# Improving the Lives of Patients with Schizophrenia:
## *Therapeutic Updates and Considerations for Comprehensive, Multidisciplinary Care*

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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*).
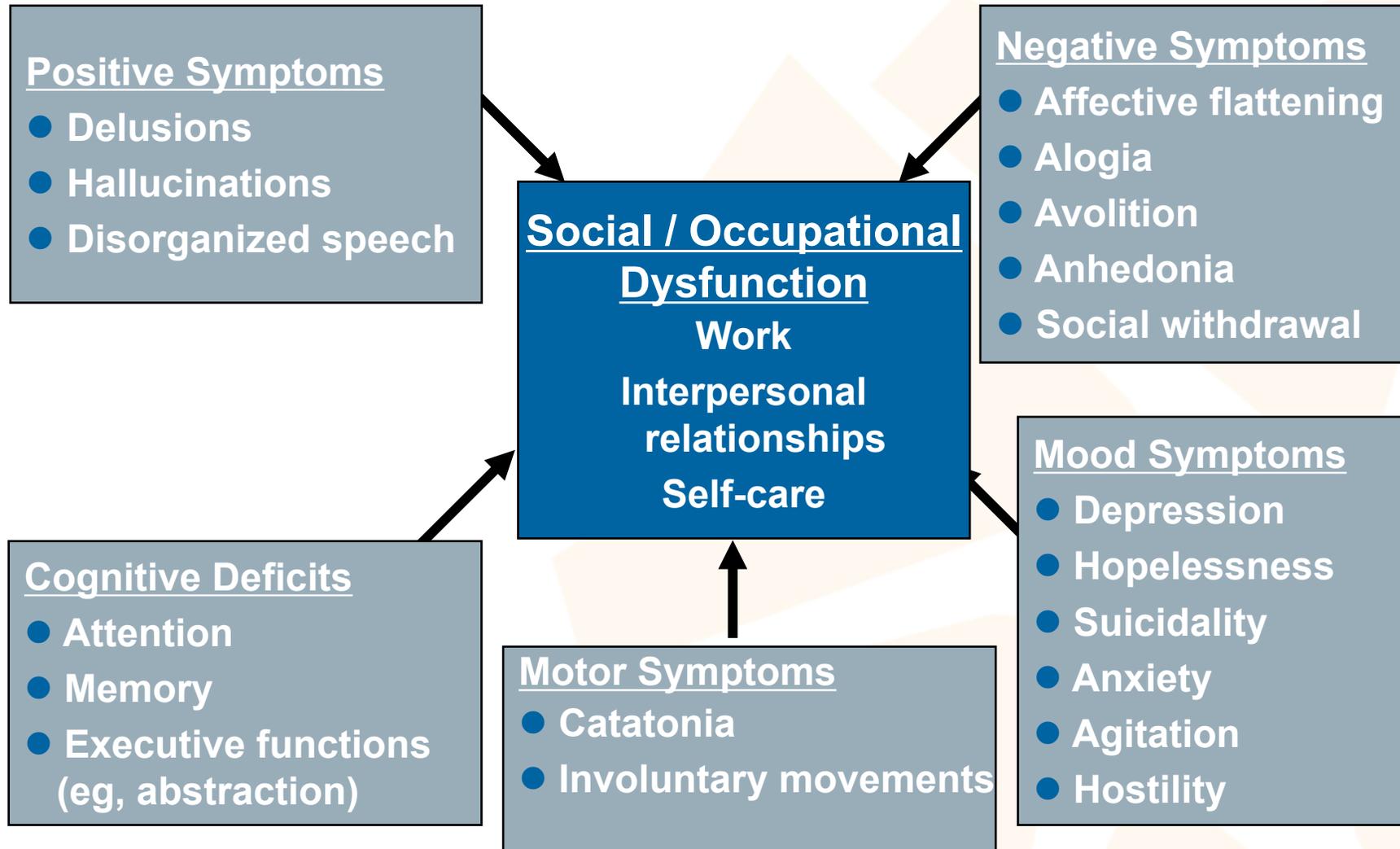
# Disclosure

- 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. Roluperidone is an investigational agent. Antidepressants are not approved treatments for schizophrenia.

- 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

- Outline the mechanisms of action and risk/safety profiles of novel and emerging agents and formulations for the treatment of schizophrenia

- Integrate pharmacologic and nonpharmacologic strategies to optimize treatment adherence and functional recovery into treatment plans for patients with schizophrenia

- Analyze the role that primary care, allied health, and behavioral practitioners can play in providing comprehensive, multidisciplinary treatment for patients with schizophrenia

# Clinical Features of Schizophrenia
## *All Patients are Different*

**Positive Symptoms**
- Delusions
- Hallucinations
- Disorganized speech

**Negative Symptoms**
- Affective flattening
- Alogia
- Avolition
- Anhedonia
- Social withdrawal

**Social / Occupational Dysfunction**
Work
Interpersonal relationships
Self-care

**Cognitive Deficits**
- Attention
- Memory
- Executive functions (eg, abstraction)

**Motor Symptoms**
- Catatonia
- Involuntary movements

**Mood Symptoms**
- Depression
- Hopelessness
- Suicidality
- Anxiety
- Agitation
- Hostility

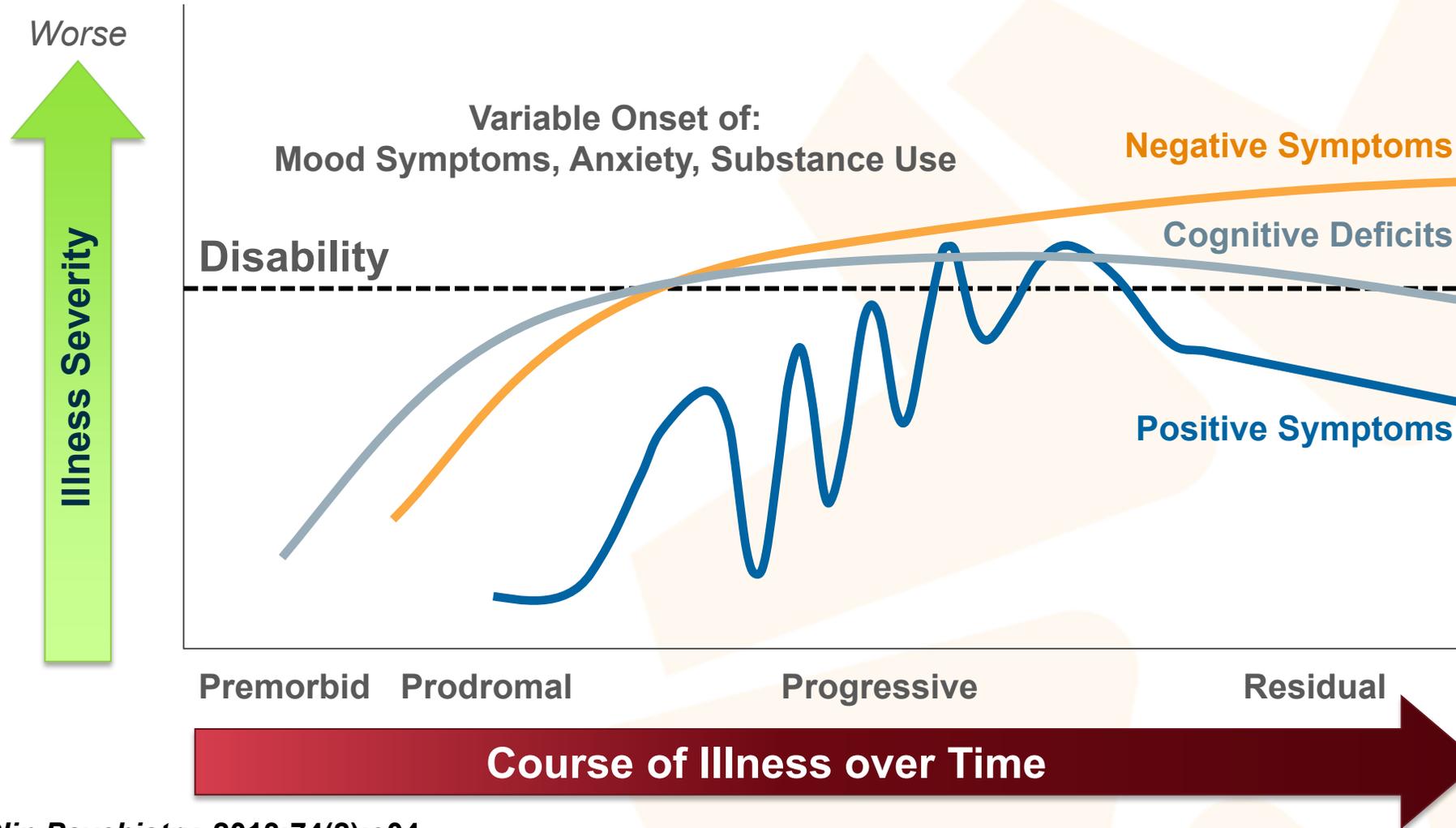Maguire GA. *Am J Health Syst Pharm*. 2002;59(17 Suppl 5):S4-S11.

# Meet *Zoe*

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

# *Zoe* Has Multiple Types of Symptoms
## *What are their typical time course*?

Correll CU. *J Clin Psychiatry*. 2013;74(2):e04.
See: www.cmeinstitute.com/psychlopedia/Documents/psychosis/5cpem/sec3/psy5-3_AV1.htm. Accessed April 13, 2020.

