Drug Development for Behavioral and Psychological Symptoms of Dementia in Japan

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Disclosure & Disclaimer

- I have no conflict of interest.

- The views and opinions expressed in this presentation are those of the speaker and should not be attributed to Pharmaceuticals and Medical Devices Agency (PMDA). This is not an official PMDA guidance or policy statement.

Behavioral and Psychological Symptoms of Dementia

- More than 80% of patients with Alzheimer's Disease (AD) have behavioral and psychological symptoms, which are extremely difficult to manage.

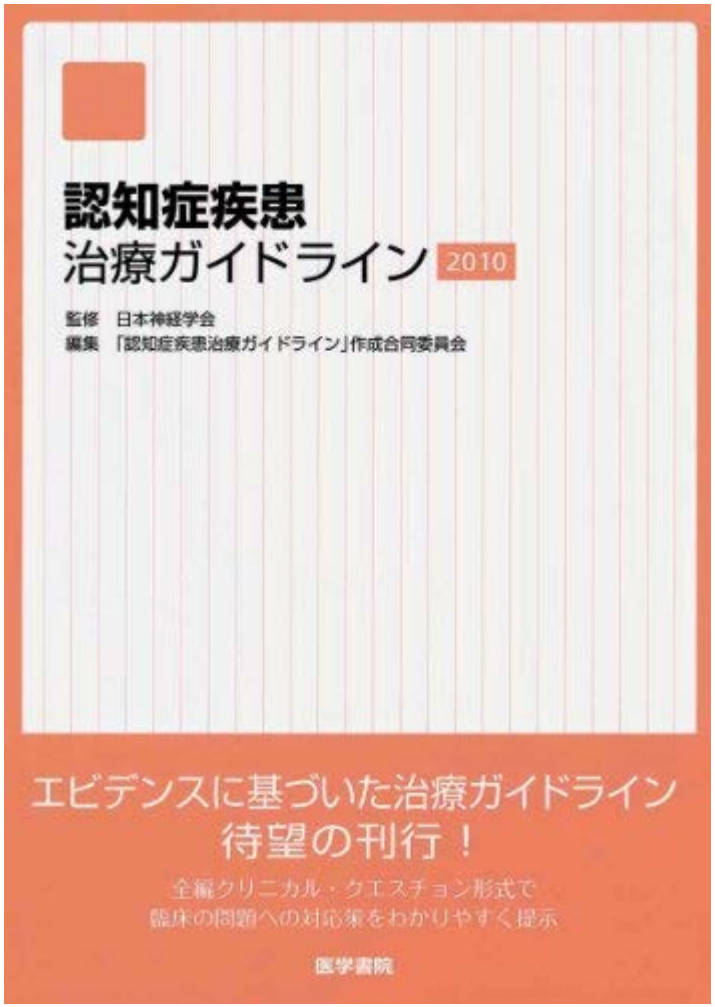
Behavioral symptoms	Agitation Irritation restlessness aggression screaming wandering
Psychological symptoms	delusions hallucinations apathy depressive symptoms anxiety

Behavioral and Psychological Symptoms of Dementia

- Behavioral and psychological symptoms of dementia (BPSD) is a source of distress and burden for patients, families, professional caregivers and others who are responsible for taking care of individuals with dementia.

Clinical Practice Guideline On Dementia In Japan

- A clinical practice guideline on dementia was published by the Japanese Society of Neurology.



Clinical Practice Guideline On Dementia In Japan

- Recommendations
  - Non-pharmacological approaches should be applied before considering pharmacological interventions.
  - It is important to assess for potentially reversible factors that may lead to development of BPSD.
  - Pharmacological interventions should only be applied for patients who are unresponsive to non-pharmacological approaches.

