PsychCase 360: Choosing the Right Long-Acting Injectable for Patients With Schizophrenia

Roueen Rafeyan, MD
Clinical Assistant Professor
Department of Psychiatry
Northwestern University
Feinberg School of Medicine
Chicago, IL

Melissa Vitale, PMHNP
Reset Psychiatry
Chicago, IL

Disclosures

Roueen Rafeyan, MD

- Consultant: Alkermes, Axsome, BMS, Intracellular, Janssen, Neurocrine, Otsuka, Teva
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Melissa Vitale, PHMNP

- Speakers' bureau: Johnson & Johnson

Case 2: José

29-year-old grocery store clerk. Living with schizophrenia for 5-years.

Has been seen at our clinic since referral from his PCP 5-years ago.

- Struggled with adherence to oral medication since his diagnosis.
- He has experienced multiple relapses over the past few years due to missed doses, leading to repeated hospitalizations and significant disruptions in his work and social life.
- Despite understanding the importance of taking his medication, he has difficulty maintaining his daily regimen, particularly during periods when his symptoms worsen.
- José and his care team decided a long-acting injectable would be a good option for him as it will increase his adherence and lower the risk of subsequent relapses. (commentary on positive interviewing technique, patient insight into their illness, shared-decision making, benefits of LAI, adherence, lower risk of relapse, etc.)
- José was switched him from oral risperidone to risperidone subcutaneous once monthly injection.[1]

Image with permission of Microsoft

1. UZEDY [package insert]. Teva Neuroscience, Inc. Parsippany, NJ; 2025.

Case 2: José

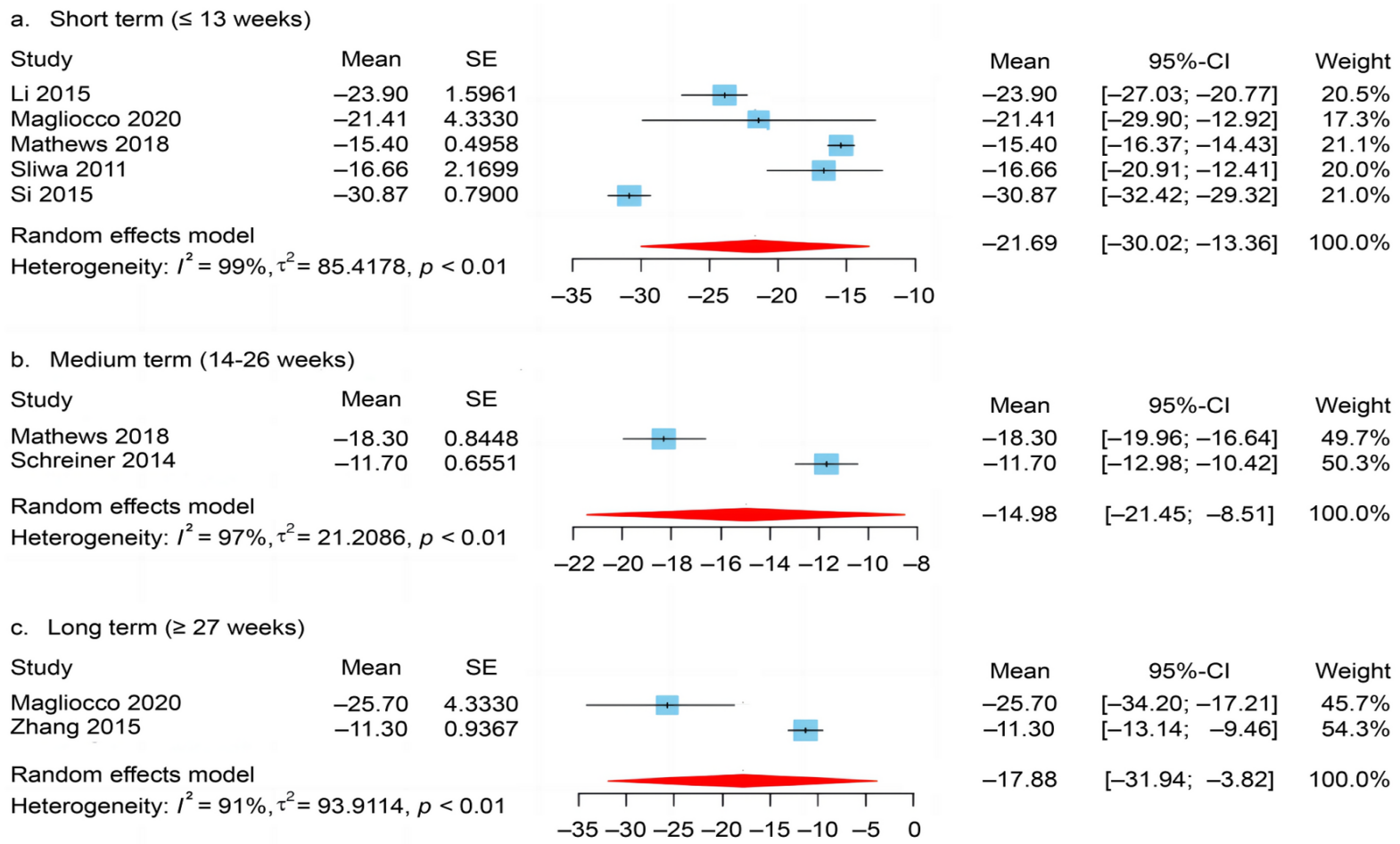
- At his next appointment, he complained of injection site pain and itching, and was switched to paliperidone palmitate once monthly (PPOM).
- Completed the two loading doses[1] without complaint of injection site pain or itching and was scheduled for his next injection 30-days later.
- José continues to struggle with keeping appointments. He misses his scheduled appointment and comes to clinic nearly 6-weeks following his last injection.
- He notes symptom breakthrough including paranoia and hallucinations
- Care team notes poor hygiene
- States he is tolerating injections well; no injection site pain, itching, etc.
- The current dose (156 mg) had been doing well with controlling symptoms, but efficacy had waned due to missing his injection 2-weeks prior.
- Counsel on need to maintain appointments for next 2–3 months. Discuss need to get to steady-state, ensure efficacy on dose, and titrate if necessary to ensure clinical stability and tolerability.

