精神藥物治療的系統性回顧：國際經驗分享
Tardive Dyskinesia Risk of Typical and Atypical Antipsychotics

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Zucker Hillside Hospital

- a Clinical Research Center for the Study of Schizophrenia
  - one of only four such facilities nationwide
- Chair: John Kane
  - Psychiatry Research: Correll CU, MD

系統性文獻回顧 Systemic review

- **為醫學文獻的整理及統合**
  - 探討或提出某一個臨床問題
  - 用明確的方式搜尋文獻
  - 以嚴謹的選擇標準，擷取高品質的研究
  - 運用適當的統計方式整合
- 優點：
  - 因為資料較完整，證據力較高。

TD: Symptoms and Signs

- Abnormal, involuntary, irregular choreoathetoid movements of the muscles of the head, limbs, and trunk
  - **Perioral movements** are the most common
    - 不能自主的伸縮或捲舌頭或口做咀嚼吞嚥狀，以及嚓嘴、裝鬼臉狀或不斷眨眼
  - Finger movements and hand clenching are also common.

Effects of TD

- It could cause
  - poor quality of life,
  - poor compliance,
  - social stigma, and
  - increased morbidity and mortality.

Epidemiology

- TD develops in about **10 to 20 %** patients
  - who are treated for > 1 year
- About **20 to 40 %** patients
  - who require long-term hospitalization.
- High-risk groups:
  - Women
  - Children
  - > 50 years of age (the elderly)
  - brain damage
  - mood disorders

Other Risk factors

- Duration of treatment
- Type of antipsychotic
- Cumulative/antipsychotic dose
- Ethnicity
- Anticholinergic medication

TD management

1. use the lowest effective dose of antipsychotic;
2. prescribing cautiously with children, elderly patients, and patients with mood disorders;
3. examining patients regularly;
4. considering alternatives and dosage reduction when TD is diagnosed; and
5. if TD worsens → discontinue the AP or switching to a different drug.
   ◦ Clozapine

Lower Risk for Tardive Dyskinesia Associated With Second-Generation Antipsychotics: A Systematic Review of 1-Year Studies

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Objective: Based on lower rates of acute extrapyramidal side effects associated with second-generation antipsychotics, compared to first-generation antipsychotics, and based on preliminary data, second-generation antipsychotics are expected to cause less tardive dyskinesia than first-generation antipsychotics. This hypothesis was examined in a systematic review of studies involving open or controlled treatment with any second-generation antipsychotic.

Method: Studies of treatment with second-generation antipsychotics lasting ≥1 year and reporting on new cases of tardive dyskinesia or dyskinesia were systematically reviewed.

Results: In 11 studies, 2,769 patients received treatment with risperidone (five studies, N=1,235), olanzapine (two studies, N=610), quetiapine (two studies, N=386), amisulpride (one study, N=331), or ziprasidone (one study, N=207) for a weighted mean and median duration of 263 and 306 days, respectively. Study designs were double blind and randomized (N=3); open-label extensions of double-blind, randomized trials (N=4); and open label (N=4). Of the four trials that had a comparator (all involving adults with schizophrenia spectrum disorders), three used halo-peridol (N=408) and one used placebo (N=71). Studied populations included children (N=77), adults (N=1,419), adults and elderly persons (N=794), and exclusively patients age 54 years or older (N=479). The weighted mean annual incidence of tardive dyskinesia for second-generation antipsychotics was 0% in the children, 0.8% (range=0.0%–1.5%) in the adults, 6.8% in the mixed adult and elderly population, and 5.3% (range=0.0%–13.4%) in the patients age 54 years and older, compared to 5.4% (range=4.1%–7.4%) in adults treated with haloperidol.

Conclusions: Results from 11 long-term studies support the idea that second-generation antipsychotics have a reduced risk for tardive dyskinesia, compared to first-generation antipsychotics, although the doses of haloperidol used in the comparator studies were relatively high. More carefully designed studies, ideally lasting beyond 1 year and comparing the effects of different second-generation antipsychotics in patients who have never taken first-generation antipsychotics, are needed to estimate the true risk. It would not appear premature for clinicians to consider these findings in making long-term treatment decisions.

