UW PACC

Psychiatry and Addictions Case Conference

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ANTIPSYCHOTIC POLYPHARMACY

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GENERAL DISCLOSURES

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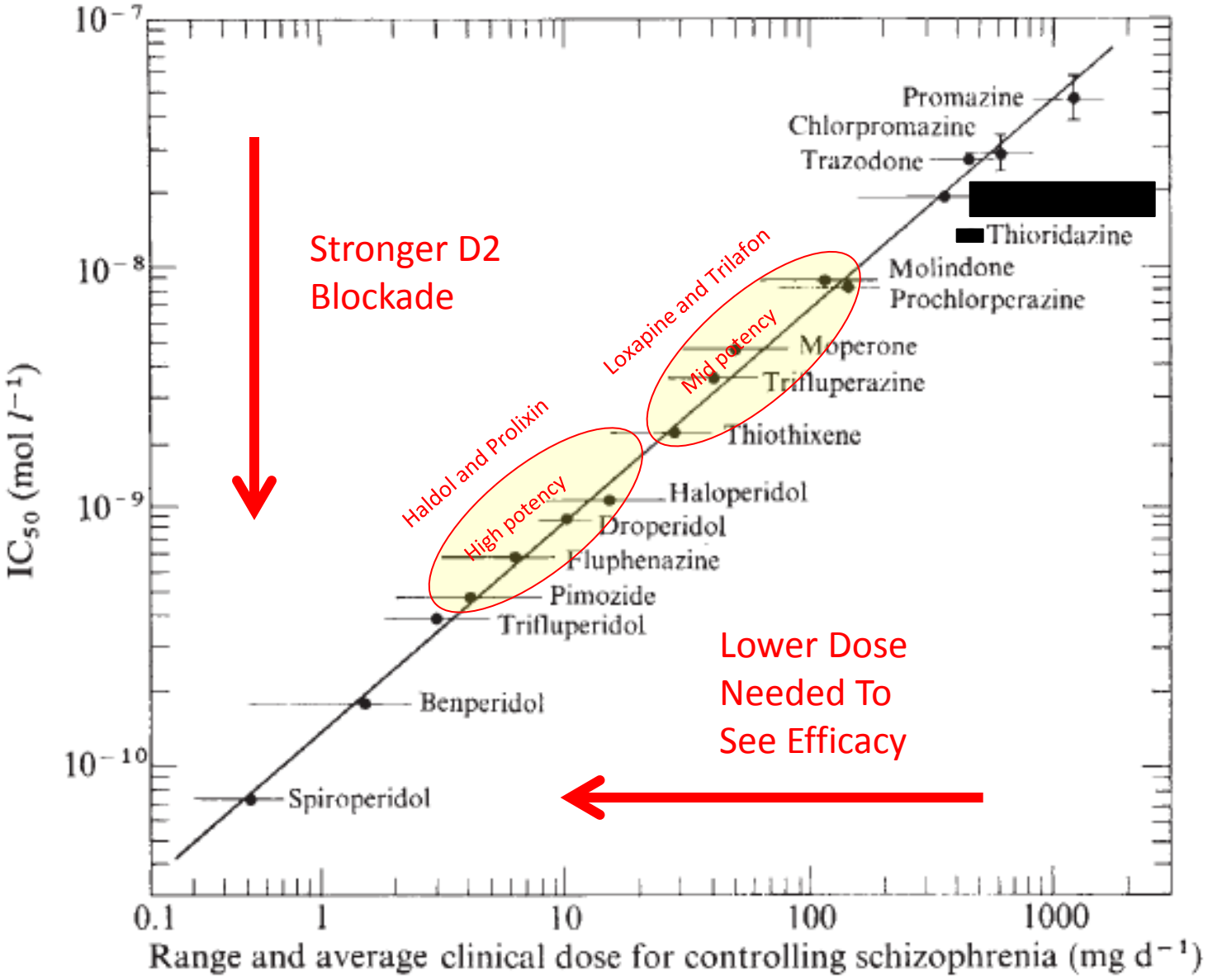
SPEAKER DISCLOSURES

