THE CARLAT REPORT HOSPITAL PSYCHIATRY

A CME Publication

Subscribe today! Call 866-348-9279

UNBIASED INFORMATION COVERING HOSPITAL PSYCHIATRY

Worth 2 CME credits!

Victoria Hendrick, MD
Editor-in-Chief

Volume 1, Issue 5&6
July/August/September 2021
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Metabolic Side Effects

Learning Objectives

After reading these articles, you should be able to:

1. Determine effective pharmacologic strategies for the prevention and treatment of obesity and antipsychotic-induced weight gain.
2. Identify metabolic syndrome and appropriate psychosocial and pharmacologic interventions in patients with schizophrenia.
3. Describe how schizophrenia presents differently in female versus male patients.
4. Summarize some of the current research findings on psychiatric treatment.

Battle of the Bulge: Obesity and Antipsychotic-Induced Weight Gain

Farah Khorassani, PharmD. Associate Clinical Professor of Pharmacy Practice, St. John's University, Queens, NY.

Dr. Khorassani has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Many psychiatric medications cause weight gain, including mood stabilizers, antidepressants, and especially antipsychotics. Most weight gain secondary to antipsychotic use occurs in the first 6 months of therapy, so it's important to monitor weight closely and intervene early in a patient's treatment. We counsel patients at every visit about healthy diets, portion control, and regular exercise. This article offers practical pharmacologic strategies for the prevention and treatment of obesity and antipsychotic-induced weight gain (AIWG).

Highlights From This Issue

Dr. Stephen Marder outlines interventions that attenuate weight gain and insulin resistance in patients on antipsychotic medications.

Dr. Jayashri Kulkarni describes the "estrogen hypothesis" of schizophrenia and tells us how it has led to novel treatments for female patients.

We review medications for obesity, including two that received FDA approval in June.

Prevention, switch, and augmentation strategies

The cornerstone of preventing AIWG is antipsychotic selection. Atypical antipsychotics with a low metabolic risk, including aripiprazole, brexpiprazole, cariprazine,

Continued on page 4

Q&A With the Expert

Weight Gain and Metabolic Side Effects
Stephen Marder, MD

Daniel X. Freedman Professor of Psychiatry. Vice Chair for Education, Semel Institute for Neuroscience at UCLA. Director, VA VISN 22 Mental Illness Research, Education, and Clinical Center, San Diego, CA.

Dr. Marder has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CHPR: Dr. Marder, can you please tell us about your work?
Dr. Marder: Sure. My work has focused on pharmacologic and nonpharmacologic approaches to improving the outcomes of serious mental illnesses, particularly schizophrenia. I'm very interested in ways to combine psychosocial interventions with pharmacological approaches and to reduce adverse side effects of antipsychotic medications, such as weight gain and diabetes.
CHPR: How big of a problem is antipsychotic-induced weight gain (AIWG) and metabolic syndrome?
Dr. Marder: It's a big problem. Individuals with schizophrenia are at high risk of obesity, elevated lipids, increased insulin resistance, diabetes, and cardiovascular disease. On average, people with schizophrenia die 20–25 years sooner than people without schizophrenia. It's important for clinicians to be mindful of the metabolic effects—those that are related to the illness itself and those

Continued on page 2

Expert Interview—Weight Gain and Metabolic Side Effects

Continued from page 1

that result from treatments, particularly antipsychotic drugs *(Editor's note: See "Metabolic Syndrome Risk Factors" table at right).*

CHPR: Might other factors contribute to the shortened lifespan?

Dr. Marder: Certainly. Many people with schizophrenia tend to be sedentary, are smokers, and have poor diets. Some risk factors, like lack of exercise and poor diet, are modifiable; some are not, like genetic risk. But diabetes, obesity, and cardiovascular disease are major factors contributing to these patients' shorter lifespans.

CHPR: You mentioned genetic risk. Is there a genetic predisposition for obesity or diabetes among individuals with schizophrenia?

Dr. Marder: Yes. Even drug-naïve people with schizophrenia have three times the risk of developing diabetes, and that's probably due to shared susceptibility genes between diabetes and schizophrenia. When you add antipsychotic drugs, the risk for diabetes increases by an additional 20% (Rajkumar AP et al, *Am J Psychiatry* 2017;174(7):686–694).

