PsychCase 360:
Balancing Psychiatric Stability and Cardiometabolic Health in Patients with Bipolar I Disorder

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Disclosures

- Consultant: Alkermes, Genomind, Luye Pharmaceuticals, Neurelis, Neuroma, Otsuka, Sunovion, Supernus
- Speakers bureau: Abbvie, Alkermes, Axsome, Intracellular Therapies
- Royalties: American Psychiatric Publishing, Cambridge University Press

Case 1

Vanessa, 26-year-old single personal trainer, history of untreated depressive episodes during college.

Brought by her mother to an outpatient crisis appointment after recent marked change in behavior and mood:

- Exhibits an elevated, expansive, and flirtatious affect, despite reporting feelings of depression
- Spends much of the night awake, making workout videos that she is convinced will make her rich and famous (grandiosity verges on delusional)
- Reports having “more thoughts and ideas than [she] can keep up with”
- Spends beyond her means on workout equipment, has ambitious plans to open a chain of fitness clubs
- Neglects personal hygiene, eating, self-care, and paying bills, disregard for basic needs and responsibilities
- Has poor insight into the nature of her condition but is open to treatments that might improve her mood
- Opposed to any medication that could cause weight gain

Vanessa: Key Features

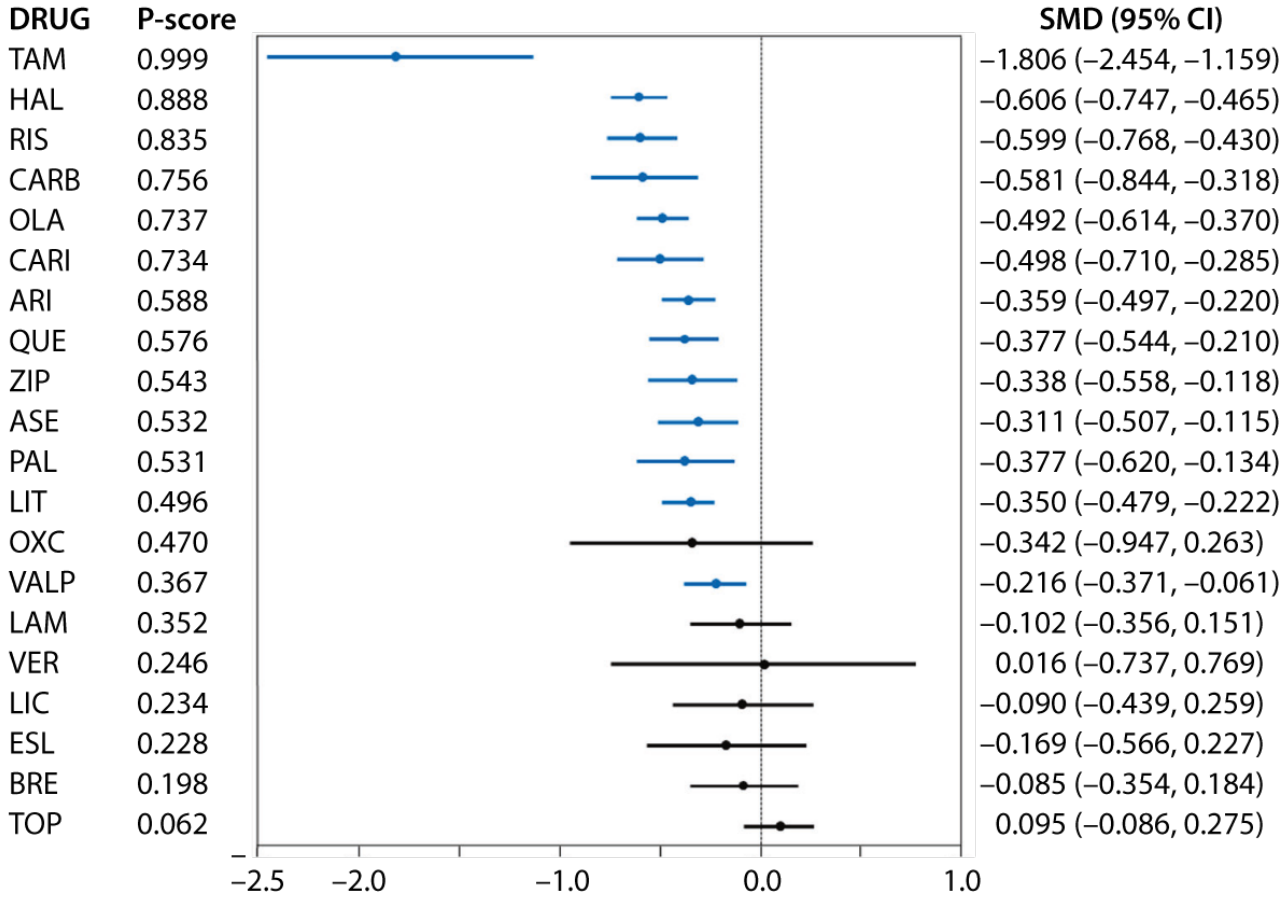
- Vanessa's presentation and historical data are consistent with a bipolar I manic episode, highlighted by untreated depressive episodes during college, recent elevated and expansive mood, and grandiose behaviors.
- Evaluate whether Vanessa's recent manic episode is due to nonadherence to any previous treatment regimen or if such a regimen was indeed ineffective, considering her history of untreated depression.
- Confirm the absence of unstable medical conditions and perform a negative drug toxicology screen to rule out substance-induced mood disorder components.
- Given Vanessa's severe, grandiose mania and lack of response to untreated depressive episodes, consider the use of high-efficacy antimanic agents to manage her symptoms.
- Conduct a risk-benefit analysis for high-potency antimanic options (eg, lithium, aripiprazole) while considering Vanessa's specific concerns about weight gain. The goal is to effectively prevent or manage antipsychotic-associated weight gain.
- Develop strategies to prevent or manage antipsychotic-associated weight gain, especially given Vanessa's opposition to medications that could cause weight gain, highlighting the need for careful selection of treatment options.