Image with permission of Microsoft
PPOM, paliperidone palmitate once monthly

1. INVEGA SUSTENNA [package insert]. Janssen Pharmaceuticals, Inc. Titusville, NJ; 2024.

PPOM Compared to Oral Antipsychotics

Single arm meta-analysis plot of change from baseline in the PANSS total score at short-, medium-, and long-term periods.



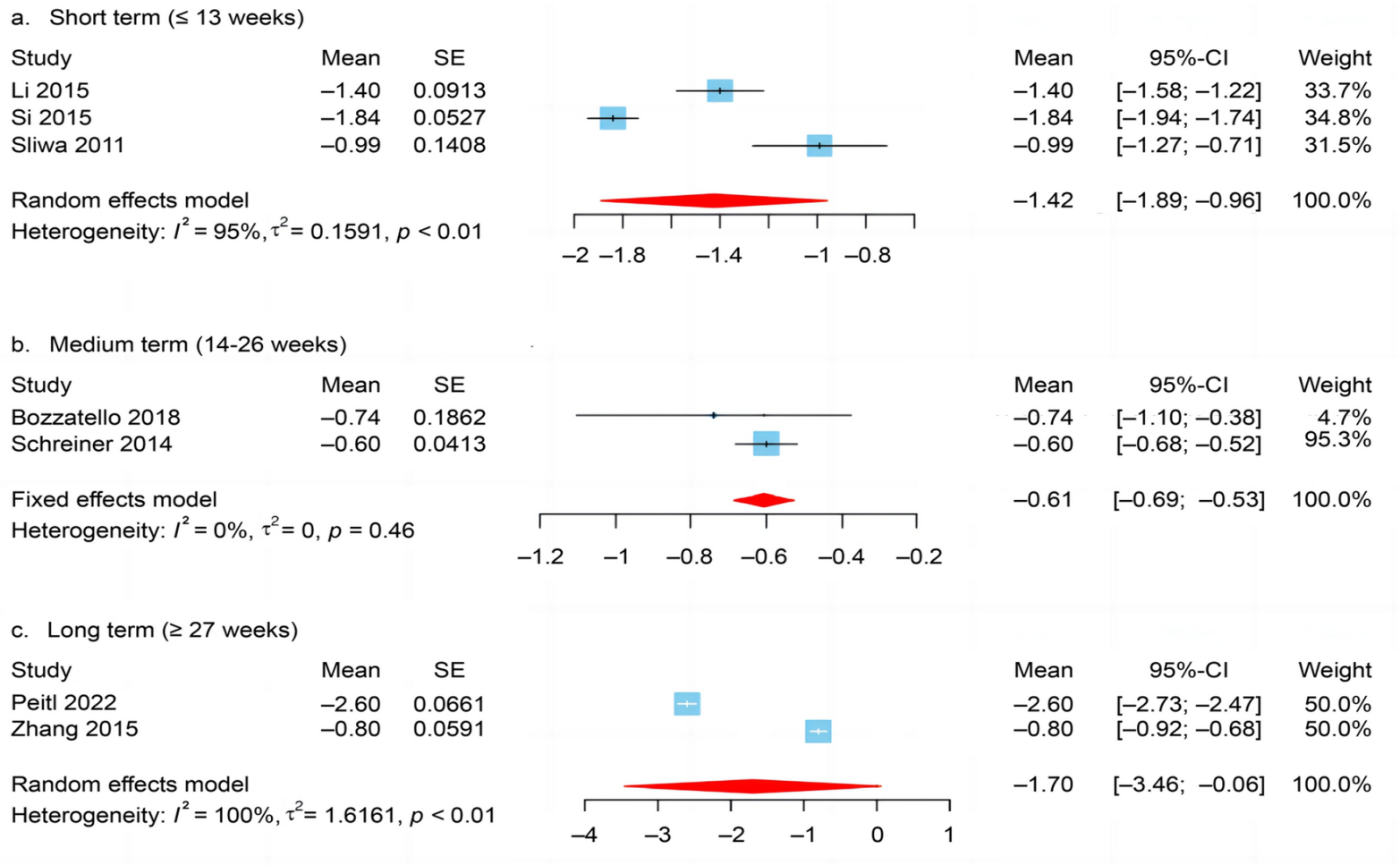
CI: confidence interval; SE: standard error.

PANSS, Positive and Negative Syndrome Scale

Li Q, et al. *CNS Drugs*. Aug 2023;37(8):695-713.

PPOM Compared to Oral Antipsychotics

Single arm meta-analysis plot of change from baseline in the CGI-S score at short-, medium-, and long-term periods.