Clinical Practice Guideline On Dementia In Japan

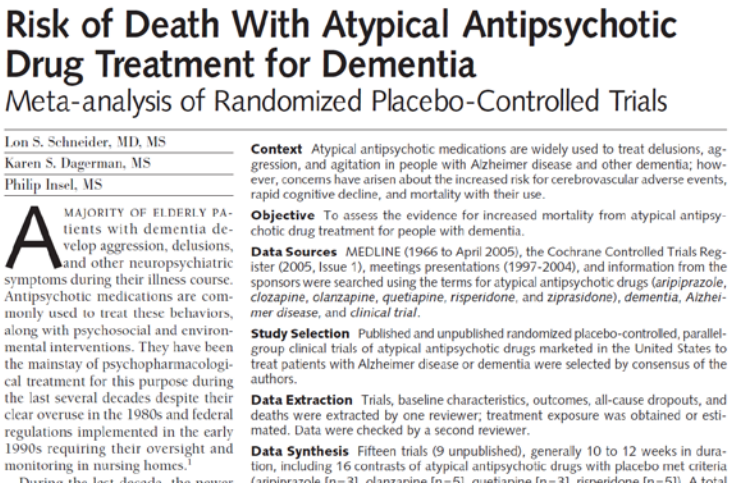
- Recommended pharmacological treatments

Symptoms	Recommended drugs
Anxiety	Risperidone, Olanzapine, (Quetiapine)
Agitation	Risperidone, Olanzapine, Quetiapine, Aripiprazole, (Valproate, Carbamazepine)
Hallucinations Delusions	Risperidone, Olanzapine, Aripiprazole, (Quetiapine, Haloperidol)
Depressive behavior	(SNRIs, SSRIs, Donepezil)

( ) : low evidence level

High Mortality Risk of Antipsychotics in Elderly Patients with Dementia

- A number of studies have revealed that antipsychotics are associated with increased mortality in elderly patients with dementia.



Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia

Meta-analysis of Randomized Placebo-Controlled Trials

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A MAJORITY OF ELDERLY PATIENTS with dementia develop aggression, delusions, and other neuropsychiatric symptoms during their illness course. Antipsychotic medications are commonly used to treat these behaviors, along with psychosocial and environmental interventions. They have been the mainstay of psychopharmacological treatment for this purpose during the last several decades despite their clear overuse in the 1980s and federal regulations implemented in the early 1990s requiring their oversight and monitoring in nursing homes.[1]

Context Atypical antipsychotic medications are widely used to treat delusions, aggression, and agitation in people with Alzheimer disease and other dementia; however, concerns have arisen about the increased risk for cerebrovascular adverse events, rapid cognitive decline, and mortality with their use.

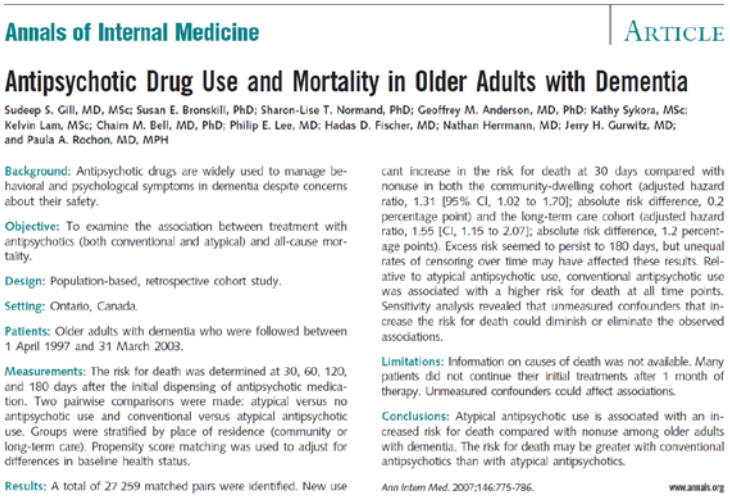
Objective To assess the evidence for increased mortality from atypical antipsychotic drug treatment for people with dementia.

Data Sources MEDLINE (1966 to April 2005), the Cochrane Controlled Trials Register (2005, Issue 1), meetings presentations (1997-2004), and information from the sponsors were searched using the terms for atypical antipsychotic drugs (*aripiprazole, clozapine, olanzapine, quetiapine, risperidone,* and *ziprasidone*), *dementia, Alzheimer disease,* and *clinical trial*.