# Negative Psychopathology: Some Definitions

- **Avolition**: Or apathy; A lack of energy and a seeming absence of interest in routine activities
- **Alogia**: A negative "thought disorder"
  – Poverty of speech
  – Poverty of content
- **Anhedonia**: Inability to experience pleasure
- **Affective Flattening or Blunting**: Markedly decreased emotional response to a stimulus
- **Asociality**: Severe impairments in social relationships

Kirkpatrick B, et al. *Schizophr Bull*. 2006;32(2):214-219.

# Negative Symptoms: Primary vs Secondary

- **Primary** negative symptoms are the enduring symptoms present at the onset of the illness (often prior to the psychotic symptoms)
- **Secondary** negative symptoms are due to other factors, such as
  - Extrapyramidal side effects
  - Sedation
  - Paranoid symptoms (these are positive symptoms)
  - Depression
  - Anxiety
  - Comorbid cerebral lesions, including strokes in the frontal cortex, thalamus, or putamen
  - Chronic pain
  - Environmental deprivation/understimulation

Kirkpatrick B, et al. *Schizophr Bull*. 2006;32(2):214-219. Correll CU. *J Clin Psychiatry*. 2013;74(2):e04.
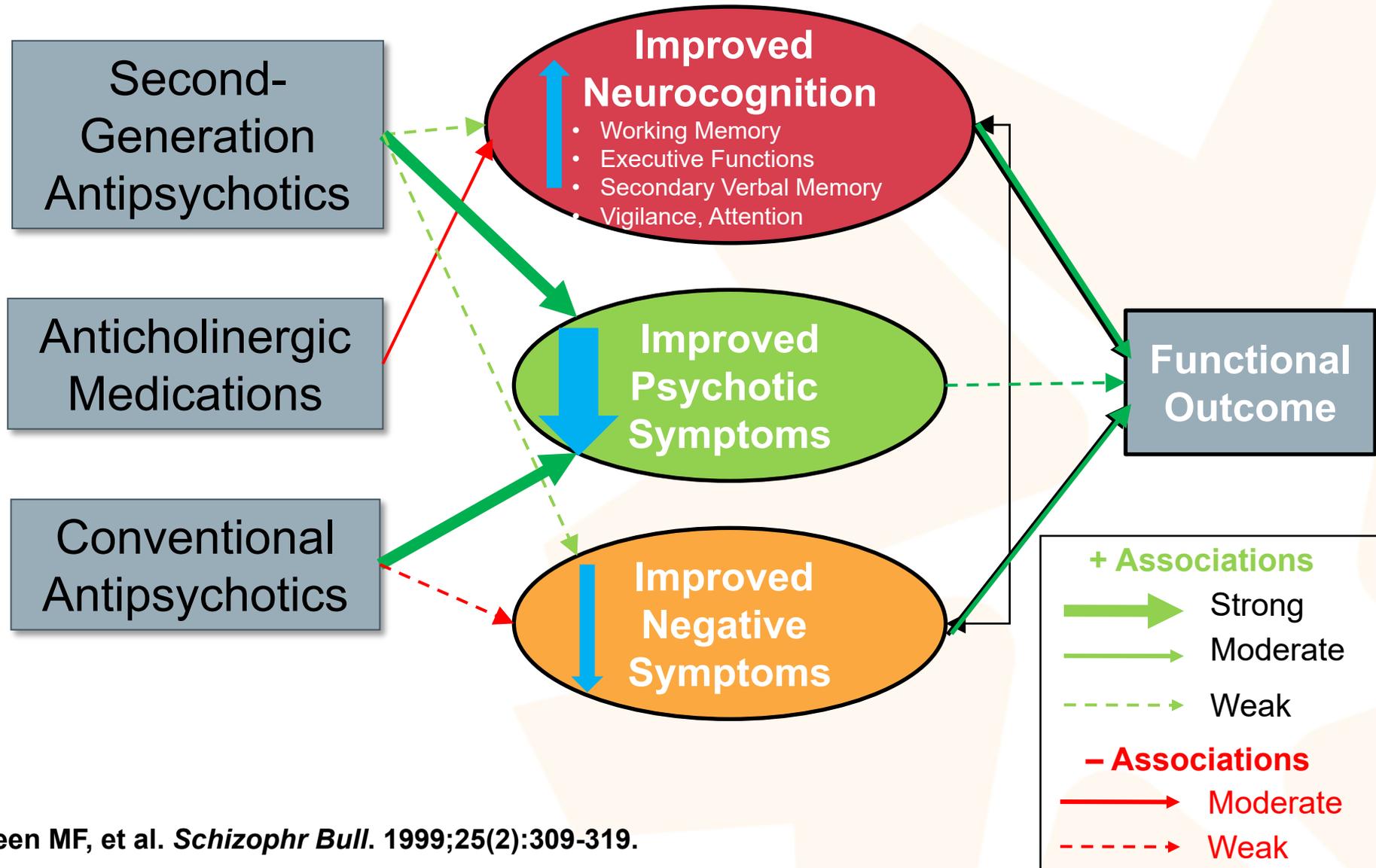
# Negative Symptoms Often Coexist with Cognitive Psychopathology

- First-episode and chronic schizophrenia have nearly identical profiles showing generalized impairment, particularly in verbal memory and learning (but also attention-vigilance, speed of visual-motor processing and attention)

- Cognitive deficits are highly clinically significant, with a 1.5 to 2.5 standard deviation gap between patients and healthy controls on neuropsychological testing

- Unfortunately, cognitive deficits are made worse with anticholinergic medications such as benztropine, often used to treat drug-induced parkinsonism

Keefe RS. *J Clin Psychiatry*. 2014;75 Suppl 2:8-13. Saykin AJ, et al. *Arch Gen Psychiatry*. 1994;51(2):124-131. Vinogradov S, et al. *Am J Psychiatry*. 2009;166(9):1055-1062.

# Burden of Negative and Cognitive Symptoms

- Functional outcomes are driven by both negative symptoms and cognitive psychopathology

- Both amotivation/apathy and cognitive psychopathology independently contribute to longitudinal functional outcomes among patients with schizophrenia, such as quality of life, relationships, work performance, and social functioning

- Specifically, cognitive performance affects patients' ability to perform everyday living skills (functional capacity), while negative symptoms affect patients' likelihood of performing these skills (functional performance)

- Negative symptoms contribute more to impaired quality of life and poor functioning than do positive symptoms

Fervaha G, et al. *Acta Psychiatr Scand*. 2014;130(4):290-299. Ritsner MS, et al. *J Nerv Ment Dis*. 2011;199(11):845-853. Strauss GP, et al. *Schizophr Res*. 2011;128(1-3):117-123. Bowie CR, et al. *Am J Psychiatry*. 2006;163(3):418-425. Rabinowitz J, et al. *Schizophrenia Res*. 2012;137(1-3):147-150.

# Current Treatment Options for Schizophrenia



Adapted from: Green MF, et al. *Schizophr Bull*. 1999;25(2):309-319.

# *Zoe* also has Medication Adverse Effects:
## *Which are the most important RE: nonadherence*?

- **Most commonly associated with nonadherence**
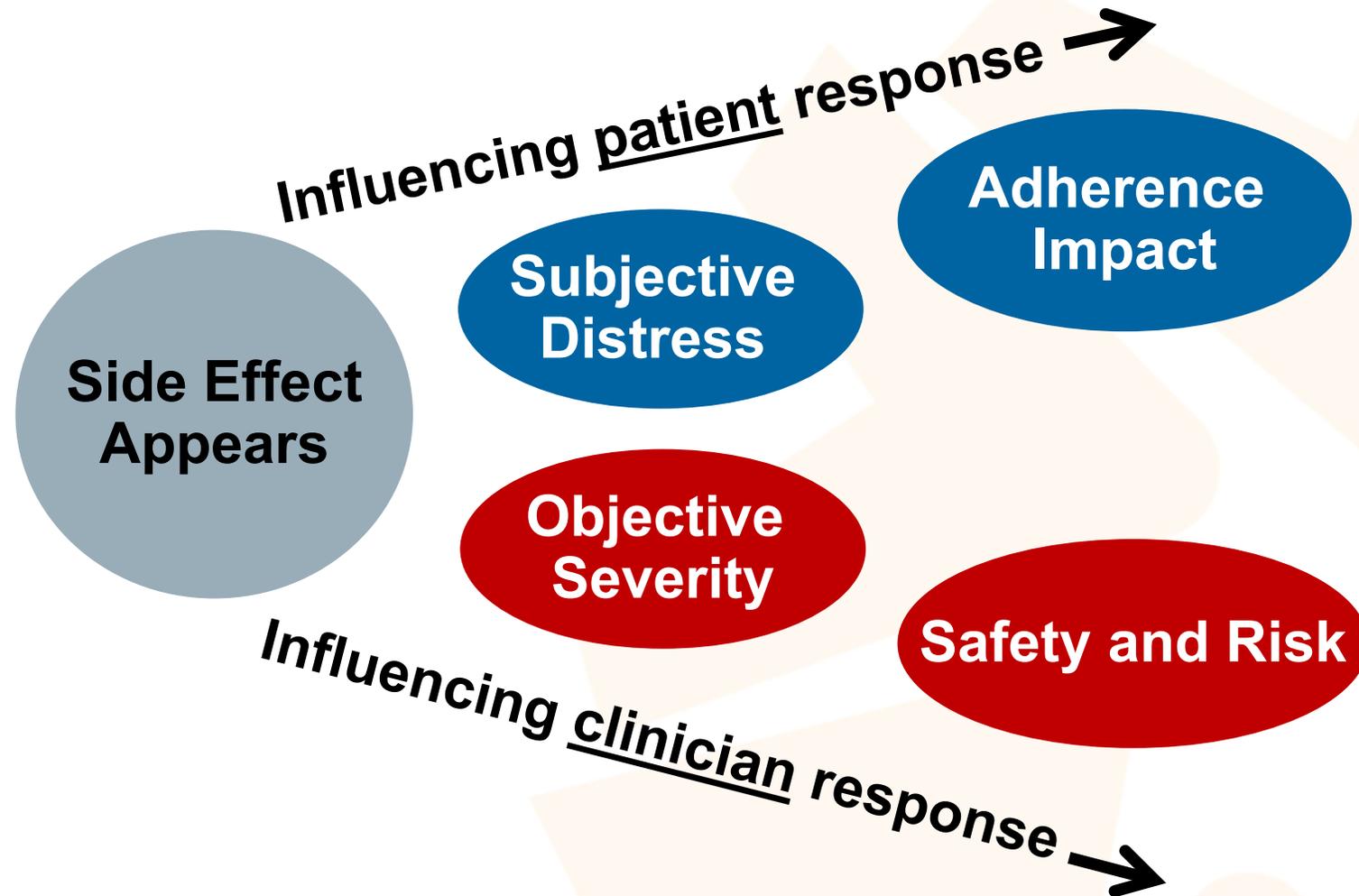  - Weight gain
  - Sedation
  - Akathisia
  - Sexual dysfunction
  - Parkinsonian symptoms
  - Cognitive problems