Treatment Considerations

	Pros	Cons
Lithium	Efficacy in euphoric mania, first episodes	Slow onset Weight gain
Divalproex	Rapid loading can yield swift efficacy	Weight gain Undesirable in women of reproductive age
Carbamazepine	Weight neutral	Strong metabolic inducer
Aripiprazole	Antimanic efficacy, maintenance efficacy	Weight gain, metabolic dysregulation
Asenapine	Antimanic efficacy	Weight gain, somnolence, metabolic dysregulation
Risperidone	Antimanic efficacy, maintenance efficacy	Weight gain, metabolic dysregulation
Quetiapine	Antimanic efficacy, maintenance efficacy	Weight gain, metabolic dysregulation, sedation
Cariprazine	Antimanic and antidepressant efficacy	No maintenance data
Olanzapine	Antimanic efficacy, fast onset, maintenance efficacy	Weight gain, metabolic dysregulation

Choosing Among Agents in Bipolar Mania

On an *overall basis*, no clear differences among second-generation antipsychotics for acute antimanic efficacy



Changes in mania rating scale scores.
Drugs were compared with placebo. Colors indicate presence or absence of a significant difference: blue, the drug was different from placebo; black, the drug was similar to placebo. 95% CI=95% confidence interval.

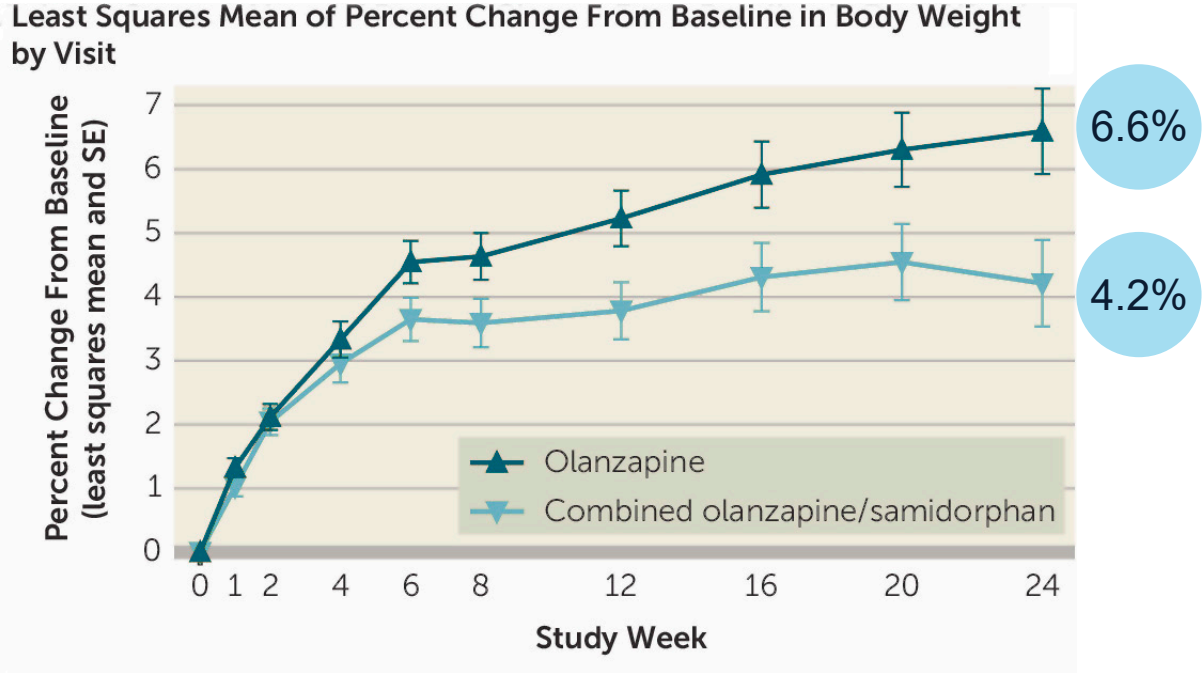
Abbreviations:
ARI=aripiprazole; ASE=asenapine; BRE=brexpiprazole; CARB=carbamazepine; CARI=cariprazine; ESL=eslicarbazepine; HAL=haloperidol; LAM=lamotrigine; LIC=licarbazepine; LIT=lithium; OLA=olanzapine; PAL=paliperidone; QUE=quetiapine; RIS=risperidone; TAM=tamoxifen; TOP=topiramate; VALP=valproate; VER=verapamil; ZIP=ziprasidone

Kishi T, et al. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. *Mol Psychiatry* 2022;27:1136-1144.

