Antipsychotic polypharmacy in schizophrenia

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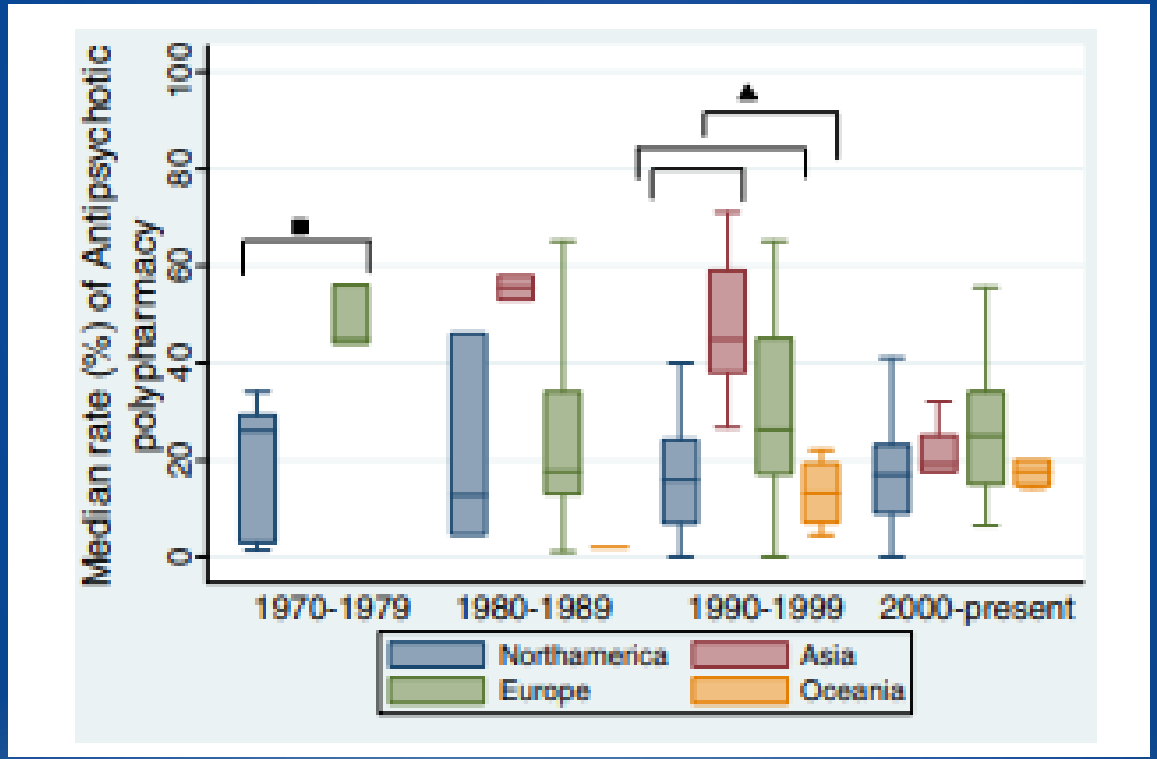
DISCLOSURES

- Payment for advisory boards/ fees/speaker fees/performed PANSS training from Teva, Jansen, Dexel and Lundbeck.
- Receives support for his work from EU and the Stanley Medical Research Institute.

IS POLYPHARMACY COMMON?

Prevalence and correlates of antipsychotic polypharmacy: A systematic review and meta-regression of global and regional trends from the 1970s to 2009☆



Gallego et al., Schiz Res, 2012

Keeping patients on medication

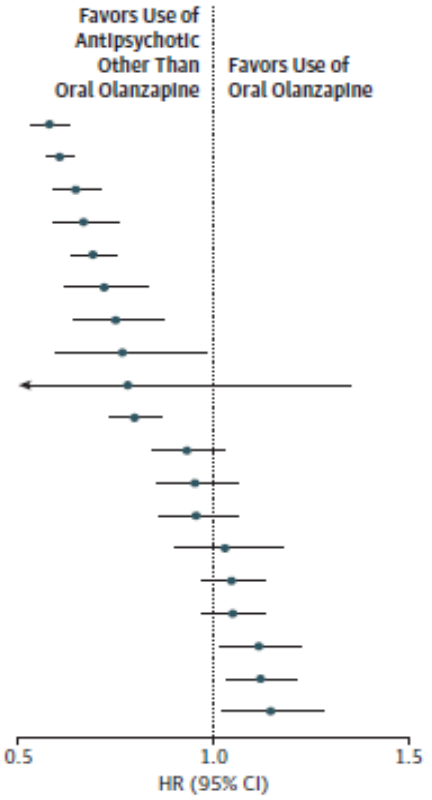
JAMA Psychiatry | Original Investigation

Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia

Jari Tiihonen, MD, PhD; Ellenor Mittendorfer-Rutz, PhD; Maila Majak, MSc; Juha Mehtälä, PhD; Fabian Hoti, PhD; Erik Jedenius, PhD; Dana Enkusson, MSc; Amy Leval, PhD; Jan Sermon, PhD; Antti Tanskanen, PhLic; Heidi Taipale, PhD

Figure 3. Adjusted Hazard Ratios (HRs) and 95% CIs for Treatment Failure During Each Monotherapy Compared With Oral Olanzapine Use