- **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?*



Influencing <u>patient</u> response →

**Adherence Impact**

**Subjective Distress**

**Side Effect Appears**

**Objective Severity**

**Safety and Risk**

Influencing <u>clinician</u> response →

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

# *Zoe* 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 Zoe 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 Impose a Significant Overall Burden

**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 Impose a Burden

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**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

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

**Proportion of patients at risk for an AE who received a medication associated with that AE**
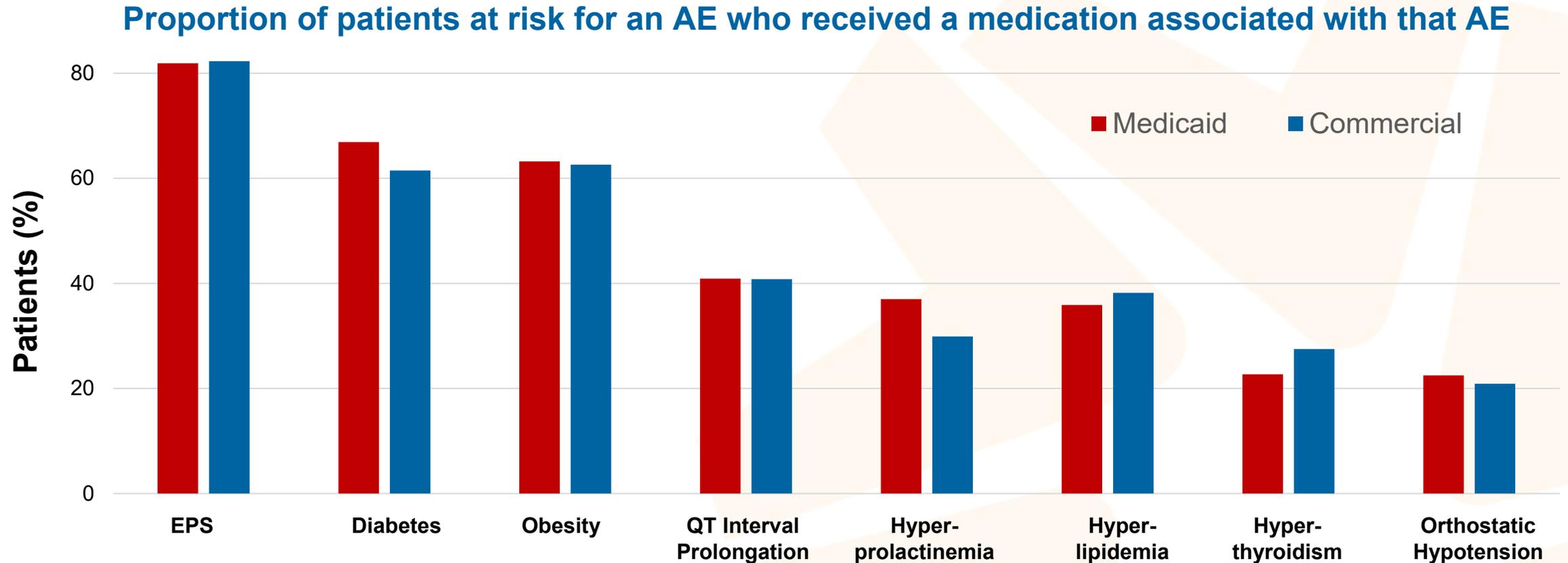


Real-world data from Medicaid and commercial insurance claims showing proportion of patients likely to experience a given AE (ie, prior history, risk factors) who received a medication associated with that AE.

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 |
| $\alpha_1$ adrenergic | Postural hypotension, dizziness, syncope, akathisia (protective) |
| $\alpha_2$ adrenergic | Increased blood pressure |
| $H_1$ | Sedation, weight gain |
| $M_1$ | Memory, cognition, dry mouth |
| $M_{2-4}$ | Blurred vision, constipation, urinary retention |
| $5\text{-}HT_{2C}$ | 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 |
| $\alpha_{1A}$ | 25.7 | 3.8 | 155 | NR | 22 | 0.60 |
| $\alpha_{1B}$ | 34.8 | 0.17 | NR | NR | 14.6 | 9.0 |
| $\alpha_{1D}$ | NR | 2.6 | 208.9 | NR | NR | NR |
| $\alpha_{2C}$ | 37.9 | 0.59 | NR | 10.8 | 28.7 | 9.1 |
| $H_1$ | 61 | 19 | 23.2 | $\geq$ 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 $5\text{-}HT_{2A}$ 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 (All Symptoms)

## Overall Change in Symptoms



| Drug | Standardized Mean Difference (95% CrI) | Effect Size of Antipsychotic Compared with Placebo |
|---|---|---|
| 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) | |

"Clozapine boundary"

"Olanzapine boundary"

Favors Active Drug

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

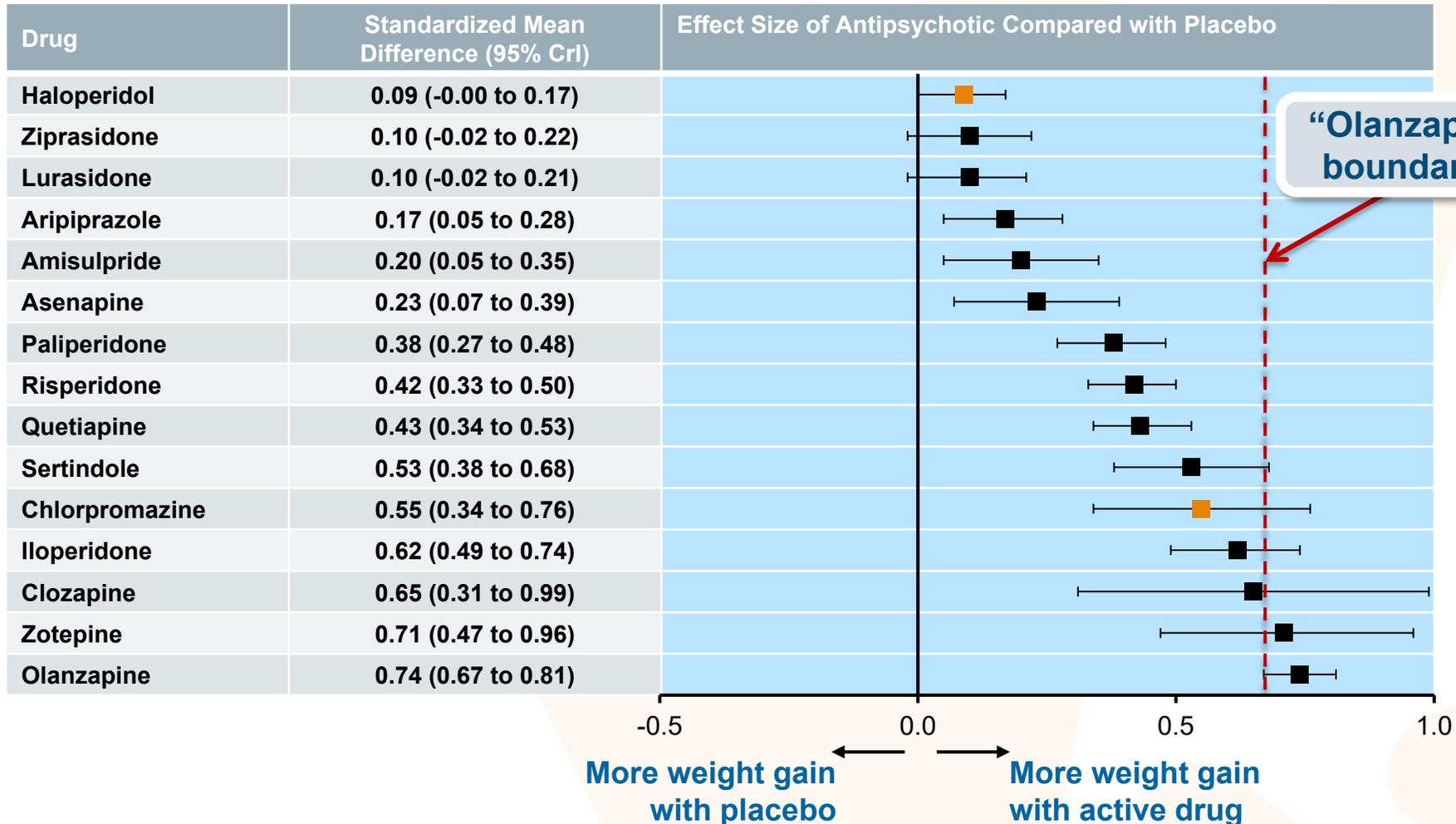| Drug | Standardized Mean Difference (95% CrI) | Effect Size of Antipsychotic Compared with Placebo |
|------|----------------------------------------|----------------------------------------------------|
| Haloperidol | 0.09 (-0.00 to 0.17) | |
| Ziprasidone | 0.10 (-0.02 to 0.22) | |
| Lurasidone | 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) | |

