Psych Congress Elevate | 2020 VIRTUAL EXPERIENCE

Improved Techniques for Schizophrenia Treatment: *A Focus on Side Effect and Comorbidity Management*

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Disclosure

- **Dr. Citrome**: Consultant—Acadia, Alkermes, Allergan, Avanir, BioXcel, Eisai, Impel, Indivior, Intra-Cellular Therapies, Janssen, Lundbeck, Luye, Merck, Neurocrine, Noven, Osmotica, Otsuka, Pfizer, Sage, Shire, Sunovion, Takeda, Teva, Vanda; Speakers Bureau—Acadia, Alkermes, Allergan, Janssen, Lundbeck, Merck, Neurocrine, Otsuka, Pfizer, Sage, Shire, Sunovion, Takeda, Teva; Stocks (small number of shares of common stock)—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased > 10 years ago; Royalties—Wiley (Editor-in-Chief, *International Journal of Clinical Practice*, through end 2019), *UpToDate* (reviewer), Springer Healthcare (book), Elsevier (Topic Editor, Psychiatry, *Clinical Therapeutics*).

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - Olanzapine/samidorphan (ALKS 3831) is under review by the FDA and is not yet approved for commercial use. The off-label use of metformin, liraglutide, orlistat, topiramate, and aripiprazole for the treatment of antipsychotic-related weight gain will be discussed.
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Review the mechanisms of action and risk/safety profiles of novel and emerging agents and formulations for the treatment of schizophrenia
- Explore both pharmacologic and nonpharmacologic tactics for enhanced treatment adherence, including the successful management of side effects and comorbidities for improved patient quality of life
- Integrate patient-centered communication methods such as shared decision making and motivational interviewing into real-world treatment plans for patients with schizophrenia

Meet *Ronald*

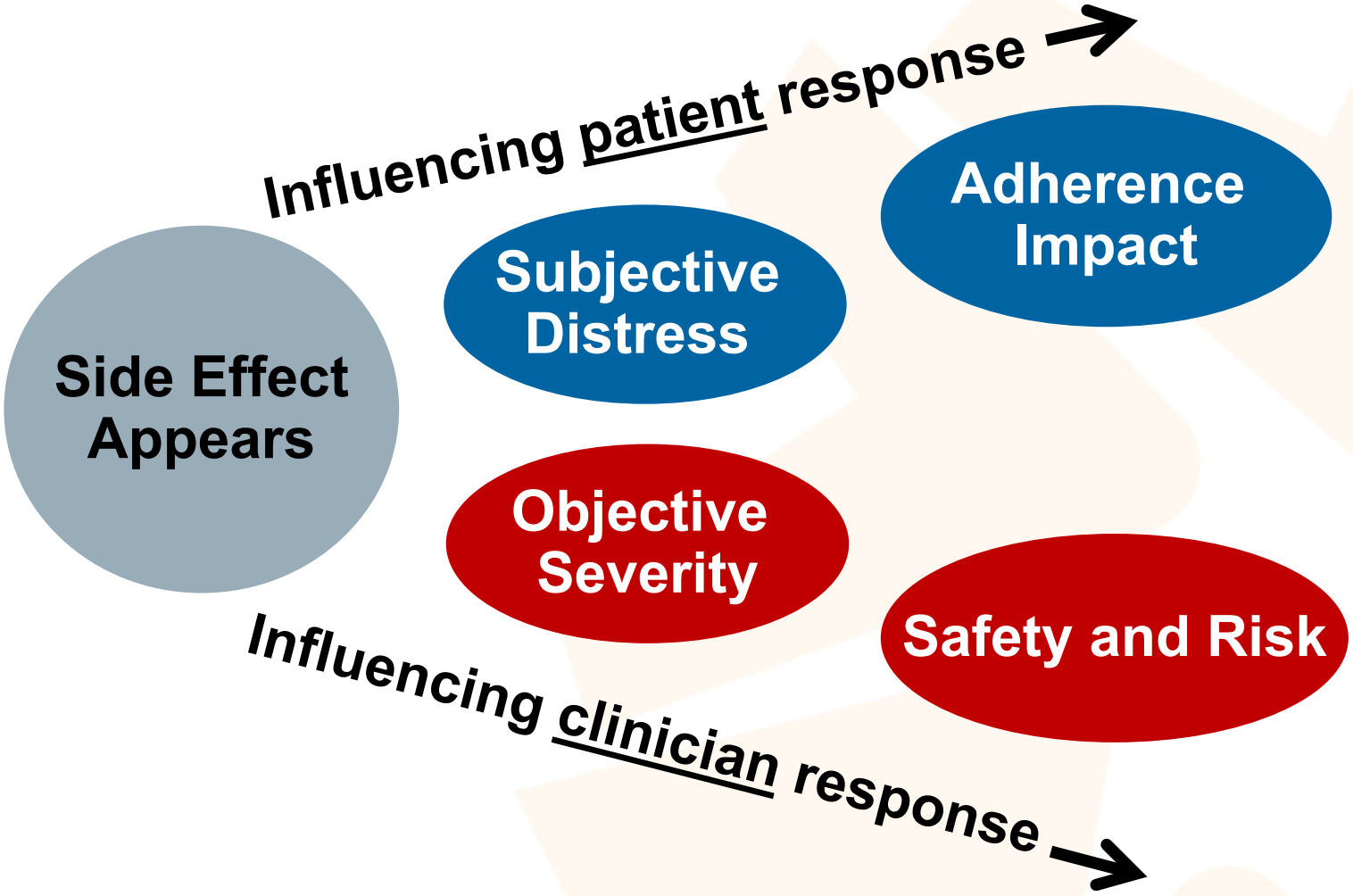
- Ronald is a 21-year-old second-year student at College, studying Liberal Arts
- Over a period of 6 months, Ronald's hygiene deteriorated, he became more isolative, and stopped attending classes; his friends did a well meaning "intervention" where Ronald accused them of being controlled by the CIA
- Upon evaluation at the Student Health Services, Ronald was diagnosed with acute schizophrenia and given quetiapine
- Ronald's psychosis was well controlled with quetiapine 400 mg/day, but after a month or so he complained bitterly that he was tired throughout the day and felt like a "zombie" and did not want to take the medicine any longer
- He was switched to aripiprazole with the idea of eventually convincing him to take the medicine by monthly injection; unfortunately he continued to complain of feeling sedated and also at the same time restless
- He also gained 20 lbs
- *What can we offer Ronald*?

Which medication-related side effects are the most important with regard to nonadherence?

- **Most commonly associated with nonadherence**
  - Weight gain
  - Sedation
  - Akathisia
  - Sexual dysfunction
  - Parkinsonian symptoms
  - Cognitive problems
- **Potential drivers**
  - Level of distress rather than severity
  - Attribution to the medication
  - Vary from patient to patient

Velligan DI, et al.; Expert Consensus Panel on Adherence Problems in Serious and Persistent Mental Illness. *J Clin Psychiatry*. 2009;70 Suppl 4:1-46.

Reverberations from Side Effects
How do patient and clinician responses differ?



Weiden PJ, et al. *J Clin Psychiatry*. 2007;68 Suppl 6:14-23.

Ronald should be engaged using Motivational Interviewing

- Basic premise of **MOTIVATIONAL INTERVIEWING**: A patient's ambivalence to change is normal and that all patients vary in their readiness to change
- Use open-ended questions and reflective listening
- Remember **RULE**
  - ***Resist*** making too many suggestions
  - ***Understand*** the patient's motivation
  - ***Listen*** with a patient-centered empathic approach
  - ***Empower*** the patient
- With Ronald we need to explore attitudes about efficacy, tolerability, and thoughts about daily adherence

Haque SF, et al. Motivational interviewing: The RULES, PACE, and OARS. *Current Psychiatry*. 2019;18(1):27-28. Lewis-Fernández R, et al. *J Clin Psychiatry*. 2018;79(3).

In Addition to the Problem of Nonadherence, Side Effects of Treatments for Schizophrenia Can Impose a Significant Overall Burden on Patients

In a study of 1825 participants with psychosis:

- **77%** reported medication side effects
- **61%** reported impairment in their daily life as a result of medication side effects
- **30%** reported moderate or severe impairment in their daily life as a result of medication side effects

Morgan VA, et al. *Aust N Z J Psychiatry*. 2012;46(8):735-752.

