MEDICATION USE AND ALZHEIMER’S DISEASE - MEDALZ STUDY

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CONFLICT OF INTEREST DISCLOSURE

I have the following potential conflicts of interest to report

- Lecture fee from MSD

- Lecture fee form Professio
MEDALZ-study
MEDication use and ALZheimer’s disease

• Largest Alzheimer Cohort in the world 70,718 community-dwelling persons with Alzheimer’s Disease

• Cohort includes persons who have got a new diagnosis for Alzheimer’s Disease during the years 2005-2011

• Four community-dwelling comparison persons matched by gender, age and region

• Based on several nationwide registers in Finland
Special Reimbursements 2005-2011

SII benefits database 2005-2011

Study sample

1-4 COMPARISON PERSONS/AD CASE

PERSONS WITH AD

Special reimbursements 1972-2020

Prescriptions 1995-2020

Social care 1995-2020

Implant register 1980-2020

Hospital discharges 1972-2020

Statistics Finland 1972-2020

Cancer register 1972-2020

DE-IDENTIFICATION by register maintainers

Database linkage at UEF

MEDALZ-database

SII

NIHW

QUERIES WITH PIN
Mean age at the time of AD diagnosis is 80 years
65% are women

MEDALZ POPULATION
## Somatic co-morbidities in AD population

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiovascular disease</td>
<td>35,921</td>
<td>(50.8)</td>
</tr>
<tr>
<td>- Hospital treatment due to ischaemic heart disease</td>
<td>18,468</td>
<td>(26.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9,461</td>
<td>(13.4)</td>
</tr>
<tr>
<td>- Hospital treatment due to diabetes</td>
<td>7,384</td>
<td>(10.4)</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>6,199</td>
<td>(8.8)</td>
</tr>
<tr>
<td>- Hospital treatment due to asthma/COPD</td>
<td>5,267</td>
<td>(7.5)</td>
</tr>
<tr>
<td>Hip fracture before AD diagnosis</td>
<td>3,714</td>
<td>(5.3)</td>
</tr>
</tbody>
</table>
# Psychiatric comorbidities

## History of psychiatric co-morbidities (ICD 10 codes)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital care due to any mental or behavioral disorder</td>
<td>16,668</td>
<td>(23.6)</td>
</tr>
<tr>
<td>- Disorders due to psychoactive substance use</td>
<td>1,832</td>
<td>(2.6)</td>
</tr>
<tr>
<td>- Schizophrenia, schizotypal and delusional disorders</td>
<td>1,882</td>
<td>(2.7)</td>
</tr>
<tr>
<td>- Depression</td>
<td>3,760</td>
<td>(5.3)</td>
</tr>
<tr>
<td>- Mania and bipolar disorder</td>
<td>504</td>
<td>(0.8)</td>
</tr>
<tr>
<td>- Neurotic, stress-related and somatoform disorders</td>
<td>1756</td>
<td>(2.5)</td>
</tr>
<tr>
<td>- Disorders of adult personality and behaviour</td>
<td>270</td>
<td>(0.4)</td>
</tr>
</tbody>
</table>
Incidence of psychotropic drug use in relation to diagnosis of Alzheimer’s Disease
Incidence of antipsychotic use in relation to AD diagnosis

Koponen et al. 2015 Br J Psychiatry
Incidence of antidepressant use in relation to AD diagnosis

Persons with AD

Comparison persons

Puranen et al. Int J Geriatr Psychiatry 2017
Incidence of benzodiazepines and related drugs use in relation to dg of AD

Saarelainen et al. J Alzheimer Dis 2015
To investigate effectiveness and safety of drug use, we’ll need to know

• When drug use started and ended?
• Where there breaks in drug use?
• What was the used dose?
Basics of the PRE2DUP method

Exceptions for:
- stockpiling
- dose dispensing
- single purchases
etc.

Input:
- Drug purchases
  *drug, date, amount
- Hospitalization periods

PRE2DUP method

Output: drug use periods

Period 1: 100 days
Period 2: 160 days
Break: 20 days
Drug use and associations with adverse events
Incidence of hip fractures per 100 person-years is higher in persons with than without Alzheimer’s Disease.

Tolppanen et al. BMC Geriatrics, 2016
Antipsychotics and risk of hip fracture among AD population
We treated antipsychotic use as a time-dependent variable in the analyses.

Start of follow-up = AD diagnosis

1-year washout period

- Nonuse
- Nonuse
- Nonuse
- Nonuse
- Nonuse
- Nonuse
- Nonuse

AP use

Hip fracture

Censored: Long-term institutionalization

Censored: Death

Censored: Discontinued AP use

Exclusion criteria: Antipsychotic use during washout period, diagnosis of schizophrenia or bipolar disorder, hip fracture before AD diagnosis

Censored:
End of study period December 31, 2012

NICE, FRANCE - SEPTEMBER 20/22, 2017
Methods

- **OUTCOME** Hip fracture was defined according to ICD-10 codes
  - Fracture of neck of femur S72.0
  - Pertrochanteric fracture S72.1
  - Subtrochanteric fracture S72.2

- **DRUG EXPOSURE** were defined according to the ATC classification
  - Antipsychotics N05A
Hazard ratio for the risk of hip fracture in persons with AD.