"Olanzapine boundary"

-0.5    0.0    0.5    1.0

More weight gain with placebo ← → More weight gain with active drug

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

# … and Different for EPS

## EPS

| Drug | Odds Ratio (95% CrI) | Effect Size of Antipsychotic Compared with Placebo |
|---|---|---|
| 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) | |

"Haloperidol boundary"

More EPS with placebo

More EPS with active drug
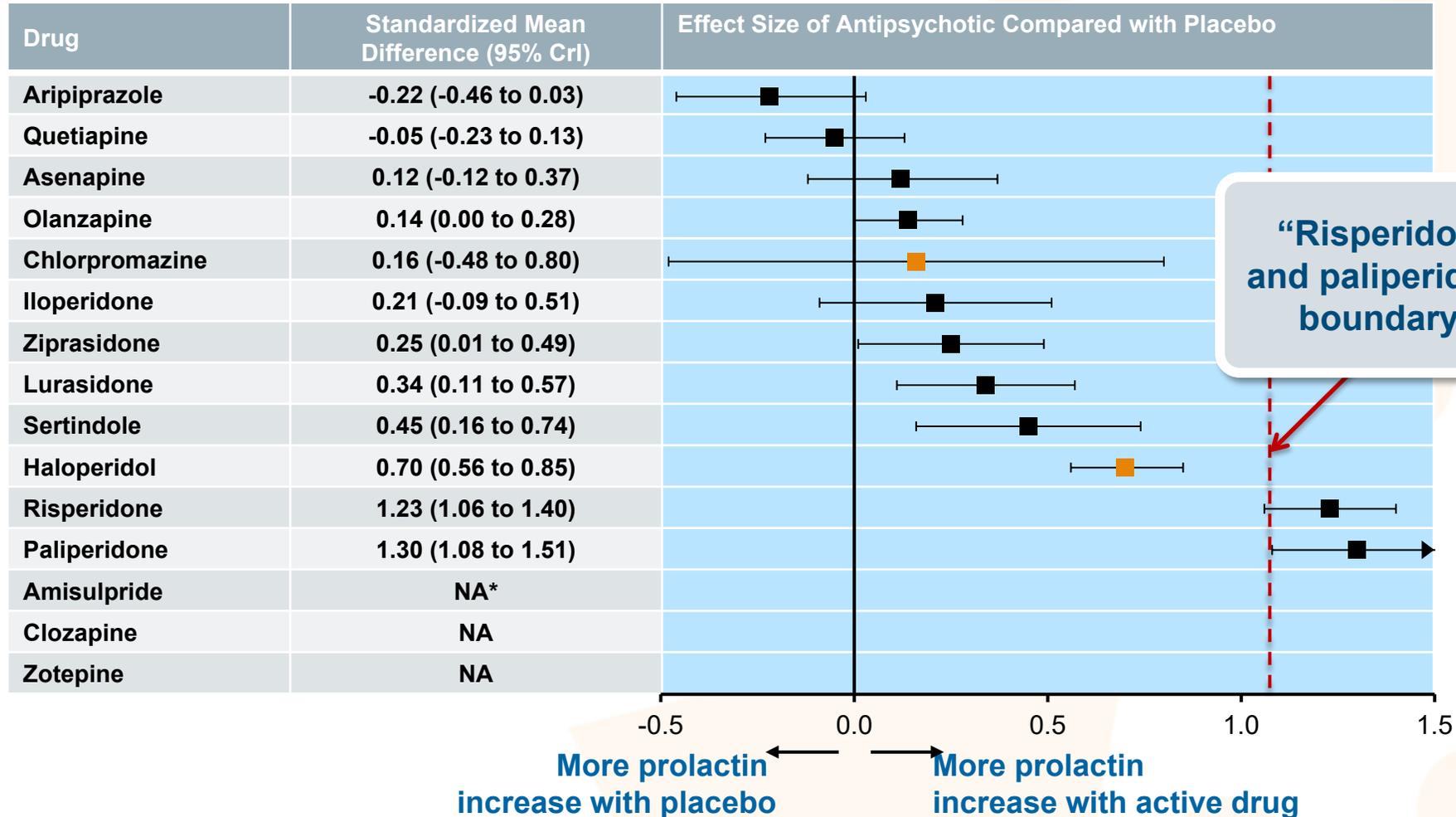
EPS assessed through use of anti-Parkinson medication.
Leucht S, et al. *Lancet*. 2013;382(9896):951-962.
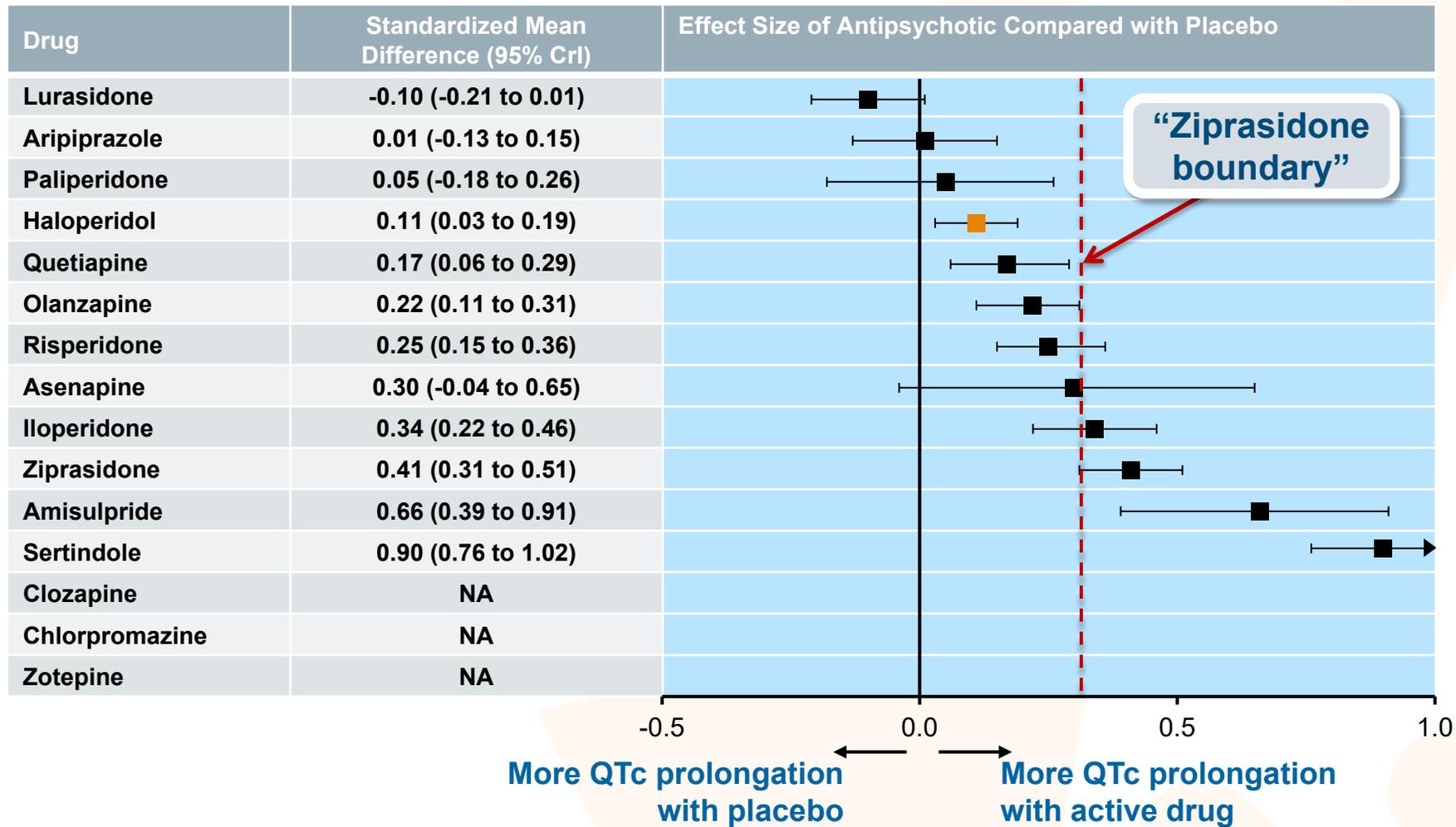
# … and Different for Prolactin Elevation

## Prolactin Increase

| Drug | Standardized Mean Difference (95% CrI) | Effect Size of Antipsychotic Compared with Placebo |
|------|------|------|
| 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 | |

"Risperidone and paliperidone boundary"

-0.5    0.0    0.5    1.0    1.5

More prolactin increase with placebo ← → More prolactin increase with active drug