Side Effects of Treatments for Schizophrenia Can Impose a Significant Overall Burden on Patients

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- **61%** reported impairment in their daily life as a result of medication side effects
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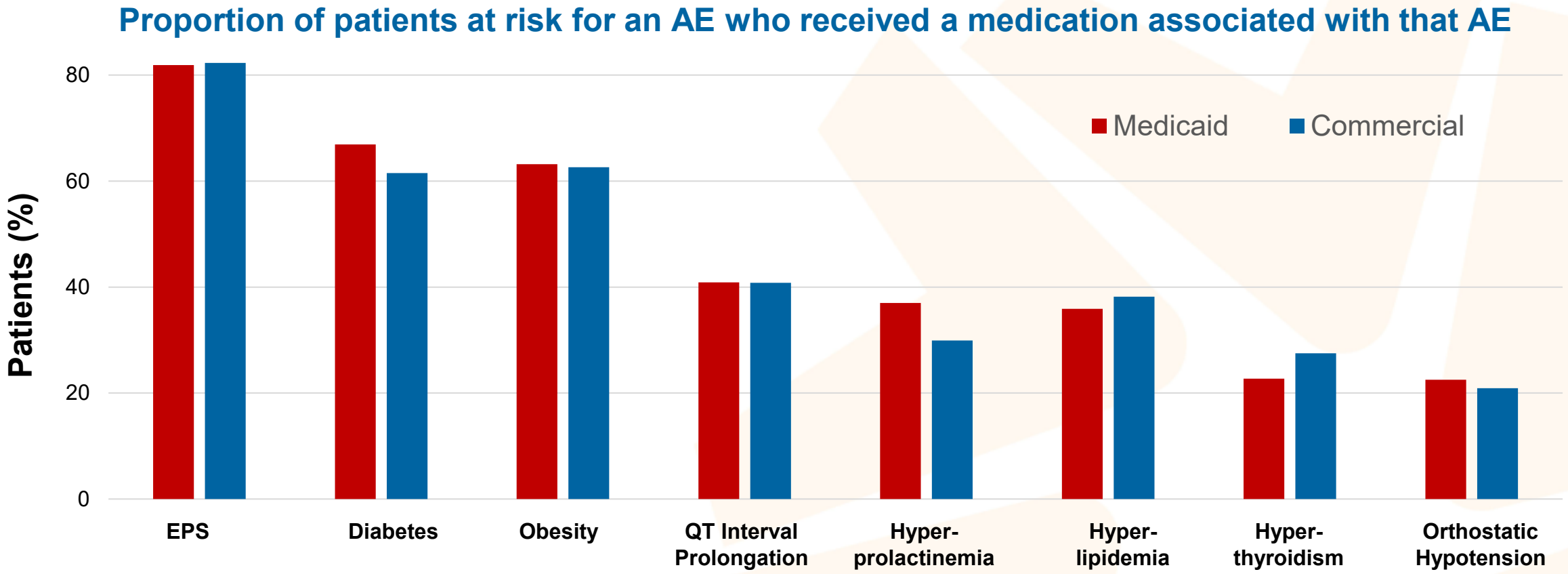
Side effects – **disabling; markedly affect quality of life**

If not addressed early, side effects can cause **long-term distress** and contribute to **chronic health complications**

Small shift in functional status – may have marked effects on **quality of life**

Morgan VA, et al. *Aust N Z J Psychiatry*. 2012;46(8):735-752. Awad AG, et al. *Acta Psychiatr Scand Suppl*. 1994;380:27-32. Barnes TR; Schizophrenia Consensus Group of British Association for Psychopharmacology. *J Psychopharmacol*. 2011;25(5):567-620.

Unfortunately, Patients with Specific AE Risk Factors are Often Treated with Agents Associated with That AE



Real-world data from Medicaid and commercial insurance claims showing proportion of patients likely to experience a given AE (ie, prior history, risk factors) who received a medication associated with that AE.

AE = adverse event; EPS = extrapyramidal symptoms.

Citrome L, et al. *Neuropsychiatr Dis Treat*. 2015;11:3095-3104.

Suboptimal Choices are Made Because of a Very Limited Number of Options for Patients at Risk

Individual Patient Segments Having:	Proportion of Patients with Schizophrenia within a Segment	Tolerable Treatment Options (prior to the availability of brexpiprazole, cariprazine, or lumateperone)
Segment 1 Diabetes, CVD, overweight, orthostatic hypotension, QTc prolongation	22% diabetes 13% CVD 23%–53% overweight 18%–40% orthostatic hypotension 3%–5% QTc prolongation	Aripiprazole, asenapine, lurasidone, paliperidone **4 options**
Segment 2 Considerations related to prolactin elevation	31%–39% increased prolactin 52% osteoporosis, 40% osteopenia 30%–80% sexual dysfunction 18% menstrual irregularities	Aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, quetiapine, ziprasidone **7 options**
Segment 3 Need to avoid excessive sedation	5%–25% in college or other school 20%–55% with part or full-time jobs 60% fatigue, 47% sedation	Aripiprazole, iloperidone, paliperidone, ziprasidone **4 options**
Segment 4 High risk of EPS / akathisia	34%–58% EPS 7%–35% akathisia	Iloperidone, quetiapine **2 options**

CVD = cardiovascular disease.

Citrome L, et al. *Neuropsychiatr Dis Treat*. 2015;11:3095-3104.

Treatment Options are Even More Limited for Patients with *Multiple* Commonly Co-occurring Risk Factor Segments

Patients with Characteristics from Multiple Segments			**Tolerable Treatment Options** (prior to the availability of brexpiprazole, cariprazine, or lumateperone)
Diabetes, CVD, overweight, orthostatic hypotension, QTc prolongation	1 and 2	Considerations related to prolactin elevation	Aripiprazole, asenapine, lurasidone **3 options combining segments 1 and 2**
Need to avoid excessive sedation	3 and 2	Considerations related to prolactin elevation	Aripiprazole, iloperidone, ziprasidone **3 options combining segments 3 and 2**
Need to avoid excessive sedation	3 and 4	High risk of EPS / akathisia	Iloperidone **1 option combining segments 3 and 4**
Diabetes, CVD, overweight, orthostatic hypotension, QTc prolongation	1 and 4	High risk of EPS / akathisia	**No options combining segments 1 and 4**

Citrome L, et al. *Neuropsychiatr Dis Treat*. 2015;11:3095-3104.

This Heterogeneity in Tolerability Can Be Due to Pharmacodynamic Factors

Association between Receptor Blockade and Side Effects

Receptor	Effects of Blockade
D_2	EPS/akathisia, tardive dyskinesia, increased prolactin
α_1 adrenergic	Postural hypotension, dizziness, syncope, akathisia (protective)
α_2 adrenergic	Increased blood pressure
H_1	Sedation, weight gain
M_1	Memory, cognition, dry mouth
$M_{2–4}$	Blurred vision, constipation, urinary retention
5-HT_{2C}	Increased appetite/weight(?)

Modified from: Correll CU. *Eur Psychiatry*. 2010;25 Suppl 2:S12-S21.

Stahl SM. *Stahl's Essential Psychopharmacology*. Fourth Edition. Cambridge University Press; 2013. Shayegan DK, et al. *CNS Spectr*. 2004;9(10 Suppl 11):6-14.

Antipsychotics Vary in Receptor Binding Affinities *In Vitro*

Binding affinity (K_i, nM), indicating partial agonist (pink) or antagonist (blue) activity

Receptor	Aripiprazole	Brexpiprazole	Cariprazine	Lurasidone	Quetiapine	Risperidone
D_2	0.34	0.30	0.49 (D_{2L}), 0.69 (D_{2S})	1	626	2.2
α_{1A}	25.7	3.8	155	NR	22	0.60
α_{1B}	34.8	0.17	NR	NR	14.6	9.0
α_{1D}	NR	2.6	208.9	NR	NR	NR
α_{2C}	37.9	0.59	NR	10.8	28.7	9.1
H_1	61	19	23.2	≥ 1000 (IC_{50})	4.41	19
M_1	6780	67% inhibition at 10 μM	> 1000 (IC_{50})	> 1000 (IC_{50})	1086	2800

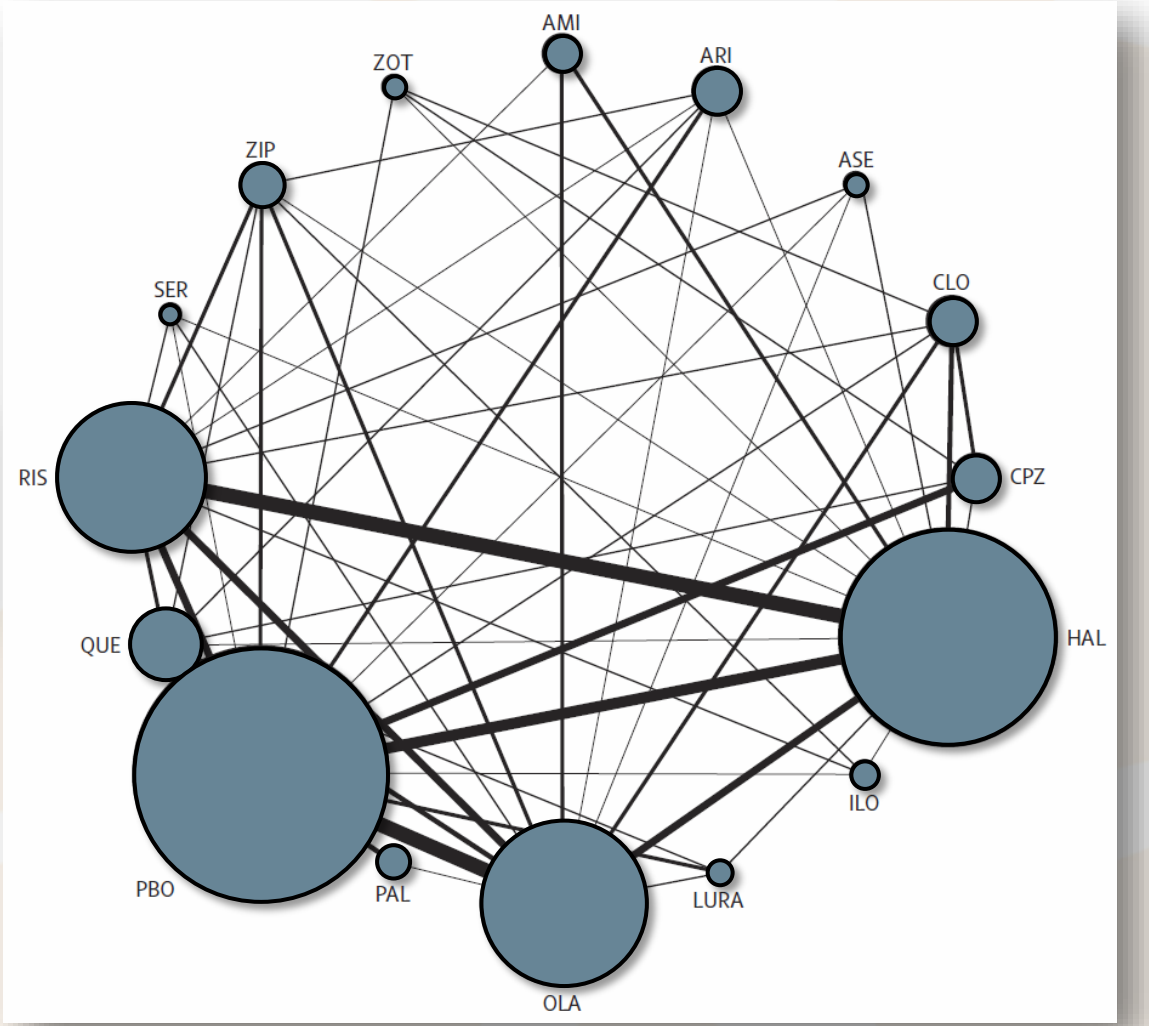
Data are from different experiments and are not intended for direct comparison; alternate sources may report different values, and there may be discrepancies due to species differences; partial agonist/antagonist activity from Stahl (2013), Maeda et al (2014), and Kiss et al (2010); brexpiprazole data are mean values calculated by nonlinear regression analysis using data from 3 assays performed in duplicate or triplicate; norquetiapine (active metabolite of quetiapine) has similar activity at D_2 receptors, but greater activity at 5-HT_{2A} receptors, compared to quetiapine; in addition, norquetiapine has a high affinity for muscarinic M_1 receptors (K_i=38.3 nM); IC_{50}=half-maximal inhibitory concentration; NR = not reported.