Treatment	HR (95% CI)
Oral clozapine	0.58 (0.53-0.63)
Polytherapy	0.61 (0.57-0.64)
LAI perphenazine	0.65 (0.59-0.71)
LAI haloperidol	0.67 (0.59-0.75)
LAI zuclopenthixol	0.69 (0.64-0.75)
LAI paliperidone	0.72 (0.62-0.83)
LAI flupentixol	0.75 (0.64-0.87)
LAI olanzapine	0.77 (0.60-0.98)
LAI fluphenazine	0.78 (0.45-1.35)
LAI risperidone	0.80 (0.73-0.87)
Oral perphenazine	0.93 (0.84-1.03)
Oral zuclopenthixol	0.95 (0.85-1.06)
Oral haloperidol	0.96 (0.86-1.06)
Oral flupentixol	1.03 (0.90-1.18)
Oral quetiapine	1.05 (0.97-1.13)
Oral risperidone	1.05 (0.97-1.13)
Other oral formulations	1.12 (1.02-1.22)
Oral aripiprazole	1.12 (1.04-1.21)
Oral levomepromazine	1.15 (1.02-1.28)



Clozapine ($P < .001$), long-acting injectable (LAI) perphenazine ($P < .001$), LAI haloperidol ($P < .001$), LAI zuclopenthixol ($P < .001$), LAI paliperidone ($P < .001$), LAI flupentixol ($P < .001$), and LAI risperidone ($P < .001$) differed significantly from oral olanzapine after Bonferroni correction. The vertical dashed line shows the reference value (oral olanzapine use). The arrow indicates that the lower end of the 95% CI (0.45) is beyond the scale (to 0.50).

Tiihonen et al., JAMA Psych, 2017

JAMA Psychiatry | Original Investigation

Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia

Jari Tiihonen, MD, PhD; Heidi Taipale, PhD; Juha Mehtälä, PhD; Pia Vattulainen, MSc; Christoph U. Correll, MD; Antti Tanskanen, PhLic

Figure 2. Risk of Psychiatric Rehospitalization in the Total Cohort, Compared With Clozapine, Aripiprazole, and Olanzapine Monotherapy (Within-Individual Analysis)

Treatment	HR (95% CI)
Clozapine monotherapy as a reference	
Clozapine and aripiprazole	0.86 (0.79-0.94)
Clozapine and olanzapine	0.99 (0.89-1.09)
Clozapine and any LAI	1.01 (0.85-1.21)
Clozapine and risperidone	1.02 (0.88-1.19)
Clozapine and quetiapine	1.06 (0.97-1.16)
Clozapine and other oral	1.08 (1.03-1.14)
Aripiprazole monotherapy as a reference	
Aripiprazole and clozapine	0.57 (0.49-0.67)
Aripiprazole and quetiapine	0.88 (0.75-1.03)
Aripiprazole and olanzapine	0.94 (0.80-1.11)
Aripiprazole and any LAI	0.95 (0.75-1.19)
Aripiprazole and other oral	0.98 (0.79-1.22)
Aripiprazole and risperidone	1.15 (0.83-1.59)
Olanzapine monotherapy as a reference	
Olanzapine and any LAI	0.75 (0.69-0.81)
Olanzapine and clozapine	0.76 (0.69-0.85)
Olanzapine and quetiapine	0.96 (0.88-1.04)
Olanzapine and other oral	1.01 (0.95-1.06)
Olanzapine and risperidone	1.02 (0.92-1.14)
Olanzapine and aripiprazole	1.10 (0.98-1.22)

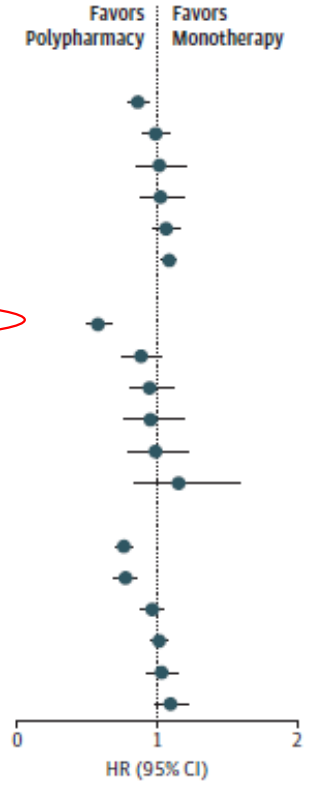
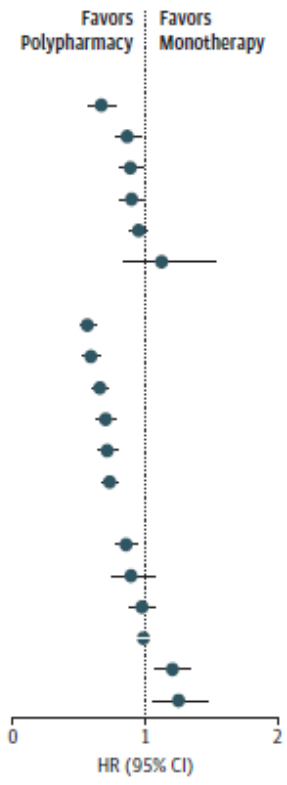


Figure 3. Risk of Psychiatric Rehospitalization in the Total Cohort, Compared With Risperidone, Quetiapine, and Any Long-Acting Injectable Agent (LAI) Monotherapy (Within-Individual Analysis)

Treatment	HR (95% CI)
Risperidone monotherapy as a reference	
Risperidone and clozapine	0.67 (0.57-0.78)
Risperidone and olanzapine	0.86 (0.77-0.97)
Risperidone and quetiapine	0.88 (0.79-0.97)
Risperidone and any LAI	0.89 (0.79-1.01)
Risperidone and other oral	0.95 (0.89-1.02)
Risperidone and aripiprazole	1.13 (0.83-1.54)
Quetiapine monotherapy as a reference	
Quetiapine and clozapine	0.56 (0.51-0.62)
Quetiapine and any LAI	0.59 (0.53-0.65)
Quetiapine and olanzapine	0.66 (0.60-0.72)
Quetiapine and aripiprazole	0.70 (0.63-0.78)
Quetiapine and risperidone	0.72 (0.64-0.80)
Quetiapine and other oral	0.74 (0.68-0.80)
Any LAI monotherapy as a reference	
Any LAI and olanzapine	0.85 (0.79-0.91)
Any LAI and clozapine	0.89 (0.74-1.06)
Any LAI and quetiapine	0.97 (0.88-1.07)
Any LAI and other oral	0.98 (0.94-1.02)
Any LAI and risperidone	1.20 (1.07-1.34)
Any LAI and aripiprazole	1.25 (1.06-1.48)