CHPR: But if a patient on antipsychotic drugs does not gain weight, do we still need to worry about diabetes?

Dr. Marder: That's a good question. Visceral fat and increased waist circumference are associated with insulin resistance, so in most cases diabetes develops primarily in people who gain weight, but patients can develop insulin resistance even in the absence of weight gain.

Metabolic Syndrome Risk Factors
Having three or more of these is problematic

Risk Factor	Description
Large waist	A waistline that measures at least 35 inches for women and 40 inches for men
High triglyceride level	150 mg/dL or higher
Reduced "good" or HDL cholesterol	Less than 40 mg/dL in men or less than 50 mg/dL in women
Increased blood pressure	130/85 mmHg or higher
Elevated fasting blood sugar	100 mg/dL or higher

Source: www.nhlbi.nih.gov/health-topics/metabolic-syndrome

CHPR: And there are certain subgroups who are at more risk of weight gain and metabolic syndrome, right?

Dr. Marder: Having a lower body mass index (BMI) prior to treatment places people at more risk for weight gain *(Editor's note: See "Body Mass Index" table below).* Also, first-episode patients and younger patients are at greater risk, particularly adolescents. And rapid weight gain in the first month of treatment predicts significant long-term weight gain. Other factors associated with medication-induced weight gain are gender (women being at greater risk) and non-Caucasian ethnicities (Vandenberghe F et al, *Pharmacogenet Genomics* 2016;26(12):547–557).

Body Mass Index (BMI)

Weight Category	BMI[1]
Obese	≥ 30
Overweight	25–29.9
Normal	18.5–24.9
Underweight	< 18.5

[1]Calculate BMI by dividing [weight (lb)] by [height (in)] squared and multiply by a conversion factor of 703. For example, a 200-pound, 6-foot individual has a BMI of 27.

CHPR: What interventions do you recommend to minimize the risk?

Dr. Marder: A reasonable first intervention is to change antipsychotics to one that is less likely to cause weight gain. Some patients only respond to certain medications, however, so this might not be an option. Adding metformin also helps.

CHPR: So which medications are the most and least likely to cause metabolic changes and weight gain?

Dr. Marder: Clozapine, olanzapine, and quetiapine stand out as the medications with the most concerning metabolic profile, and aripiprazole, lurasidone, and ziprasidone have the lowest risk *(Editor's note: See "Metabolic Side Effects of Antipsychotics" table on page 3).* But there are patients who gain weight on drugs that are not considered high risk. For example, when we began doing phase II trials with risperidone in the 1990s, I remember a patient who developed diabetic ketoacidosis on risperidone. Almost all antipsychotics have at least some metabolic risk, so even though aripiprazole, lurasidone, and ziprasidone are associated with minimal weight gain, some patients will gain weight on these medications.

CHPR: It sounds like we should monitor all patients on antipsychotic agents, not just patients on the worst-offending agents.

Dr. Marder: Yes. We recommend that early in treatment, clinicians check for signs of prediabetes or insulin resistance. That would include ordering either a fasting blood glucose or a hemoglobin A1C within 6–8 weeks of starting a new antipsychotic drug.

CHPR: Do you do any other testing?

Continued on page 3

EDITORIAL INFORMATION

Publisher: **Daniel Carlat, MD**

Editor-in-Chief: **Victoria Hendrick, MD**

Deputy Editor: **Talia Puzantian, PharmD, BCPP,** professor, Keck Graduate Institute School of Pharmacy, Claremont, CA

Executive Editor: **Janice Jutras**

Assistant Editor: **Ilana Fogelson**

Editorial Contributor: **Farah Khorassani, PharmD**

Editorial Board:

Timothy Botello, MD, Chief of Inpatient Psychiatry, University of Southern California—County Hospital

Jeff Cardenas, MD, Psychiatric Emergency Room Director, Olive View UCLA Medical Center, Los Angeles, CA

Adrienne Grzenda, MD, Clinical Assistant Professor of Psychiatry & Biobehavioral Sciences, UCLA David Geffen School of Medicine and Olive View UCLA Medical Center, Los Angeles, CA

Sandra Hyams, PMHNP, psychiatric nurse practitioner, John Peter Smith Hospital, Fort Worth, TX

Anne Li, MD, inpatient psychiatrist, Lemuel Shattuck Hospital, Boston, MA

Alexander Thompson, MD, MBA, MPH, Clinical Professor and Director, C-L Psychiatry, University of Iowa

All editorial content is peer reviewed by the editorial board. Dr. Carlat, Dr. Hendrick, Dr. Puzantian, Ms. Jutras, Ms. Fogelson, Dr. Khorassani, Dr. Botello, Dr. Cardenas, Dr. Grzenda, Ms. Hyams, Dr. Li, and Dr. Thompson have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.

