Citation

Title: Benzodiazepine use and risk of Alzheimer’s disease: case-control study

Primary Objective

- To determine the association between the use of benzodiazepines and the increase risk of Alzheimer’s disease.

The primary objective is simple and specific. It will provide a good overview of Alzheimer’s disease.

Funding

- Funded by: INSERM (Institut National de la Santé et de la Recherche Médicale) and University of Bordeaux, grants from IRESP (Institut de Recherche en Santé Publique), The French Ministry of Health, Funding Agency for Health Research of Quebec

The case-control study is a collaborative effort among different entities where there is no conflict of interest yet provide with invaluable data and findings that will contribute to the public health. This study also gives further insight to Alzheimer's Disease research.

Journal Impact Factor

- BMJ 2016: 20,785 (9)

N/A

Background

- Alzheimer's disease is a progressive brain disorder that damages and eventually destroys brain cells. It affects the normal function of the brain leading to memory loss, mood swings and changes in the way of thinking. Its development or progression may be slow but gradually gets worse as brain function declines and brain cells eventually deteriorate and die. Females over 65 years old have a higher risk for Alzheimer’s Disease. In the long run, Alzheimer's is fatal and currently there is no cure.

- Several professors and researchers carried out a case-control study among people older than 66 years old and living in the community in the province of Quebec (Canada) to compare Alzheimer's Disease and the use of Benzodiazepines. The goal of is this study is to demonstrate a correlation between patients using Benzodiazepines and an increasing risk of Alzheimer’s Disease.

- Benzodiazepines are primarily used for treating anxiety, but they also are effective in treating insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures. They appear to work by affecting neurotransmitters in the brain. For example, gamma-aminobutyric acid (GABA) is a neurotransmitter that suppresses the activity of nerves. Excessive activity of nerves may be the cause of anxiety and other psychological disorders, and benzodiazepines reduce the activity of nerves in the brain and spinal cord by enhancing the effects of GABA. The sedative side effects can carry into the next day and impair driving and other daily activities. This is a concerning risk in the elderly.

- More recent research is focusing on the possible adverse effects on cognition (thinking and reasoning ability) in patients using benzodiazepines for long periods of time. In some patients, severe allergies like anaphylaxis and angioedema have been reported. Similar to benzodiazepines, some studies have found to demonstrate that anticholinergic drugs, like Benadryl, increase the risk of dementia.

Previous Trials

- “Cumulative Use of Strong Anticholinergics and Incident Dementia” is a prospective cohort study that examine whether cumulative anticholinergic use is associated with a higher risk for incident dementia. The study included 3434 participants 65 years or older with no dementia at study entry. Initial recruitment occurred from 1994 through 1996 and from 2000 through 2003. Beginning in 2004, continuous replacement for deaths occurred. All participants were followed up every 2 years. Data through September 30, 2012, were included in these analyses. The study concluded that a higher cumulative anticholinergic use is associated with an increased risk for dementia. (3)
### METHODS

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<tr>
<th>Study Population/Inclusion Criteria</th>
<th>ARTICLE OVERVIEW</th>
<th>CRITIQUE</th>
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| **Trial Design**                   | - Study design: case-control study  
- Where: the province of Quebec, Canada | **Pros**  
- Randomized Control Trial is a strongest study to assess the association and causality, but ethical issue will be a concern. This study meets ethical issues because it determined the relation between risk of Alzheimer’s disease and exposure to benzodiazepines without using any interventions on patients.  
- This study allows researchers to use time and resources efficiently. There is no loss to follow up.  
- The study in one location will lower the cost. | **Cons**  
- Data on potential risk factors are collected retrospectively, so the collecting results cannot determine causality and may give rise to protopathic bias (antecedent-consequence).  
- Does not determine incidence or prevalence of Alzheimer’s disease.  
- Study was only carried out in one region, thus only represented to one community living in that area. |
| **Study Population/Inclusion Criteria** | **Case group** (n=1796): people aged >66 with diagnosis or treatment for dementia randomly selected from RAMQ database from 2000-2009 (10 years) that met all three of inclusion criteria:  
1. First diagnosed of Alzheimer’s disease recorded during the study period without any record of another type of dementia at the index date or before  
2. Absence of any anti-dementia treatment before index date.  
3. At least 6 years of follow-up before the index date.  
- **Control group** (n=7184): people aged >66 without diagnosis or treatment related to dementia. Each case was matched on sex, age group and duration of follow-up at the index date with 4 controls.  
- 3 criteria were used to describe exposure: ever use (yes/no), cumulative dose (1-90PDD exposure<3months, 90-180PDD exposure 3-6 months, >180PDD exposure >6 months), and drug elimination half-life (short acting <20hr and long acting >20hr).  
- Sample only represented the elderly population in Quebec, Canada with regard to length of disease, not the severity of disease. | **Pros**  
- Sample was randomly selected from elderly population, thereby avoiding selection bias.  
- Inclusion criteria are appropriate and precise, thus avoiding the effects of other previous anti-dementia medications that can be considered as confounders.  
- Sample size is large, thus the chance to find association between risk of Alzheimer’s disease and benzodiazepine will increase. | **Cons:**  
- Data was collected from RAMQ database without interviewing patients, thus not avoid bias due to recording or delay errors.  
- The population of the study is elderly. They may have other diseases such as HTN and Diabetes, which can be considered as potential confounders. |
| **Exclusion Criteria** | - People with non-Alzheimer’s dementia  
- Received anti-dementia treatment before diagnosis  
- People with < 6 years’ follow-up. | **Pros**  
- For patient with non-Alzheimer dementia the study did not specified what anti dementia medication they were taking. Exclusion criteria could help the result to be extrapolated for the future use of this study, since it excludes non-Alzheimer’s dementia. | **Cons:** |
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<th>Interventions</th>
<th>- Case control study, so there are no interventions.</th>
<th>N/A</th>
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<td>Outcome Measures</td>
<td>- Relationship between Benzodiazepine use and Alzheimer with regard to length of benzodiazepine use, benzodiazepine density of exposure, and formulations (short or long acting) of benzodiazepine</td>
<td>- This final outcome in this study can be found in the case-control study that is used to determine the association between two variables, not causality.</td>
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<td>Statistical Analyses</td>
<td>- Multivariable conditional logistic regression analysis dependent variable: diagnosis of Alzheimer independent variable: benzodiazepine use</td>
<td>- This study has &gt;= 2 measurement variables for one nominal variable, so this analysis method is reliable and good enough to detect the association between two variables. Since in this study we have one dependent variable and multiple independent variables we can conclude the logistic regression analysis was a good method of study for this trial.</td>
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**RESULTS**