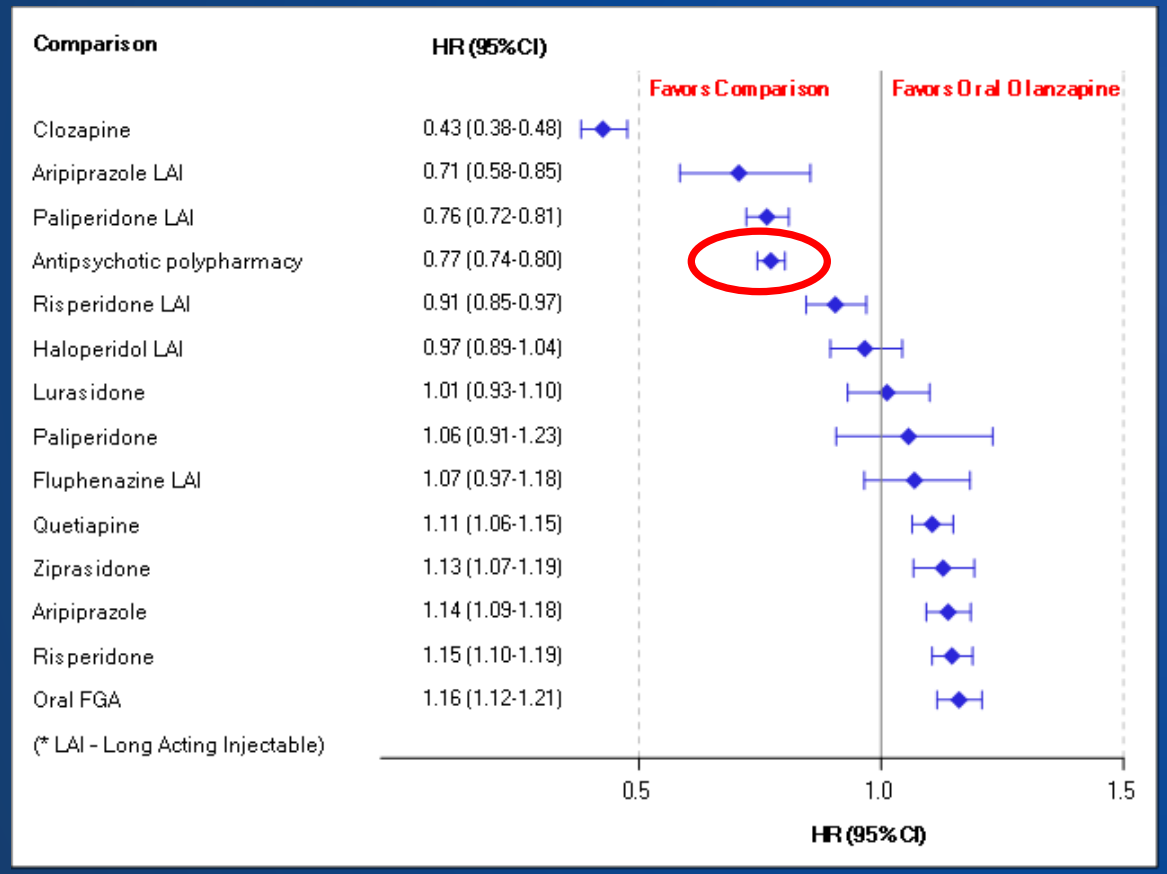


Tiihonen et al., JAMA Psych, 2019

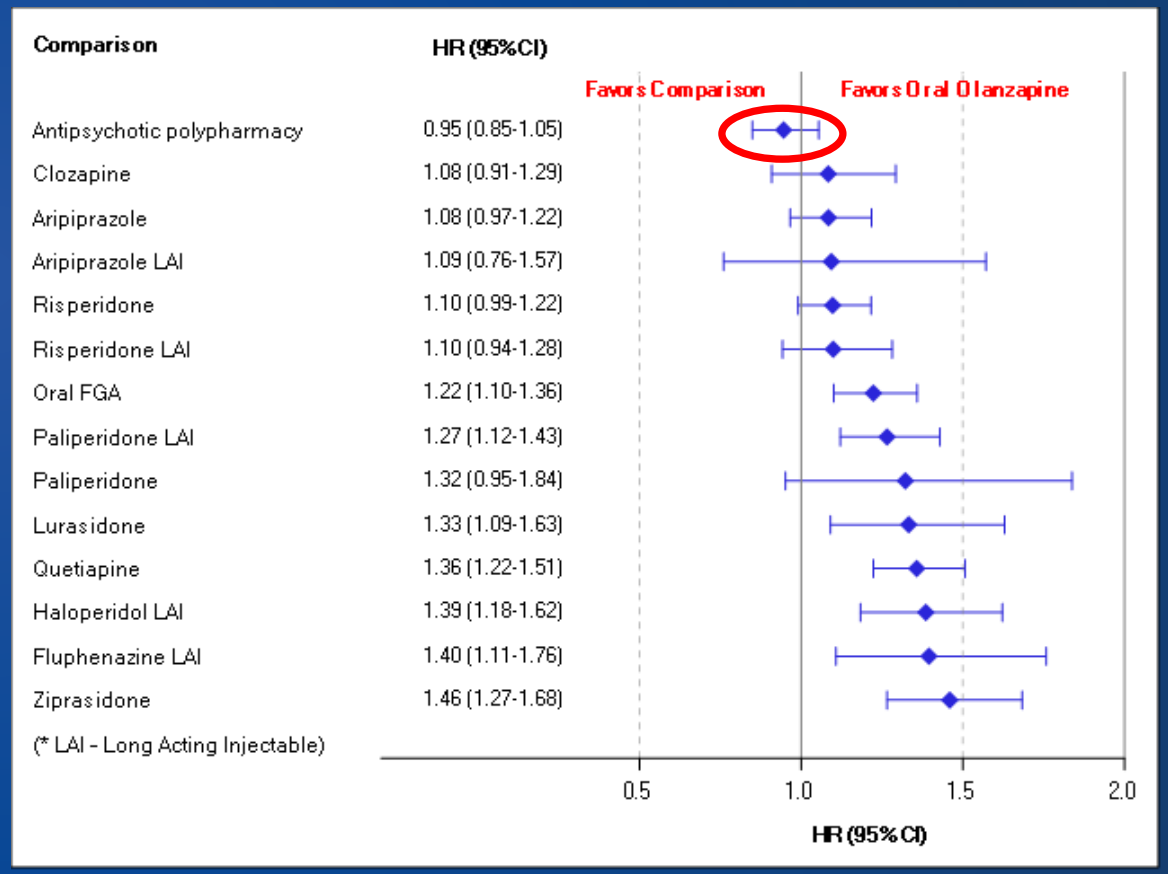
VA DATABASE ALSO SHOWS LONGER TIME TO DISCONTINUATION WITH POLYPHARMACY

N= 37,368

Time to Discontinuation compared with oral olanzapine



Time to Hospitalization compared with oral olanzapine