Prescribing information data used where available, otherwise published data. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/. Stahl SM. *Stahl's Essential Psychopharmacology*. Fourth Edition. Cambridge University Press; 2013. Shapiro DA, et al. *Neuropsychopharmacology*. 2003;28(8):1400-1411. Kiss B, et al. *J Pharmacol Exp Ther*. 2010;333(1):328-340. Ishibashi T, et al. *J Pharmacol Exp Ther*. 2010;334(1):171-181. Duncan GE, et al. *Mol Psychiatry*. 1999;4(5):418-428. Kroeze WK, et al. *Neuropsychopharmacology*. 2003;28(3):519-526. Maeda K, et al. Presented at: 2014 American Psychiatric Association Annual Meeting. PDSP 2014. Schotte A, et al. *Psychopharmacology*. 1996;124(1-2):57-73.

Deeper Dive—Therapeutic Features of Antipsychotics
All Drugs are Different

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

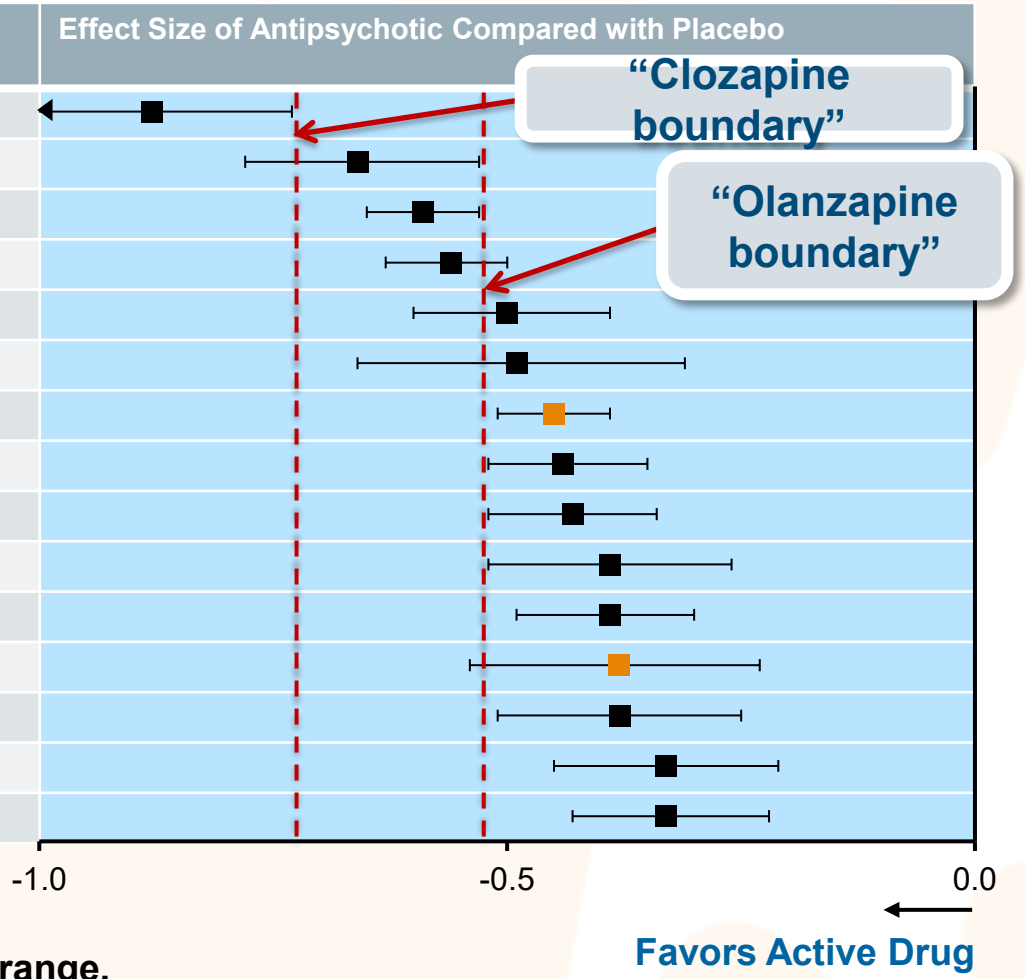


Leucht S, et al. *Lancet*. 2013;382(9896):951-962.

Rank Order for Efficacy

Overall Change in Symptoms

Drug	Standardized Mean Difference (95% CrI)
Clozapine	-0.88 (-1.03 to -0.73)
Amisulpride	-0.66 (-0.78 to -0.53)
Olanzapine	-0.59 (-0.65 to -0.53)
Risperidone	-0.56 (-0.63 to -0.50)
Paliperidone	-0.50 (-0.60 to -0.39)
Zotepine	-0.49 (-0.66 to -0.31)
Haloperidol	-0.45 (-0.51 to -0.39)
Quetiapine	-0.44 (-0.52 to -0.35)
Aripiprazole	-0.43 (-0.52 to -0.34)
Sertindole	-0.39 (-0.52 to -0.26)
Ziprasidone	-0.39 (-0.49 to -0.30)
Chlorpromazine	-0.38 (-0.54 to -0.23)
Asenapine	-0.38 (-0.51 to -0.25)
Lurasidone	-0.33 (-0.45 to -0.21)
Iloperidone	-0.33 (-0.43 to -0.22)



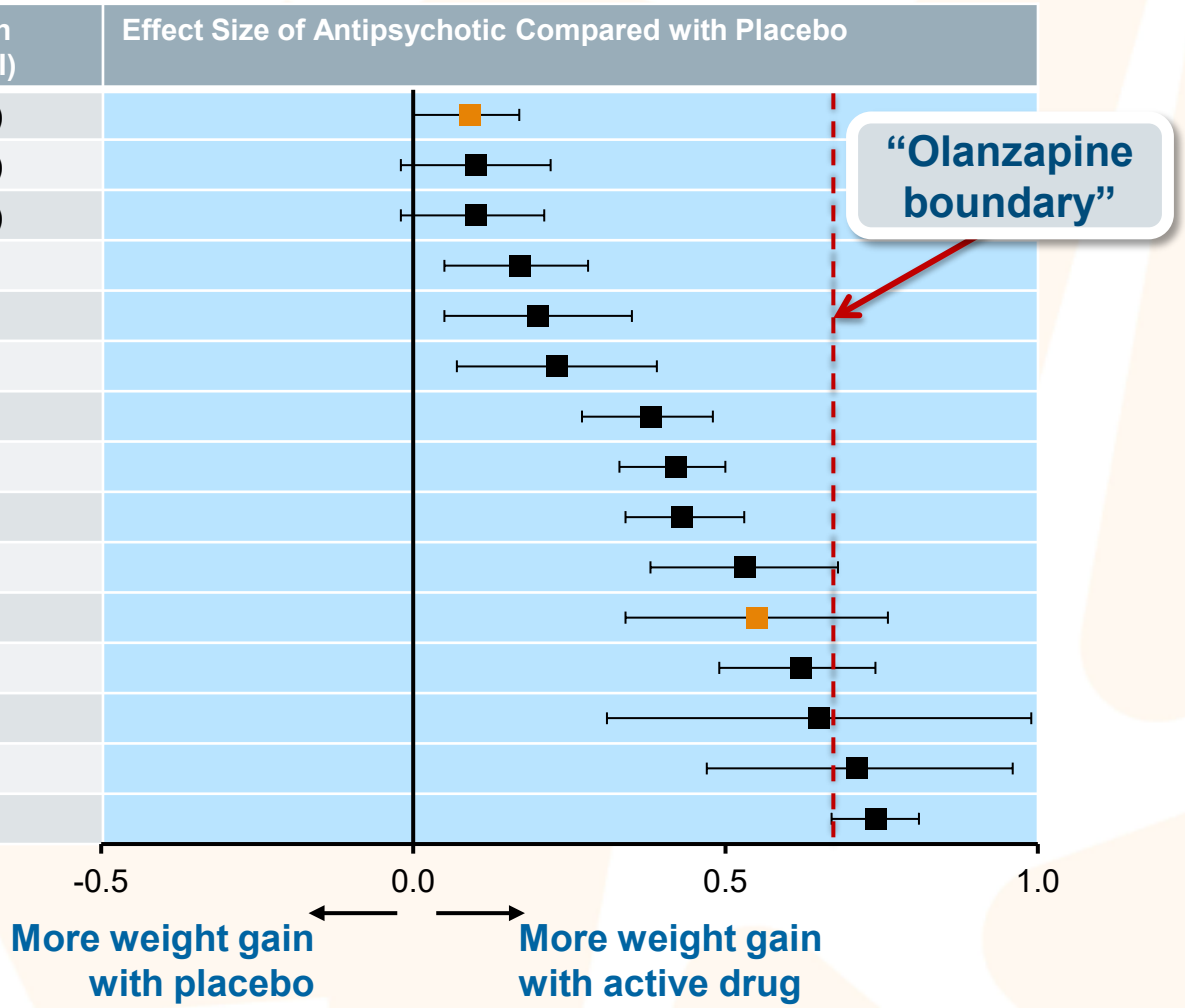
CrI = credible interval. Typical antipsychotics are shown in orange.