- ≥1yr studies Rx with SGA
  - Risperidone: 5
  - Olanzapine: 2
  - Quetiapine: 2
  - Amisulpride: 1
  - Ziprasidone: 1
- at least 20 pts

- 4 trials that had a comparator, 3 used haloperidol and 1 used placebo.

weighted mean annual incidence of TD for SGA
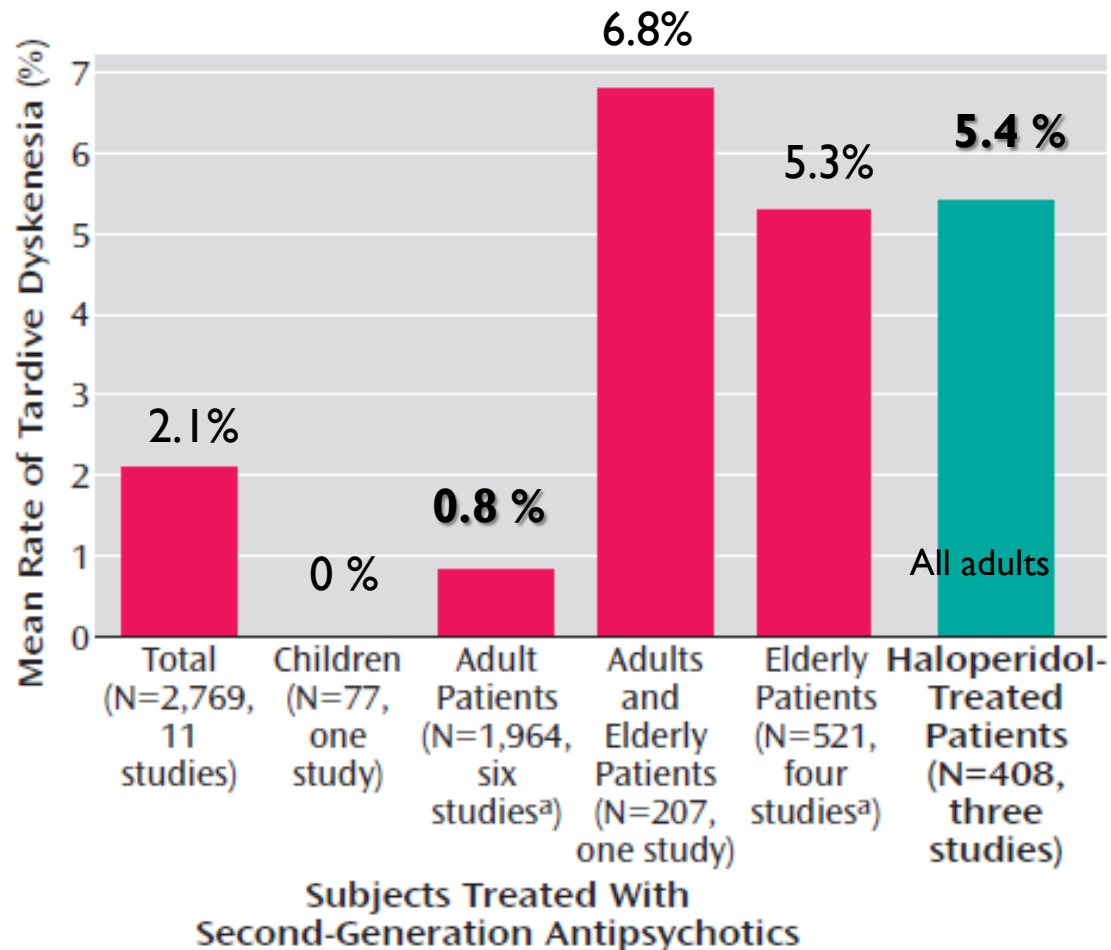
Tardive dyskinesia and new antipsychotics
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Purpose of review
To provide an update on tardive dyskinesia rates in patients treated with first-generation or second-generation antipsychotics in studies published since the last systematic review in 2004.
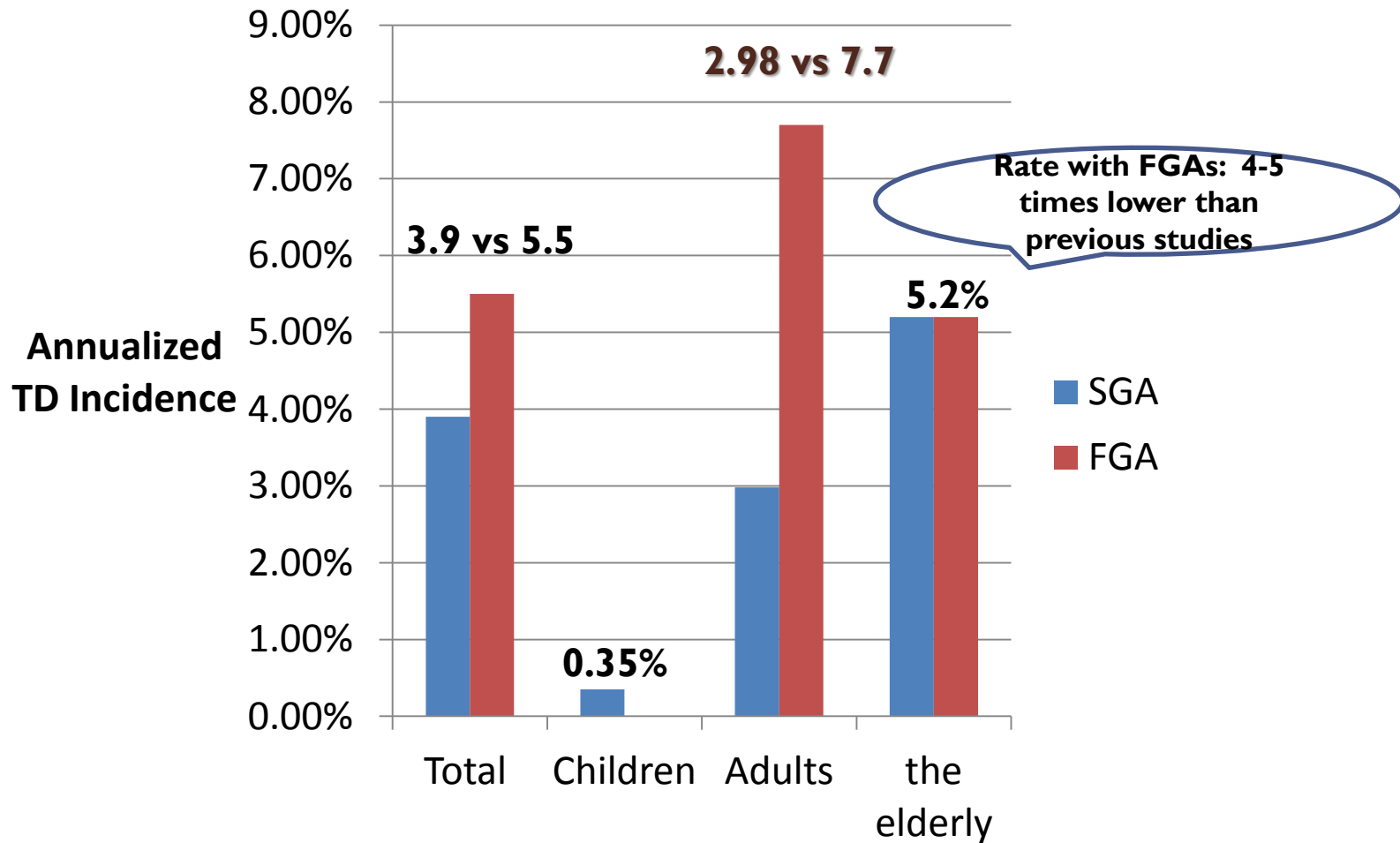
Recent findings
Across 12 trials ($n = 28\,051$, age 39.7 years, 59.7% male, 70.9% white, followed for 463 925 person-years), the annualized tardive dyskinesia incidence was 3.9% for second-generation antipsychotics and 5.5% for first-generation antipsychotics. Stratified by age, annual tardive dyskinesia incidence rates were 0.35% with second-generation antipsychotics in children, 2.98% with second-generation antipsychotics versus 7.7% with first-generation antipsychotics ($P < 0.0001$) in adults, and 5.2% with second-generation antipsychotics versus 5.2% with first-generation antipsychotics ($P = 0.865$) in the elderly (based almost exclusively on one retrospective cohort study). In four adult studies ($n = 2088$, age 41.2 years, 71.2% male, 62.0% white), tardive dyskinesia prevalence rates were 13.1% for second-generation antipsychotics, 15.6% for antipsychotic-free patients, and 32.4% for first-generation antipsychotics ($P < 0.0001$).