Weiser et al., under review

Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis

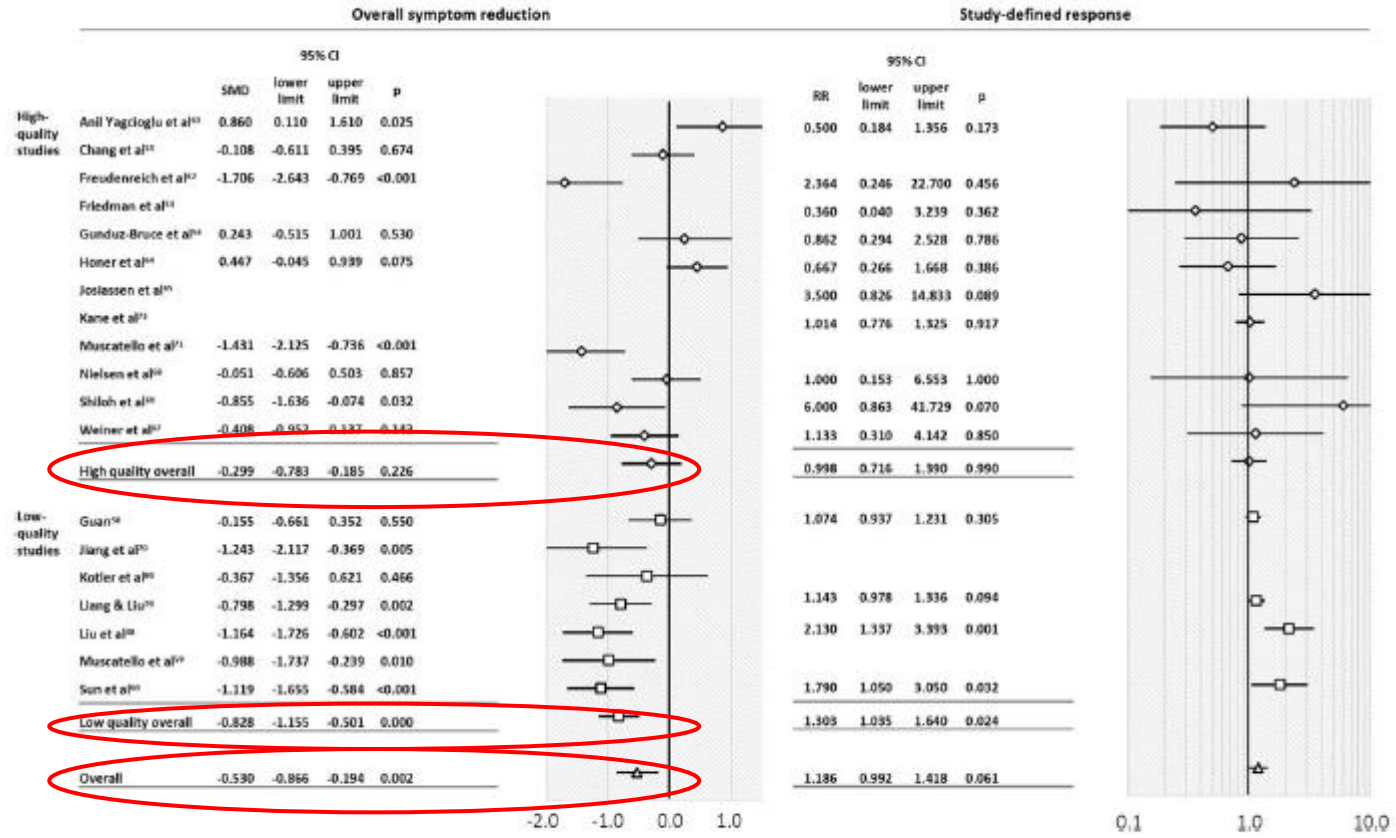


Figure 2 Forest plots of overall symptom reduction and study-defined response. SMD – standardized mean difference, RR – risk ratio