This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists, and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

The Carlat Hospital Psychiatry Report (ISSN 2768-3877)

POSTMASTER: Send address changes to *The Carlat Psychiatry Report,* P.O. Box 626, Newburyport, MA 01950

Expert Interview—Weight Gain and Metabolic Side Effects

Continued from page 2

Dr. Marder: We also recommend obtaining a lipid panel within 6–8 weeks. An elevation in triglycerides is early evidence indicating that the person will be at greater risk for diabetes and weight gain.

CHPR: And with what sort of frequency should clinicians do the monitoring?

Dr. Marder: At every visit to the clinician, patients should get their weight checked. We also want to make sure patients have a bathroom scale at home so they can weigh themselves regularly and take ownership of this issue.

CHPR: You mentioned metformin earlier. Can you say more about this?

Dr. Marder: We encourage the use of metformin as it's the pharmacologic intervention with the most evidence, particularly for managing body weight, HbA1c, and fasting blood sugars (Jiang WL et al, *Transl Psychiatry* 2020;10(1):117). It is easy to prescribe and is usually well tolerated.

CHPR: Which patients should not get metformin?

Dr. Marder: It should not be prescribed to patients with severe kidney or liver disease, congestive heart failure, or metabolic acidosis. Younger patients tend to have the best responses to metformin, so we should be especially mindful of starting metformin for them.

CHPR: Are there any other agents that work?

Dr. Marder: There is some evidence that topiramate is effective, but because of its cognitive side effects, such as impaired attention and memory, it is not our first drug of choice. Liraglutide (Victoza, Saxenda) also appears to be effective. In a large randomized controlled trial, patients on liraglutide gained 5.3 kg less than patients on placebo after 16 weeks of treatment daily (Larsen JR et al, *JAMA Psychiatry* 2017;74(7):719–728). The investigators reevaluated the subjects one year later and found that they continued to weigh significantly less than the placebo group.

Metabolic Side Effects of Antipsychotics

Antipsychotic	Weight Gain	Glucose Abnormalities	Hyperlipidemia
Aripiprazole	Low	Low	Low
Asenapine	Moderate	Moderate	Moderate
Brexpiprazole	Low	Low	Moderate
Cariprazine	Moderate	Low	Low
Chlorpromazine	Moderate	Moderate	Low
Clozapine	High	High	High
Haloperidol	Low	Low	Low
Iloperidone	Moderate	Moderate	Low
Lumateperone	Low	Low	Low
Lurasidone	Low	Moderate	Moderate
Olanzapine	High	High	High
Paliperidone	Moderate	Low	Moderate
Quetiapine	Moderate	Moderate	High
Risperidone	Moderate	Moderate	Low
Ziprasidone	Low	Low	Low

Source: Adapted from UpToDate 2020

CHPR: That sounds like a promising treatment! What about the new combination drug, olanzapine-samidorphan, that is awaiting FDA approval?

Dr. Marder: This is a combination pill where samidorphan, an opioid antagonist, is added to olanzapine. Recent data published in *The American Journal of Psychiatry* shows that it substantially attenuates, though does not entirely prevent, the weight gain from olanzapine (Correll CU et al, *Am J Psychiatry* 2020;177(12):1168–1178).

CHPR: Can you talk about how the timing of an intervention affects its likelihood of working?

Dr. Marder: It's important to identify early that somebody is at risk for weight gain. In the guidelines that I participated in, we recommend that clinicians look at signs of weight gain starting in the first weeks of treatment (Keepers GA et al, *Am J Psychiatry* 2020;177(9):868–872). If somebody gains as little as 1 BMI unit, that's a concern because it indicates a risk for further weight gain. And intervening early, before a person has put on weight, is more effective than helping patients lose weight after they've gained it.