*In one small study, amisulpride produced less prolactin increase than haloperidol, but prolactin concentrations were highly imbalanced at baseline.
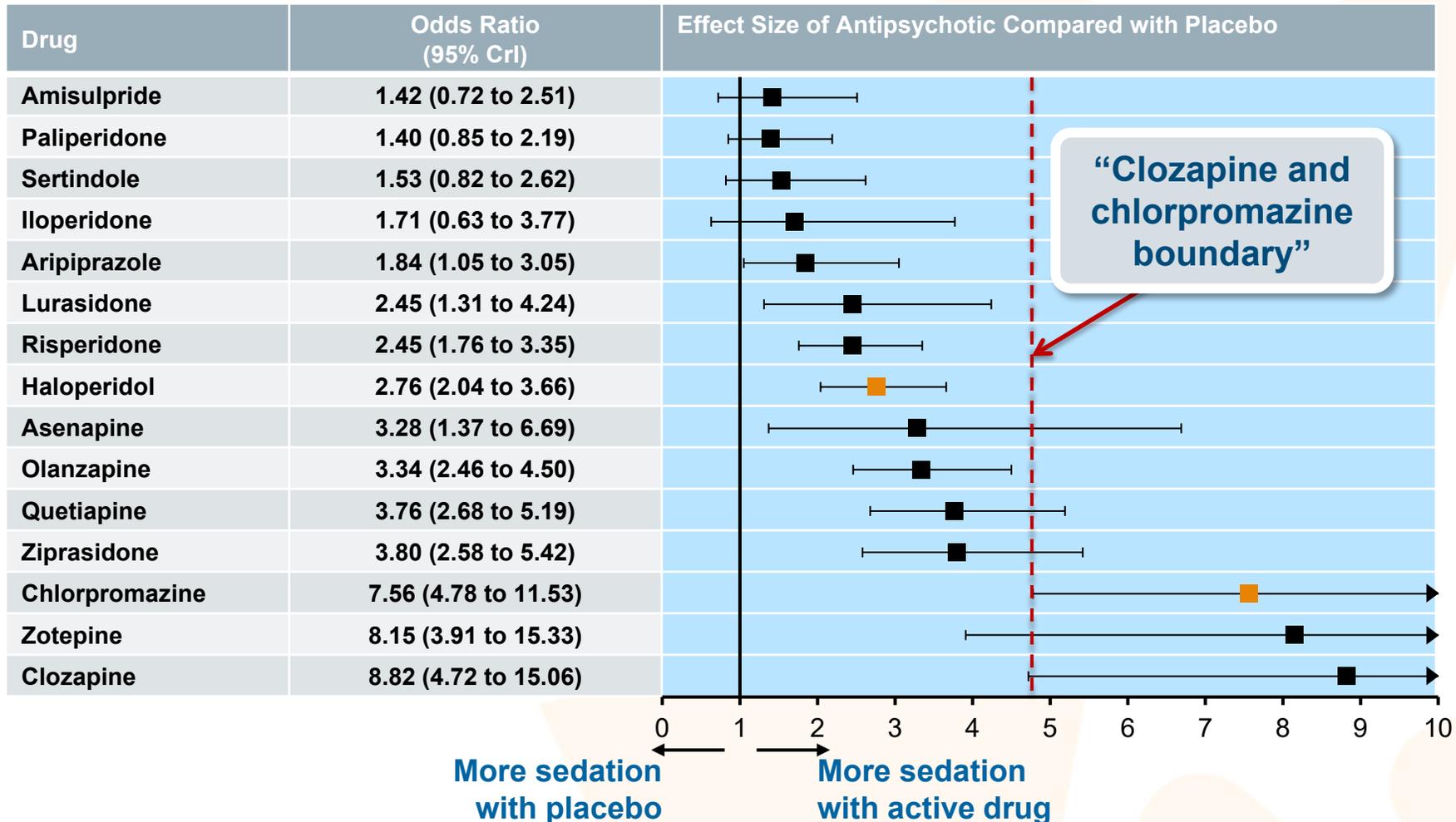Leucht S, et al. *Lancet*. 2013;382(9896):951-962.

# ... and Different for QTc Prolongation

## QTc Prolongation

| Drug | Standardized Mean Difference (95% CrI) | Effect Size of Antipsychotic Compared with Placebo |
|------|----------------------------------------|----------------------------------------------------|
| 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 | |

"Ziprasidone boundary"

More QTc prolongation with placebo ← → More QTc prolongation with active drug

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

# … and Different for Sedation

## Sedation

| Drug | Odds Ratio (95% CrI) | Effect Size of Antipsychotic Compared with Placebo |
|------|----------------------|-----------------------------------------------------|
| 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) | |

"Clozapine and chlorpromazine boundary"

More sedation with placebo

More sedation with active drug

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 values vs placebo < 10 will mean that you will encounter this adverse event in routine clinical practice, and in patients who are sensitive to this adverse effect, it will need to be addressed**

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

# 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)**
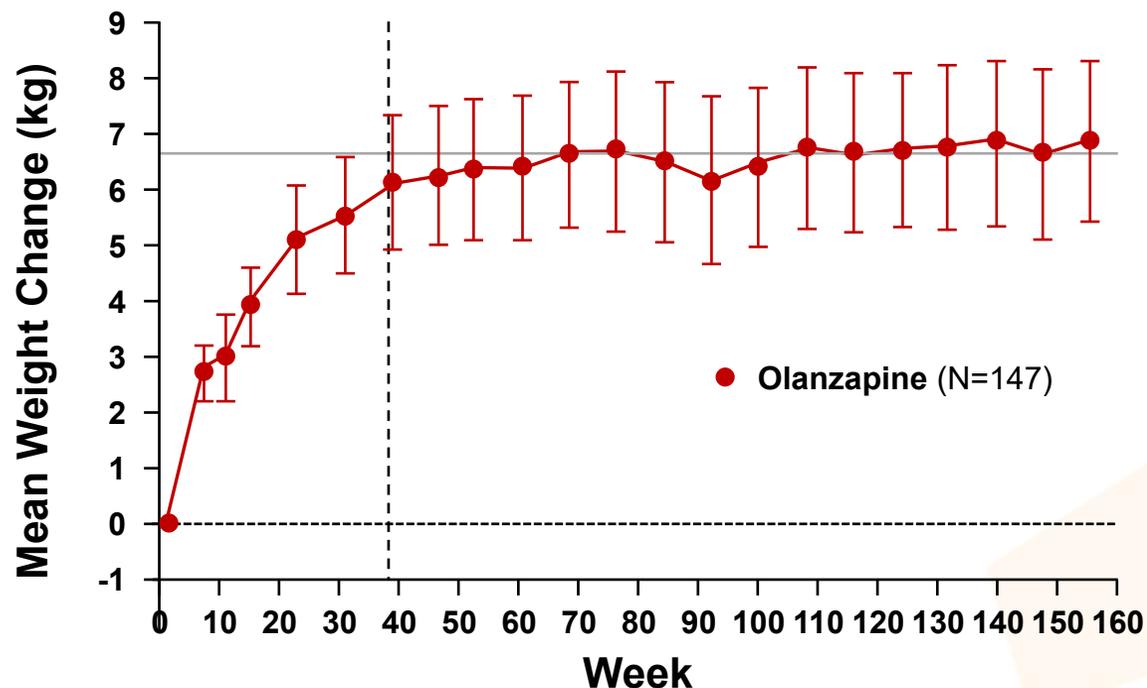


- Patients with higher baseline BMI (> 27.6) gained significantly less weight during treatment with olanzapine than their lighter counterparts
- The effect of olanzapine dose on weight was not significant

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
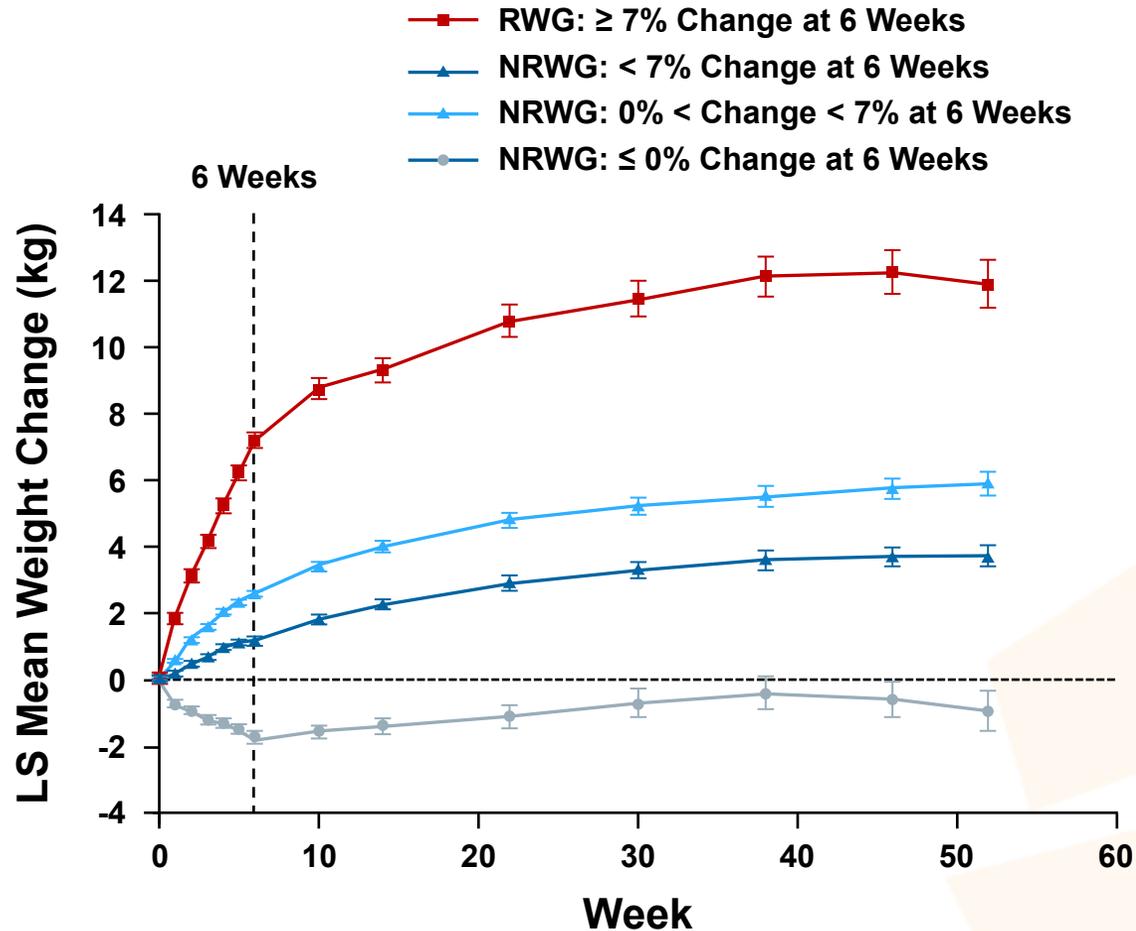