Summary
Current evidence supports a lower tardive dyskinesia risk for second-generation antipsychotics than for first-generation antipsychotics. Tardive dyskinesia incidence was higher with second-generation antipsychotics than previously reported, possibly due to recent studies with relatively short mean durations and use of nonstandard tardive dyskinesia definitions.

an update on TD rates in patients treated with FGA or SGA

TD incidence in 12 trials

Annualized TD Incidence

2.98 vs 7.7

3.9 vs 5.5

5.2%

Rate with FGAs: 4-5 times lower than previous studies

0.35%

- SGA
- FGA

9.00%
8.00%
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%

Total   Children   Adults   the elderly

Total N=28,051

This updated review

- PubMed/Medline literature search since 2007
- report on prevalence rates of TD
  - cross-sectional or cohort studies
- a manual search of reference lists of relevant studies and reviews
- search terms
- at least 20 patients,
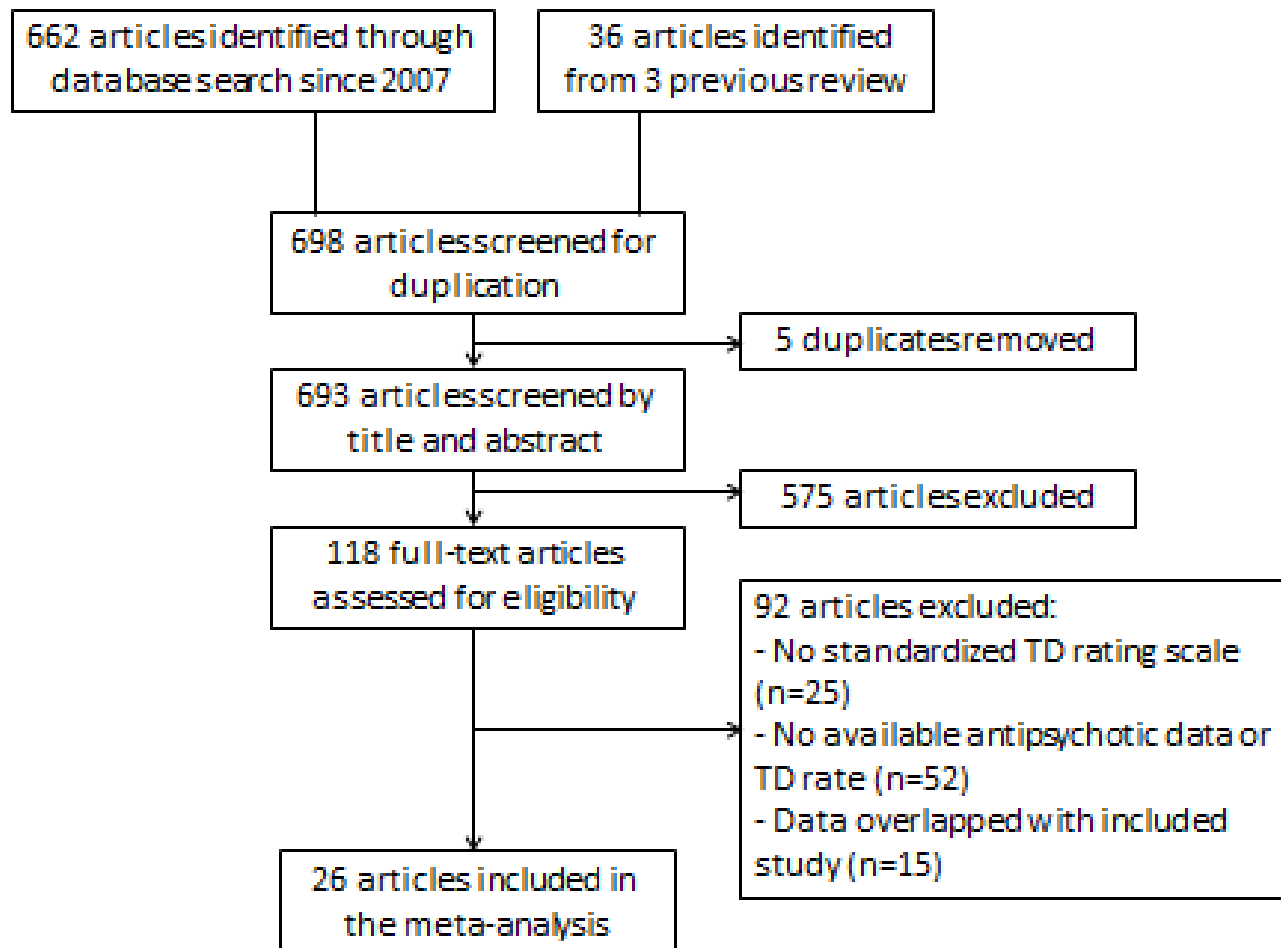- using a standard rating scale to evaluate TD.