Leucht S, et al. *Lancet*. 2013;382(9896):951-962.

Different Rank Order for Weight Gain

Weight Gain

Drug	Standardized Mean Difference (95% CrI)
Haloperidol	0.09 (-0.00 to 0.17)
Ziprasidone	0.10 (-0.02 to 0.22)
Lurasidone	0.10 (-0.02 to 0.21)
Aripiprazole	0.17 (0.05 to 0.28)
Amisulpride	0.20 (0.05 to 0.35)
Asenapine	0.23 (0.07 to 0.39)
Paliperidone	0.38 (0.27 to 0.48)
Risperidone	0.42 (0.33 to 0.50)
Quetiapine	0.43 (0.34 to 0.53)
Sertindole	0.53 (0.38 to 0.68)
Chlorpromazine	0.55 (0.34 to 0.76)
Iloperidone	0.62 (0.49 to 0.74)
Clozapine	0.65 (0.31 to 0.99)
Zotepine	0.71 (0.47 to 0.96)
Olanzapine	0.74 (0.67 to 0.81)

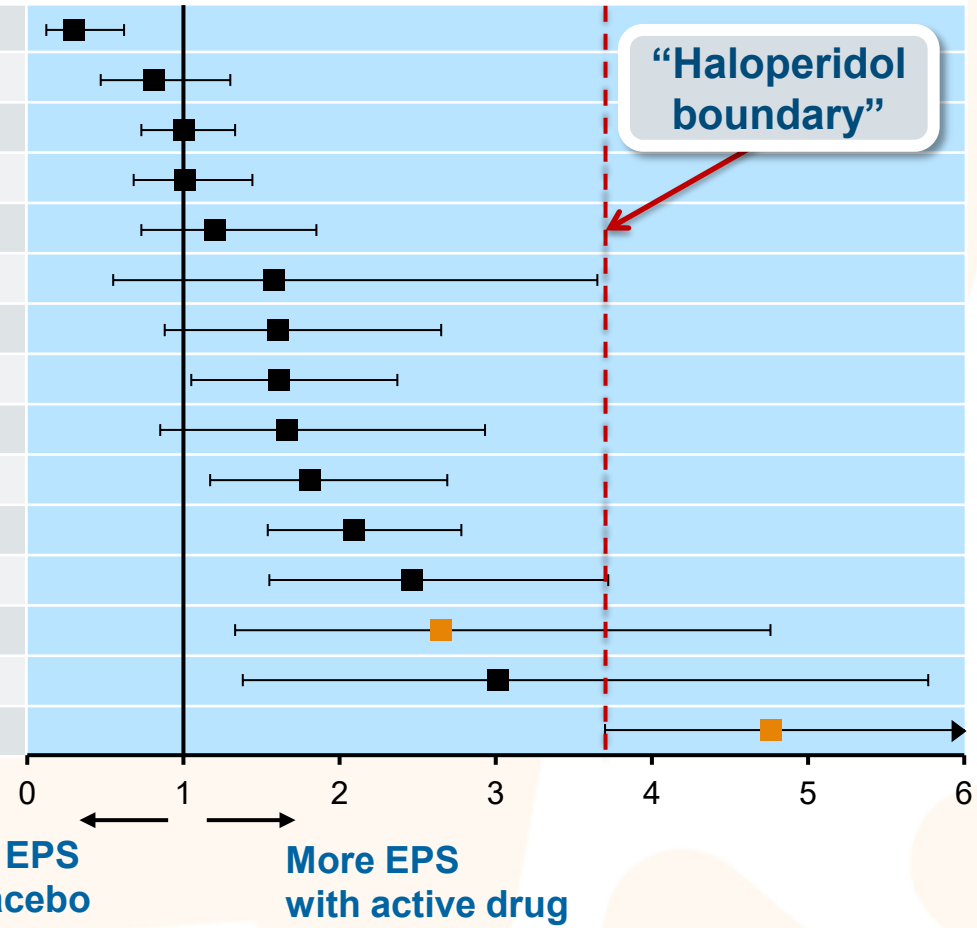


Leucht S, et al. *Lancet*. 2013;382(9896):951-962.

… and Different for EPS

EPS

Drug	Odds Ratio (95% CrI)
Clozapine	0.30 (0.12 to 0.62)
Sertindole	0.81 (0.47 to 1.30)
Olanzapine	1.00 (0.73 to 1.33)
Quetiapine	1.01 (0.68 to 1.44)
Aripiprazole	1.20 (0.73 to 1.85)
Iloperidone	1.58 (0.55 to 3.65)
Amisulpride	1.60 (0.88 to 2.65)
Ziprasidone	1.61 (1.05 to 2.37)
Asenapine	1.66 (0.85 to 2.93)
Paliperidone	1.81 (1.17 to 2.69)
Risperidone	2.09 (1.54 to 2.78)
Lurasidone	2.46 (1.55 to 3.72)
Chlorpromazine	2.65 (1.33 to 4.76)
Zotepine	3.01 (1.38 to 5.77)
Haloperidol	4.76 (3.70 to 6.04)



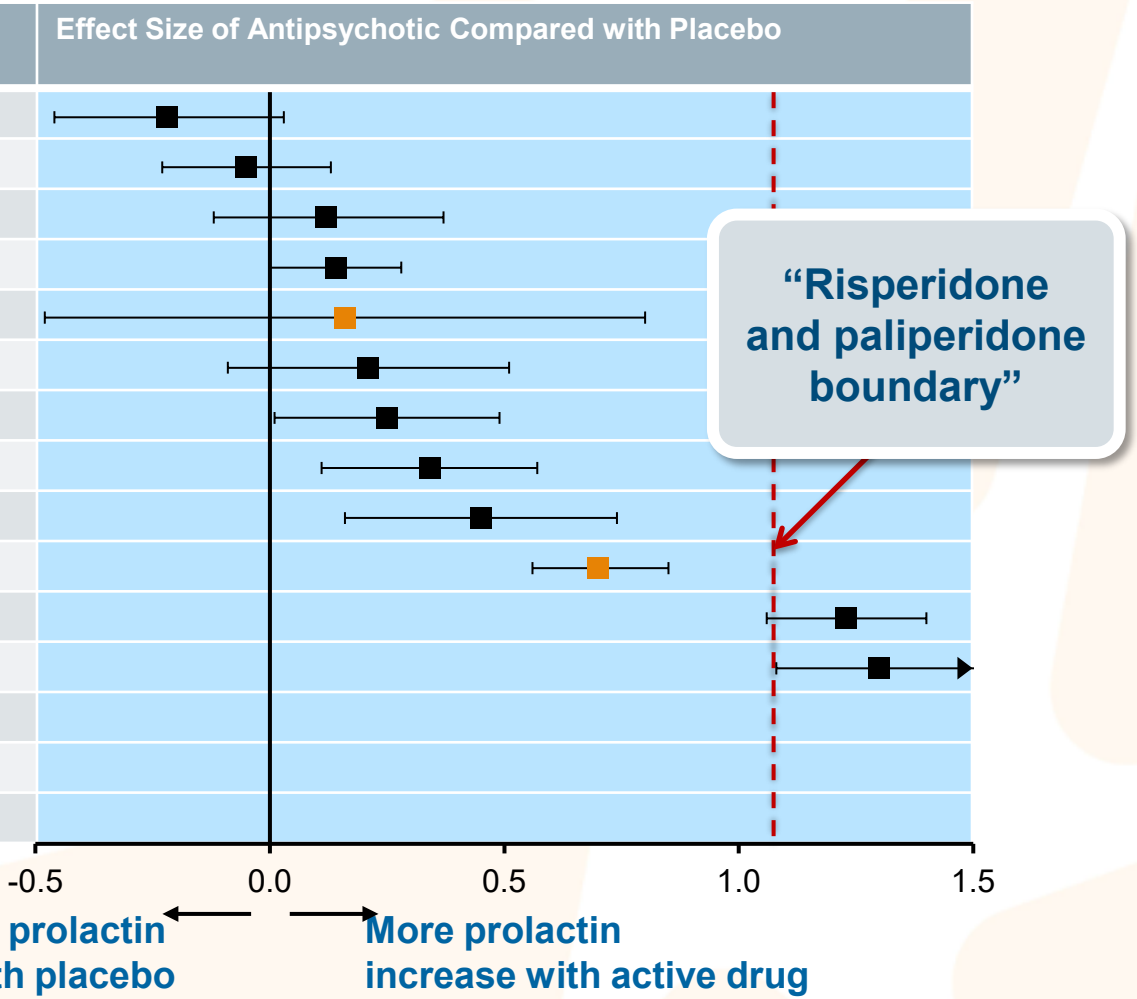
EPS assessed through use of anti-Parkinson medication.