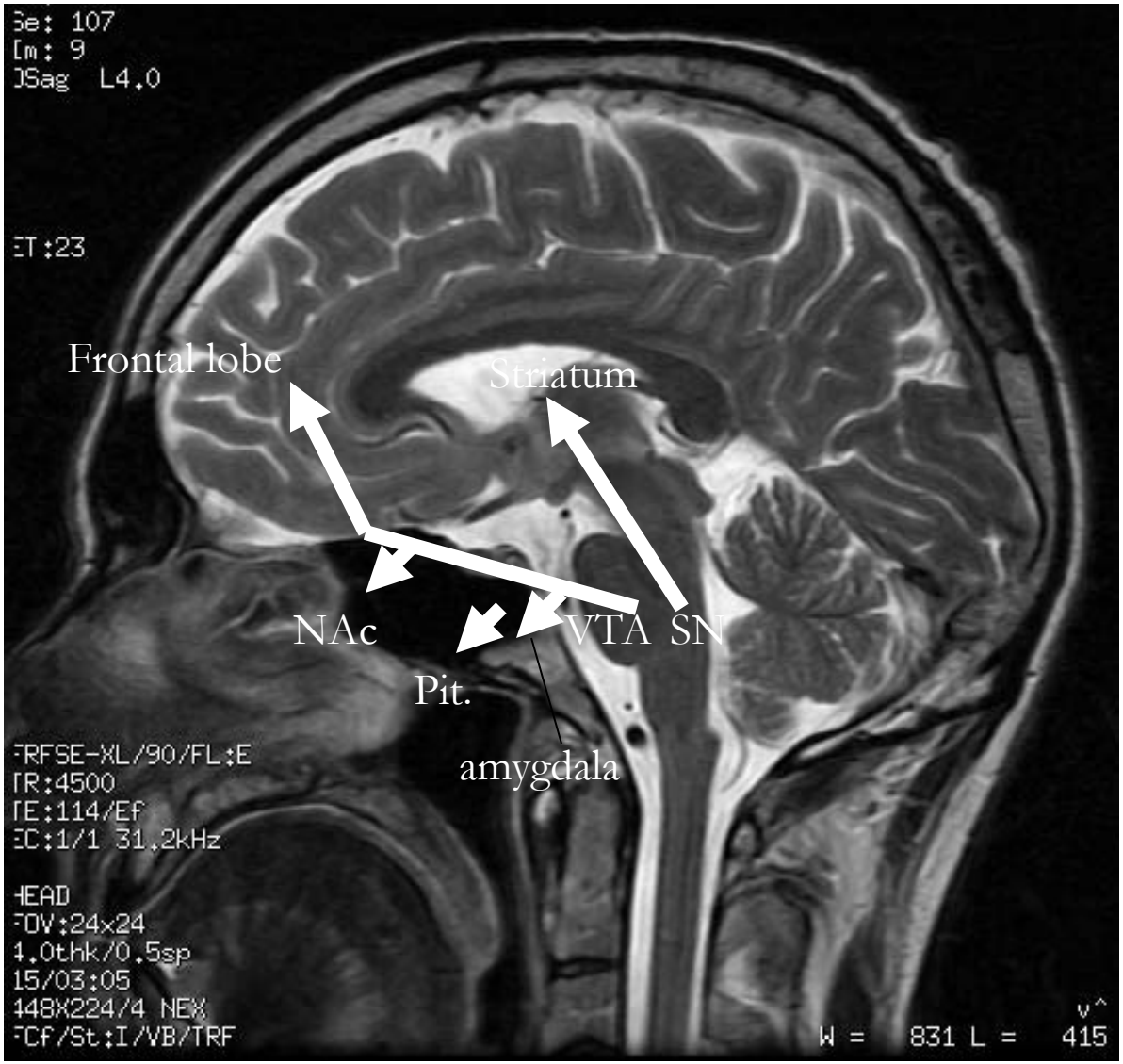
- ✓ No conflicts of interest.

HERE'S WHAT PSYCHIATRISTS KNEW IN 1976



(Seeman, Proc. Nat. Acad. Sci. USA, 1976)

DOPAMINE



AND THEN CLOZAPINE CAME ALONG AND DIDN'T NEED TO BLOCK AS MUCH DOPAMINE (45% OCCUPANCY VS. 70% OCCUPANCY), BUT WORKED BETTER…

- Clozapine has high 5-HT2A antagonism and 5-HT1A agonism. It also has 5-HT2C, 5-HT6, 5-HT7, D4, D3, D1, M1, and H1 binding.

- Since we don't really know why clozapine works, every subsequent antipsychotic has included a smattering of clozapine's binding profile…and a smattering of its problems.