Statistical analysis

- Comprehensive Meta-Analysis Version 2.0

  Borenstein et al., 2005

- Effect size
  - Prevalence: the proportion
    - Odds ratio (OR)
  - Incidence: annualized rate, events by person years
    - Rate ratio (RR)
- Heterogeneity
- Subgroup analyses
- Exploratory meta-regression analyses

Search Results

Figure 1. Search Flow Diagram

662 articles identified through database search since 2007

36 articles identified from 3 previous review

698 articles screened for duplication

5 duplicates removed

693 articles screened by title and abstract

575 articles excluded

118 full-text articles assessed for eligibility

92 articles excluded:
- No standardized TD rating scale (n=25)
- No available antipsychotic data or TD rate (n=52)
- Data overlapped with included study (n=15)

26 articles included in the meta-analysis

Studies & Patients Characteristics

- 26 studies (a total of 9,550 patients)
  - 13 prevalence studies (N=3,034)
  - 7 genetic or association studies (N=2,264)
  - 6 clinical studies (N=4,270)

- Mean age: 43.8 years, male: 66.9%, white: 39.4%
- 19 studies: schizophrenia spectrum disorders (N=7,854, 78.9%)

Publication Bias

Funnel Plot of Standard Error by Logit event rate
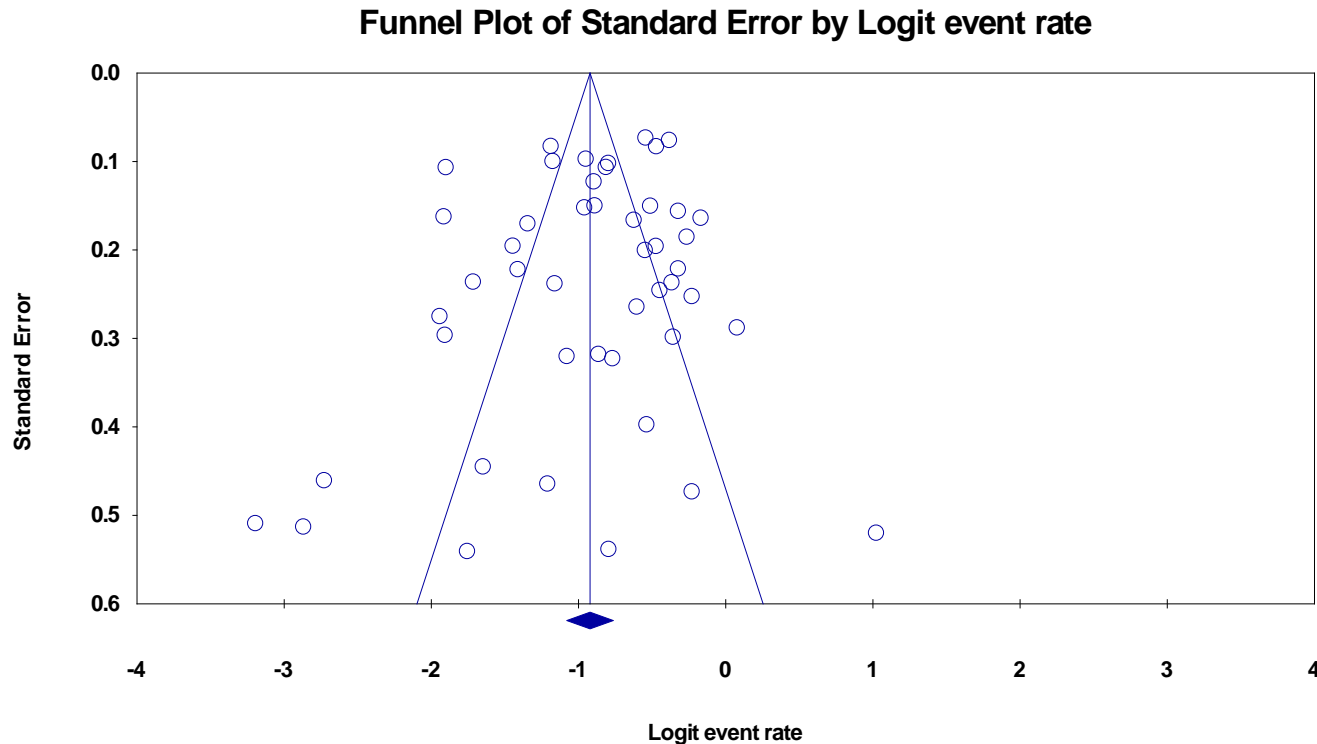
- Begg and Mazumdar test: Kendall's tau b with continuity correction=-0.13, p=0.106.
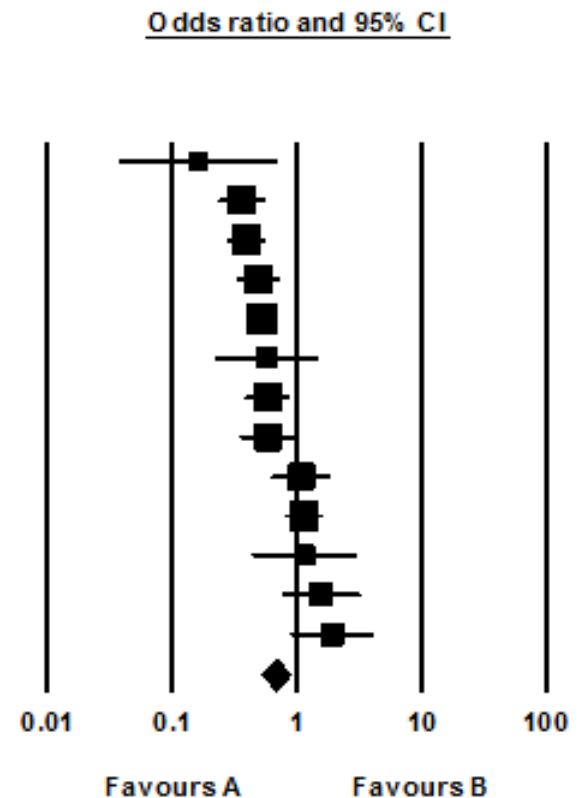- Egger's bias=-1.03, 95% CI=-2.88~0.82, t=1.12, p=0.13.

Pooled TD Prevalence

- estimated weighted mean prevalence rate
  - SGA: **24.2%**
  - FGA: **32.6%**
  - SGA+FGA: **25.7%**
- Rates between SGA and FGA groups:
  - Q=5.163, p=0.023