Galling et al., World Psych, 2017

Switching to antipsychotic monotherapy vs. staying on antipsychotic polypharmacy in schizophrenia: A systematic review and meta-analysis☆

Kentaro Matsui [a,1], Takahiro Tokumasu [b,1], Yoshiteru Takekita [c], Ken Inada [a], Tetsufumi Kanazawa [d], Taishiro Kishimoto [e], Shotaro Takasu [e], Hideaki Tani [e], Seiichiro Tarutani [f], Naoki Hashimoto [g], Hiroki Yamada [b], Yoshio Yamanouchi [h], Hiroyoshi Takeuchi [e,*]

Favors monotherapy

Favors polypharmacy

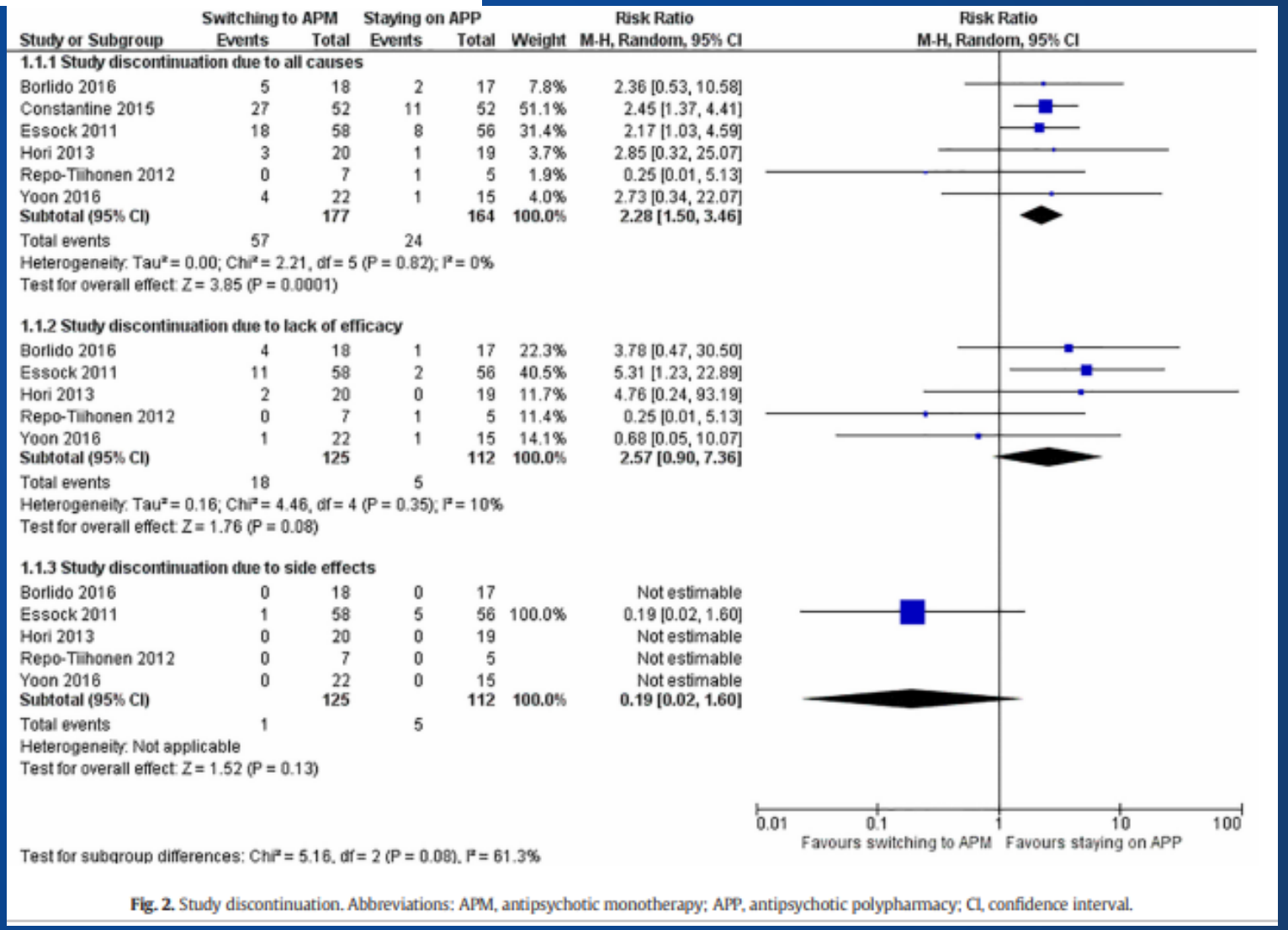


Fig. 2. Study discontinuation. Abbreviations: APM, antipsychotic monotherapy; APP, antipsychotic polypharmacy; CI, confidence interval.

Matsui et al., Schiz. Research, 2019

Disadvantages of RCTs

- 80% to 90% of patients are excluded:
  - Involuntary admission
  - Refusal
  - Substance abuse
  - Suicidality
  - Antisocial behavior
  - Comorbidity
- Represent an atypical minority of the patient population
- A direct comparison of oral vs long-acting antipsychotics is problematic