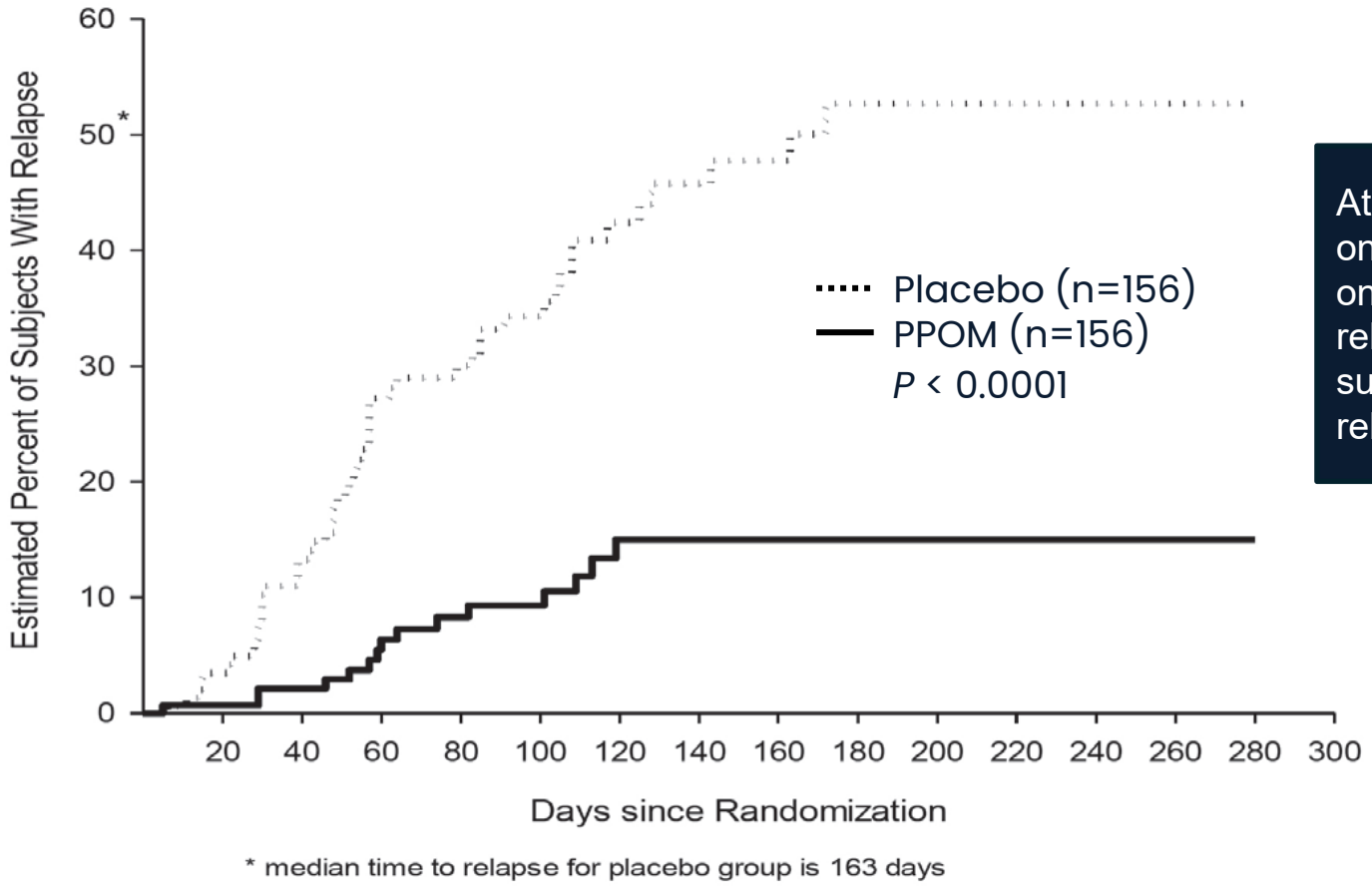
CI: confidence interval; SE: standard error.

CGI-S, Clinical Global Impression-Severity

Li Q, et al. *CNS Drugs*. Aug 2023;37(8):695-713.

PPOM vs Placebo in Relapse Prevention

Kaplan-Meier Plot of Cumulative Proportion of Subjects with Relapse Over Time



At the interim analysis*, only 15 of 156 subjects on PPOM had suffered a relapse, while 141 of 156 subjects remained relapse free.

*The preplanned interim analysis was conducted after 68 relapse events and included 312 patients. Time-to-relapse favored palidperidone palmitate($P<0.0001$, log-rank test) at interim and final analysis (n=408). The hazard ratio (placebo/paliperidone palmitate) at the final analysis was 3.60 (95% CI: 2.45, 5.28).

INVEGA SUSTENNA [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2024

Hough D, et al. *Schizophr Res*. Feb 2010;116(2-3):107-17.

Paliperidone Palmitate Once Monthly Safety Profile

Most common adverse events[1]*:

- Injection-site reactions
- Somnolence/sedation
- Dizziness
- Akathisia
- EPS

Paliperidone has a prolactin-elevating effect[1], which is associated with higher levels of prolactin elevation than other antipsychotic agents

Weight	Placebo N=451	PPOM dose (mg) 234/39 N=137	234/156 N=144	234/234 N=145
Change from baseline (kg)	-0.4	0.4	0.7	1.4
≥ 7% increase from baseline	3.3%	5.8%	8.3%	13.1%

*Incidence ≥5% and occurring at least twice as often as placebo in the 5 pivotal schizophrenia trials.
EPS, extrapyramidal side effect; PPOM; paliperidone palmitate once monthly

INVEGA SUSTENNA [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2024

José Clinic Follow Up

- José has been on PPOM for 5 months and is keeping his appointments
- States he is doing much better. Has been consistent with his work and has resumed normal social activities.
- His care team notes an improvement in his hygiene.
- José states he is traveling home to Puerto Rico for his grandmother's birthday at the end of the month and will be unable to get his next scheduled injection.
- Team discusses longer duration formulations of paliperidone, an every 3-month or 6-month injection.