ATYPICALS HAVE A RANGE OF D2 BINDING AFFINITIES, TOO

Drug	Daily Dose (mg)	D2 (Ki)
risperidone	4	6
paliperidone	6	6
asenapine	10	7
iloperidone	12	22
olanzapine	20	40
quetiapine	600	245
clozapine	600	343

Notes: 1. Dose is linear and Ki is logarithmic, so you can't draw a straight line graph with the atypicals

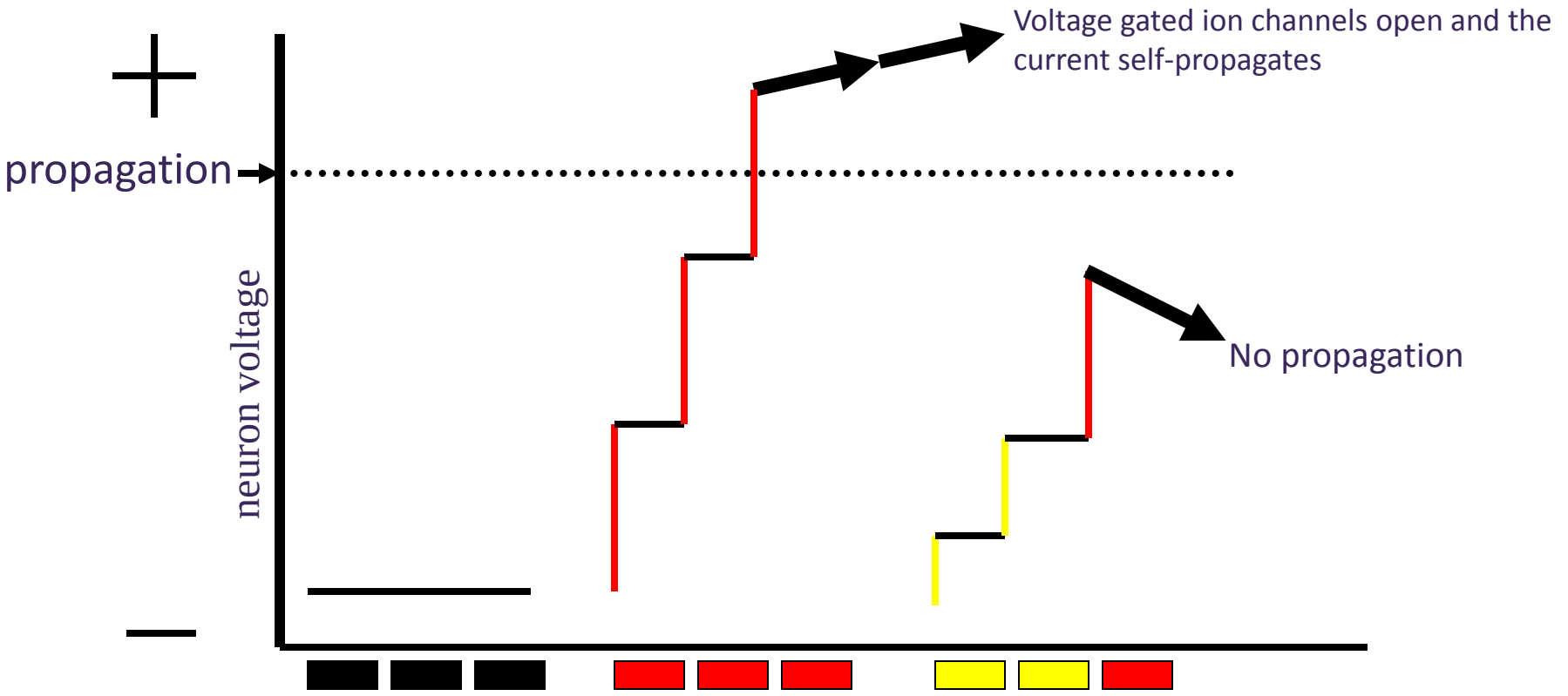
2. Use this chart to predict relative rate of D2 side effects.

INSERTING ABILIFY

Drug	Daily Dose (mg)	D2 (Ki)
aripiprazole	20	1.6
risperidone	4	6
paliperidone	6	6
asenapine	10	7
iloperidone	12	22
olanzapine	20	40
quetiapine	600	245
clozapine	600	343

VISUALIZING A PARTIAL AGONIST

(THERE MAY A WIDE DIFFERENCE BETWEEN THE SIMPLICITY OF THIS SLIDE AND THE COMPLEXITY OF REAL LIFE BIOLOGY.)