Meta-regression

- mean age
  - RC=0.062, p<0.001
- mean AP dose
  - RC=0.002, p=0.023
- duration of psychiatric illness
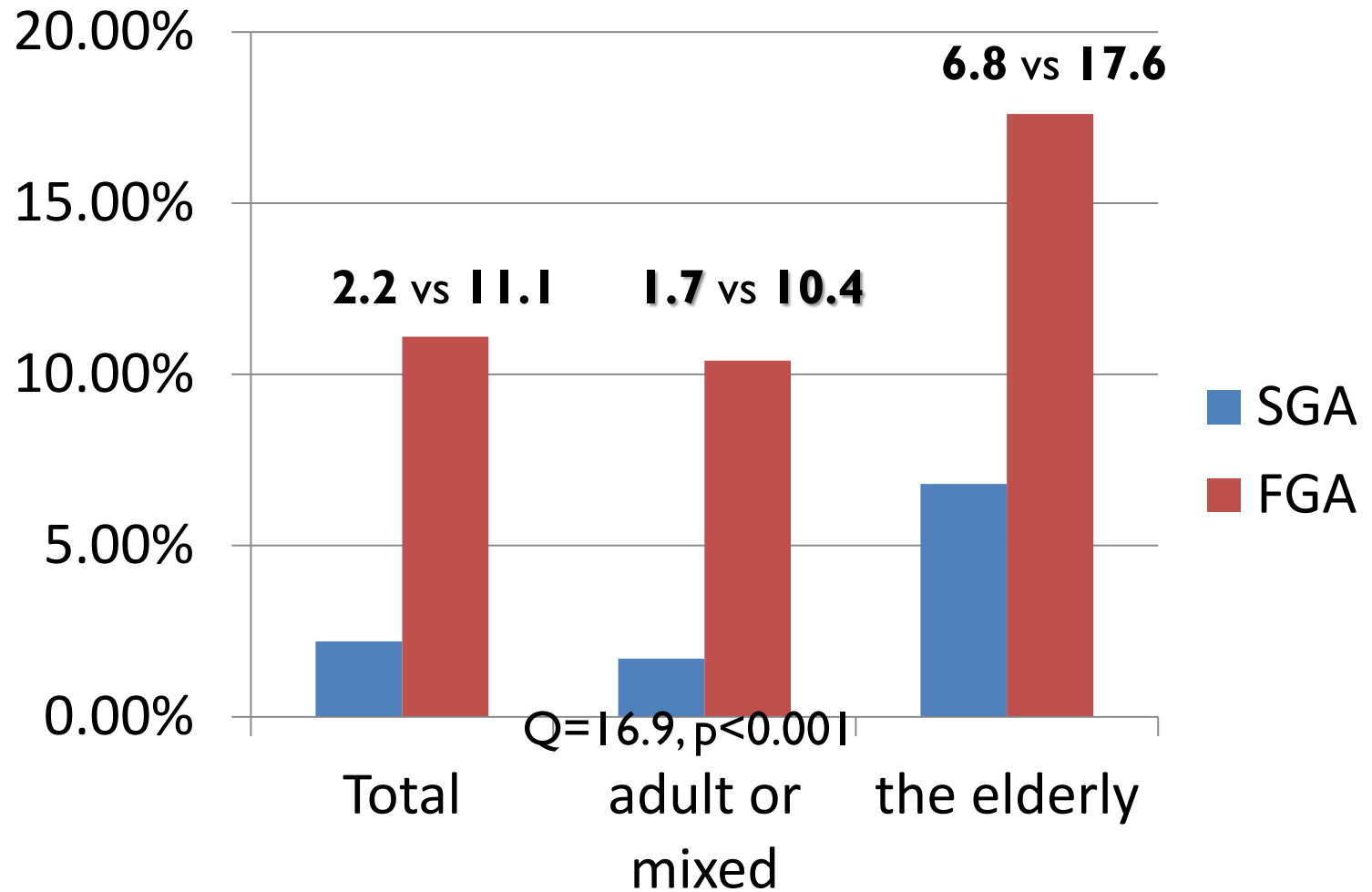 - RC=0.084, p<0.001
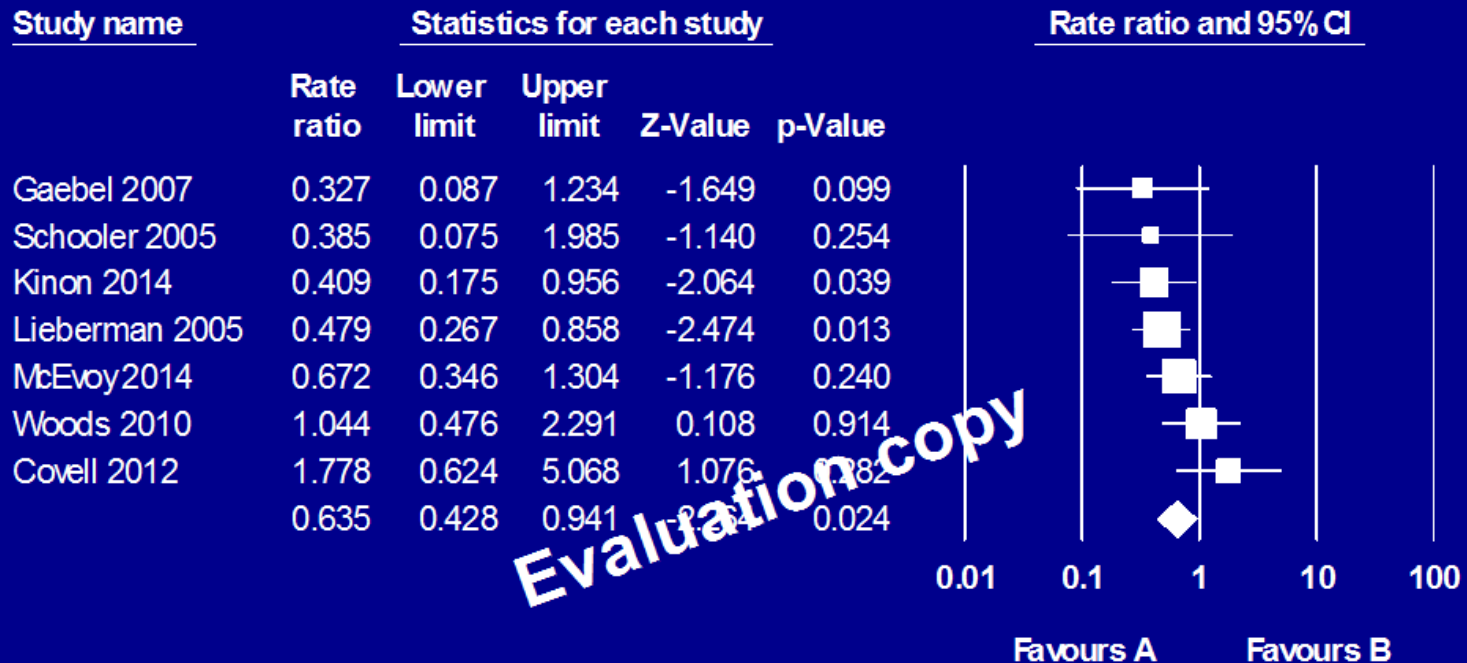- EPS
  - RC=0.028, p=0.007