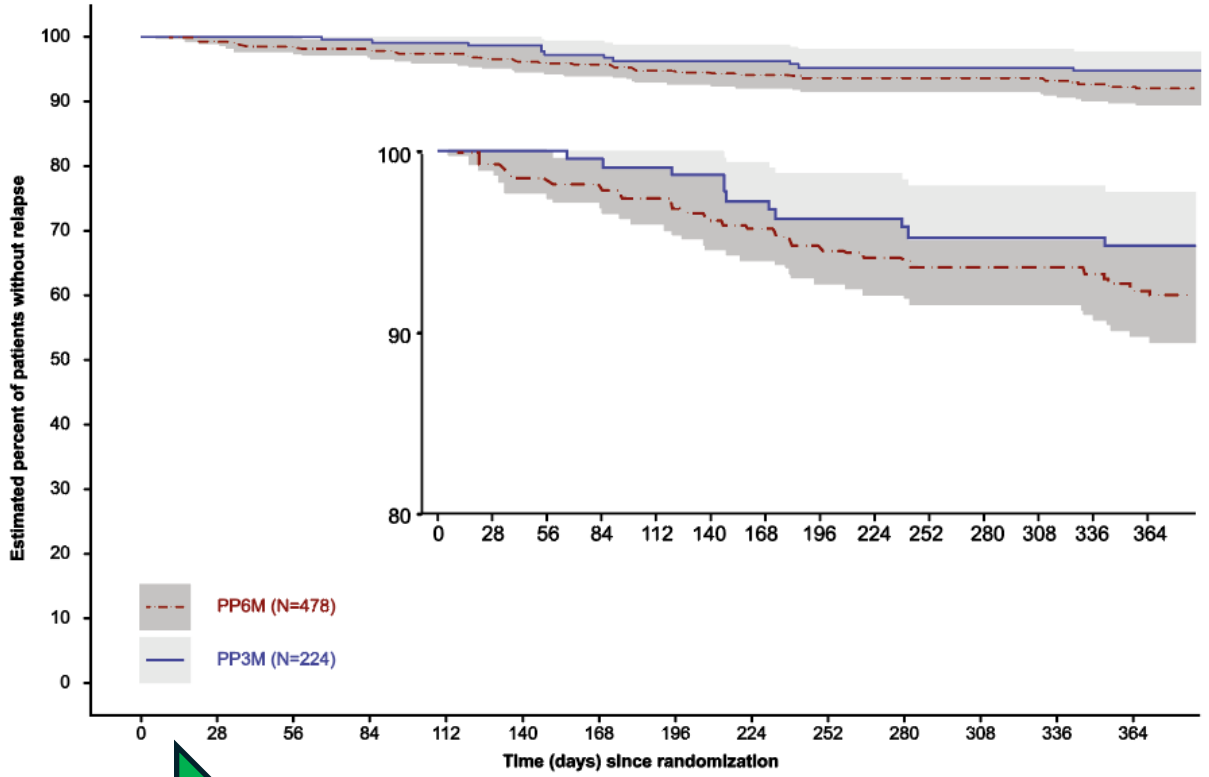
Results from a 1-year noninferiority study comparing PP6M to PP3M

95% of patients taking PP3M

and

92.5% of patients taking PP6M

Remained relapse free at 1-year



In an open-label extension study, 96.1% of patients receiving PP6M remained relapse free for 2-years

Kaplan-Meier plot and 95% pointwise confidence-based percentage of patients without relapse during the double-blind phase.

ITT, intent-to-treat; PP3M, paliperidone palmitate 3-month formulation; PP6M, paliperidone palmitate 6-month formulation.

Najarian D, et al. *Int J Neuropsychopharmacol*. Mar 17 2022;25(3):238-251.

Paliperidone Safety Profile

The overall safety profile for PP3M and PP6M were comparable to PPOM

Preferred Term	PP3M (n=224)	PP6M (n=478)
Upper respiratory tract infection	13%	12%
Injection-site reaction	5%	11%
Weight increased	8%	9%
Headache	5%	7%
Extrapyramidal symptoms	5%	7%
Akathisia	4%	4%
Psychosis	3%	3%
Urinary tract infection	1%	3%
Back pain	1%	3%
Musculoskeletal pain	1%	3%
Anxiety	0%	3%
Insomnia	2%	3%
Diarrhea	1%	2%

Change in Fasting Glucose	PP3M (n=195)	PP6M (n=423)
Normal to high	3%	4%
Impaired glucose tolerance to high	4%	5
Normal/impaired glucose tolerance to high	7%	9%
<126 mg/dL to ≥140 mg/dL	4%	5%
<126 mg/dL to ≥200 mg/dL	0%	1%
<126 mg/dL to ≥300 mg/dL	0%	<1%

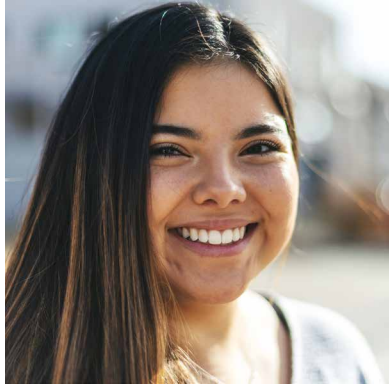
Treatment-emergent adverse reactions (≥2%) during noninferiority study

INVEGA TRINZA [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2024
INVEGA HAFYERA [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2024
Najarian D, et al. *Int J Neuropsychopharmacol.* Mar 17 2022;25(3):238-251.

How is José Doing Now?

- José states it was great to catch up with family and old friends, and he is grateful he was able to attend his grandmother's birthday party.
- States he is back at work, continues to improve and focus on his recovery.
- He has been consistent with his appointments and is happy with only getting two injections a year.

