NSAIDs) that has been observed in a number of independent longitudinal cohorts [1, 2]. These studies have

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initiated molecular research on the role of inflammation in Alzheimer's disease (AD) as well as prospective prevention trials in at-risk groups [3, 4]. The prevention trials using NSAIDS, however, have not yet been successful, which may be related to the insufficient duration of the trials or the wrong age of participants at baseline. Other drug classes with epidemiological evidence for dementia risk modification include statins [5, 6] and antihypertensive agents [7, 8].

Recently, epidemiological studies investigated the effect of the drugs with anticholinergic properties on cognition and dementia risk in elderly. Overall, drugs with anticholinergic properties are considered inappropriate in elderly patients. However, they are widely prescribed in non-specialized and specialized medical settings [9]. The reasons are most likely lack of awareness of anticholinergic effects in general and of knowledge about anticholinergic side effects of specific compounds. With regard to the central nervous system, anticholinergic drug effects may cause delirium as a major complication [10] and cognitive impairment, particularly on task of attention [11]. In fact, it has been demonstrated that the use of drugs with anticholinergic properties may induce a reversible state of mild cognitive impairment (MCI) [12], similar to the widely recognized MCI syndrome that is considered an at-risk condition for dementia.

In addition to acute anticholinergic effects on cognition, epidemiological studies investigated the risk for dementia by anticholinergic drug use. In a large-population-based sample of individuals above 65 years of age, chronic use of anticholinergic drugs has been associated with an increased risk for dementia within an interval of 4 years, while use of anticholinergic drugs at baseline only was not associated with increased risk [13]. In a different study in African Americans over 70 years of age, an increased risk for cognitive impairment and dementia was also observed in continuous users of drugs with known anticholinergic effects [14]. It needs to be stressed that the group of drugs with anticholinergic properties is heterogenous: It includes agents that are used in indications with need for anticholinergic effects and agents with anticholinergic side effects. The two longitudinal studies referenced above used different classification systems to define anticholinergic drugs, i.e., by three different French databases [13] and by the Anticholinergic Cognitive Burden Scale [14, 15].

We analyzed the risk for dementia by anticholinergic drug use, in the German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe). This study is unique as it sampled the participants in the primary care setting, which is of superior relevance for actions of prevention as the vast majority of individuals are first and only seen by their general practitioner. The detailed recruitment and assessment procedures of the AgeCoDe study have been reported [16]. Briefly, at baseline, randomly selected individuals from the GP registries above the age of 75 without dementia were recruited and followed longitudinally. All clinical and neuropsychological assessments as well as recording of medication were performed at the subjects' homes by trained interviewers. The follow-up period of the present analyses covered 54 months with three time points of investigation at 18 months intervals. In the analyses on risk for dementia by anticholinergic drug use prior to the diagnosis of dementia presented here, all individuals with information on medication, apolipoprotein E (ApoE) genotype, and follow-up data on diagnosis of incident dementia were included. Individuals using anticholinergic medication first at the time point of incident dementia were excluded. A total of 2.605 cases formed the sample for the present analyses. Anticholinergic drugs were defined according to a recent report on anticholinergic effect of frequently used drugs in the elderly population [17]. We found that 37% ($n = 963$) of the participants used anticholinergic drugs at least at one time point. The anticholinergic drugs were mainly cardiovascular agents, analgetics/anti-inflammatories, antidiabetics, and antidepressants.

We calculated a Cox regression model to assess the risk for incident dementia by the use of an anticholinergic drug at any time prior to the diagnosis of incident dementia vs. no use of anticholinergic drug ever. We included sex, age, level of education as defined by the CASMIN classification [16], presence of depression, as defined by a score on the Geriatric Depression Scale (GDS) >6, and the apolipoprotein E (ApoE) genotype (carrier status of the 4 allele) as additional predictors. The use of anticholinergic drugs was associated with an increased risk for dementia (hazard ratio: 2.081, $P < 0.001$). All results are listed in Table 1. Figure 1 displays the Kaplan–Meier survival curves.