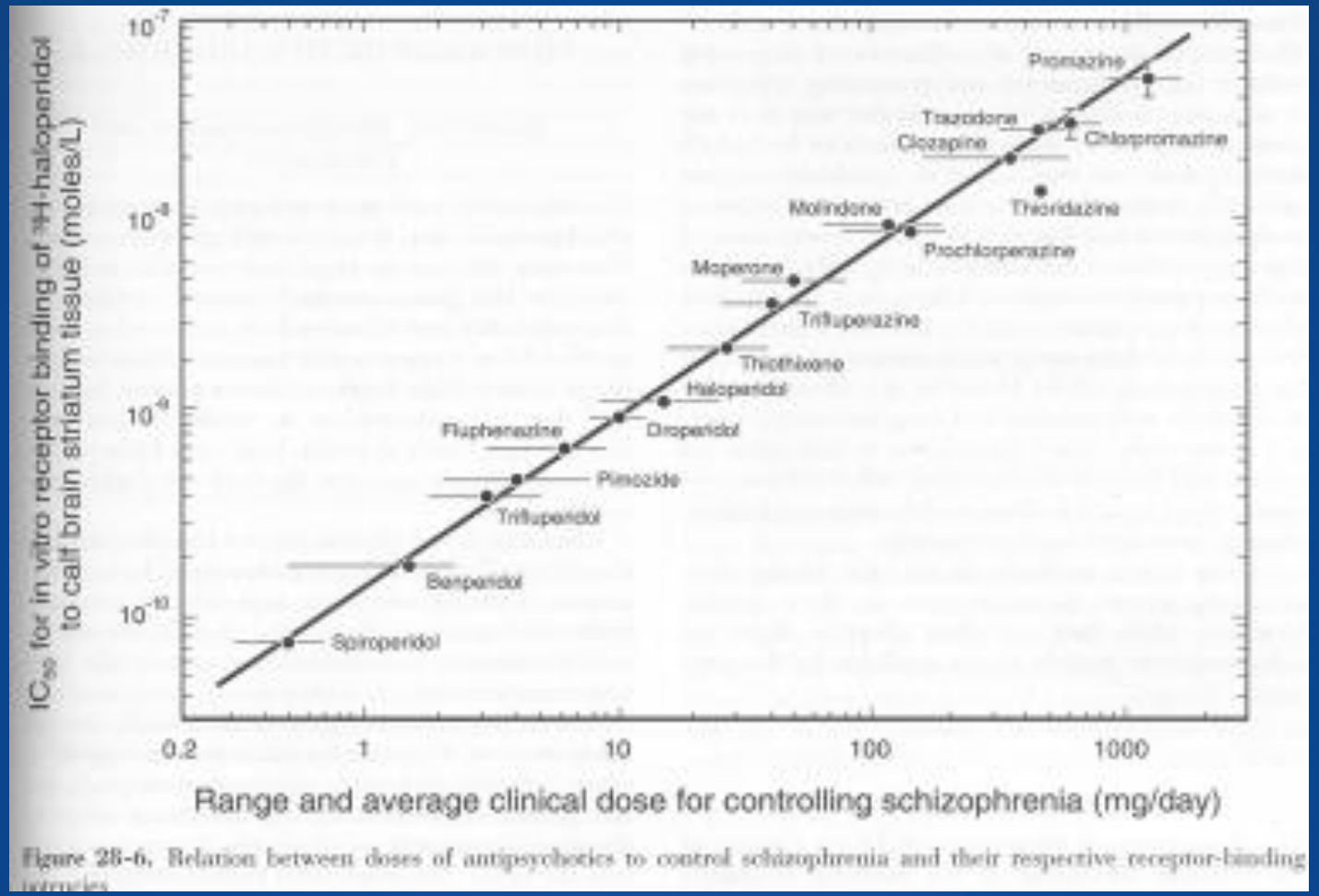
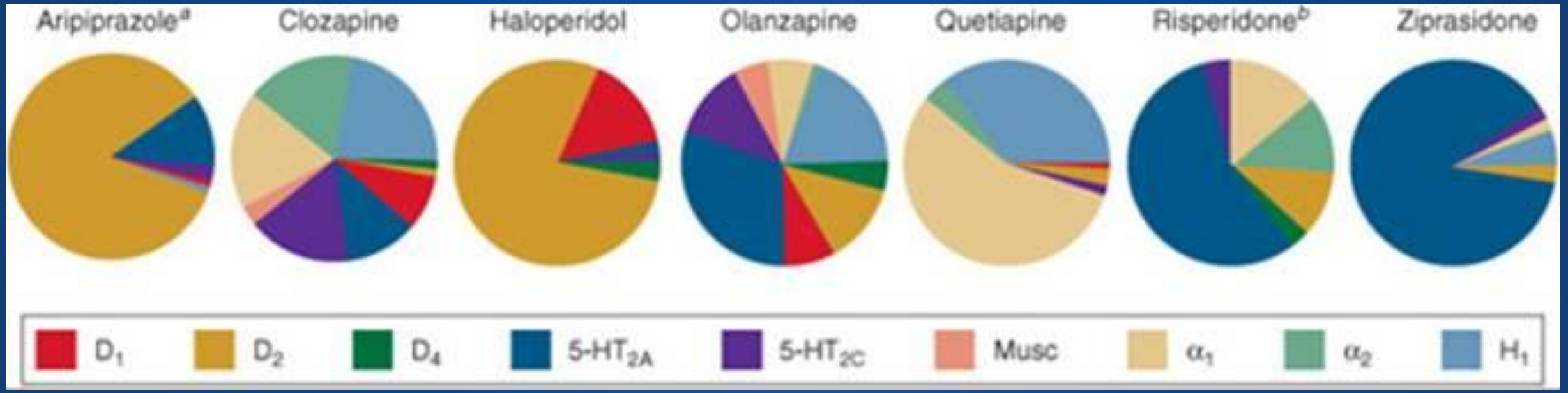


Figure 28-6. Relation between doses of antipsychotics to control schizophrenia and their respective receptor-binding potencies.