Case 1: Sarah

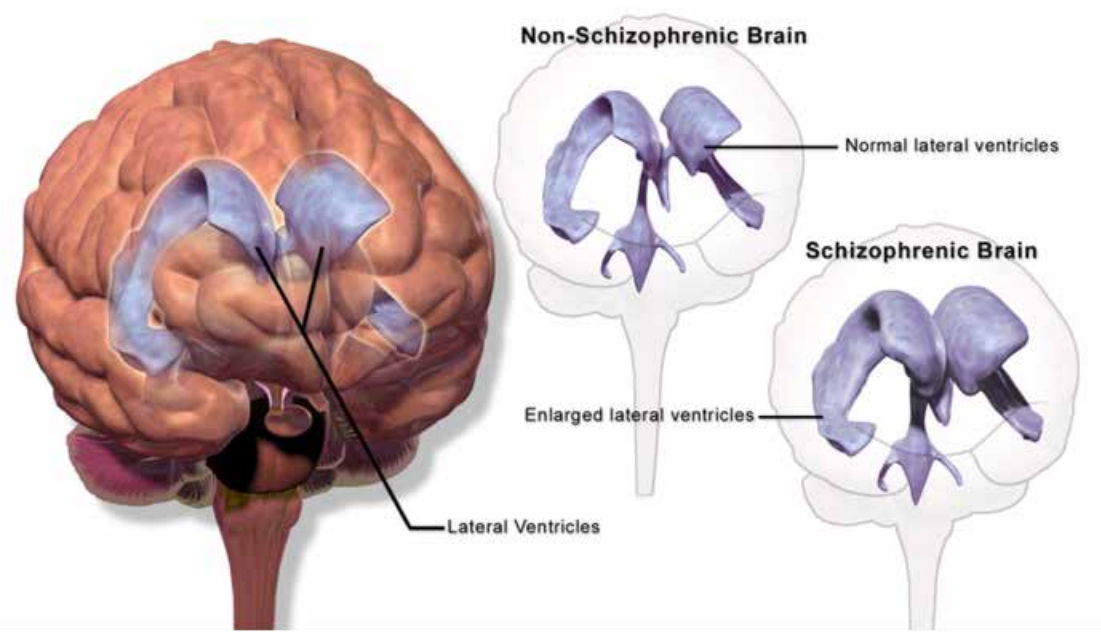


21-year-old college student, diagnosed with schizophrenia 6 months ago after experiencing a 2nd psychotic episode while home for summer break.

- Started on risperidone after her diagnosis. Demonstrated good clinical improvement with stability and tolerated the medication well.
- Stopped taking medication once back at school due to stigma of her roommate finding out what her medication was for and gaining 4 pounds, despite a good diet and exercise routine.
- Resulted in a relapse and hospitalization, during which she was restarted on risperidone and counseled on the need to be adherent to her medication.
- She was referred to your outpatient psychiatric clinic with an appointment scheduled 12 days post-discharge.

Sarah: Key Features for New Care Team

- Receive her chart from recent hospitalization as well as her home psychiatrist.
- Key features confirming her diagnosis include a CT ordered after her first episode to rule out any organic causes, eg:
  - Tumor
  - Arteriovenous malformation
  - Cyst
- CT indicated enlarged lateral ventricles consistent with schizophrenia[1,2] and was negative for any other organic findings.



Enlarged ventricles in schizophrenia.
The lateral ventricles (highlighted in purple) are enlarged in individuals with schizophrenia compared to individuals without schizophrenia.[3]

1. Wright IC, et al. *Am J Psychiatry*. Jan 2000;157(1):16-25.
2. Gaser C, et al. *Am J Psychiatry*. Jan 2004;161(1):154-6.
3. Hedges V. Introduction to Neuroscience, Open Edition. https://openbooks.lib.msu.edu/intronerosciencel/. Accessed Feb. 28, 2025.

Sarah: Key Features for New Care Team

Labs from her recent hospital stay:

- Tox screen
- Comment on synthetic/designer drugs, kratom, etc

Patient: Sarah

Urine Toxicology

Test	Result
Amphetamines	Negative
Barbiturates	Negative
Benzodiazepines	Negative
Cocaine	Negative
Marijuana	Negative
Methadone	Negative
Methamphetamines	Negative
Opiates	Negative
Oxycodone	Negative
Phencyclidine	Negative

Sarah: Key Features for New Care Team

Labs from her recent hospital stay:

- CBC

Patient: Sarah

Routine Hematology: CBC

Test	Result	Unit	Ref
W.B.C	6.5	x1000/mm^3	4.0 – 10
R.B.C	5.01	Mill/mm^3	F: 4.2 – 5.4
Hb	15.4	gm/dl	F: 12 – 16
Hct	45.2	%	F: 36 – 46
M.C.V	90.2	fL	77 – 97
M.C.H	31	Pgm	26 – 32
M.C.H.C	34	%	32 – 36
Platelet	209	x1000/mm^3	140 – 440

Sarah: Key Features for New Care Team

Labs from her recent hospital stay:

- Fasting lipid panel
- FBG
- A1c
- LFT
- 12-lead EKG was normal

Patient: Sarah

Fasting Lipid Panel

Test	Result	Unit
Total-C	151	mg/dl
HDL-C	58	mg/dl
LDL-C	83	mg/dl
Trigs	48	mg/dl

FBG, A1c

Test	Result	Unit
FBG	87	mg/dl
A1c	5.4	%

LFT

Test	Result	Unit
AST	14	IU/L
ALT	18	IU/L

FBG, fasting blood glucose; LFT, liver function tests

Clinical Interview Findings

- Upon interview, it is clear that Sarah is high functioning and motivated
- She maintains good grades and regularly attends spin and yoga classes at the school gym
- Notes concerns over her weight gain
- Other adverse events identified include:
  - Dysregulation of her menstrual cycle[1,2]
  - Galactorrhea[2,3]
  - Sedation
  - Order prolactin, reveals hyperprolactinemia

Patient: Sarah

Endocrinology

Test	Result	Unit	Ref
Prolactin	146.4	ng/ml	F <25 ng/ml

1. Hariharan J, Mohsin J. *WMJ*. 2002;101(8):41-3.
2. Stojkovic M, et al. *Front Psychiatry*. 2022;13:874705.
3. Batra S, Sidana A. *Prim Care Companion CNS Disord*. Jan 30 2024;26(1)