Leucht S, et al. *Lancet*. 2013;382(9896):951-962.

… and Different for Prolactin Elevation

Prolactin Increase

Drug	Standardized Mean Difference (95% CrI)
Aripiprazole	-0.22 (-0.46 to 0.03)
Quetiapine	-0.05 (-0.23 to 0.13)
Asenapine	0.12 (-0.12 to 0.37)
Olanzapine	0.14 (0.00 to 0.28)
Chlorpromazine	0.16 (-0.48 to 0.80)
Iloperidone	0.21 (-0.09 to 0.51)
Ziprasidone	0.25 (0.01 to 0.49)
Lurasidone	0.34 (0.11 to 0.57)
Sertindole	0.45 (0.16 to 0.74)
Haloperidol	0.70 (0.56 to 0.85)
Risperidone	1.23 (1.06 to 1.40)
Paliperidone	1.30 (1.08 to 1.51)
Amisulpride	NA*
Clozapine	NA
Zotepine	NA



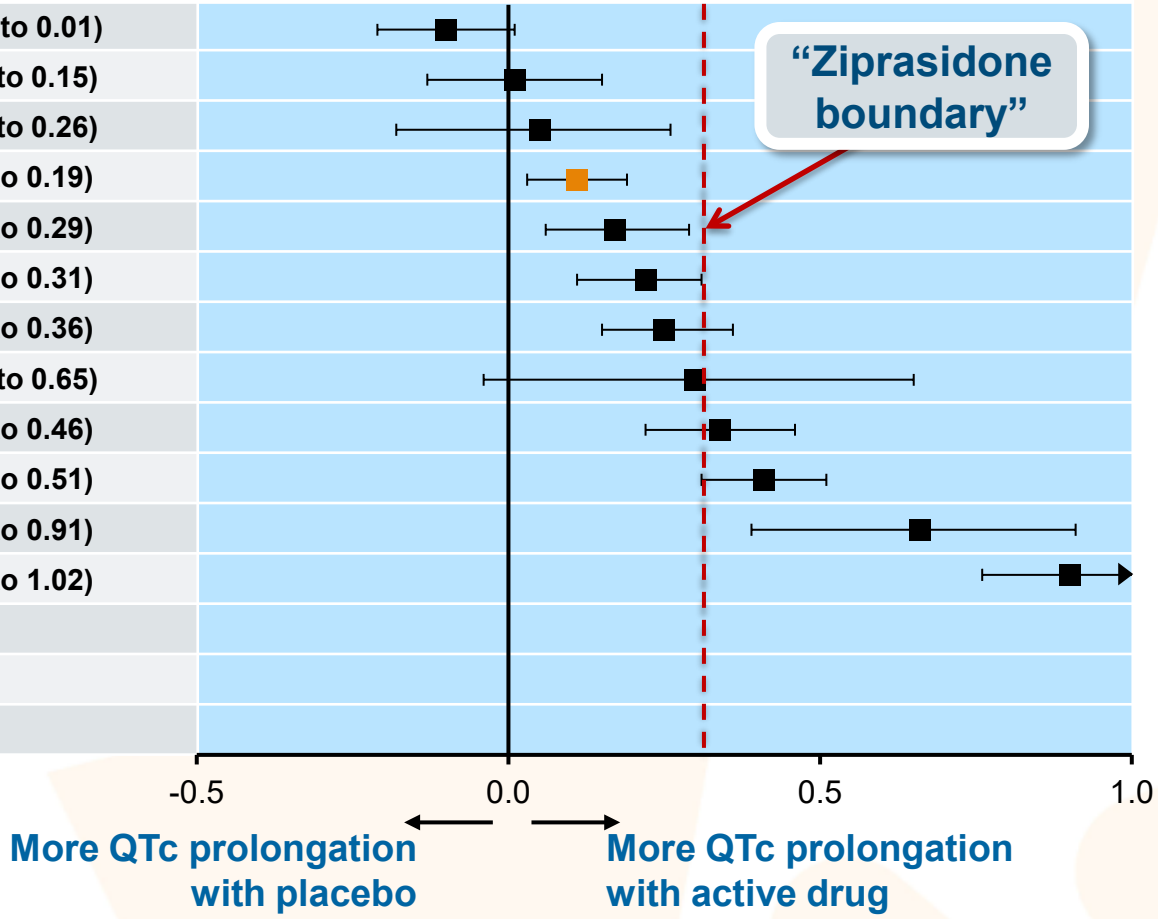
*In one small study, amisulpride produced less prolactin increase than haloperidol, but prolactin concentrations were highly imbalanced at baseline.

Leucht S, et al. *Lancet*. 2013;382(9896):951-962.

… and Different for QTc Prolongation

QTc Prolongation

Drug	Standardized Mean Difference (95% CrI)
Lurasidone	-0.10 (-0.21 to 0.01)
Aripiprazole	0.01 (-0.13 to 0.15)
Paliperidone	0.05 (-0.18 to 0.26)
Haloperidol	0.11 (0.03 to 0.19)
Quetiapine	0.17 (0.06 to 0.29)
Olanzapine	0.22 (0.11 to 0.31)
Risperidone	0.25 (0.15 to 0.36)
Asenapine	0.30 (-0.04 to 0.65)
Iloperidone	0.34 (0.22 to 0.46)
Ziprasidone	0.41 (0.31 to 0.51)
Amisulpride	0.66 (0.39 to 0.91)
Sertindole	0.90 (0.76 to 1.02)
Clozapine	NA
Chlorpromazine	NA
Zotepine	NA

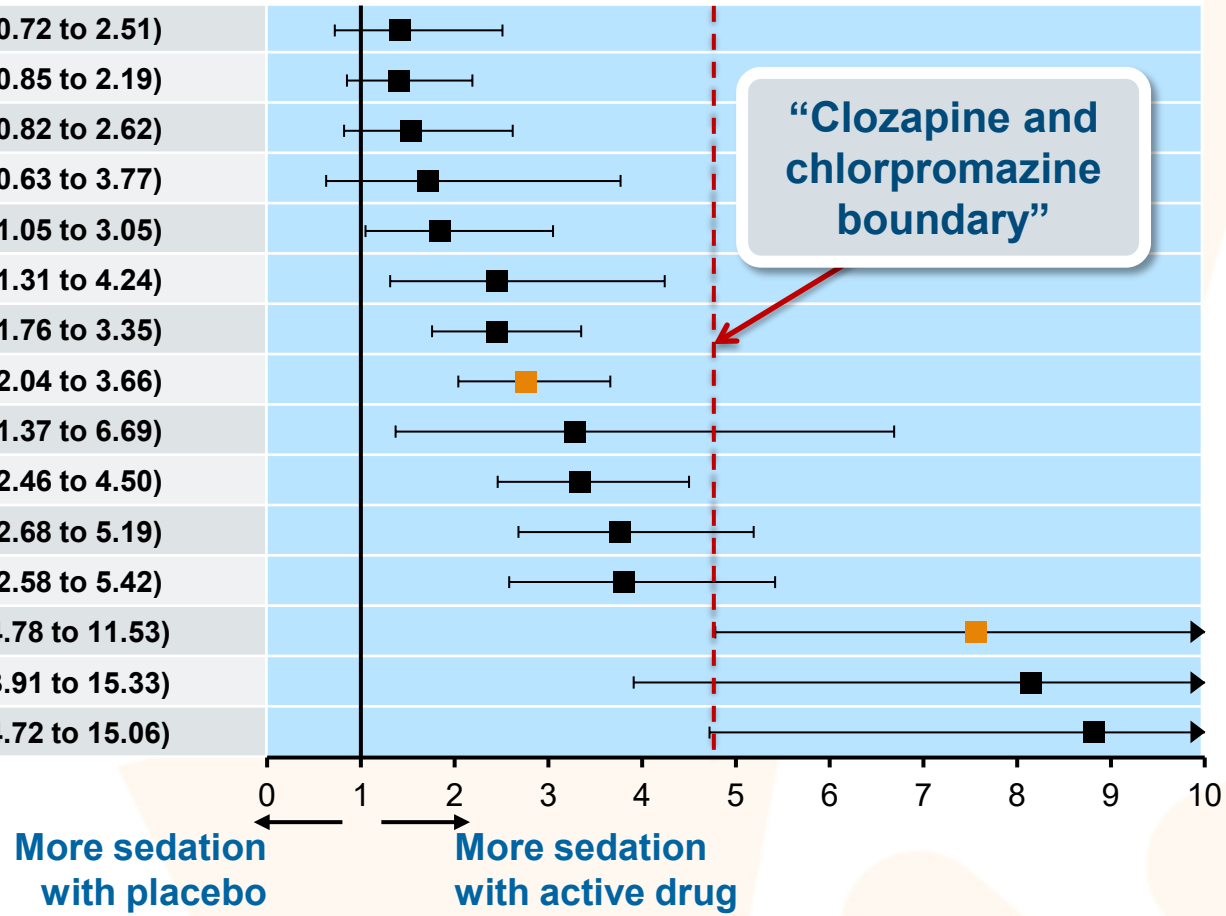


Leucht S, et al. *Lancet*. 2013;382(9896):951-962.