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<th>ARTICLE OVERVIEW</th>
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<td><strong>Enrollment</strong></td>
<td>The study was conducted in Quebec, Canada. Both groups were followed up in at least 6 years before the index date with case group: n=1,796 control group: n= 7184 people</td>
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<td><strong>Baseline Characteristics</strong></td>
<td>- Case group and control group: 67% female, 70.8% aged 70-84 years old</td>
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<td><strong>Primary Outcome Measures</strong></td>
<td>- Benzodiazepine use: 49.8% (cases) and 40.0% (controls) (p&lt;0.001); (OR=1.52, 95%CI=1.37 to 1.69) - Benzodiazepines density exposure: 1-90PDD (&lt;3 months) and 90-180 PDD (3-6 months): no significant difference between groups (p&gt;0.05) &gt;180 PDD (&gt;6 months): 32.9% (cases) versus 21.8% (controls), (p&lt;0.001); (OR=1.85, 95%CI=1.63 to 2.09) → statistically significant difference between long term benzodiazepine use and Alzheimer long acting Benzodiazepine: 17.2% (cases) versus 12.2% (controls), significant difference (p&lt;0.001); (OR=1.72, 95%CI=1.48 to 1.96)→ stronger association between Benzodiazepine use and Alzheimer short acting Benzodiazepine: 32.6% (cases) versus 27.6%(controls). (p&lt;0.001) (OR=1.43, 95%CI=1.27 to 1.61)</td>
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<td><strong>Secondary Outcome Measures</strong></td>
<td>- Hyper-cholesterolemia: 20.9% (cases) versus 16.5% (controls), significant difference (p&lt;0.001) - Anxiety: 21.2% (cases) versus 15.1% (controls), significant difference (p&lt;0.001) - Myocardial infarction was less common (3.4% v 4.6%) while stroke (7.0% v 5.8%) was more common, but no significant difference between groups (p&gt;0.05) - Depression: 2.9% (cases) versus 2.4% (controls) (p&gt;0.05) - Insomnia: 4.0% (cases) versus 3.2% (controls) (p&gt;0.05)</td>
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<td><strong>Safety Outcome Measures</strong></td>
<td>- case-control study, no interventions, no safety outcome measures in this study.</td>
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ONCLUSION

The authors thoughts and conclusions regarding the study are extrapolated beyond the study by accessing:

1. Covariability (sex, age, duration of follow up),
2. Potential confounders (high blood pressure, myocardial infarction, stroke, use of platelet inhibitors or oral anticoagulants, hypercholesterolemia, anxiety, depression and insomnia).
3. Broad comorbidities category including at least one of the following diseases: liver disease, rheumatic disease, chronic pulmonary disease, among others.

Therefore, demonstrating consistency between thoughts, conclusions and results. Furthermore, the limitations encountered by the researchers during the study were listed and adequately addressed.

- Limitations:
  - Use of database instead of direct access to patients.
  - Database containing information of patients under benzodiazepines treatment, representing 75% of the data used for the study.

Benzodiazepines role in Alzheimer’s disease was associated with its use at high cumulative doses exposure for the treatment of dementias’ prodromes and/or other conditions, which showed an increased risk of Alzheimer’s disease.

The author extends the conversation for further research, which is needed to address other factors, such as comorbidities and/or limitations.

DISCUSSION/ OVERALL CRITIQUE

- Study was conducted on large number of people. This study meets ethical issues because it determined the relation between risk of Alzheimer’s disease and exposure to benzodiazepines without using any interventions on patients. This study was conducted in one location which will lower the cost, and it allows researchers to use time and resources efficiently. However, data was collected from RAMQ database without directly interviewing patients, thus not avoid bias due to recording or delay errors.
- Although this study found the association between Alzheimer and benzodiazepine use, we would not use this trial as an only resource for making a clinical decision in the practice. We could use this trial as a reference when we have to solve a case with a patient who suffers from Alzheimer.
- This study is a source of information to consider when prescribing Benzodiazepines, it shows that the use of benzodiazepines for long terms and at high doses increases the risk of Alzheimer's disease. However, Benzodiazepines used at lower doses is not associated with the risk of Alzheimer’s disease, based on this information we suggest: the use of short acting benzodiazepines at doses below 180 mg per day to avoid the risk of Alzheimer’s disease.
- We also would want to see a research that follows this trial, it will fill the pieces of data which this trial is missing.
- Exclusion criteria could help the result to be extrapolated for the future use of this study, since it excludes non-Alzheimer’s dementia.

REFERENCES