In a second analysis, we applied the classification of strength of anticholinergic activity as provided by Chew et al. [17] with level 1 indicating lowest activity and level 4 indicating highest activity. In a Cox regression model with the identical variables as in the first analysis, we observed an overall group effect of strength of cholinergic activity ($P < 0.001$). With reference to no use, following are the risk increase by drugs with different anticholinergic activity levels: level 1: HR 1.800, $P < 0.001$; level 2: HR 1.534, $P = 0.105$; level 3: HR 2.584, $P = 0.002$; level 4: HR 3.361, $P < 0.001$. This indicates that with increasing anticholinergic activity, the risk for dementia increases. Figure 2 depicts the respective Kaplan–Meier survival curves.

Anticholinergic drugs acutely impair cognitive function in elderly individuals and even in young volunteers, as shown experimentally with the muscarinergic blocker scopolamine [18]. It is, however, not known how the risk for dementia by the prior use of anticholinergic drugs is

Table 1 Risk for dementia at follow-up

	No use[a]	Use[a]	Hazard ratio (HR)[b]	*P*-value
No use[a]/Use[a]	1,642[a] (63.0%)	963[b] (37.0%)	2.081	<0.001
Age (m, SD)	79.42	79.62	1.117	<0.001
Education				0.045
Low	985 (60.0%)	627 (65.1%)	Reference	
Middle	461 (28.1%)	240 (24.9%)	0.708	0.035
High	196 (11.9%)	96 (10.0%)	0.662	0.099
Sex (female)	1,053 (64.1%)	649 (67.4%)	1.133	0.395
Depression[c]	101 (6.2%)	125 (13.0%)	1.952	<0.001
ApoE4	355 (21.6%)	186 (19.3%)	2.130	<0.001
Incident dementia	101	119		
No dementia at follow-ups	1,541	844		

[a] Use of anticholinergic drugs before the diagnosis of dementia

[b] Risk increase for dementia at any follow-up

[c] Defined by Geriatric Depression Scale (GDS) score of >6

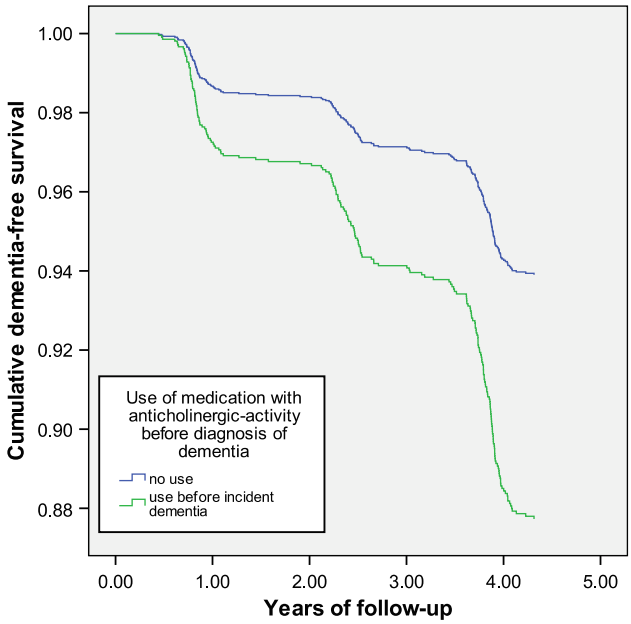

Fig. 1 Dementia-free survival by the use of anticholinergic drugs at any time before dementia diagnosis