… and Different for Sedation

Sedation

Drug	Odds Ratio (95% CrI)
Amisulpride	1.42 (0.72 to 2.51)
Paliperidone	1.40 (0.85 to 2.19)
Sertindole	1.53 (0.82 to 2.62)
Iloperidone	1.71 (0.63 to 3.77)
Aripiprazole	1.84 (1.05 to 3.05)
Lurasidone	2.45 (1.31 to 4.24)
Risperidone	2.45 (1.76 to 3.35)
Haloperidol	2.76 (2.04 to 3.66)
Asenapine	3.28 (1.37 to 6.69)
Olanzapine	3.34 (2.46 to 4.50)
Quetiapine	3.76 (2.68 to 5.19)
Ziprasidone	3.80 (2.58 to 5.42)
Chlorpromazine	7.56 (4.78 to 11.53)
Zotepine	8.15 (3.91 to 15.33)
Clozapine	8.82 (4.72 to 15.06)



Leucht S, et al. *Lancet*. 2013;382(9896):951-962.

Let's Quantify by Calculating NNH vs Placebo

- How many patients would you need to treat with a medication instead of placebo before you would encounter 1 additional **adverse** outcome?
- The smaller the NNH, it takes fewer patients to treat with a medication vs placebo before encountering an additional adverse outcome
- Thus, the higher the NNH, the less likely one would encounter that outcome
- NNH is a measure of **clinical significance**
  - NNH does not measure statistical significance; it is not the same as a *P*-value
- NNH is an **absolute** effect size measure
  - NNH is not a relative effect size measure such as the relative risk or odds ratio that are sometimes used to describe adverse outcomes

NNH = number needed to harm.

Citrome L, et al. *Int J Clin Pract*. 2013;67(5):407-411.

NNH vs Placebo
Easy to Calculate

- What is the NNH for an outcome for Drug A vs placebo?
  - f_A = frequency of outcome for Drug A
  - f_B = frequency of outcome for placebo
  - Attributable Risk Increase (ARI) = $f_A - f_B$
  - NNT = 1/AR, by convention, when not presenting fractions, we round up the NNT to the next higher whole number in order to avoid exaggerating a difference (lower NNH values = larger effect)

For example, Drug A results in a headache 50% of the time, but placebo results in a headache 20% of the time:

NNH = 1/[0.50-0.20] = 1/0.30 = 3.33 → Round up to 4

NNT = number needed to treat.

Citrome L. *Curr Drug Saf*. 2009;4(3):1229-1237.

NNH vs Placebo
Easy to Calculate

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"For every 4 persons randomized to Drug A instead of placebo, you would encounter 1 additional person with a headache."

Citrome L. *Curr Drug Saf*. 2009;4(3):1229-1237.

How often can we expect weight gain ≥ 7%, somnolence, or akathisia in the short-term in schizophrenia?

NNH vs placebo can help answer this

Antipsychotic	NNH: Weight Gain	NNH: Somnolence AE	NNH: Akathisia AE
Aripiprazole	21	20†	25
Brexpiprazole	17	50‡	112
Cariprazine (to 6 mg/day)	34	100‡	15
Risperidone (to 8 mg/day)	18†	13	15
Olanzapine	6†	7†	25
Quetiapine IR	6	10†	ND
Quetiapine XR	22	7	188
Ziprasidone	16	15	100
Paliperidone	35	42	39
Iloperidone	10	16	ND
Asenapine	35	17	34
Lurasidone	67	11	10

†Reported in product labeling for schizophrenia and bipolar mania pooled together; ‡Somnolence, sedation, hypersomnia.
IR = immediate release; ND = no difference from placebo; XR = extended release.

Citrome L. *Clin Schizophr Relat Psychoses*. 2016;10(2):109-119.

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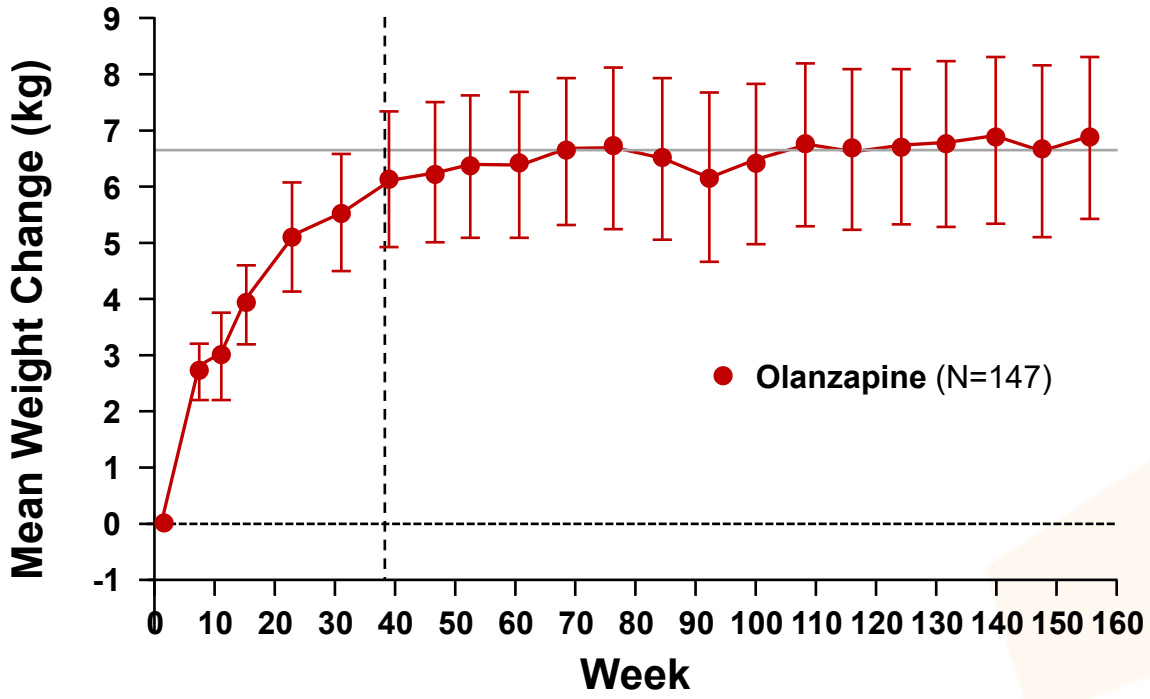
CAVEAT: Antipsychotic-Related Weight Gain

- Almost **all** antipsychotics are associated with weight gain
  - More pronounced in antipsychotic naïve patients
  - Can occur over time
  - Not clearly dose-dependent
- Antipsychotic-related weight gain is **polygenic** and associated with specific genetic variants, especially in genes coding for antipsychotic pharmacodynamic targets
- Nonetheless, there are differences that can be quantified when comparing groups of patients in clinical trials
- "Your individual mileage may vary"

Bak M, et al. *PLoS One*. 2014;9(4):e94112. Zhang JP, et al. *Schizophr Bull*. 2016;42(6):1418-1437.

Olanzapine Pattern of Weight Gain

Mean Change in Body Weight (kg) of Patients Treated with Olanzapine (N=147) Who Completed the Entire 3-Year Observation Period (observed cases)



