MORTALITY ASSOCIATED WITH USE OF ANTIPSYCHOTICS IN DEMENTIA: REVIEWING THE EVIDENCE

KRISTA L. LANCTÔT, PHD
PROFESSOR OF PSYCHIATRY AND PHARMACOLOGY, UNIVERSITY OF TORONTO;
SENIOR SCIENTIST, HURVITZ BRAIN SCIENCES PROGRAM, SUNNYBROOK RESEARCH INSTITUTE

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Faculty: Dr Krista Lanctôt

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- Krista Lanctot has received funding from • Abbvie Canada • Elan • F Hoffman La Roche • Janssen Ortho • Lundbeck Canada Inc.
- Janssen Ortho developed/licenses/distributes/benefits from the sale of a products that will be discussed in this program: risperidone (Risperdal)
Many of the therapeutic agents discussed in this presentation are genericized and no longer marketed by the drug companies.

Talking about drug-associated death does not make the drug companies happy.
By the end of this talk participants will be familiar with:

- evidence from observational studies linking atypical and conventional antipsychotic use with mortality
- factors suggesting causality in observational studies
- risks changes associated with choice of antipsychotic, timing and dose
USE OF ANTIPSYCHOTICS

- frequently used
  - 33% of elderly NH residents with dementia in the US (National Survey Data) (Kamble et al 2009)
  - 18% of elderly VA patients (Kales et al 2012)
  - 13% elderly with dementia in outpatient and office-based settings (Desi et al 2012)
- controversial
JUDICIOUS USE ENDORSED BY CLINICAL PRACTICE GUIDELINES

Canadian Consensus Conference on the Diagnosis and Treatment of Dementia – CCCDTD (2008 and 2012)

- severe agitation, aggression and psychosis ...risk of harm to the patient and/or others....significant risks

American Psychiatric Association (2007, 2014)

- severe agitation, aggression and psychosis after weighing risks and benefits and with appropriate informed consent

*off-label use: antipsychotics are not approved for agitation and aggression in AD
INCREASED MORTALITY ASSOCIATED WITH ANTIPSYCHOTICS

**FDA**
- black box warning April 2005
- ‘Treatment of behavioral disorders in elderly patients with dementia with atypical antipsychotic medications is associated with increased mortality’
- Extended to conventional June 2008

**Health Canada**
- black box warning June 2005
### Deaths

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
<td>Total No.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>31/1184</td>
<td>6/478</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>21/391</td>
<td>7/246</td>
</tr>
<tr>
<td>Risperidone</td>
<td>45/1175</td>
<td>22/779</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>118/3353</strong></td>
<td><strong>41/1851</strong></td>
</tr>
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</table>

Test for Heterogeneity $\chi^2_{15} = 8.45$, $I^2 = 0\%$ ($p = 0.90$)

Test for Overall Effect $z = 2.28$ ($p = 0.02$)

**Significant** OR 1.54 (54% ↑ risk of mortality for atypicals vs. placebo in patients with dementia; NNH = 100)

RCTs vs Observational Trials

- Rates in individual RCTs are low (3.5% drug, 2.3% placebo), no long term follow-up, little comparison of medications, selection bias

- Warning concerning conventional antipsychotics comes from “observational studies that do not prove conclusively that the older drugs carry the same risk as the newer drugs”

- Issues: causality, uncontrolled confounding
CAUSALITY IN OBSERVATIONAL STUDIES

- strength of association
- temporal relationship
- biologic gradient
- biologic plausibility
- consistency with other knowledge
**STRENGTH OF ASSOCIATION**

**ATYPICAL ANTIPSYCHOTICS VS NO USE**

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<table>
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<th>Study</th>
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</table>
| Gill [2007] | 9,100 matched pairs, **Non-institutionalized** dementia patients (age>=65) | Yes (Propensity score matching, sensitivity analysis) | 180 days  | 8.0%                     | HR 1.32 (1.12-1.54)
Risk Difference: 1.1 per 100 (0.1-2.1)                          |
| Gill [2007] | 4,036 matched pairs, **Institutionalized** dementia patients (age>=65) | Yes (Propensity score matching, sensitivity analysis) | 180 days  | 15.1%                    | HR 1.23 (1.05-1.45)
Risk difference: 1.5 per 100 (-0.5-3.4)                           |