Creese et al., 1976

Classic thought: Antipsychotic polypharmacy causes increased risk for side effects, while all antipsychotics are D2 blockers and affect the same brain mechanisms

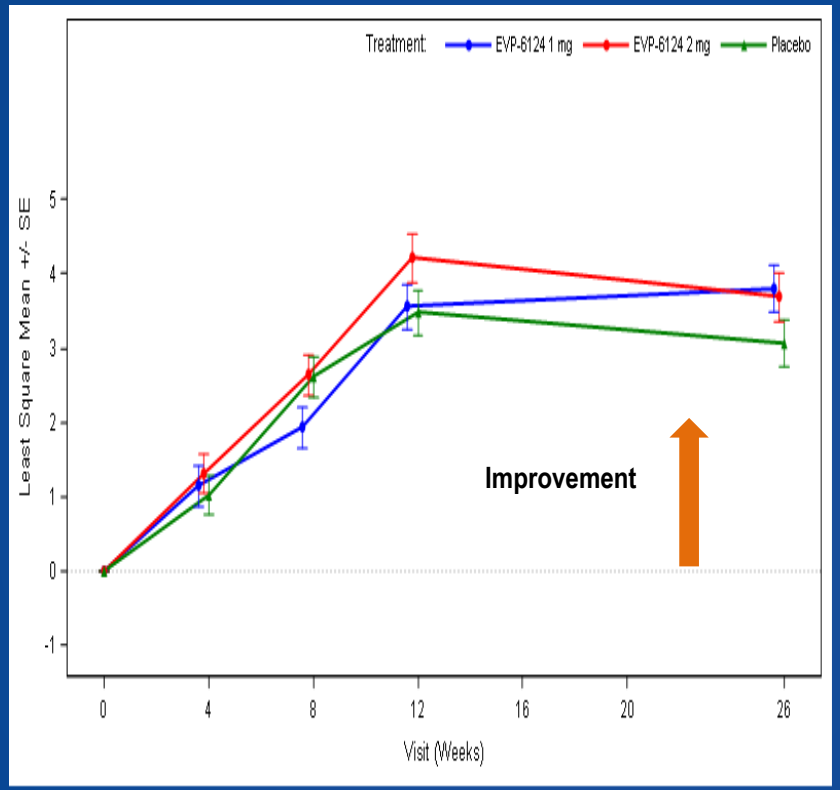
BUT DIFFERENT ANTIPSYCHOTICS BIND DIFFERENT RECEPTORS



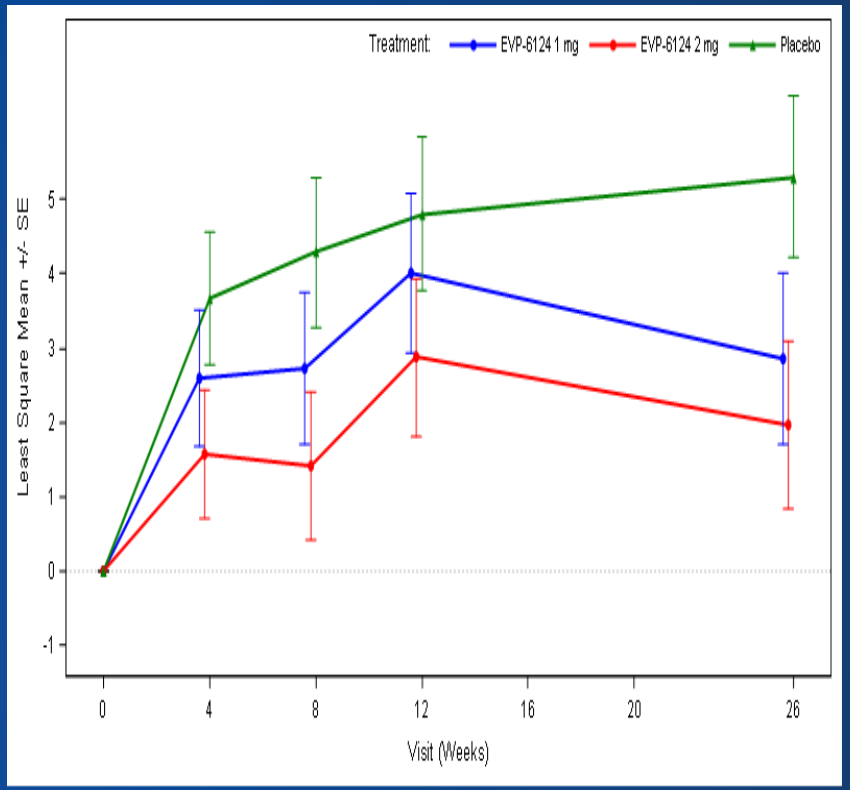
32.2 TWO GLOBAL PHASE III TRIALS OF ENCENICLINE FOR COGNITIVE IMPAIRMENT IN CHRONIC SCHIZOPHRENIA PATIENTS: RED FLAGS AND LESSONS LEARNED