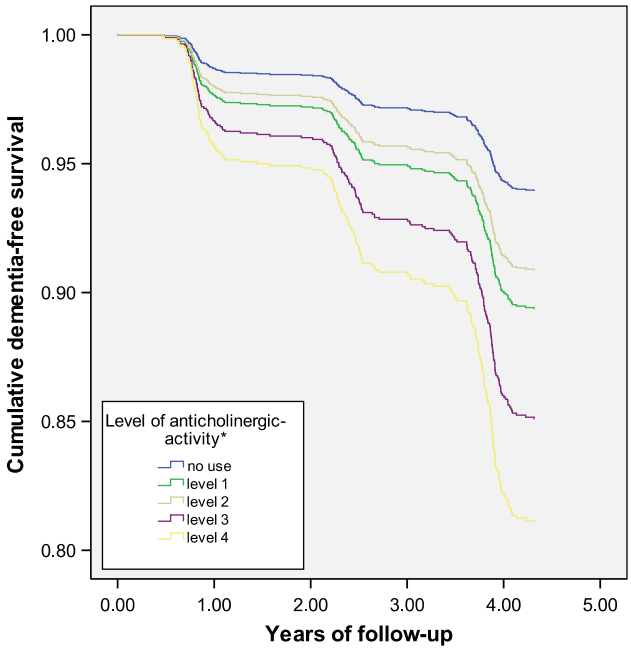

Fig. 2 Dementia-free survival by the level of anticholinergic activity of the drug used before dementia diagnosis. * Anticholinergic activity level [17]

biologically transported. Alzheimer's disease is characterized by a cholinergic deficit caused by the degeneration of the cholinergic Nucleus Meynert at the basal forebrain. At the stage of clinical dementia, this hypocholinergic state is the basis for the current treatment with acetylcholinesterase inhibitors. Increasing evidence from postmortem investigations and neuroimaging suggests that the basal forebrain nucleus is already affected at stages prior to dementia in the course of AD. In subjects with MCI, postmortem investigations revealed the effect of tau pathology on the basal nucleus [19]. In structural magnetic resonance imaging (MRI) studies, volume reduction in the basal forebrain nucleus has been observed in MCI subjects [20, 21]. On the functional level, it has been shown with positron emissions tomography (PET) that the enzyme acetylcholinesterase is downregulated in subjects with MCI, particularly in those who later develop dementia [22]. In addition, there is evidence for an upregulation of the choline acetyltransferase (ChAT) in MCI followed by the progressive reduction in ChAT as the clinical stage of dementia is reached [23, 24]. This upregulation can be interpreted as compensatory to stabilize presynaptic

acetylcholine concentration in the face of degeneration of cholinergic neurons. The observation that the intake of anticholinergic drugs is a risk factor for dementia provokes the hypothesis that a yet compensated cholinergic deficit at the pre-dementia stages of AD is critically affected by these drugs with the consequence of accelerated functional decline of cholinergic transmission.

A second explanation for the dementia risk increase by anticholinergic drugs may be related to inflammatory processes. It has been demonstrated that peripheral immune response can be inhibited by cholinergic vagus neurons [25]. In the brain, cholinergic nicotinic receptors on microglia cell inhibit inflammatory reactions [26]. Anticholinergic drugs may inhibit this immune regulatory process and may thereby accelerate neurodegeneration. This mode of action has recently been proposed as the underlying cause for poor outcome after anticholinergic delirium in elderly individuals [27].

To further elucidate the mode of action of anticholinergic drugs with regard to risk increase for dementia, it is necessary to capture all drugs with anticholinergic properties and to distinguish between those that penetrate the blood–brain barrier and those that do not. In epidemiological studies, the length and time point of use required to actually develop an increased risk for dementia should be more closely defined. Basic science may focus on the deregulation of the cholinergic system by these drugs and on their effects on brain inflammation. Based on the current data, however, it is becoming apparent that anticholinergic drugs not only are of acute harm for elderly patients by impairment of cognition and risk for delirium but may also have negative long-term effects by increasing dementia risk. Thus, the strict avoidance of drugs with central anticholinergic effects is an important component of dementia prevention.

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