- **15%** showed rapid increases in weight (RWG group)

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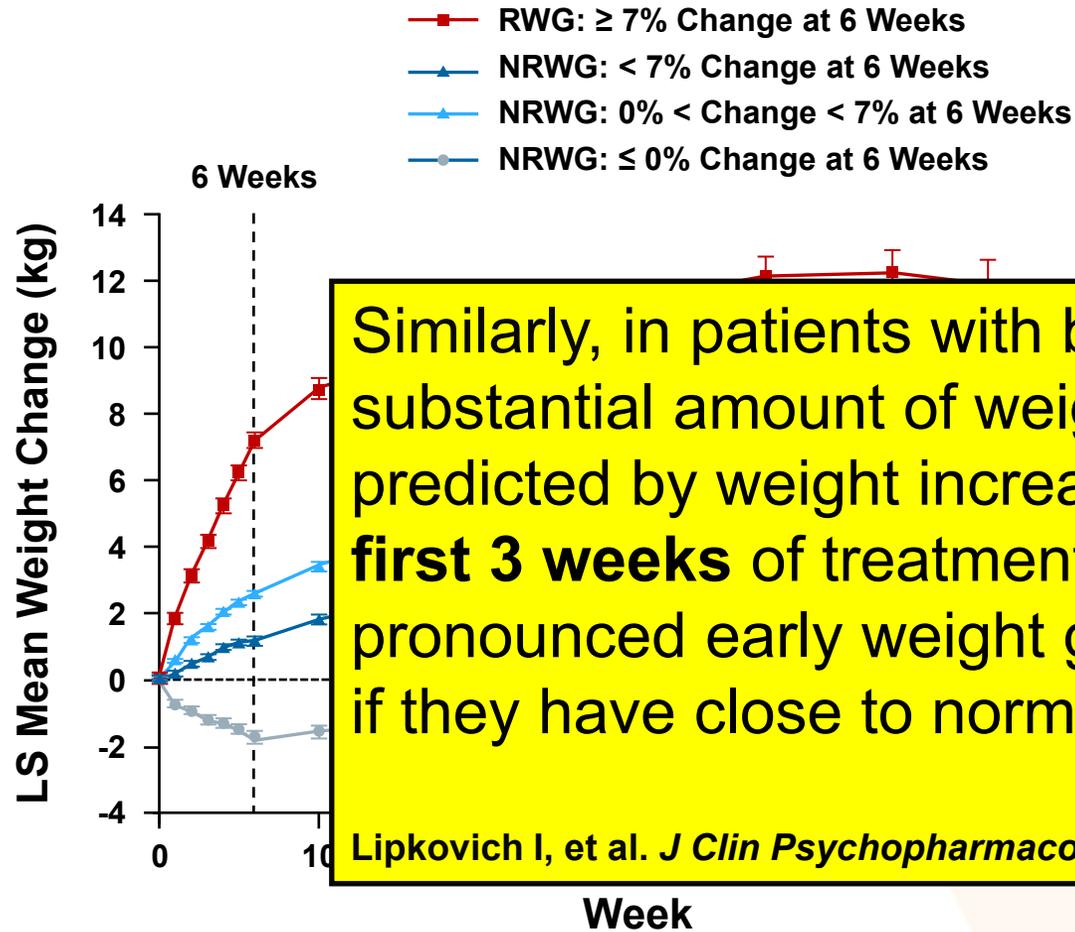
RWG = rapid weight gain group; NRWG = nonrapid weight gain group.
Kinon BJ, et al. *J Clin Psychopharmacol*. 2005;25(3):255-258.

# Olanzapine Early Weight Gainers

**Legend:**
- RWG: ≥ 7% Change at 6 Weeks
- NRWG: < 7% Change at 6 Weeks
- NRWG: 0% < Change < 7% at 6 Weeks
- NRWG: ≤ 0% Change at 6 Weeks



*Y-axis: LS Mean Weight Change (kg); values 14, 12, 10, 8, 6, 4, 2, 0, -2, -4*
*X-axis: Week; values 0, 10*
*Marker: 6 Weeks*

- **15%** showed rapid increases in weight (RWG group)
- In the RWG group, patients gained an average of 4% of their body weight [within 3] **weeks** of [treatment]

[...] were [...] **baseline**

[...] [wee]ks, patients [...] significantly [...] a higher [...] [in]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 **CBT**

CBT = 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

# 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, but after 1 year although body weight reduction was partially sustained, the improvements in other metabolic parameters returned to baseline levels
  - **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

Larsen JR, et al. *JAMA Psychiatry*. 2017;74(7):719-728. Svensson CK, et al. *Acta Psychiatr Scand*. 2019;139(1):26-36. 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]**



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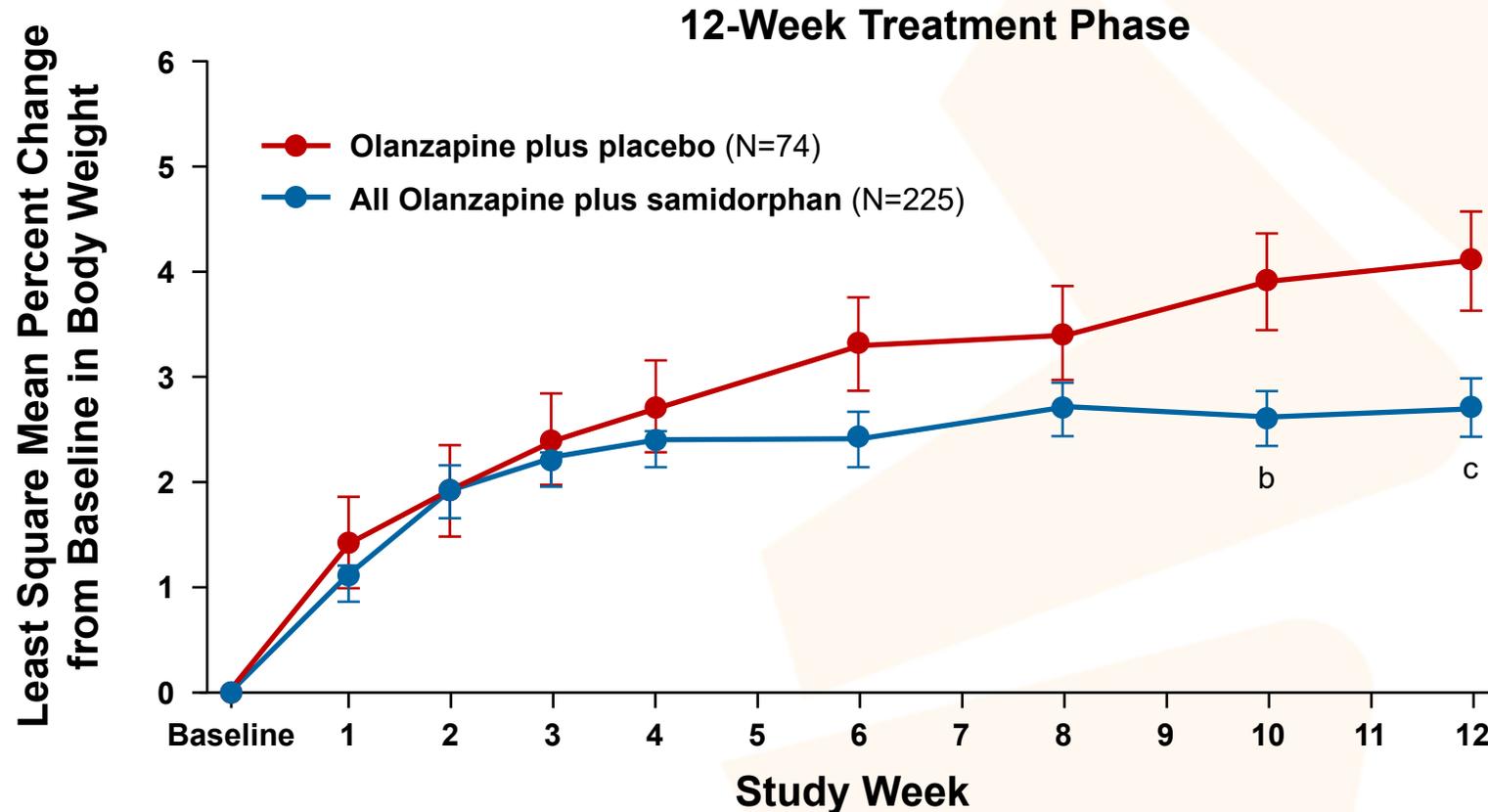
*In vitro*, samidorphan binds with high affinity to human μ-, κ-, and δ-opioid receptors and acts as an antagonist at μ-opioid receptors and a partial agonist at κ- and δ-opioid receptors