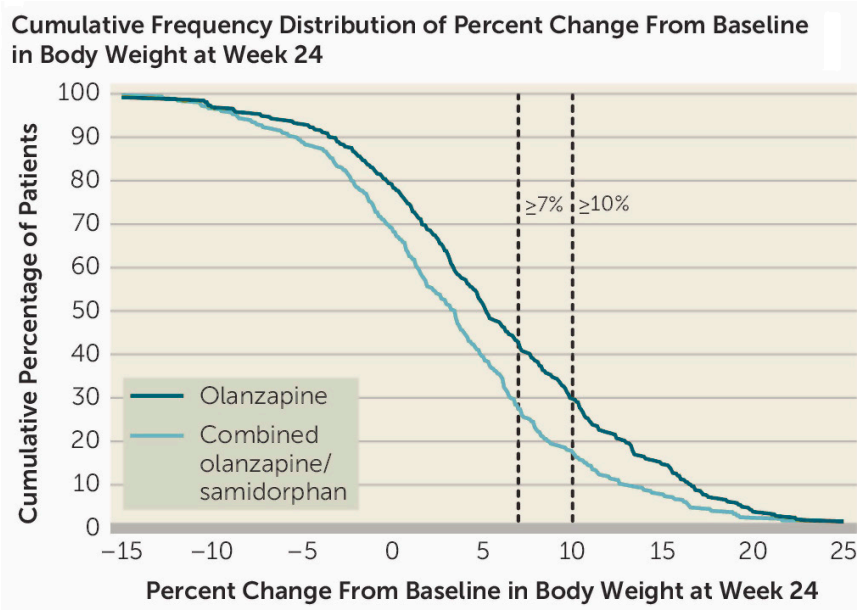
Treatment Considerations and Options

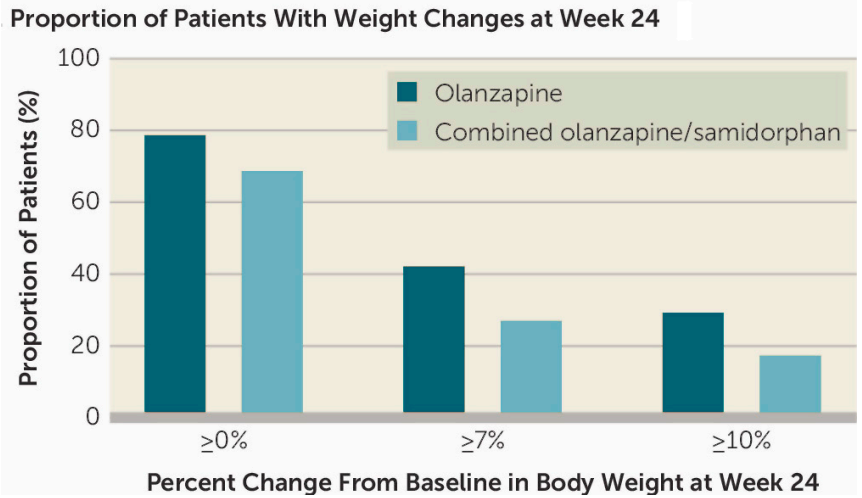
- Choose a fast-acting, broad spectrum, high-potency second-generation antipsychotic to avert hospitalization if possible; reconsider longer-term use once stable based on efficacy and tolerability
  - “We will know within a short time if this option is working; if so, but side effects were unacceptable, we can re-evaluate within a few weeks”
  - “We also have strategies to minimize the risk of metabolic side effects”
- Favor a second-generation antipsychotic with low metabolic liability, but possibly lower breadth of spectrum, in the absence of past treatment nonresponse
- Consider pairing second-generation antipsychotic with lithium in first episode mania with possible eventual transition to lithium monotherapy if efficacious

Minimizing the Potential for Weight Gain: Olanzapine/Samidorphan: 24-Week Data



At 24 weeks: mean = +3.18 kg olanzapine + samidorphan
mean = +5.08 kg olanzapine alone





Missing postbaseline assessments were imputed based on multiple imputation. Data in panel A were analyzed using an analysis of covariance model with treatment, race (black/African American, nonblack/non-African American), and age group (<30 years, ≥30 years) as factors and baseline body weight as the covariate. Baseline was defined as the last nonmissing value before the first dose of study drug.

Correll CU, et al. Effects of olanzapine combined with samidorphan on weight gain in schizophrenia: a 24-week phase 3 study. *Am J Psychiatry.* 2020; 177:1168-1178.

Case 2

- James, 47-year-old African American divorced professional, initially presented with a hospitalized manic episode in college followed by three subsequent manic episodes despite taking lithium and/or divalproex in combination with aripiprazole or quetiapine
- Previous response to olanzapine but discontinued due to 15-lb weight gain
- Now brought to emergency department by his brother with irritability, sleeplessness, provoking arguments with coworkers, spending thousands of dollars at strip clubs, claiming he has ideas to invent new phone apps that he is convinced will revolutionize the tech industry and make him rich
- Admitted, begun on olanzapine 20 mg/day plus divalproex 1500 mg/day (serum [valproate]=84 mg/dL), stabilized and transitioning to step-down program
- Personal history of hypertension (on losartan 50 mg/day) and hypercholesterolemia (on simvastatin 20 mg/day). Family history of heart attack in his father at age 52; familial hypercholesterolemia

James: Key Features

- Presentation and history consistent with bipolar I manic episode
- Assure relapse is not merely lack of adherence to existing regimen (and that existing regimen is in fact ineffective)
- Assure no unstable medical conditions, negative drug toxicology screen
- Severe, recurrent psychotic mania that has not responded well to multiple prior appropriate treatments warrants use of antimanic agents with high efficacy
- Risk-benefit analysis of high-potency antimanic options (eg, olanzapine, clozapine, ECT) and need for relapse prevention after response
- How to prevent or manage antipsychotic-associated weight gain if the severity of James' condition favored an agent with high metabolic liability?

Pooled Cohort Risk Equation for James

Risk Factors for ASCVD

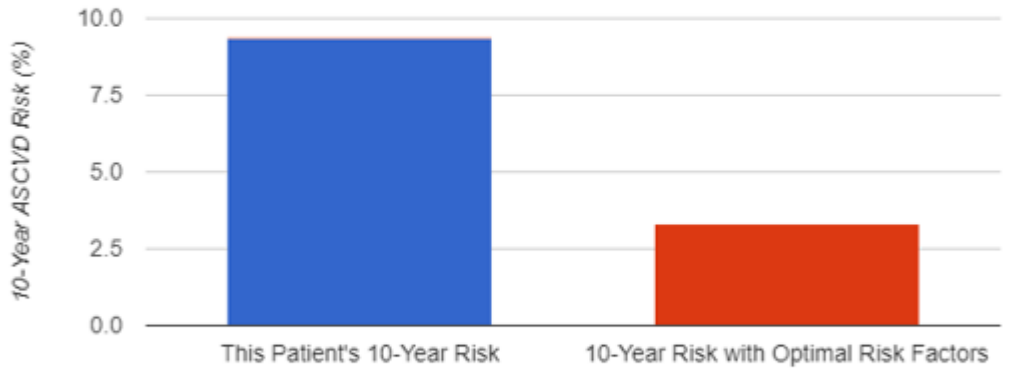
Gender	Male / Female	Systolic BP	132 mmHg
Age	47 years	Receiving treatment for high blood pressure (if SBP > 120 mmHg)	No / Yes
Race	African American	Diabetes	No / Yes
Total Cholesterol	247 mg/dL	Smoker	No / Yes
HDL Cholesterol	36 mg/dL		

Reset | Calculate

⇄ US units

10-year risk of atherosclerotic cardiovascular disease: 9.4%

10-year risk in a similar patient with optimal risk factors: 3.3%



Lifetime risk of atherosclerotic cardiovascular disease: 69% (95% CI 62% to 73%)