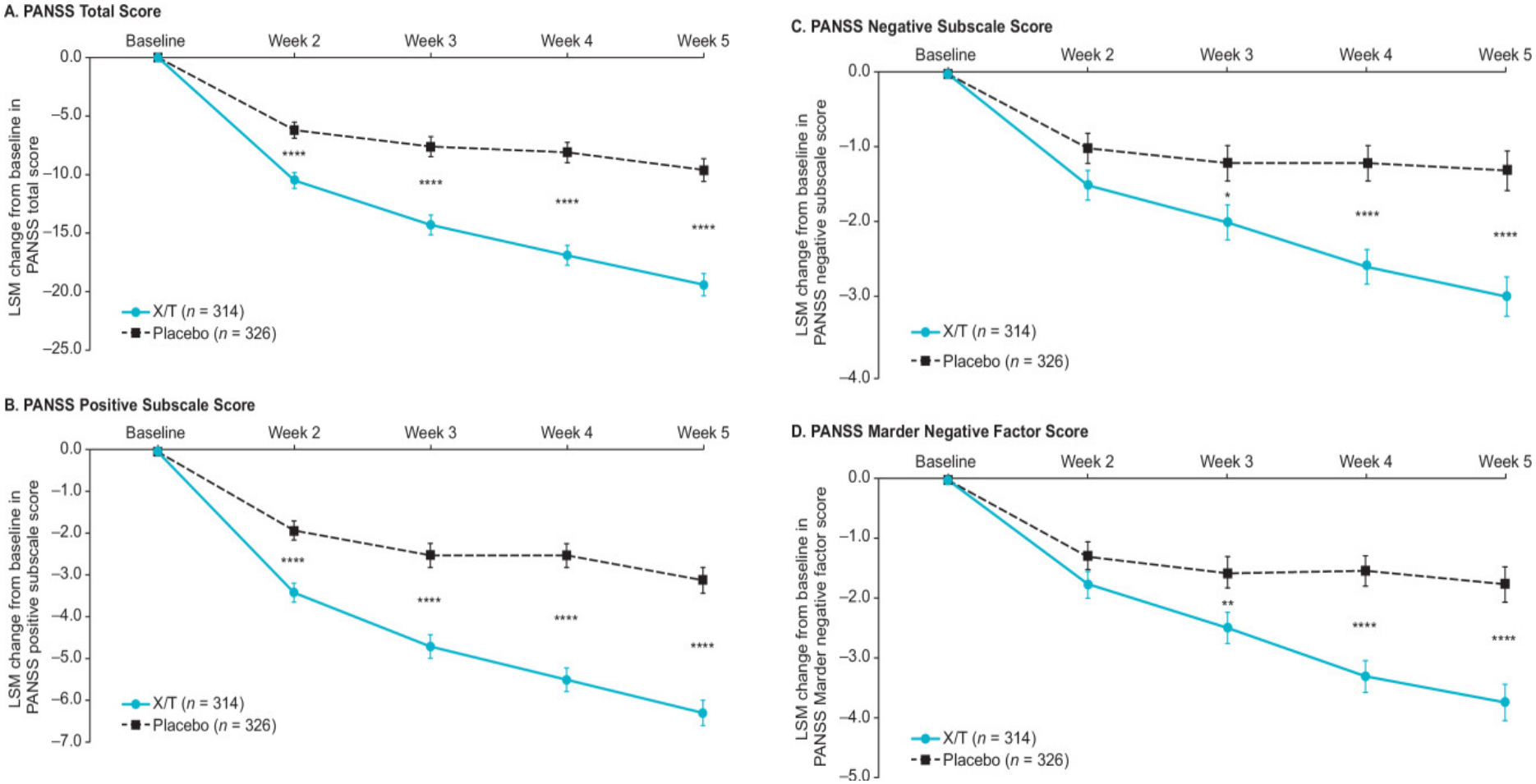
Treatment Considerations

- Need a medication that will maintain clinical stability with a lower risk of metabolic issues (prolactin elevation, weight gain) while avoiding histaminergic activity due to her sedation
- Oral options
  - Xanomeline-Trospium
  - Cariprazine
- Long-acting injectable (LAI)
  - Aripiprazole
    LAIs offer superior relapse control, improved adherence to concomitant medications, avoidance of peak-trough variance which can be associated with withdrawal AEs

LAI, long-acting injectable

Xanomeline-Trospium Efficacy

Pooled Efficacy Results from EMERGENT-1, -2, and -3



Pooled PANSS scores change from baseline.
Values are LSM ± SE. LS mean difference vs. placebo: *$P < 0.05$; ** $P < 0.01$; **** $P < 0.0001$. SE standard error, LSM least squares mean, PANSS Positive and Negative Syndrome Scale; X/T xanomeline/trospium.

Kaul I, et al. *Schizophrenia (Heidelb).* 2024 Nov 2;10(1):102.

Xanomeline-Trospium Safety

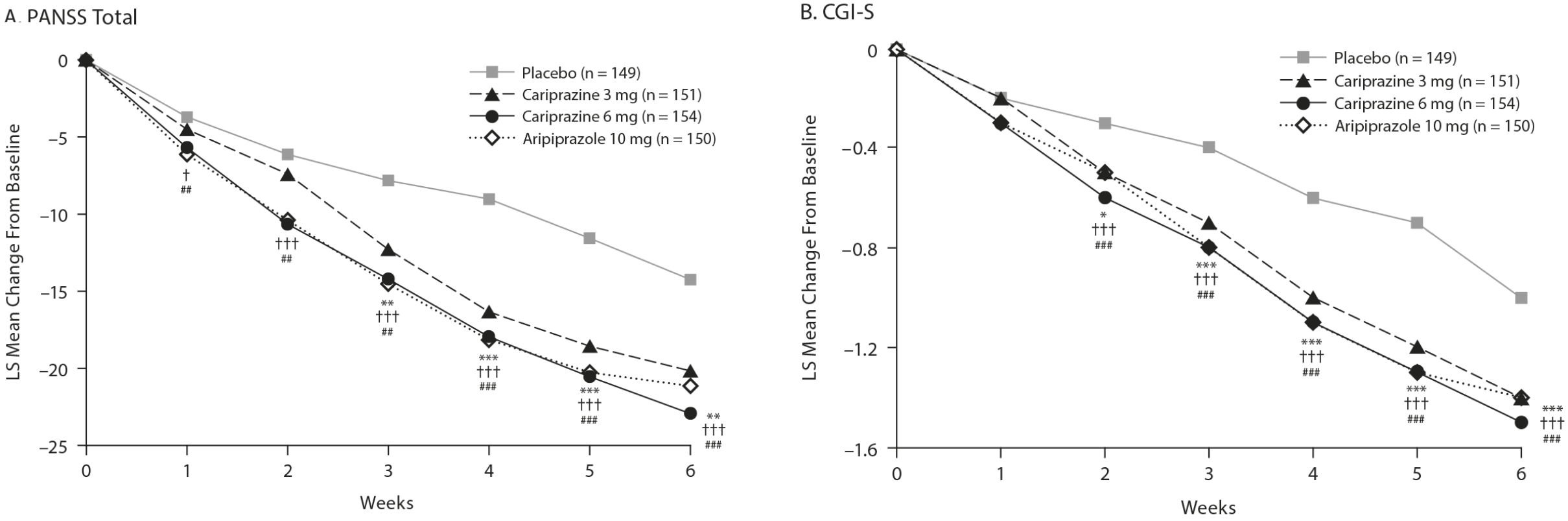
Pooled Incidence of Adverse Events from EMERGENT-1, -2, and -3