Forest plot of odds ratio comparing SGA vs FGA in the 13 studies

Annualized TD incidence

Direct Incidence comparison: SGA vs FGA: exclude 4 studies with HAL ≧ 8.9mg/day

Meta Analysis

Study name	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Gaebel 2007	0.327	0.087	1.234	-1.649	0.099
Schooler 2005	0.385	0.075	1.985	-1.140	0.254
Kinon 2014	0.409	0.175	0.956	-2.064	0.039
Lieberman 2005	0.479	0.267	0.858	-2.474	0.013
McEvoy 2014	0.672	0.346	1.304	-1.176	0.240
Woods 2010	1.044	0.476	2.291	0.108	0.914
Covell 2012	1.778	0.624	5.068	1.076	0.282
	0.635	0.428	0.941		0.024

Rate ratio and 95% CI

0.01   0.1   1   10   100

Favours A   Favours B

Meta Analysis

- RR: 0.64, p,0.024 (7 studies)
  - Q=8.5, p=0.20, I^2=29.5

Discussions (1)

- TD prevalence
  - SGA 24.2% < FGA 32.6%
  - SGA lower than FGA (OR=0.67)
  - Other factors affecting TD risk
    - older age,
    - higher AP dose,
    - longer illness duration
    - EPS

Discussions (2)

- TD incidence is lower in SGA than FGA
    - **2.2%** vs **11.1%**
    - *1.7%* vs *10.4%* (adults or mixed)
    - FGA>SGA: RR=0.64, p=0.02 (直接比較)

Limitations

- may also neglect previous AP exposure
  - not obtain exposure time of current AP
- Category: SGA vs FGA ?
  - quetiapine was found lower than that of amisulpiride in a systemic review

Discussions (3)_ SR

- Team work
  - Topic, data extraction, statistics,
- Reputation & relationship
  - Get more the (raw) data as we can
- Other resources
  - Library, different language, CMA
- Learn by doing

Thanks for your attention