Study Selection Published and unpublished randomized placebo-controlled, parallel-group clinical trials of atypical antipsychotic drugs marketed in the United States to treat patients with Alzheimer disease or dementia were selected by consensus of the authors.

Data Extraction Trials, baseline characteristics, outcomes, all-cause dropouts, and deaths were extracted by one reviewer; treatment exposure was obtained or estimated. Data were checked by a second reviewer.

Data Synthesis Fifteen trials (9 unpublished), generally 10 to 12 weeks in duration, including 16 contrasts of atypical antipsychotic drugs with placebo met criteria (aripiprazole [n=3], olanzapine [n=6], quetiapine [n=3], risperidone [n=5]). A total



Annals of Internal Medicine | ARTICLE

Antipsychotic Drug Use and Mortality in Older Adults with Dementia

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Background: Antipsychotic drugs are widely used to manage behavioral and psychological symptoms in dementia despite concerns about their safety.

Objective: To examine the association between treatment with antipsychotics (both conventional and atypical) and all-cause mortality.

Design: Population-based, retrospective cohort study.

Setting: Ontario, Canada.

Patients: Older adults with dementia who were followed between 1 April 1997 and 31 March 2003.

Measurements: The risk for death was determined at 30, 60, 120, and 180 days after the initial dispensing of antipsychotic medication. Two pairwise comparisons were made: atypical versus no antipsychotic use and conventional versus atypical antipsychotic use. Groups were stratified by place of residence (community or long-term care). Propensity score matching was used to adjust for differences in baseline health status.

Results: A total of 27 259 matched pairs were identified. New use of antipsychotics was associated with a significant increase in the risk for death at 30 days compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio, 1.31 [95% CI, 1.02 to 1.70]; absolute risk difference, 0.2 percentage point) and the long-term care cohort (adjusted hazard ratio, 1.55 [CI, 1.15 to 2.07]; absolute risk difference, 1.2 percentage points). Excess risk seemed to persist to 180 days, but unequal rates of censoring over time may have affected these results. Relative to atypical antipsychotic use, conventional antipsychotic use was associated with a higher risk for death at all time points. Sensitivity analysis revealed that unmeasured confounders that increase the risk for death could diminish or eliminate the observed associations.

Limitations: Information on causes of death was not available. Many patients did not continue their initial treatments after 1 month of therapy. Unmeasured confounders could affect associations.

Conclusions: Atypical antipsychotic use is associated with an increased risk for death compared with nonuse among older adults with dementia. The risk for death may be greater with conventional antipsychotics than with atypical antipsychotics.

Ann Intern Med. 2007;146:775-786. www.annals.org

High Mortality Risk of Antipsychotics in Elderly Patients with Dementia

- The warning about the mortality risk of antipsychotics in elderly patients with dementia is included in the package insert in the US, the EU and Japan.

↓US

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. *[See Warnings and Precautions (5.1)]*

4.4 Special warnings and precautions for use

Elderly patients with dementia

Overall mortality

Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including RISPERDAL. In placebo-controlled trials with RISPERDAL in this population, the incidence of mortality was 4.0% for RISPERDAL-treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67-100).

↑EU

Japan→

2) 外国で実施された認知症に関連した精神病症状(承認外効能・効果)を有する高齢患者を対象とした17の臨床試験において、本剤を含む非定型抗精神病薬投与群はプラセボ投与群と比較して死亡率が1.6～1.7倍高かったとの報告がある。また、外国での疫学調査において、定型抗精神病薬も非定型抗精神病薬と同様に死亡率の上昇に関与するとの報告がある。

Trends in Use of Psychotropic Agents for BPSD in Japan

- The use of antipsychotics slightly increased even after the warning about the mortality risk.