[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
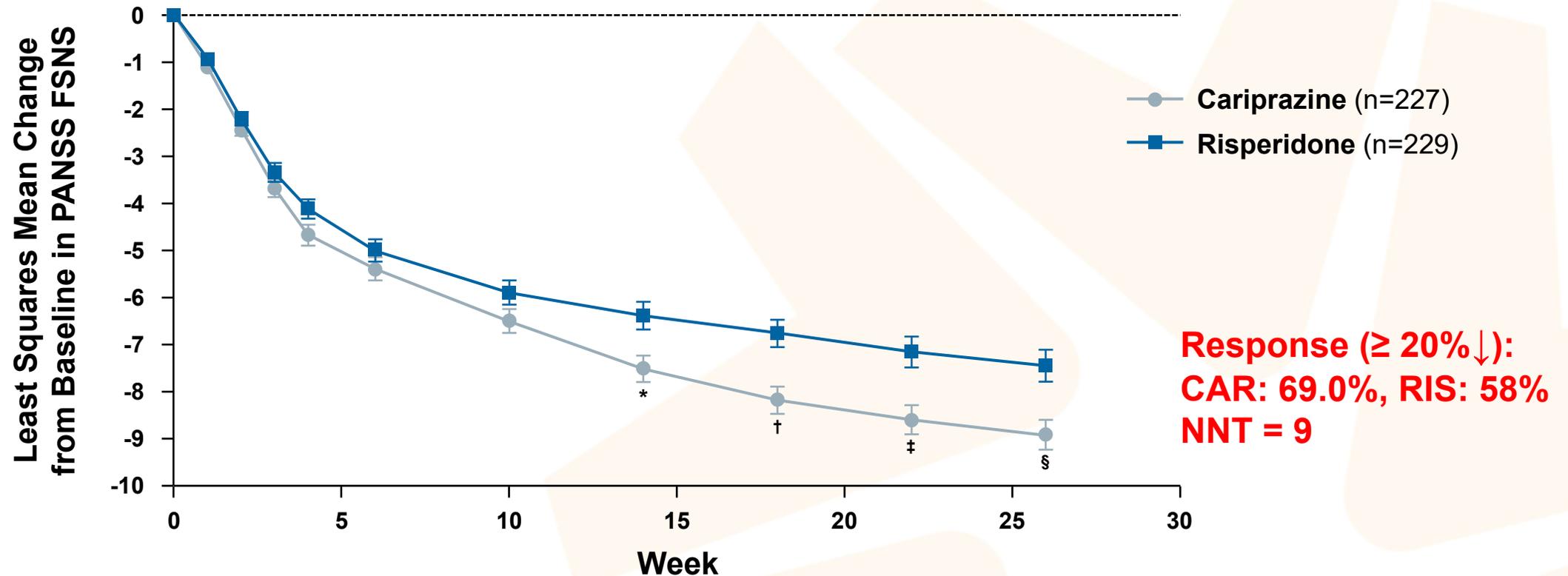
# Back to Negative Symptoms: Rx So Far

- Current foundational treatment options for schizophrenia consist of first- and second-generation antipsychotics

- Both types of antipsychotics can reduce positive symptoms, but second-generation antipsychotics (and avoidance of anticholinergic medications) may have at least a small beneficial effect on negative symptoms and neurocognition, and thus can potentially yield better functional outcomes

- Antidepressants do appear to be somewhat useful to treat negative symptoms and should be considered, especially in the face of possible depressive symptoms

Fusar-Poli P, et al. *Schizophr Bull*. 2015;41(4):892-899. Green MF, et al. *Schizophr Bull*. 1999;25(2):309-319. Leucht S, et al. *Am J Psychiatry*. 2017;174(10):927-942. Zhang JP, et al. *Int J Neuropsychopharmacol*. 2013;16(6):1205-1218. Krause M, et al. *Eur Arch Psychiatry Clin Neurosci*. 2018;268(7):625-639. Helfer B, et al. *Am J Psychiatry*. 2016;173(9):876-886. Correll CU, et al. *JAMA Psychiatry*. 2017;74(7):675-684. Galling B, et al. *Acta Psychiatr Scand*. 2018;137(3):187-205.

# New Data: Head-to-Head Comparison 6-Month RCT

## Cariprazine (a $D_3$ preferring $D_3/D_2$ receptor partial agonist) vs Risperidone (a $D_2$/5-$HT_{2A}$ antagonist): Change in PANSS-FSNS



**Cariprazine** (n=227)
**Risperidone** (n=229)

*Y-axis: Least Squares Mean Change from Baseline in PANSS FSNS*
*X-axis: Week*

**Response (≥ 20%↓):**
**CAR: 69.0%, RIS: 58%**
**NNT = 9**

*This was a **specific** effect on **negative symptoms**. Both cariprazine and risperidone were otherwise comparable in terms of scores on PANSS factor scale positive symptoms, Calgary Depression Scale for Schizophrenia, and Simpson Angus Scale for the Measurement of Extrapyramidal Symptoms*

*$P$=.0079; †$P$=.0011; ‡$P$=.0016; § $P$=.0022. FSNS = Factor Score Negative Symptoms [N1 (blunted affect), N2 (emotional withdrawal), N3 (poor rapport), N4 (passive or apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), G7 (motor retardation), and G16 (active social avoidance)]; PANSS = Positive and Negative Syndrome Scale.
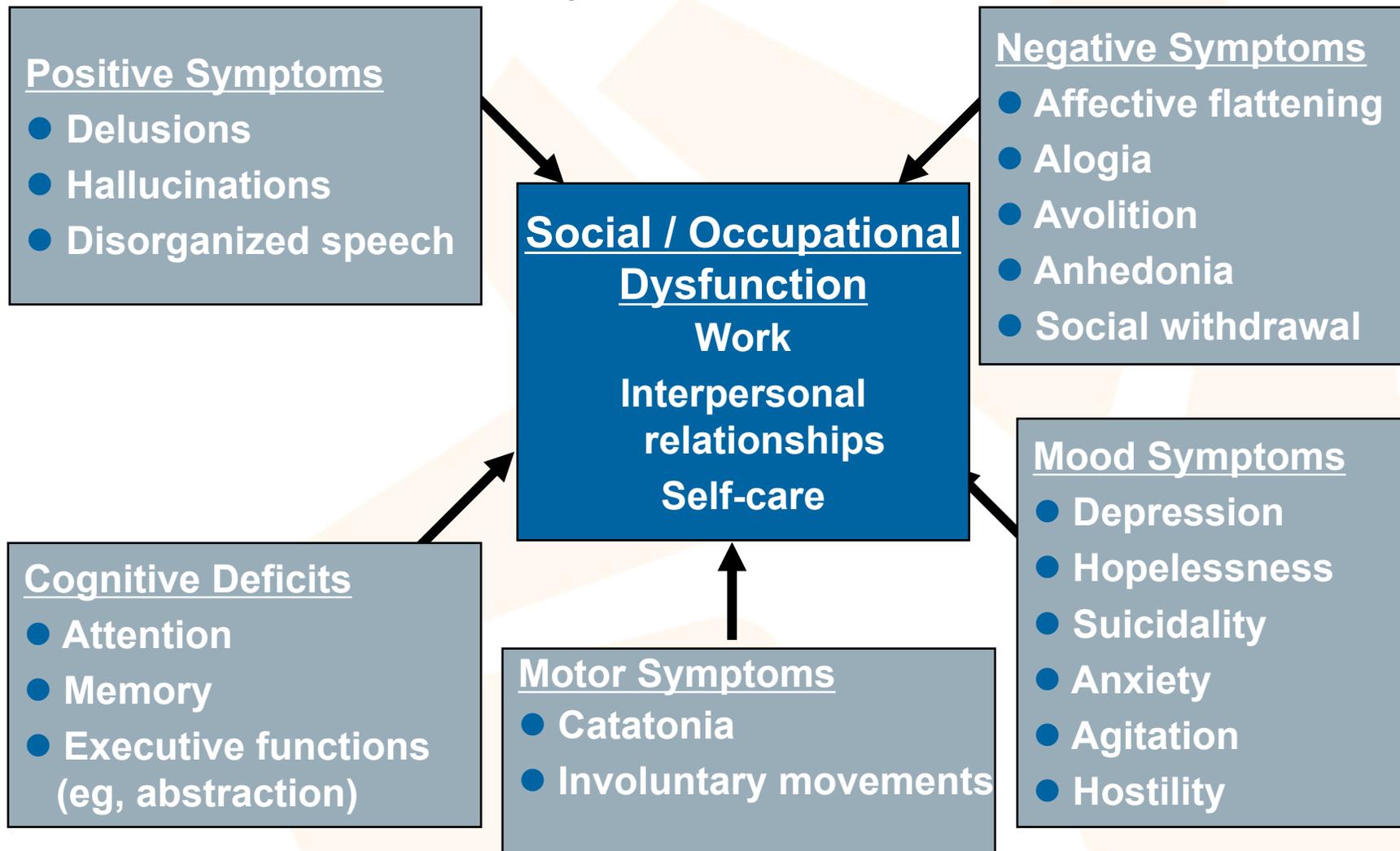Németh G, et al. *Lancet*. 2017;389(10074):1103-1113.

# On the Horizon: Roluperidone

- In late stage of clinical development is roluperidone, a serotonin 5-HT$_{2A}$/sigma receptor antagonist

- Roluperidone was compared with placebo in treating negative symptoms in 244 stabilized patients with schizophrenia

- In this 12-week study, a statistically significant difference in PANSS negative factor score was observed, with lower scores for roluperidone

- There were no statistically significant differences in PANSS positive scale score between the roluperidone and placebo groups

Davidson M, et al. *Am J Psychiatry*. 2017;174(12):1195-1202.