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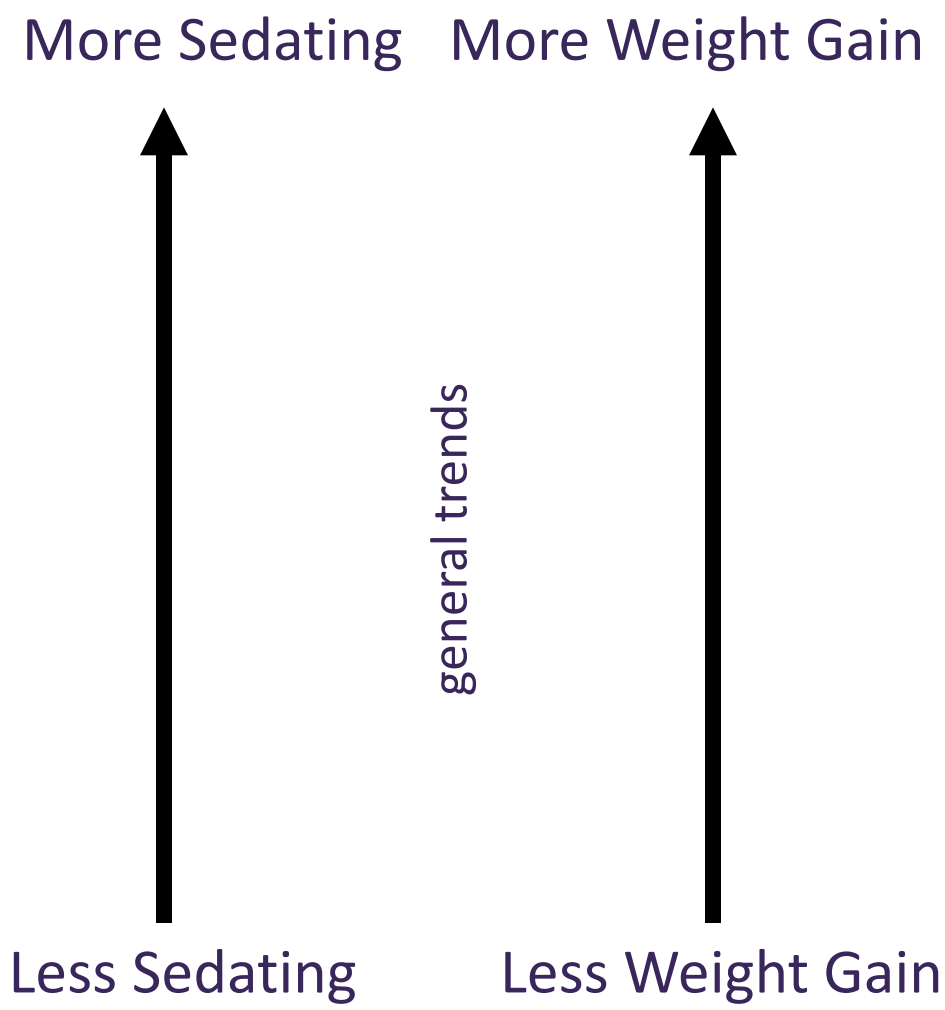
METABOLIC SIDE EFFECTS AND ANTI-HISTAMINE BINDING TRACK TOGETHER

Med	H1 (Ki)
• clozapine	1
• olanzapine	2
• quetiapine	7
• Iloperidone	12
• risperidone	20
• aripiprazole	28
• ziprasidone	63
• lurasidone	none
• haloperidol	none



Notes: Use this chart to predict relative rate of H1 side effects.