Lifetime risk for a 50-year-old with optimal risk factors: 5% (95% CI 0% to 12%)

ASCVD Risk Calculator. ClinCalc.com. https://clincalc.com/cardiology/ascvd/pooledcohort.aspx

Olanzapine Is Among the Few Evidence-Based Options in Treatment-Resistant Mania

12-week monotherapy open trial (dosing 5-40 mg/day) in 18 bipolar manic patients previously unresponsive to lithium, anticonvulsants, or other atypical antipsychotic medications

	Baseline		End of Study		
	Mean	SD	Mean	SD	*P*
YMRS total score (N=18)	28.5	5.9	5.2	0.2	<0.001
Elevated mood	2.5	1.0	0.2	0.5	<0.001
Increased motor activity-energy	3.1	0.4	0.3	0.8	<0.001
Sexual interest	1.7	1.1	0.2	0.5	<0.001
Sleep	2.6	0.9	0.7	1.0	<0.001
Irritability	4.1	1.1	1.4	2.3	<0.001
Speech	4.7	1.2	0.6	0.8	<0.001
Language-thought disorder	2.5	0.5	0.6	0.8	<0.001
Content	3.2	2.1	0.3	0.8	<0.001
Disruptive-aggressive behavior	1.9	1.2	0.4	1.1	<0.001
Appearance	1.6	0.8	0.3	0.6	0.037
Insight	0.7	1.0	0.2	0.5	<0.001
HAM-D total score (N=18)	5.2	5.5	8.8	9.0	0.093
CGI-S (N=18)					
Mania Score	4.9	0.7	1.7	1.5	<0.001
Depression score	2.0	1.1	2.5	1.8	0.116
Overall score	5.1	0.7	2.9	1.7	<0.001
PANSS (N=18)					
Total score*	58.1	12.4	43.6	11.7	<0.001
Positive scale**	16.6	6.0	9.1	4.6	<0.001
Negative scale**	11.2	3.2	10.2	3.3	0.314
General psychopathology scale***	30.2	7.2	24.3	6.8	<0.001

*minimum score –30
**minimum score –7
***minimum score –16

YMRS=Young Mania Rating Scale; HAM-D=17-item Hamilton Depression Rating Scale; CGI-S=Clinical Global Impression for Bipolar Disorder-Severity Scale; PANSS=Positive and Negative Syndrome Scale.

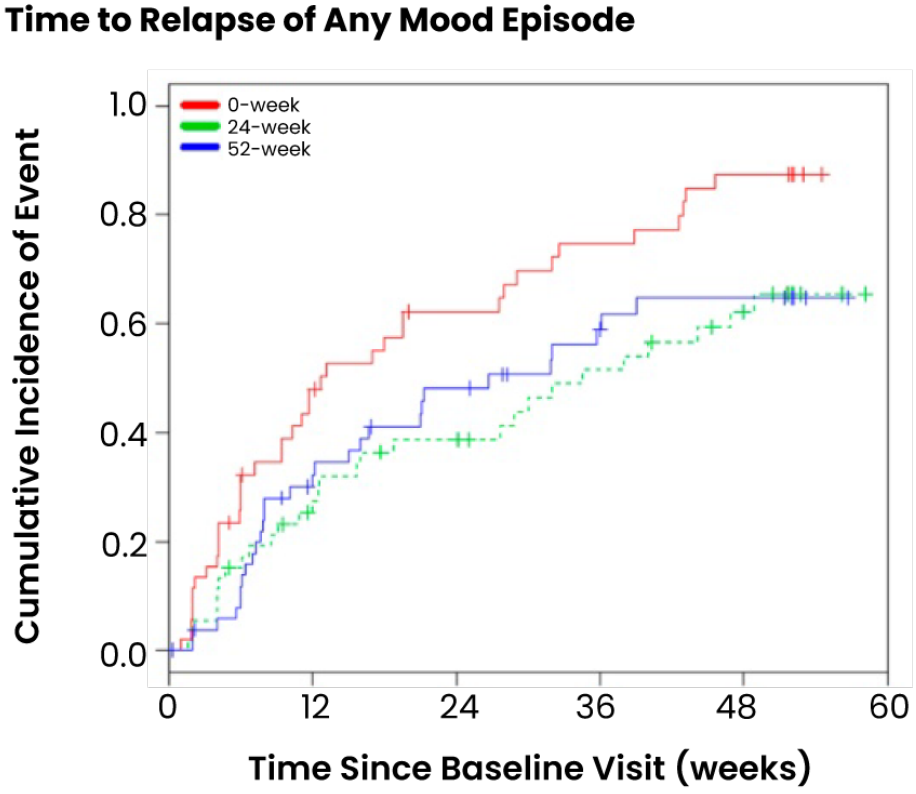
Chen J, et al. Safety and efficacy of olanzapine monotherapy in treatment-resistant bipolar mania: a 12-week open-label study. *Hum Psychopharmacol Clin Exp.* 2011;26:588-595.

Stopping Adjunctive Olanzapine Sooner Than 6 Months After Remission Increases Mania Relapse Risk

N=159 bipolar I manic patients treated with lithium or divalproex plus olanzapine or risperidone

<u>After 24 weeks</u>
<u>Relapse hazard ratio</u>:

- Overall=0.53 (95% CI=0.33-0.86)
- RIS=1.85 (95% CI=1.00-3.41)
- OLZ=0.48 (95% CI=0.17-1.32)