- Results consistent with RCTs, estimate similar
TEMPORAL RELATIONSHIP

- temporal relationship
  - risk evident as early as 30 days after the initiation of treatment (Gill et al 2007)
    - elevation in risk persists for 180 days
  - mortality risk 1.5 x higher in the first 120 days cp subsequent 60 days for atypicals (Kales et al 2012)
    - haloperidol risk highest in the first 30 days (relative risk=2.24)
biologic gradient

- 180 day non CA mortality n=136,000 elderly (Gerhard et al 2014)
  - High vs low dose: RR 1.36 (1.24-1.49)
- n=37,241 elderly dementia patients (Schneeweiss et al 2007)
  - risk greater with higher doses and during the initial 40 days of treatment
- atypicals show dose-response ↑ in mortality in dementia (Maust et al 2015)
  - 3.5% greater mortality high vs low-dose
BIOLOGIC PLAUSIBILITY

- **biologic plausibility**
  - Anticholinergic properties (affecting blood pressure and heart rate)
  - Q–T prolongation (causing conduction delays)
  - extrapyramidal symptoms (causing swallowing problems)
  - more common with conventional than with atypical antipsychotic agents
BIOLOGIC PLAUSIBILITY—QT PROLONGATION

Covariate-Adjusted Survival Function by Days of Exposure in a Study of Mortality Risk Among Individual Antipsychotics (Elderly)

- crude 6-month mortality:
  - haloperidol, 20.0%
  - olanzapine, 12.6%
  - risperidone, 12.5%
  - quetiapine, 8.8%
  - $\chi^2=294.4$, df=4, p<0.0001
- peaks during 1st 120 d for atypicals
- Mirrors QT prolongation

Kales et al Am J Psychiatry
• compared with RIS
  • ↑ risk of mortality haloperidol (HR 2.07, 1.89 to 2.26)
  • ↓ risk with quetiapine (0.81, 0.75 to 0.88)
• effects strongest shortly after the start of treatment
CONSISTENCY WITH OTHER KNOWLEDGE

- consistency with other knowledge
  - RCTs
  - QT prolongation
  - other populations
Consistency with Other Knowledge—Antipsychotics and Mortality in PD

- Nested case control study of deaths within 30 days of starting an AP in elderly with Parkinsonism
- N=25,000, cases=5,300
- Exposure to APs significantly associated with risk of death: aOR=2.0 (95%CI 1.4-2.7)
  - Quetiapine aOR=1.8 (95%CI 1.1-3.0)
  - Typical AP aOR=2.4 (95%CI 1.1-5.7)

Marras et al 2012
ANTIPSYCHOTIC WITHDRAWAL-DART-AD TRIAL

- AD patients in LTC
- randomized, placebo-controlled, discontinuation trial
- n=128 (78%) started treatment (64 continued, 64 placebo)
- Mortality @12 mo
  - 30% (20-42%) AP group
  - 23% (15-36%) placebo group
  - (mITT log rank p=0.03; ITT p=0.02)

Ballard et al Lancet Neurol 2009
LONG-TERM EFFECTS OF CONVENTIONAL AND ATYPICAL APS IN PATIENTS WITH PROBABLE AD

- Observational study of 957 AD patients
- Average F/U 4.3 years for death or institutionalization
- Results:
  - Use of APs not associated with time to death or institutionalization after controlling for covariates
  - Presence of NPS (including psychosis and agitation) strongly associated with time to death and institutionalization
SUMMARY

- **Strength of association**
  - HR = 1.32

- **Temporal relationship**
  - Risk highest first 120-180 d

- **Biologic gradient**
  - 3.5% greater mortality high vs low-dose

- **Biologic plausibility**
  - Putative mechanisms, typicals > atypicalcs, 2-3 deaths/100

- **Consistency**
  - Consistent with meta-analyses, also found in PD
CONCLUSIONS

Observational studies
• suggest an increased risk of mortality (HR 1.32)
• provide additional evidence of the risk of these drugs in older patients
  • risks vary by medication
  • atypicals > conventional
  • risks increase with dose
• can address long-term safety
  • risk highest in first 3 to 5 months
• cannot prove causality, though suggest it
• cannot rule out the possibility of residual confounding
IMPACT OF DESIGN: COHORT VERSUS CASE CONTROL