Adverse Event	Xanomeline/ Trospium (n)	Events (n)	Placebo (n)	Events (n)	RR	95% CI	
Constipation	340	58	343	15	3.30	[1 .63; 4.45]	P = 0.000116
Dyspepsia	340	52	343	15	3.30	[1 .23; 8.84]	P = 0.017689
Nausea	340	63	343	13	4.37	[2 .97; 50.90]	P < 0.000001
Vomiting	340	46	343	6	7.53	[1 .50; 37.94]	P = 0.014367
Diarrhea	340	16	343	9	1.66	[1 .50; 37.94]	P = 0.436441
Headache	340	37	343	35	1.06	[0.69; 1.65]	P = 0.779017
Serious Adverse Events	340	4	343	3	1.25	[0.30; 5.1 8]	P = 0.760045

	Xanomeline/ Trospium (n)	Placebo (n)	MD	95% CI	
Akathisia	340	343	0	[-0.13; 0.13]	P= 0.991726
Parkinsonism	340	343	0.03	[-0.06; 0.1 2]	P = 0.518893
Body Weight Gain	340	343	-0.36	[-1.18; 0.46]	P = 0.386626

de Almeida A, M. et al. *J Psychiatr Res*. 2024 Nov 28;181:262-272.

Cariprazine Efficacy



Change from baseline at each study week (ITT, MMRM).
*P < 0.05; **P < 0.01; *** P < 0.001: cariprazine 3 mg/d vs placebo.
†P < 0.05; ††P < 0.01; ††† P < 0.001: cariprazine 6 mg/d vs placebo.
#P < 0.05; ##P < 0.01; ### P < 0.001: aripiprazole 10 mg/d vs placebo.

CGI-S, Clinical Global Impression-Severity of Illness; ITT, intent to treat; LS=least squares; MMRM, mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale.

Durgam S, et al. *J Clin Psychiatry*. Dec 2015;76(12):e1574-82.

Cariprazine Safety

Weight change in 6-week pivotal studies[1]

	n	Mean Change	Proportion of patients with ≥ 7% change
Placebo	573	+0.7 lb	5%
Cariprazine 1.5-3 mg/d	512	+1.8 lb	8%
Cariprazine 4.4-6 mg/d	570	+2.2 lb	8%

No meaningful increase in mean levels of[1,2]:

- Fasting blood glucose
- Total cholesterol
- Fasting triglycerides
- Prolactin

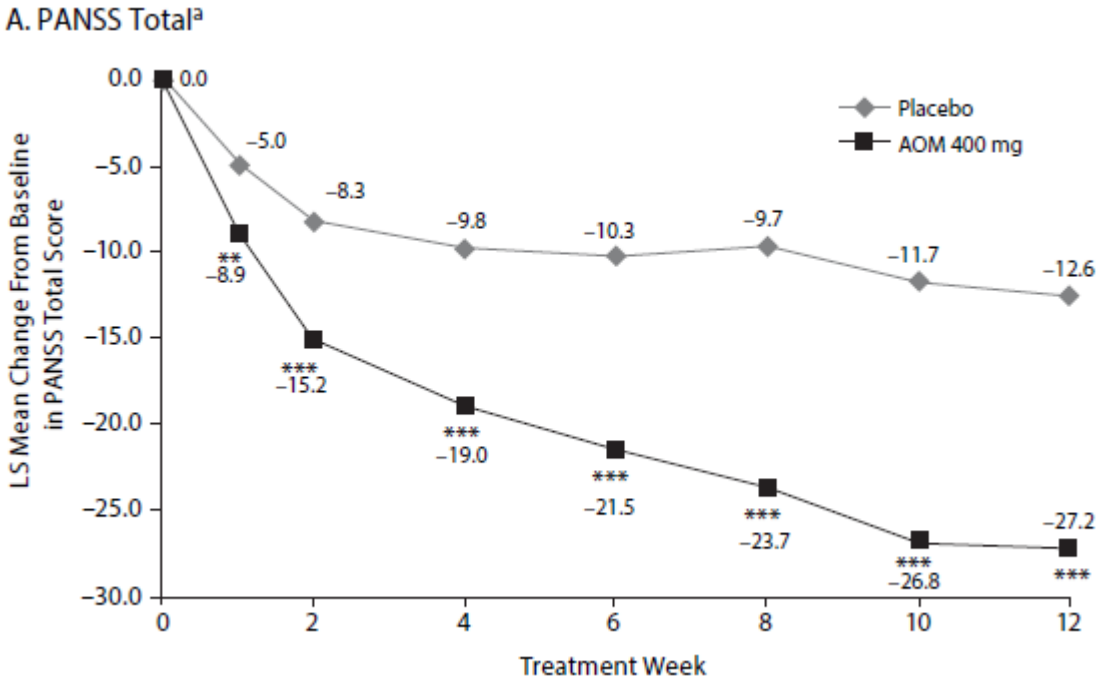
*Most common adverse reactions from short-term schizophrenia studies[2-4]