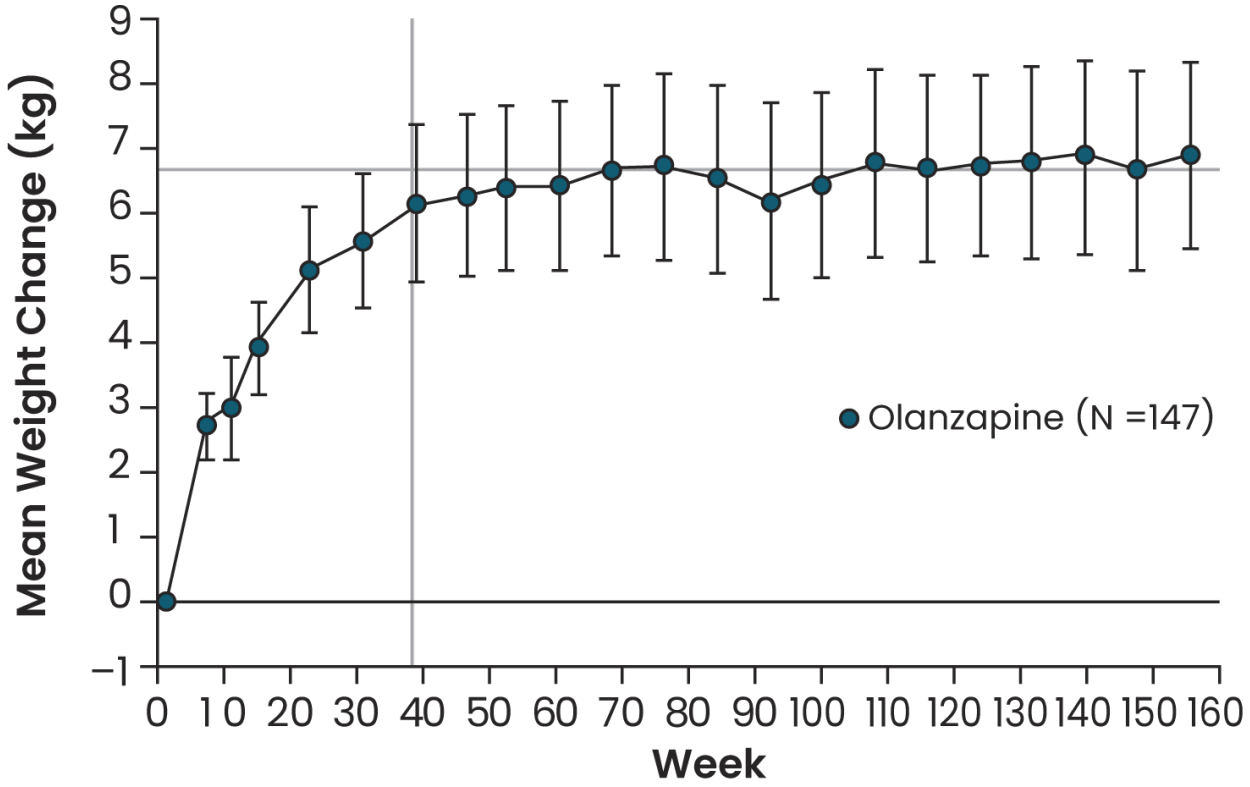


Number at risk						
0-week	52	23	15	10	5	0
24-week	54	34	26	19	13	0
52-week	53	32	22	15	12	0

Yatham LN, et al. Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: a CANMAT randomized double-blind trial. *Mol Psychiatry.* 2016;21:1050-1056.

Balancing Tolerability: Olanzapine Weight Gain May Not Plateau Until 39 Weeks

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

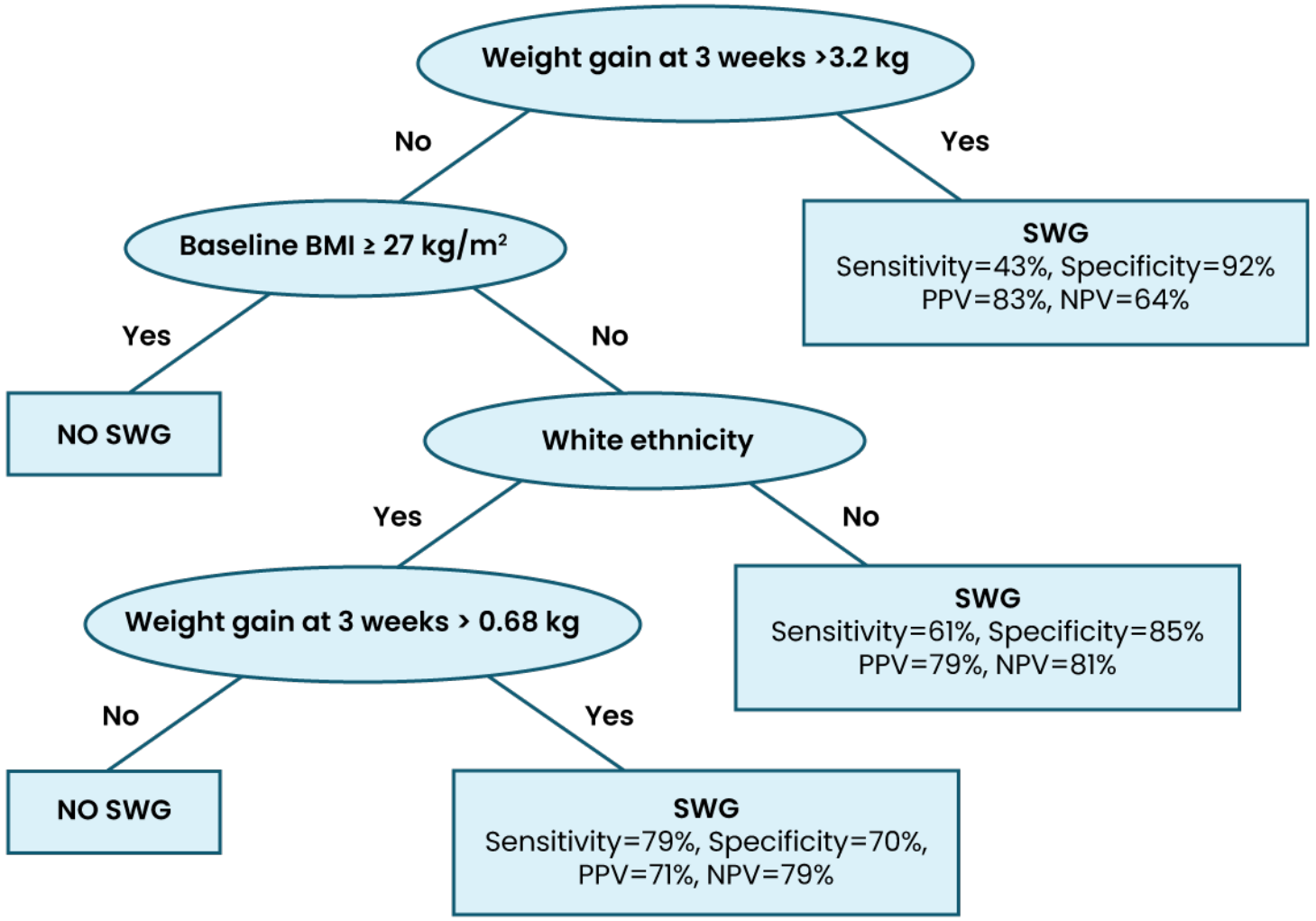


Kinon BJ, et al. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. *J Clin Psychiatry.* 2001;62:92-100.

