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## REVIEW ARTICLE

# Anesthesia and Alzheimer disease – current perceptions<sup>☆</sup>

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### KEYWORDS

Alzheimer disease;  
General anesthesia;  
Postoperative  
cognitive dysfunction

### Abstract

**Background and objectives:** It has been speculated that the use of anesthetic agents may be a risk factor for the development of Alzheimer disease. The objective of this review is to describe and discuss pre-clinical and clinical data related to anesthesia and this disease.

**Content:** Alzheimer disease affects about 5% of the population over 65 years old, with age being the main risk factor and being associated with a high morbidity. Current evidence questions a possible association between anesthesia, surgery, and long-term cognitive effects, including Alzheimer disease. Although data from some animal studies suggest an association between anesthesia and neurotoxicity, this link remains inconclusive in humans. We performed a review of the literature in which we selected scientific articles in the PubMed database, published between 2005 and 2016 (one article from 1998 due to its historical relevance), in English, which address the possible relationship between anesthesia and Alzheimer disease. 49 articles were selected.

**Conclusion:** The possible relationship between anesthetic agents, cognitive dysfunction, and Alzheimer disease remains to be clarified. Prospective cohort studies or randomized clinical trials for a better understanding of this association will be required.

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## PALAVRAS-CHAVE

Doença de Alzheimer;  
Anestesia geral;  
Disfunção cognitiva  
pós-operatória

## Anestesia e doença de Alzheimer – Percepções atuais

### Resumo

*Justificativa e objetivos:* Tem sido especulado que o uso de agentes anestésicos possa ser um fator de risco para o desenvolvimento de doença de Alzheimer. O objetivo desta revisão é descrever e discutir dados pré-clínicos e clínicos relacionados com a anestesia e essa doença.

*Conteúdo:* A doença de Alzheimer afeta cerca de 5% da população com mais de 65 anos, a idade é o principal fator de risco e está associada a uma elevada morbidade. A evidência atual questiona uma possível associação entre anestesia, cirurgia e efeitos cognitivos em longo prazo, o que inclui a doença de Alzheimer. Embora os dados obtidos em alguns dos estudos animais sugiram uma associação entre anestesia e neurotoxicidade, esse elo permanece inconclusivo em humanos. Fizemos uma revisão da literatura em que foram selecionados artigos científicos na base de dados Pubmed, publicados entre 2005 e 2016 (um de 1998 pela relevância histórica), em inglês, que abordam a eventual relação entre anestesia e doença de Alzheimer. Foram eleitos 49 artigos.

*Conclusão:* A possível relação entre agentes anestésicos, disfunção cognitiva e doença de Alzheimer permanece por esclarecer. Serão necessários estudos de coorte prospectivos ou ensaios clínicos randomizados para melhor compreensão dessa associação.

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## Introduction

Alzheimer disease is currently the most common form of dementia, estimated to reach 26.6 million people worldwide,<sup>1</sup> or about 5% of the population over 65 years of age.<sup>2</sup> The finding of a possible cognitive deterioration as a result of an anesthetic/surgical event led to the investigation of this phenomenon, also motivated by the greater concern and demand for information by patients and their families.<sup>3</sup>

Postoperative cognitive dysfunction is a well-known perioperative syndrome as a result of anesthesia and surgery but the exact cause remains unclear.<sup>4</sup> In what way postoperative cognitive dysfunction and Alzheimer disease may be linked remains a question under study. The biochemistry underlying the process of dementia, the study of the relationship between Alzheimer disease and postoperative cognitive dysfunction as a probable spectrum of the same disease, and the relationship of both with anesthetic agents motivate the exploration of this area.

We performed a search in Pubmed with the words "Alzheimer's disease", "Anesthesia", and "Postoperative Cognitive Dysfunction". We included scientific articles published in English between 2005 and 2016 (one from 1998 by historical relevance), which address the possible relationship between anesthesia and Alzheimer's disease. According to the inclusion criteria and their relevance, 49 articles were selected.

This review aims at summarizing the definition and pathophysiology of Alzheimer's disease, as well as discussing the scientific knowledge that relates the exposure to anesthetic agents with this dementia development.

## Alzheimer disease

Alzheimer disease is a progressive dementia that leads to a decline in cognitive abilities. The vast majority of Alzheimer disease cases are late onset or sporadic and it is presumed to be a multifactorial disease resulting from the interaction between genetic and environmental factors.<sup>5</sup> The main risk factor is age, although others such as female, low educational level, family history, and specific genetic mutations (apolipoprotein E genotype)<sup>6,7</sup> may also contribute. A number of modifiable risk factors, such as cardiovascular disease, history of head trauma,<sup>6</sup> diabetes,<sup>8</sup> hypertension, and dyslipidemia have been described.<sup>9</sup> The association between environmental exposure to modifiable risk factors and Alzheimer disease provided a potential analogy for the possible role of general anesthesia in the pathogenesis of this disease. In this line of thinking, reducing these modifiable risk factors would reduce the incidence of dementia.

## Pathophysiology of Alzheimer disease

Alzheimer disease is characterized by severe neurodegeneration, neuroinflammation, and progressive loss of cognitive abilities.<sup>10</sup> The diagnostic criteria for dementia released by the National Institute on Aging-Alzheimer's Association define dementia as the development of cognitive or behavioral symptoms associated with decline in the previous level of performance, involving several cognitive domains that may not be explained by delirium or psychiatric disorders.<sup>11</sup> Recently, the guidelines also included biomarkers as diagnostic criteria, such as decreased levels of amyloid protein

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