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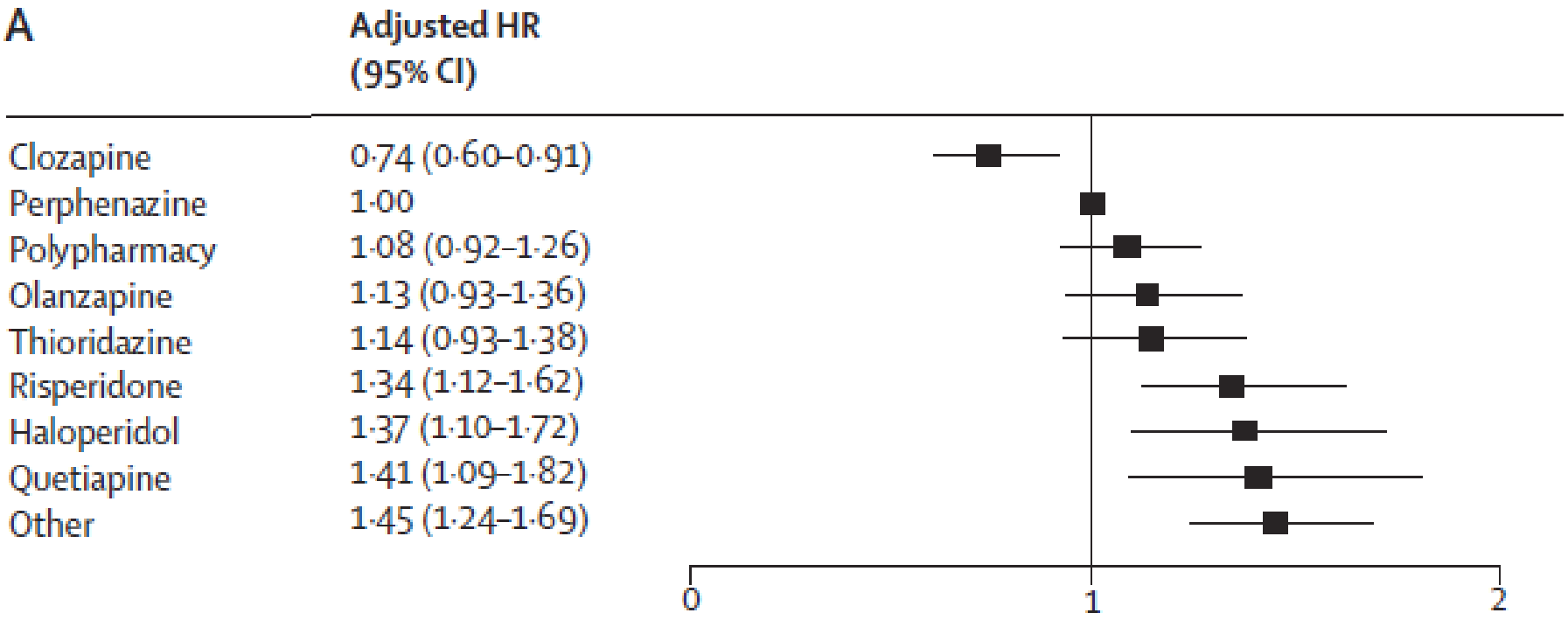
MY PITCH FOR CLOZAPINE

- Clozapine is the only medication that consistently shows efficacy in patients refractory to trials of other first-generation and second-generation antipsychotics.

- The agranulocytosis rate is 0.8%, mostly in the 1st year of treatment. More problematic is the weight gain, sedation, sialorrhea, seizures, and myocarditis.

ALL CAUSE MORTALITY OVER 11 YEARS IN PATIENTS WITH SCHIZOPHRENIA (N=76,881)



Tihonen et al., "11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). " Lancet, 2009 Aug 22;374(9690):620-7.

ANTIPSYCHOTIC POLYPHARMACY

- Despite a lack of evidence for efficacy, the incidence of antipsychotic polypharmacy is rising (Mojtabai and Olfson 2010).

- In the last 40 years, pharmaceutical companies have not been able to develop a medication (or combo-pill) that replicate's clozapine's efficacy. So…why are so many prescribers employing antipsychotic polypharmacy?

WHY WE TRY ANTIPSYCHOTIC POLYPHARMACY

- Avoiding side effects to full doses of the first med
- Mistaken assumption that adding quetiapine does not increase the EPS rate
- Trying to create a “super-atypical”
- Get stuck in cross-taper when patient got better
- Challenges of clozapine monitoring or afraid of clozapine side effects
- Underestimate the impact of poor antipsychotic adherence
- Patients with developmental disorders or dementia

SIDE EFFECTS OF ANTIPSYCHOTIC POLYPHARMACY

- Antipsychotic polypharmacy is associated with a higher risk of diabetes and a higher rate of the broader metabolic syndrome (Citrome, Jaffe et al. 2004; Correll, Frederickson et al. 2007).

- Antipsychotic polypharmacy leads to higher rates of anticholinergic med use to treat EPS (Patton, J Psychopharmacol, 2003).

Getting Stuck In A Cross Taper

Immediate vs. Gradual Discontinuation in Antipsychotic Switching: A Systematic Review and Meta-Analysis.
Takuechi et al., Schizophr Bull, 2017

- 9 studies involving 1416 patients
- "Gradual" = 1, 2, 3, or 4 weeks
- No difference in outcomes

For Patients on Antipsychotic Polypharmacy:

Every client deserves the opportunity to be tried on a lower risk regimen. A trial of a different regimen, with a clinical need to switch back, is not a failure. It documents that you tried.
– Molly Finnerty, MD