# Clinical Features of Schizophrenia
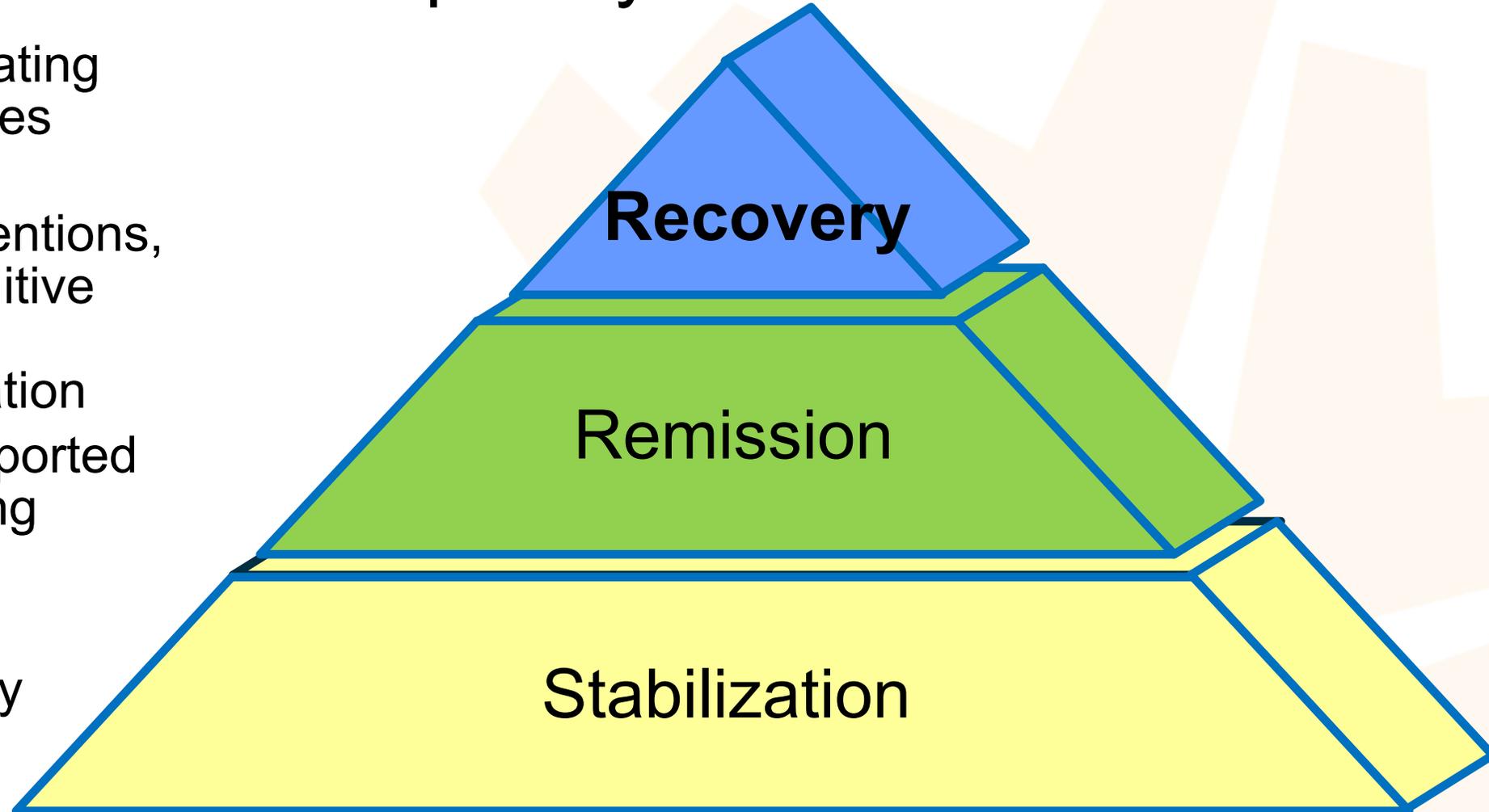## Treatment is Multidisciplinary *and* Individualized

- Rx for some Sx
- Cognitive remediation and vocational rehabilitation for functionality
- Supportive/supported employment and housing may be needed to ensure above is successful
- Intensive Case Management or Assertive Community Treatment for some

**Positive Symptoms**
- Delusions
- Hallucinations
- Disorganized speech

**Negative Symptoms**
- Affective flattening
- Alogia
- Avolition
- Anhedonia
- Social withdrawal

**Social / Occupational Dysfunction**
Work
Interpersonal relationships
Self-care

**Cognitive Deficits**
- Attention
- Memory
- Executive functions (eg, abstraction)

**Motor Symptoms**
- Catatonia
- Involuntary movements

**Mood Symptoms**
- Depression
- Hopelessness
- Suicidality
- Anxiety
- Agitation
- Hostility

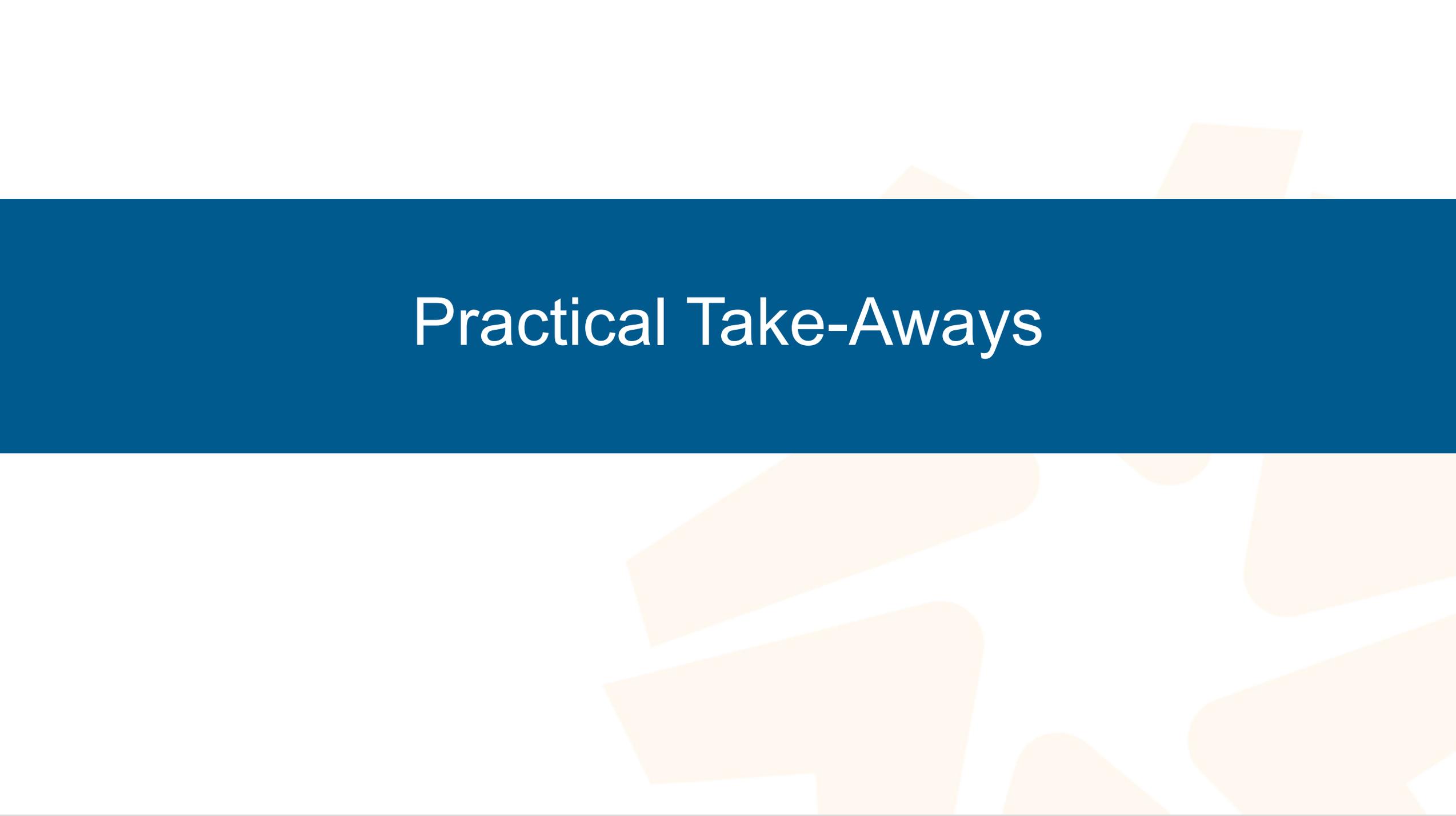Maguire GA. *Am J Health Syst Pharm*. 2002;59(17 Suppl 5):S4-S11.

# Recovery Reminder!
## Treatment is Multidisciplinary *and* Individualized

- Primary care for treating physical comorbidities
- Psychological and psychosocial interventions, including CBT, cognitive remediation, and vocational rehabilitation
- Supportive and supported employment, housing
- Intensive case management
- Assertive community treatment



Recovery

Remission

Stabilization

Adapted from Weiden PJ, et al. *J Clin Psychiatry*. 1998;59 Suppl 19:36-49.

# Practical Take-Aways

# 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

# 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
## *Do I Switch or Do I Stay?*

- What are the patient's preferences?
- What is the patient's past history of efficacy of drug response?
  - Does the patient respond to everything or generally does poorly?
- Is this an acute exacerbation or an elective choice?
- What is the patient's history of adherence or lack thereof?
- Does the patient accept the need for special monitoring if needed?
- Is the patient amenable to other interventions to address tolerability?
  - Diet, exercise, and statins for obesity and dyslipidemia
  - Beta-blockers for akathisia
  - Anticholinergics or amantadine (preferred) for acute EPS

Citrome L. *CNS Drugs*. 2013;7(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.