Table 2. Trends in psychotropic visits by psychotropic classes

	PSYCHOTROPIC VISITS, %			ODDS RATIOS FOR TIME TREND (95% CI)		
PSYCHOTROPICS	2002–2004	2005–2007	2008–2010	2002–2004 (vs.) 2005–2007	2005–2007 (vs.) 2008–2010	2002–2004 (vs.) 2008–2010
Antipsychotics	25.6	26.0	24.9	1.11 (0.99, 1.24)	1.03 (0.94, 1.12)	1.14 (1.02, 1.27)*
SGAs	5.0	9.1	12.0	2.02 (1.66, 2.47)*	1.46 (1.30, 1.65)*	2.95 (2.44, 3.59)*
FGAs	20.6	16.9	12.9	0.88 (0.78, 1.00)	0.80 (0.72, 0.89)*	0.71 (0.62, 0.80)*
Antidepressants	11.5	12.6	13.0	1.21 (1.04, 1.41)*	1.08 (0.96, 1.21)	1.30 (1.12, 1.51)*
NGAs	6.1	7.6	7.3	1.37 (1.13, 1.66)*	1.00 (0.87, 1.14)	1.36 (1.13, 1.65)*
TCAs	1.7	1.9	1.7	1.14 (0.80, 1.64)	1.00 (0.76, 1.32)	1.14 (0.81, 1.63)
Others	3.7	3.1	3.9	0.96 (0.74, 1.25)	1.42 (1.17, 1.74)*	1.37 (1.08, 1.75)*
Mood stabilizers	1.7	2.0	2.9	1.46 (1.02, 2.12)*	1.58 (1.24, 2.01)*	2.30 (1.65, 3.28)*
Sedatives-hypnotics	35.2	38.4	37.5	1.08 (0.97, 1.20)	1.04 (0.96, 1.12)	1.11 (1.01, 1.24)*
Any BZDs	28.5	29.6	28.6	1.02 (0.91, 1.14)	1.00 (0.92, 1.09)	1.02 (0.92, 1.14)
Sedative BZDs	13.8	14.9	13.4	1.11 (0.96, 1.28)	0.90 (0.81, 1.00)*	1.00 (0.87, 1.14)
Hypnotics BZDs	19.5	20.6	20.6	1.02 (0.90, 1.15)	1.04 (0.95, 1.14)	1.06 (0.94, 1.19)
Z-drugs	4.8	6.8	7.6	1.43 (1.17, 1.77)*	1.17 (1.01, 1.34)*	1.67 (1.37, 2.04)*
Others	1.9	2.0	1.3	1.26 (0.89, 1.82)	0.68 (0.52, 0.91)*	0.86 (0.60, 1.25)

Note. BZDs = benzodiazepines; CI = confidence interval; FGAs = first-generation antipsychotics; NGAs = new-generation antidepressants; SGAs = second-generation antipsychotics; TCAs = tricyclic antidepressants.
*$p < 0.05$.

(Okumura Y et al, *Int Psychogeriatr*, 2014,PMID: 25369886)

J-CATIA study: Study design

- A prospective cohort study on mortality risk associated with antipsychotics in patients with AD in Japan.
- Conducted by the Japan Consortium for Antipsychotics Treatment in AD.
- Study population: 10,000 patients with AD
- 5,000 patients were treated with antipsychotics and 5,000 patients were not.
- Patients were observed for 24 weeks and assessed for mortality risk.

Arai H, *29th Annual Meeting of Japanese Psychogeriatric Society*, S-10-1, 2014

J-CATIA study: Results

- There was no significant difference in the mortality rate between the two groups throughout the observation period (0-24 weeks).
- The mortality rate of new starters (who have no prior medication) of treatment group was significantly higher than non-treatment group in 11-24 weeks (non-treatment: 1.9%, new starters: 3.7%, odds ratio: 2.01 [1.15, 3.51]).

Arai H, *29th Annual Meeting of Japanese Psychogeriatric Society*, S-10-1, 2014

Drug Development for BPSD

- The proposals in the following slides are applicable only for the development of psychotropic agents (eg, antipsychotics, antidepressants, etc).

Strategy of Drug Development for BPSD in Japan

- BPSD is a legitimate target for drug development.
- The independent clinical trials are required for the indication of BPSD. The secondary endpoint in the clinical trials for cognition and function is not admissible.
- Focusing on particular symptom of BPSD like agitation or delusions is acceptable if that symptom is clinically relevant.