<table>
<thead>
<tr>
<th>Antipsychotic use vs. nonuse</th>
<th>1.65 (1.58-1.71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of use vs. nonuse</td>
<td></td>
</tr>
<tr>
<td>1-30 days</td>
<td>2.70 (2.46-2.95)</td>
</tr>
<tr>
<td>31-180 days</td>
<td></td>
</tr>
<tr>
<td>181-365 days</td>
<td></td>
</tr>
<tr>
<td>&gt;365 days</td>
<td></td>
</tr>
</tbody>
</table>

Age-adjusted incidence rate per 100 person-years (95% CI)
The most frequently used antipsychotic drugs had similar hip fracture risk in persons with AD.
Risk of mortality (HR)

Koponen M et al. J Alz Dis 2017

- Antipsychotic use vs. nonuse
- Duration of use vs. nonuse:
  - 1-30 days
  - 31-90 days
  - 91-180 days
  - 181-365 days
  - 366-730 days
  - >730 days
- Monotherapy vs. nonuse
- Polypharmacy vs. nonuse
- Quetiapine vs. risperidone
- Haloperidol vs. risperidone

Adjusted Hazard Ratio with 95% CI
Antidepressant use and risk for hip fractures and head injuries

- Antidepressant are according the ATC-codes N06A
- Definition for hip fracture is S72.0-2
- Definition in ICD-10 for head injuries is S0* Traumatic brain injuries S06
<table>
<thead>
<tr>
<th>Event rate/100 person-years for hip fracture</th>
<th>Person with Alzheimer’s Disease</th>
<th>Comparison Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted event rate/100 person-years (95% CI)</td>
<td>Age adjusted event rate/100 person years (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Non use</td>
<td><strong>1.63</strong> (1.56-1.70)</td>
<td><strong>0.69</strong> (0.66-0.71)</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td><strong>3.01</strong> (2.75-3.34)</td>
<td><strong>2.28</strong> (1.94-2.61)</td>
</tr>
<tr>
<td>Duration of use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-30 days</td>
<td><strong>4.94</strong> (3.65-6.31)</td>
<td><strong>2.93</strong> (1.83-4.02)</td>
</tr>
<tr>
<td>31-180 days</td>
<td><strong>3.90</strong> (3.24-4.62)</td>
<td><strong>2.76</strong> (2.07-3.45)</td>
</tr>
<tr>
<td>181-365 days</td>
<td><strong>2.78</strong> (2.17-3.38)</td>
<td><strong>2.07</strong> (1.42-2.72)</td>
</tr>
<tr>
<td>1-2 years</td>
<td><strong>1.51</strong> (1.19-1.83)</td>
<td><strong>1.25</strong> (0.83-1.67)</td>
</tr>
<tr>
<td>&gt;2 -4 years</td>
<td><strong>2.60</strong> (1.81-3.38)</td>
<td><strong>2.11</strong> (0.98-3.23)</td>
</tr>
</tbody>
</table>
Hip fracture risk was increased during antidepressant use

Hazard Ratio of hip fracture during antidepressant use

<table>
<thead>
<tr>
<th></th>
<th>Persons with AD</th>
<th>Persons without AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-use (=reference)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1.7</td>
<td>3.52</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>1.61</td>
<td>2.71</td>
</tr>
</tbody>
</table>

- Blue bar: Non-use (=reference)
- Red bar: Unadjusted HR
- Green bar: Adjusted HR
How about head injuries?

Taipale H et al 2017 Alzheimer’s Research & Therapy

- Among Alzheimer population using antidepressants
- HR for compared to nonuse was for head injuries **1.35** (95% CI 1.20-1.52)
- traumatic brain **1.26** (95% CI 1.06-1.50)
Benzodiazepines and Z-drug use and risk for hip fractures

- Definition for benzodiazepines according ATC codes
- Benzodiazepines N05BA and N05CD
- Z-drugs N05CF (mainly tsopiklone)
• 46,373 persons with AD and 92,746 comparison persons without AD
  – 21.1% of persons with AD and 12.8% of comparison persons initiated BZDR use

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Persons with AD</th>
<th>Comparison persons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hip fractures</td>
<td>Hip fracture rate</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>/ 100 person-years (95% CI)</td>
</tr>
<tr>
<td>Nonuse</td>
<td>1878</td>
<td>1.56 (1.49–1.63)</td>
</tr>
<tr>
<td>BZDR use</td>
<td>197</td>
<td><strong>2.51 (2.15–2.86)</strong></td>
</tr>
<tr>
<td>Benzodiazepine use</td>
<td>117</td>
<td><strong>2.36 (1.92–2.80)</strong></td>
</tr>
<tr>
<td>Z-drug use</td>
<td>61</td>
<td><strong>2.71 (2.01–3.41)</strong></td>
</tr>
</tbody>
</table>
## Hazard ratio for hip fracture

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Persons with AD</th>
<th>Comparison persons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted* HR (95% CI)</td>
<td>Adjusted* HR (95% CI)</td>
</tr>
<tr>
<td>Nonuse</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>BZDR use</td>
<td>1.43 (1.23–1.66)</td>
<td>1.58 (1.31–1.91)</td>
</tr>
<tr>
<td>Benzodiazepine use</td>
<td>1.34 (1.11–1.62)</td>
<td>1.60 (1.22–2.09)</td>
</tr>
<tr>
<td>Z-drug use</td>
<td>1.58 (1.22–2.04)</td>
<td>1.58 (1.21–2.06)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, comorbidities, socioeconomic position, other drug use (antipsychotics, opioids, antidepressants, antiparkinson drugs, estrogen, urinary antispasmodics, calcitonin, oral corticosteroids, and bisphosphonates)
Are Proton pump inhibitors (PPIs) use associated with the risk of hip fractures among persons with Alzheimer’s Disease?
PPI use was modestly associated with an increased risk of hip fracture only in short-term use.

Our findings do not support previous assumptions that long-term PPI use would be associated with an increased risk of hip fractures.
Conclusion

Among persons with Alzheimer’s Disease

• All psychotropic drugs increase risk for hips fractures
• Antidepressants increase risk for head injuries
• Proton pump inhibitors do not increase risk for hip fractures
Thank you for your attention!