Predicting Significant Weight Gain (SWG) with Olanzapine

Weight gain of >4-5 lb in the first few weeks of treatment is highly associated with significant subsequent weight gain with olanzapine

SWG defined as ≥5 kg or ≥7% of initial body weight

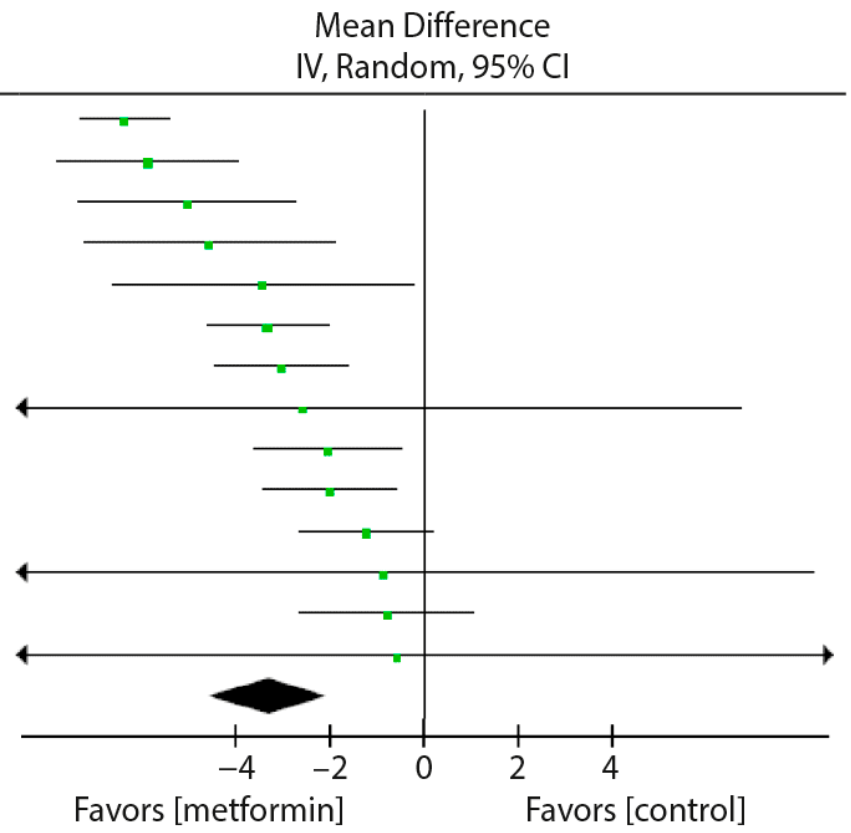


Lipkovich I, et al. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. *J Clin Psychopharmacol.* 2006;26:316-320.

Weight Mitigation with Second-Generation Antipsychotics: Metformin

	Metformin			Control				
Study or Subgroup	Mean	SD	Total N	Mean	SD	Total N	Weight, %	Mean Difference IV, Random, 95% CI
Wu et al (minus lifestyle modifications), 2008[15]	−3.2	1.9	32	3.1	1.9	32	3.6	−6.30 (−7.23 to −5.37)
Wang et al, 2012[26]	−3.3	3.9	32	2.5	4	34	3.0	−5.80 (−7.71 to −3.89)
Wu et al, 2008[15]	1.9	2.72	18	6.87	4.23	19	2.7	−4.97 (−7.25 to −2.69)
Wu et al, 2012[27]	−2.37	6.1	42	2.15	6.1	42	2.5	−4.52 (−7.13 to −1.91)
Rado et al, 2016[71]	2.49	2.35	12	5.88	5.23	13	2.2	−3.39 (−6.53 to −0.25)
Wu et al (plus lifestyle modifications), 2008[15]	−4.7	3.2	32	−1.4	1.8	32	3.4	−3.30 (−4.57 to −2.03)
Chen et al, 2013[28]	−3.2	3.1	28	−0.2	2.1	27	3.3	−3.00 (−4.39 to −1.61)
de Silva et al, 2015[30]	−1.56	19	34	1	19	32	0.5	−2.56 (−11.73 to 6.61]
Carrizo et al, 2009[25]	−1.87	2.9	24	0.16	2.9	30	3.2	−2.03 (−3.59 to −0.47)
Jarskog et al, 2013[29]	−3	4.3	75	−1	4.2	71	3.4	−2.00 (−3.38 to −0.62)
Baptista et al, 2007[74]	−1.4	3.2	36	−0.18	2.8	36	3.4	−1.22 (−2.61 to 0.17)
Chiu et al (1,000 mg), 2016[32]	−0.97	12.9	19	−0.1	14.89	18	0.5	−0.87 (−9.87 to 8.13)
Baptista et al, 2006[21]	5.5	3.3	19	6.3	2.3	18	3.1	−0.80 (−2.63 to 1.03)
Chiu et al (500 mg), 2016[32]	−0.7	14.38	18	−0.1	14.89	18	0.5	−0.60 (−10.16 to 8 96)
Total			**421**			**422**	**35.4**	**−3.27 (−4.49 to −2.06)**

Heterogeneity: $\tau^2 = 3.57$; $\chi^2 = 70.41$, $df = 13$, $P < .00001$; $I^2 = 82\%$
Test for overall effect: $Z = 5.28$, $P < .00001$