Strategy of Drug Development for BPSD in Japan

- Despite the safety issues, antipsychotics are used to treat BPSD in clinical practice and are still needed to manage BPSD.
- Developing antipsychotics for BPSD would be acceptable when the mortality risk is reduced.
  - restricting the treatment duration
  - excluding the patients with high risk factors from study
- A strict Risk Management Plan (RMP) would be necessary for authorization.

Study Population

- Independent studies should be conducted for each type of dementia because each has different symptoms.
  - AD: agitation, aggression
  - DLB: hallucinations, delusions
  - FTB: apathy, social disinhibition
- Only the patients who are unresponsive to non-pharmacological approaches and might harm themselves and others should be included in the studies.
- Patients with high risk factors, such as history of ischemia or arrhythmia, should be excluded from the studies.

Primary Outcome Measure

- NPI (Neuropsychiatric Inventory)
  - NPI was developed to provide a means of assessing neuropsychiatric symptoms and psychopathology of patients with dementia.
  - NPI assesses 10 or 12 behavioral domains common in dementia.
    - Hallucinations, Delusions, Agitation/Aggression, Dysphoria/Depression, Anxiety, Irritability, Disinhibition, Euphoria, Apathy, Aberrant motor behavior, (Sleep and night-time behavior change, Appetite and eating change)

Primary Outcome Measure

- <u>BEHAVE-AD (behavioral Pathology in Alzheimer's Disease)</u>
  - BEHAVE-AD was developed to measure behavioral and psychological symptoms of dementia in patients with AD.
  - BEHAVE-AD is composed of two parts: the first part concentrates on symptomatology, and the second consists of a global rating of the symptoms.
    - Part 1: Paranoid and delusional ideation, Hallucinations, Activity disturbances, Aggressiveness, Diurnal rhythm disturbances, Affective disturbances, Anxieties and phobias

Primary Outcome Measure

- <u>CMAI (Cohen-Mansfield Agitation Inventory)</u>
  - CMAI was developed to assess the frequency of agitated behaviors in elderly peolple and was originally used in nursing home residents.
  - CMAI consists of 29 agitated behaviors.
    - Hitting, Kicking, Grabbing onto people, Pushing, Throwing things, Biting, Scratching, Spitting, Hurt self or others, etc
- The use of CMAI as a primary outcome measure would be acceptable when the studies focus on agitation with BPSD.

Secondary Outcome Measure

- It is important to assess whether drugs for BPSD worsen cognition and function or not.
- The effect on cognition and function should be assessed as a secondary outcome measure.
  - MMSE (Mini Mental State Examination)
  - ADCS-ADL (Alzheimer's Disease Cooperative Study ADL Scale)

Treatment Duration

- The indication of risperidone in the EU is restricted to short term (< 6 weeks) treatment.
- The J-CATIA study suggests that short term (< 10 weeks) treatment of antipsychotics may not increase the mortality risk in the patients with AD, although long term (> 10 weeks) treatment increases that in the new starters.
- Treatment Duration of antipsychotics should be restricted to short term (eg, 6-10 weeks).

Dosage

- Dosage of antipsychotics should be minimized.
- For BPSD, it is usually smaller than that for schizophrenia or bipolar disorder.

Safety evaluation

- Safety evaluation is important to the development of antipsychotics for BPSD.
- Safety of outpatients should be assessed in the clinical trials because main target population in the clinical practice is outpatient.
- Cardiovascular adverse events (eg, heart failure, sudden death) and infections (eg, pneumonia) should be observed carefully.
- Sedative effects on antipsychotics should be assessed (eg, by ADCS-ADL).

Perspectives

- BPSD are responsible for increased risks of patient institutionalization and increased costs.
- Antipsychotics are used and still needed to manage BPSD, but they are not most appropriate option due to their safety issues.
- Drugs with novel mechanism of action are needed to improve the treatment of BPSD.

Thank you for your time and your attention!