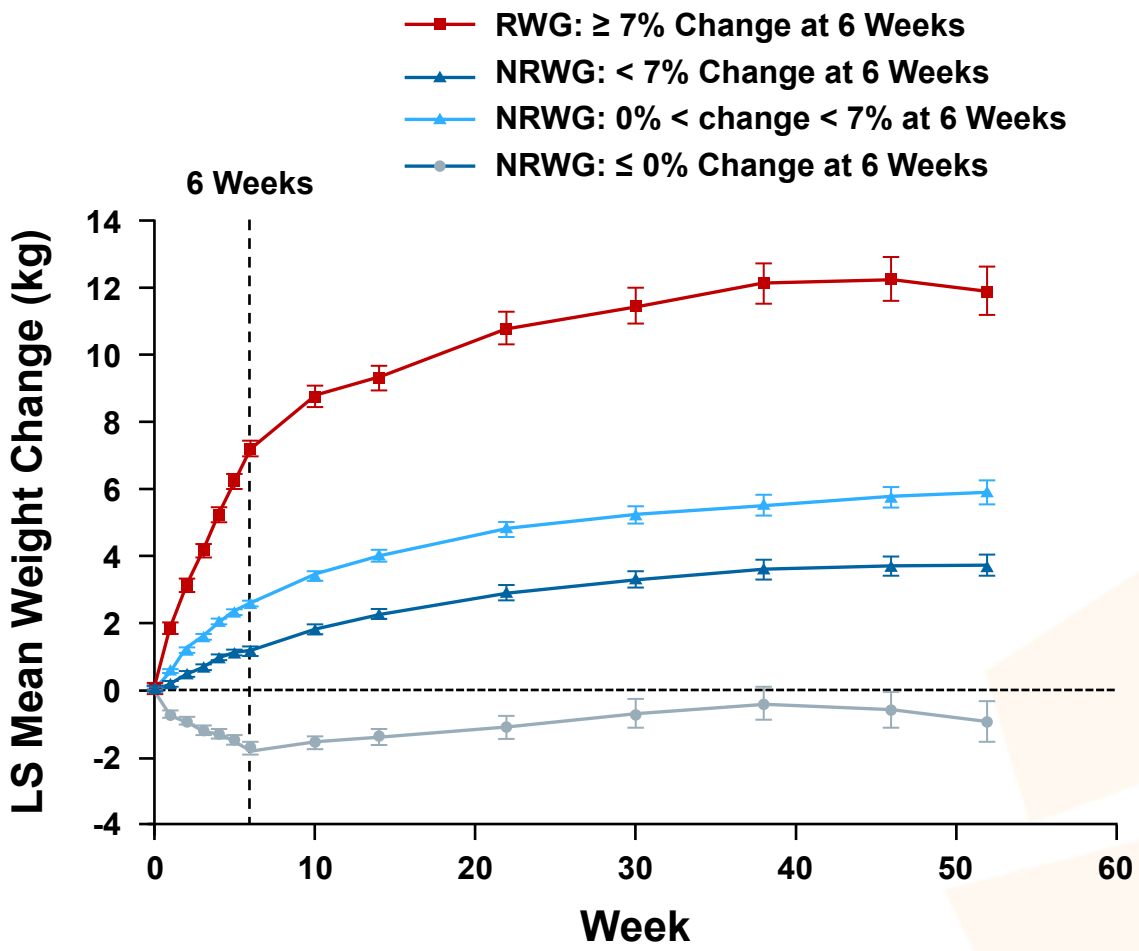
- Patients with higher baseline BMI (> 27.6) gained significantly less weight during treatment with olanzapine than their lighter counterparts
- The effect of olanzapine dose on weight was not significant

In long-term (≥ 48 weeks) studies the proportions of patients who gained at least 7%, 15%, or 25% of their baseline weight were 64%, 32%, and 12%, respectively.

BMI = body mass index.

Kinon BJ, et al. *J Clin Psychiatry*. 2001;62(2):92-100. Citrome L, et al. *Clin Drug Invest*. 2011;31(7):455-482.

Olanzapine Early Weight Gainers

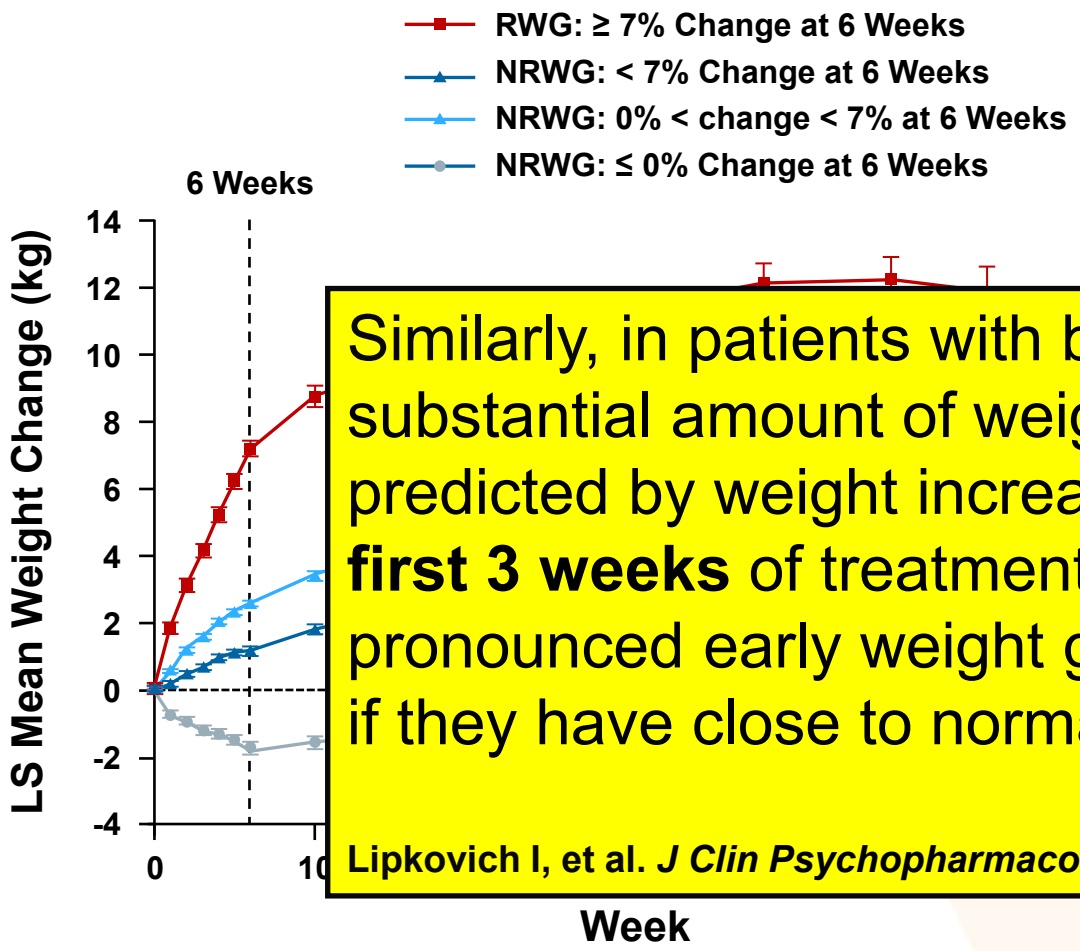


- **15%** showed rapid increases in weight (RWG group)
- In the RWG group, patients gained an average of 4% of their body weight (4–7 lbs) within the **first 2 weeks** of treatment with olanzapine
- Patients in the RWG group were **younger** and had a **lower baseline BMI**
- Over the course of 52 weeks, patients in the RWG group gained significantly **more weight** and reached a higher plateau for mean weight increase at 38 weeks

RWG = rapid weight gain group; NRWG = nonrapid weight gain group.

Kinon BJ, et al. *J Clin Psychopharmacol*. 2005;25(3):255-258.

Olanzapine Early Weight Gainers



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- were **baseline**
- ks, patients significantly a higher crease at 38 weeks

Similarly, in patients with bipolar mania or mixed mania, a substantial amount of weight gain after 30 weeks was predicted by weight increases of **2 to 3 kg within the first 3 weeks** of treatment. However, patients with less pronounced early weight gain might still be at risk if they have close to normal BMI at treatment initiation.

Lipkovich I, et al. *J Clin Psychopharmacol*. 2006;26(3):316-320.

RWG = rapid weight gain group; NRWG = nonrapid weight gain group.
Kinon BJ, et al. *J Clin Psychopharmacol*. 2005;25(3):255-258.

Can we use nonpharmacologic interventions for antipsychotic-associated weight gain?

Results of a meta-analysis

- 17 studies (n=810, mean age: 38.8 years, 52.7% male, 40.8% white, 85.6% with schizophrenia spectrum disorders)
- Significant reduction in weight (−3.12 kg) and BMI (−0.94 kg/m^2) compared with control groups
- Benefits extended to all secondary outcomes, except for high-density lipoprotein cholesterol and systolic blood pressure
- Subgroup analyses showed effects only in **outpatient** trials; effective treatments ranged from **nutritional interventions** to **cognitive-behavioral therapy**

Caemmerer J, et al. *Schizophr Res*. 2012;140(1-3):159-168.
See also Teasdale SB, et al. *Br J Psychiatry*. 2017;210(2):110-118.
Evaluation of the STructured lifestyle education for people WIth SchizophrEnia (STEPWISE) program: Gossage-Worrall R, et al. *BMC Psychiatry*. 2019;19:358.
Antidepressant and/or antipsychotic associated weight gain: Wharton S, et al. *Obesity*. 2019;27(9):1539-1544.

Does metformin work?

Meta-analysis

- 21 RCTs (n=1547) that tested metformin and placebo in patients taking antipsychotics
- Metformin was significantly superior to placebo in the primary outcome measures (body weight, BMI, fasting glucose, fasting insulin, triglycerides, and total cholesterol)
- Significantly higher frequencies of nausea/vomiting and diarrhea were found in the metformin group, but no differences were found in other adverse effects
- Adjunctive metformin is an effective, safe, and reasonable choice for antipsychotic-induced weight gain and metabolic abnormalities

RCT = randomized controlled trial.

Zheng W, et al. *J Clin Psychopharmacol*. 2015;35(5):499-509.

Using Metformin Early

- The best weight outcomes are from **preventing** initial weight gain rather than attempting weight loss later in treatment
- Initiate metformin concomitantly with or soon after the initiation of antipsychotic medication use; particularly important for young, healthy patients who receive olanzapine or clozapine
- When **combined with diet and lifestyle changes**, metformin's effects appear more pronounced
- Start with 500 mg, twice a day, or 850 mg, once a day, with meals; dosage should be increased in increments of 500 mg/weekly or 850 mg, every 2 weeks, up to 2000 mg/day, given in divided doses

Hendrick V, et al. *Ann Clin Psychiatry*. 2017;29(2):120-124.