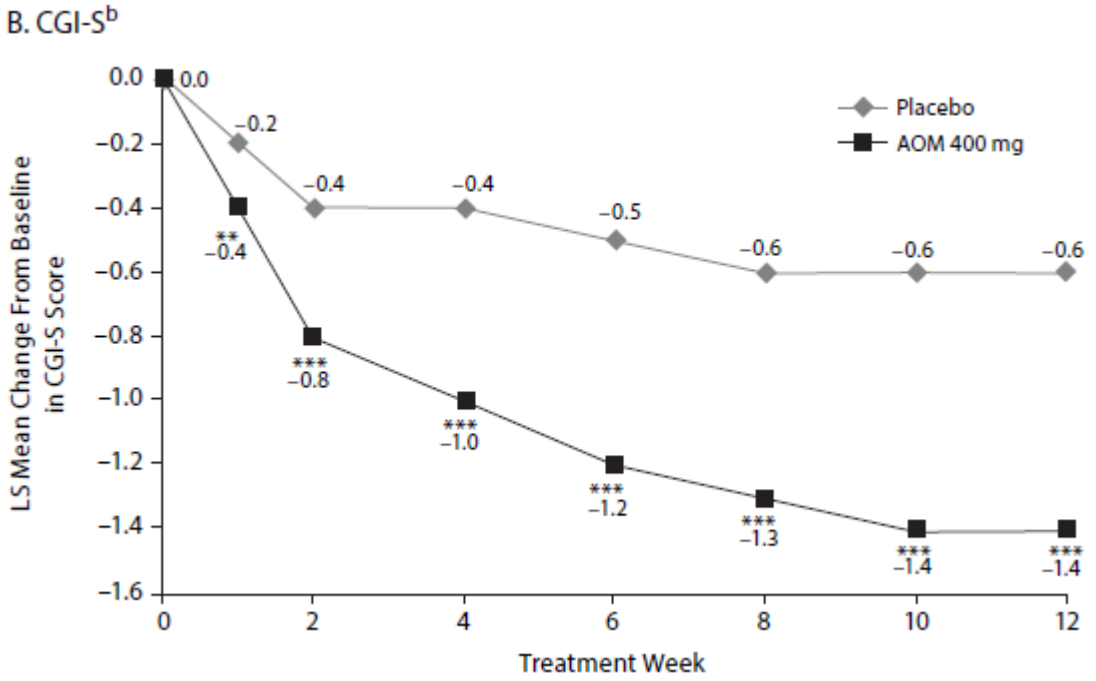
	Placebo (n=584)	Cariprazine 1.5-3 mg/d (n=539)	Cariprazine 1.5-3 mg/d (n=575)	Cariprazine 1.5-3 mg/d (n=203)
EPS	8%	15%	19%	20%
Akathisia	4%	9%	13%	14%

*≥5% and at least twice that of placebo

1. VRAYLAR [package insert]. North Chicago, IL: AbbVie, Inc.; 2024.
2. Durgam S, et al. *Schizophr Res*. 2014;152(2-3):450-457.
3. Durgam S, et al. *J Clin Psychiatry*. 2015;76(12):e1574-e1582.
4. Kane JM, et al. *J Clin Psychopharmacol*. 2015;35(4):367-373.

Aripiprazole Once Monthly Efficacy





[a]Mean baseline score: placebo (n=167), 103.4; AOM 400mg (n=162), 102.4
[b]Mean baseline score: placebo (n=168), 5.2; AOM 400mg (n=162), 5.2
LS change from baseline (MMRM).
**$P < 0.01$; ***$P < 0.001$

AOM, Aripiprazole Once Monthly; CGI-S, Clinical Global Impression-Severity of Illness; LS, least squares; MMRM, mixed-effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale.

Kane JM, et al. *J Clin Psychiatry*. Nov 2014;75(11):1254-60.

Aripiprazole Once Monthly Safety

PREFERRED TERM	AOM (%, n=167)	PLACEBO (%, n=172)
Constipation	10	7
Dry mouth	4	2
Diarrhea	3	2
Vomiting	3	1
Abdominal discomfort	2	1
Injection site pain	5	1
Upper respiratory tract infection	4	2
Increased weight	17	7
Decreased weight	4	2
Arthralgia	4	1
Back pain	4	2
Myalgia	4	2
Musculoskeletal pain	3	1
Akathisia	11	4
Sedation	5	1
Dizziness	4	2
Tremor	3	1
Nasal congestion	2	1

Adverse reactions in ≥2% of patients in a 12-week, double-blind, placebo-controlled study of adult patients living with schizophrenia.

METABOLIC MEASURE		AOM 400 MG	PLACEBO
Fasting Blood Glucose	% (n/N) of patients who shifted from normal to high (<100 mg/dL to ≥126 mg/dL)	8.0% (7/88)	0.0% (0/75)
Weight Gain	Mean change from baseline to Week 12, kg	+3.5	+0.8
	Weight gain ≥7% of body weight, % (n/N)	21.5% (31/144)	8.5 (12/141)
Prolactin	Mean change from baseline to Week 12; ng/mL (SD) (*P*=0.0176)	-6.4 (13.5%) n=99	-1.1 (14.5%) n=66

No meaningful increase in mean levels of :

- Total cholesterol
- LDL-C
- HDL-C
- Fasting triglycerides

AOM, Aripiprazole Once Monthly

Kane JM, et al. *J Clin Psychiatry*. Nov 2014;75(11):1254-60.

How is Sarah Doing Now?

- Sarah states that she doing well on aripiprazole once monthly
  - Positive symptoms are well controlled
  - Sedation is improved
- Her prolactin level has normalized
  - Menstrual cycle has regulated
  - Galactorrhea has resolved
- She has not gained any additional weight
- Consider moving her to the every 2-month formulation of aripiprazole in time?