Stephen Brannan*,[1]
[1]*Karuna Pharmaceuticals*

One Antipsychotic Drug



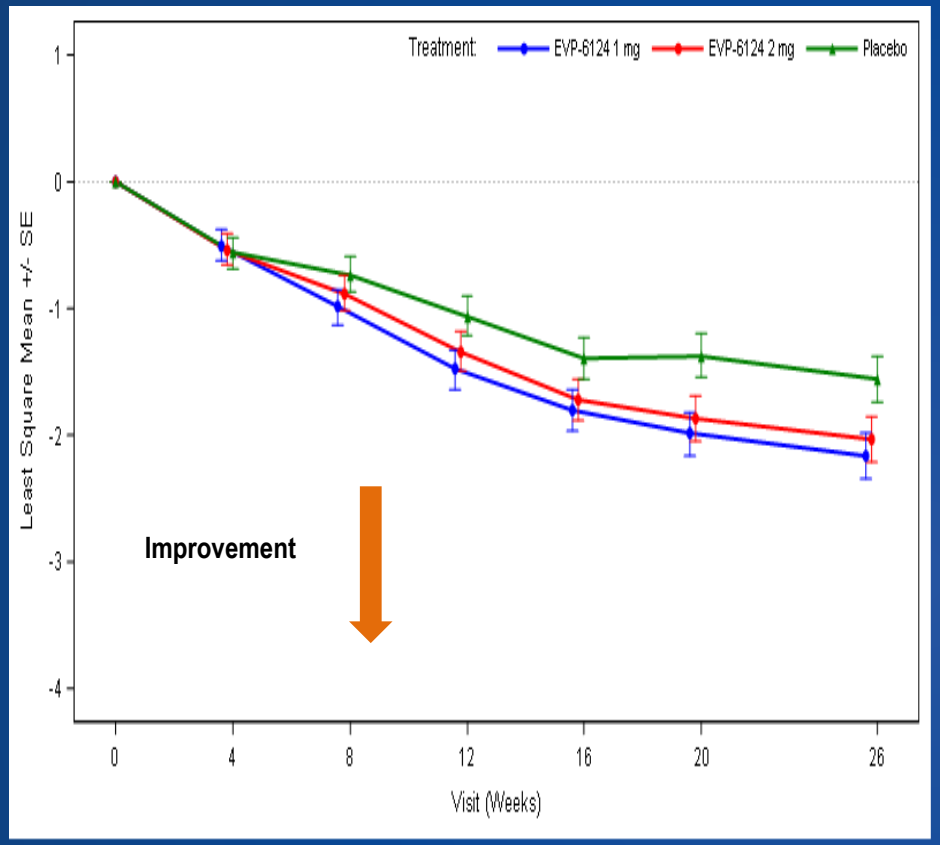
>=Two Antipsychotic Drugs



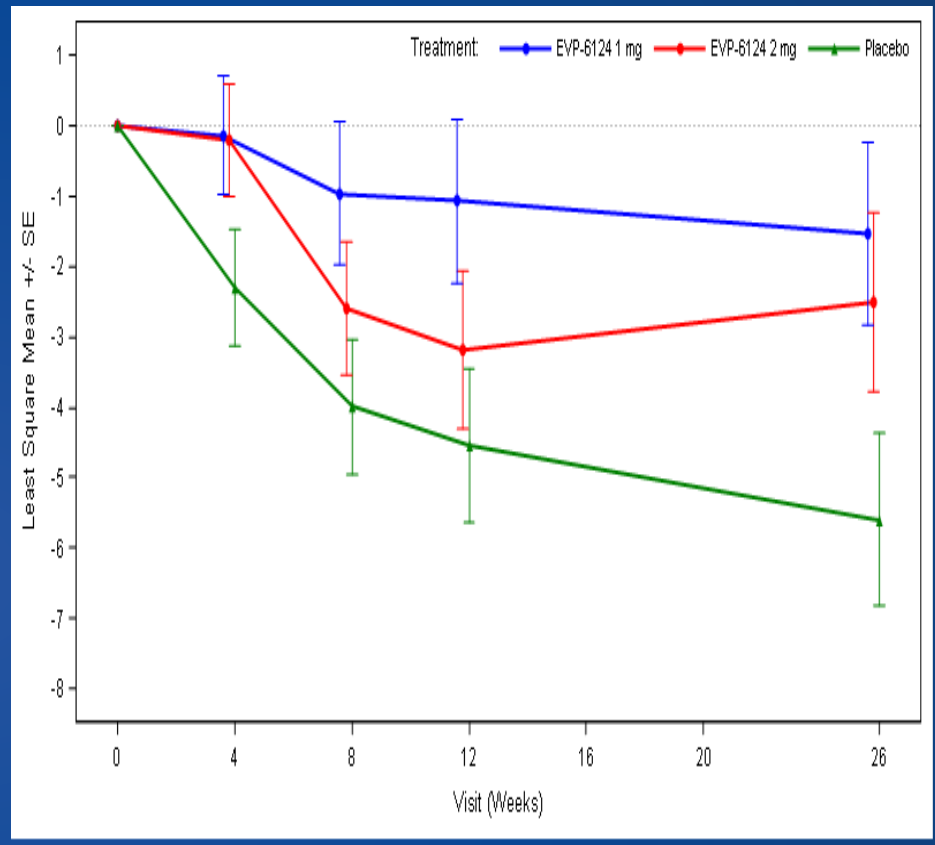
Least Squares Means (+/-SE) of Change from Baseline Overtime in the Neurocognitive Composite Scores by Treatment Group- EVP-6124-015+016

SUBJECTS STABILIZED ON 2 ANTIPSYCHOTICS SHOWED INCREASED PLACEBO RESPONSE THAN THOSE ON ONLY ONE ANTIPSYCHOTIC

One Antipsychotic Drug



>= Two Antipsychotic Drugs



ALSO IN NEGATIVE SYMPTOMS

Courtesy of Dr. Stephen Brannan

Polypharmacy

- Cohort studies show that antipsychotic polypharmacy might be more beneficial than monotherapy.
- Meta-analyses of RCTs show equivocal results.
- In any case, polypharmacy is very common in clinical use.
- Different antipsychotic compounds bind different receptors, suggesting that other mechanisms besides D2 blockade are efficacious.
- Polypharmacy is common in general medicine, ie treatment of hypertension or arthritis, where pathophysiology is better understood, justifying use of drugs with different and complementary mechanisms

Methodological Issues

- Add-on studies often exclude patients on polypharmacy
  - treatment resistant
  - mask a potential effect of the tested drug.
- This is problematic as large number of patients do get polypharmacy hence these RCTs are not representative,
- affect recruitment.
- Investigators sometimes stop polypharmacy in order to recruit patients who then relapse
- Polypharmacy is sometimes the last option for some patients who are non-responders, hence the long time to discontinuation reflects the lack of alternatives, rather then efficacy