Using Metformin Safely

- **GI adverse effects** are common with metformin: nausea, vomiting, abdominal discomfort, flatulence, and diarrhea
  - Minimize by using **gradual dose up-titration**, administration of the drug with meals, and use of a time-release formulation
- Lactic acidosis is very rare with metformin
  - Reduce risk by avoidance in patients with significantly impaired renal, liver, or cardiac functioning; check **creatinine levels annually**
- Metformin can impair vitamin B_{12} absorption: assess **serum B_{12} levels annually**

GI = gastrointestinal.

Andrade C. *J Clin Psychiatry*. 2016;77(11):e1491-e1494.

Other Rx for Weight Loss

- Medications approved for weight loss have generally not been assessed in RCTs in persons with schizophrenia
  - An exception is **liraglutide** (a GLP-1 receptor agonist) in patients with schizophrenia in stable treatment with clozapine or olanzapine, and who were overweight or obese, and had prediabetes; trial demonstrated efficacy
  - **Orlistat** (a GI lipase inhibitor) added to clozapine or olanzapine did not show efficacy
- **Topiramate** (may also be helpful in decreasing symptoms of schizophrenia); watch for cognitive effects
- Adding **aripiprazole** to clozapine (or olanzapine) may be another option

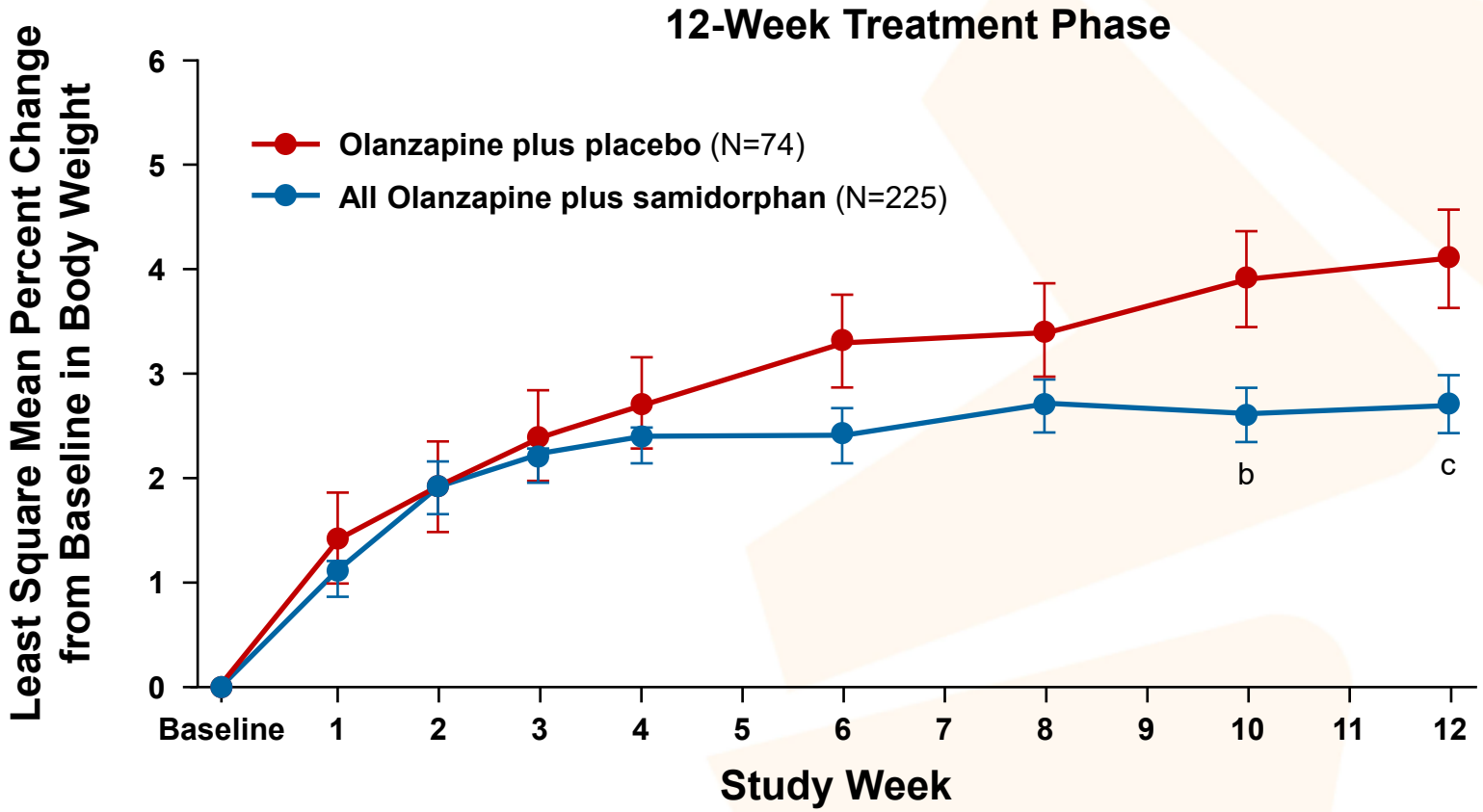
GLP-1 = glucagon-like peptide-1.

Larsen JR, et al. *JAMA Psychiatry*. 2017;74(7):719-728. Joffe G, et al. *J Clin Psychiatry*. 2008;69(5):706-711. Citrome L. *Int J Clin Pract*. 2014;68(12):1401-1405. Andrade C. *J Clin Psychiatry*. 2016:77(9):e1090-e1094.

Let's Make Olanzapine Great Again

Mitigation of olanzapine-induced weight gain with samidorphan, an opioid antagonist

Change in body weight from baseline for patients treated with olanzapine plus samidorphan or with olanzapine plus placebo, by visit, during the 12-week treatment and extension phases[a]



In vitro, samidorphan binds with high affinity to human μ-, κ-, and δ-opioid receptors and acts as an antagonist at μ-opioid receptors and a partial agonist at κ- and δ-opioid receptors

[a]Error bars indicate standard error. [b]*P*<.05 compared with olanzapine plus placebo. [c]*P*<.01 compared with olanzapine plus placebo.

Martin WF, et al. *Am J Psychiatry*. 2019;176(6):457-467.

The New Kid on the Block: Lumateperone

A quick read of the product label

- Atypical antipsychotic indicated for the treatment of schizophrenia in adults
- Recommended dosage 42 mg once daily, with food; no titration
- Lumateperone binding affinities (Ki in nM): **5-HT_{2A} (0.54) >> D_2 (32)** ~ SERT (33) ~ D_1 (41) > D_4, $alpha_{1A}$, $alpha_{1B}$ (< 100) >> muscarinic, histaminergic receptors (less than 50% inhibition at 100 nM)
- No difference from placebo in weight ≥ 7%
- Drug-induced EPS (including akathisia) similar to placebo, 6.7% vs 6.3%, NNH = 250
- Somnolence/sedation higher than for placebo, 24% vs 10%, NNH = 8

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Treatment is a Dynamic Process

- Switches offer both opportunity and risk
- A medication does not have to be perfect
  - Does it relieve symptoms well enough?
  - Is it tolerated well enough?
  - Is the patient willing to take it?
- Shared decision-making: Getting the patient to “buy-in” is key in promoting adherence
  - Individuals have their own preferences and values regarding which symptoms are important to them
  - Individuals have their own preferences and values regarding which tolerability issues are important to them

Volavka J, et al. *Expert Opin Pharmacother*. 2009;10(12):1917-1928.

Example of Empathic Patient-Centered Communication: LAIs and Adherence

- “You know, I have high blood pressure and take pills for that, and sometimes I forget. How often does that happen to you?”
- “How would you like to get your medicine once a month instead of a pill every day? I know I would!””
- “It must be hard to hear your Mother constantly ask if you have taken your medicine…”
- “It must be hard to remember if you had taken your medicine last night.”
- “This is different from when you were in the ER and got a shot…”
- “Would you like to give it a try? If you don’t want it again, you don’t have to have it.”

LAIs = long-acting injectable antipsychotics.

Choosing an Antipsychotic
Switch or Stay?

- Past history of efficacy of drug response
- Nature of psychiatric condition, acuity
- Target signs and symptoms
- Patient preference, history of adherence
- Need for special monitoring
- Amenable to other interventions to address tolerability?
  - Diet, exercise, and statins for obesity and dyslipidemia
  - Beta-blockers for akathisia
  - Anticholinergic medications for EPS

Citrome L. *CNS Drugs*. 2013;27(11):879-911.

Updated Treatment Options for Patients with *Multiple* Commonly Co-occurring Risk Factor Segments

Patients with Characteristics from Multiple Segments				Tolerable Treatment Options
Diabetes, CVD, overweight, orthostatic hypotension, QTc prolongation	1 and 2	Considerations related to prolactin elevation	**Can also now consider brexpiprazole, cariprazine, or lumateperone**	Aripiprazole, asenapine, lurasidone **3 options combining segments 1 and 2**
Need to avoid excessive sedation	3 and 2	Considerations related to prolactin elevation	**Can also now consider brexpiprazole or cariprazine**	Aripiprazole, iloperidone, ziprasidone **3 options combining segments 3 and 2**
Need to avoid excessive sedation	3 and 4	High risk of EPS / akathisia	**Can also now consider brexpiprazole**	Iloperidone **1 option combining segments 3 and 4**
Diabetes, CVD, overweight, orthostatic hypotension, QTc prolongation	1 and 4	High risk of EPS / akathisia	**Can also now consider brexpiprazole or lumateperone**	**No options combining segments 1 and 4**

Updated from: Citrome L, et al. *Neuropsychiatr Dis Treat*. 2015;11:3095-3104.

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Q&A