Mean −3.27 kg weight decrease

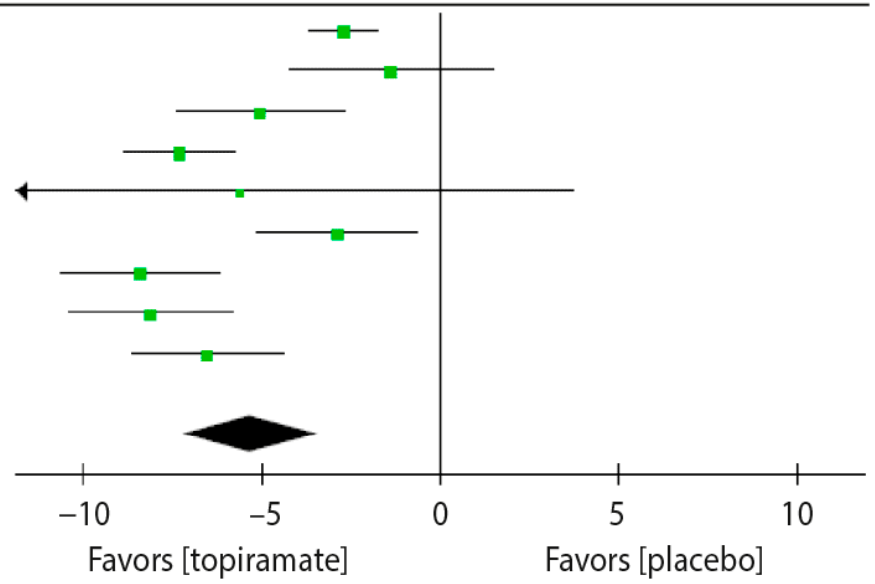
Hiluy JC, et al. Effectiveness of pharmacologic interventions in the management of weight gain in patients with severe mental illness: a systematic review and meta-analysis. *Prim Care Companion CNS Disord.* 2019;21:19r02483.

Weight Mitigation with Second-Generation Antipsychotics: Topiramate

	Topiramate			Placebo				
Study or Subgroup	Mean	SD	Total N	Mean	SD	Total N	Weight, %	Mean Difference IV, Random, 95% CI
Afshar et al, 2009[54]	−2.5	3.4	86	0.2	3	91	13.8	−2.70 (−3.65 to −1.75)
Ko et al (100 mg), 2005[51]	−1.68	5.3	16	−0.3	2.59	20	10.8	−1.38 (−4.21 to 1.45)
Ko et al (200 mg), 2005[51]	−5.35	4.35	17	−0.3	2.59	20	11.7	−5.05 (−7.41 to −2.69)
Narula et al, 2010[55]	−1.27	2.28	33	6.03	3.99	34	13.0	−7.30 (−8.85 to −5.75)
Nickel et al, 2005[52]	−4.4	16.3	25	1.2	14.76	18	3.1	−5.60 (−14.95 to 3.75)
Roy Changappa et al, 2006[53]	−2.4	3.93	16	0.49	2.37	16	11.9	−2.89 (−5.14 to −0.64)
Talaei et al (100 mg), 2016[56]	0.05	3.56	20	8.47	3.57	20	11.9	−8.42 (−10.63 to −6.21)
Talaei et al (200 mg), 2016[56]	0.35	3.82	20	8.47	3.57	20	11.8	−8.12 (−10.41 to −5.83)
Talaei et al (50 mg), 2016[56]	1.94	3.3	20	8.47	3.57	20	12.1	−6.53 (−8.66 to −4.40)
Total			**253**			**259**	**100.0**	**−5.33 (−7.20 to −3.46)**

Heterogeneity: $\tau^2 = 6.37$; $\chi^2 = 58.10$, $df = 8$, $P < .00001$; $I^2 = 86\%$

Test for overall effect: $Z = 5.58$, $P < .00001$



Mean −5.33 kg weight decrease

Hiluy JC, et al. Effectiveness of pharmacologic interventions in the management of weight gain in patients with severe mental illness: a systematic review and meta-analysis. *Prim Care Companion CNS Disord.* 2019;21:19r02483.

GLP-1 Receptor Agonists to Counter Weight Gain/Metabolic Dysregulation

Incretin: gut peptide that stimulates insulin secretion

Glucagon-like peptide 1: an incretin hormone secreted by L cells in intestinal mucosa

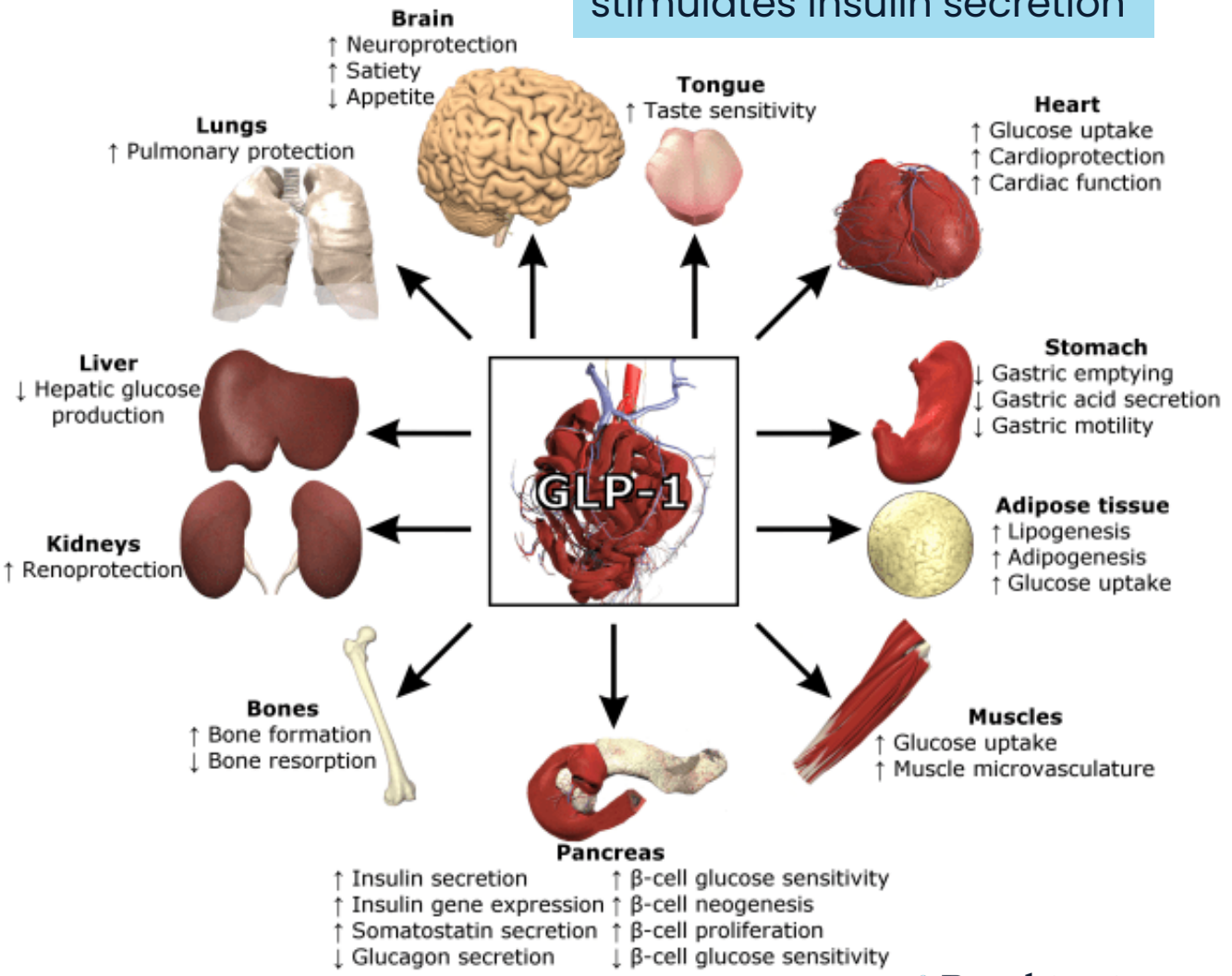
Reduces blood sugar by:

- **↑ insulin secretion**
- **↓ glucagon release** (glucagon ↑s blood sugar)
- **↓ insulin resistance**

Reduces appetite by

- stimulating satiety center
- slowing gastric emptying and GI motility

Tirzepatide also agonizes *glucose-dependent insulinotropic polypeptide* (GIP), further stimulating insulin secretion



Liraglutide for Antipsychotic-Associated Weight Gain

16 weeks of once-daily subcutaneous injection

N=97 schizophrenia spectrum patients – overweight/obese, prediabetic, taking OLZ or CLOZ

Parameter	Estimated Treatment Difference	*P* value
Body weight	-5.3 kg	<.001
Waist circumference	-4.1 cm	<.001
BMI	-1.8	<.001
Systolic BP	-4.9 mm Hg	.04
Diastolic BP	-3.0 mm Hg	ns
Fasting glucose	-2.1	<.001
HbA1C	-0.2	<.001
Total cholesterol	-19.3	<.001
LDL-cholesterol	-15.4 mg/dL	<.001

Larsen JR, et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: a randomized clinical trial. *JAMA Psychiatry.* 2017;74:719-728.

GIP/GLP-1 Agonists and Weight Loss in Non-Diabetic Obese Adults

- Semaglutide
  - Treatment with semaglutide plus lifestyle intervention was associated with substantial and sustained clinically relevant weight loss.[1]
- Tirzepatide
  - At 20 weeks after randomization, treatment with tirzepatide resulted in significantly greater weight reduction than placebo.[2]

1. Wilding JPH, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med.* 2021;384:989-1002.
2. Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med.* 2022;387:205-216.

GLP-1 Agonists Reduce Risk of Major Adverse Cardiovascular Events (MACE)

Pooled analysis of 8 randomized trials (n=60,080 diabetic patients) over a weighted 3-year average follow-up[1]

- 14% relative risk reduction in MACE (HR=0.86,95% CI=0.80-0.93, *P*<.0001)
- Cardiovascular deaths: HR=0.87 (95% CI=0.80-0.94, *P*=.001)
- Fatal or nonfatal myocardial infarction: HR=0.90 (95% CI=0.83-0.98, *P*=.02)
- Fatal or nonfatal stroke: HR=0.83 (95% CI=0.76-0.92, *P*=.002)

2.6-fold increased risk for cardiovascular disease in bipolar I disorder vs controls[2]

[1]Sattar N, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021;9:653-662.
[2]Goldstein BI, et al. Excessive and premature new-onset cardiovascular disease among adults with bipolar disorder in the US NESARC cohort. *J Clin Psychiatry.* 2015;76:163-169.

Summary

Key Insights:

- Bipolar I disorder presents complex challenges in managing psychiatric stability alongside minimizing cardiometabolic risks.
- Effective treatment requires a nuanced understanding of each patient's history, response to past treatments, and current health status.
- Various pharmacological options are available, each with pros and cons concerning efficacy, onset speed, and side effects, particularly weight gain and metabolic dysregulation.

Case Studies Overview:

- Vanessa's case highlights the importance of addressing grandiosity and manic symptoms without exacerbating weight or metabolic concerns.
- James's scenario underscores the difficulty of treating recurrent manic episodes in patients with significant cardiometabolic health risks.

Conclusions and Recommendations

Treatment Considerations:

- Prioritize fast-acting, broad-spectrum antipsychotics with a high potency for acute episodes, carefully monitoring and managing side effects.
- In patients with a first episode of mania, consider combining a second-generation antipsychotic with lithium, with a possible transition to lithium monotherapy if successful.
- Address cardiometabolic health proactively, using strategies like pairing antipsychotic treatment with agents that mitigate weight gain and metabolic effects (eg, metformin, topiramate, GLP-1 receptor agonists).

Future Directions:

- Further research is needed to explore integrated approaches that simultaneously address the psychiatric and physical health needs of patients with bipolar I disorder.
- Development and dissemination of guidelines for managing cardiometabolic risks in the context of psychiatric care will be critical for improving patient outcomes.

Call to Action:

- Psychiatrists should adopt a holistic view of patient care, recognizing the interplay between mental health and physical health risks.
- Ongoing education on the latest treatment modalities and strategies for balancing efficacy with side effect management is essential.