**Cohort Studies**
- Moderate risk of bias, moderate quality

**Case Control**
- Moderate risk of bias, lower quality
- More variability

- Gill nonI
- Gill inst
- Trifiro non-I
- Raivio inst

Pratt et al 2012
DESIGN CHOICES

- scrutinize for control of confounders and potential for misclassifying diagnoses
- sociodemographic, clinical and health care utilization factors likely independent predictors of death
  - controlled using traditional multivariable analyses as well as propensity score
- instrumental variable analysis
  - can control for unmeasured patient characteristics or physician preference
- non-differential exposure misclassification
  - health care providers may have managed the indication using harsher co-interventions (e.g., physical restraint, sedatives)
LEVEL I EVIDENCE: META-ANALYSES

LOW RISK OF BIAS

Studies that compared atypical antipsychotic (ATYP) treatment to placebo (PLA)

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<tr>
<td>Katz [5]</td>
<td>895 institutionalized dementia patients (age&gt;=55)</td>
<td>12 weeks</td>
<td>1.8%</td>
<td>HR 1.26 (0.53-2.99)</td>
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<td>Schneider [19]</td>
<td>5,204 Dementia patients (age&gt;55)</td>
<td>6-26 weeks</td>
<td>2.3%</td>
<td>OR 1.54 (1.06-2.23)</td>
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<td>2.8%</td>
<td>OR 1.30 (0.76-2.23)</td>
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<td>Haupt [20]</td>
<td>1,721 Alzheimers Patients (mean age 82.3)</td>
<td>4-12 weeks</td>
<td>3.1%</td>
<td>RR 1.21 (0.71-2.06)</td>
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- 20% to 50% increased risk of death
- absolute increase of 1 extra death per 100 patients with atypical AP compared to non-use.
QUIZ

Which of the following is true with respect to observational research findings:

a) The risk of mortality associated with second generation antipsychotics is higher in than that found with conventional antipsychotics.

b) The risk of mortality associated with second generation antipsychotics increases with increasing dose

c) There is no difference between second generation antipsychotics on risk of mortality

d) The risk of mortality associated with second generation antipsychotics peaks after 4 months of administration.

Answer b.)
COHORT VS CASE CONTROL

- Cohort
  - Grouped by whether or not exposed to AP
  - Followed over time for death
  - Selection bias
  - RR

- Case control
  - Select cases (mortality) and match controls
  - Look retrospectively at use of AP
  - Inaccurate exposure info
  - OR
## IMPACT OF DESIGN
**COHORT STUDIES OF ATYPICALS**

### Moderate risk of bias, moderate quality

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Pratt et al 2012
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<td>Trifiro [2007]</td>
<td>398 cases, 4,023 controls, dementia patients, (age&gt;85)</td>
<td>Yes (matching on age and duration of dementia)</td>
<td>9 years</td>
<td>NA</td>
<td>OR 2.2 (1.2-3.9)</td>
</tr>
<tr>
<td>Raivio [2007]</td>
<td>254 institutionalized dementia patients (Finland) (age&gt;70)</td>
<td>Yes (covariate adjustment)</td>
<td>2 years</td>
<td>49.6%</td>
<td>HR 0.49 (0.24-0.99)</td>
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- 1 estimate higher and the other NS

Pratt et al 2012
QTc prolongation with common antipsychotic drugs: 183 patients with normal ECGs at baseline were randomized to one of six antipsychotic drugs at maximum daily doses of: ziprasidone 160 mg, risperidone 16 mg, olanzapine 20 mg, quetiapine 750 mg, thioridazine...

Fig 1 QTc prolongation with common antipsychotic drugs: 183 patients with normal ECGs at baseline were randomized to one of six antipsychotic drugs at maximum daily doses of: ziprasidone 160 mg, risperidone 16 mg, olanzapine 20 mg, quetiapine 750 mg, thioridazine 300 mg and haloperidol 15 mg (Data from PsychoPharmacological Drugs Advisory Committee, 2000).

Nasser Abdelmawla, and Alex J. Mitchell APT 2006;12:35-44