"Intervening early, before a person has put on weight, is more effective than helping patients lose weight after they've gained it. It's a good idea to initiate preventive interventions in medication-naïve patients if they're placed on medications that are highly likely to cause weight gain."

Stephen Marder, MD

CHPR: I looked at this issue myself in a paper where we reported that the first 3 months of treatment represent a critical period for preventive interventions. Beyond that time, when patients have already gained weight, it's much harder for them to return to their baseline weight (Hendrick V et al, *Ann Clin Psychiatry* 2017;29(2):120–124).

Dr. Marder: Yes, many studies have found that AIWG occurs early. So it's a good idea to initiate preventive interventions in medication-naïve patients if they're placed on medications that are highly likely to cause weight gain.

CHPR: Do you routinely recommend exercise programs or nutritional counseling?

Dr. Marder: The first thing I do when I start someone on a drug like olanzapine or quetiapine is to make them aware that those drugs cause weight gain. The biology of feeding behavior is complex. Peptides from the intestines communicate with the hypothalamus to regulate eating behavior. Antipsychotics interfere with this process and prevent patients from experiencing satiety. It's important to inform patients about this effect so they can be mindful of how much they are eating. Mere portion control can prevent weight gain if patients are motivated. I want to emphasize that lifestyle interventions work. Dozens of well-controlled studies have found that various interventions are helpful, including nutritional counseling and encouraging people to keep track of what they are eating and how much exercise they're getting.

Continued on page 4

Expert Interview–Weight Gain and Metabolic Side Effects

Continued from page 3

CHPR: Have you found that your patients are generally receptive to these interventions?

Dr. Marder: The interventions are not always easy to implement, but it's important to dispense with the bias that people with psychotic illnesses are not motivated to regulate their weight. Many of them are, particularly early in the illness. Young people who gain weight are often devastated by it. All these interventions can make a difference. The ones that work best typically include a lot of patient interaction over extended periods of time. You can't simply do an intervention for 8 or 12 weeks; it's got to be a sustained intervention. And interventions that include active monitoring are particularly beneficial.

CHPR: What type of active monitoring?

Dr. Marder: There are several types of monitoring devices, like smartphone apps, Fitbits, and other wearable devices, that give patients feedback about whether they are exercising adequately and can motivate them to remain physically active.

CHPR: And we can also help motivate patients by regularly reminding them to exercise.

Dr. Marder: Yes, and the effects of exercise go beyond just weight control and cardiovascular health. Exercise is good for managing the illness itself. It promotes neuroplasticity and improves patients' memory and ability to learn. Studies done at UCLA and elsewhere show that exercise releases brain-derived neurotrophic factor (BDNF) and increases gray matter (Neuchterlein KH et al, *Schizophr Bull* 2016;42 Suppl 1:S44–S52). So the effects of exercise are helpful not only for physical health, but also for managing the symptoms of schizophrenia.

CHPR: That's interesting. Are any factors associated with exercise's effectiveness?

Dr. Marder: There's a direct correlation between the amount of exercise and improvements in cognitive functioning (Firth J et al, *Schizophr Bull* 2017;43(3):546–556). Various domains of cognition improve, including attention and memory, but the greatest improvements are in patients' social cognitive functioning.

CHPR: I recently came across a meta-analysis of randomized controlled trials that reported aerobic exercise reduces negative symptoms in patients with schizophrenia (Sabe M et al, *Gen Hosp Psychiatry* 2020;62:13–20).

Dr. Marder: Yes, that's yet another benefit of exercise.

CHPR: So to summarize, early in treatment we should be vigilant for weight and blood sugar changes in our patients on antipsychotic medications; it's a good idea to intervene early, for example by adding metformin, to prevent weight gain from developing in the first place *(Editor's note: See "Pharmacologic Interventions to Prevent Weight Gain and Metabolic Syndrome" table below)*; and it's important to track weight at every visit and encourage portion control and regular exercise.

Dr. Marder: And again, the simplest and sometimes most effective intervention is changing the antipsychotic. It's a good idea for clinicians to have a list they can easily refer to, listing the relative liabilities of different drugs *(Editor's note: "See Metabolic Side Effects of Antipsychotics" table on page 3).*

CHPR: Thank you, Dr. Marder.

Pharmacologic Interventions to Prevent Weight Gain and Metabolic Syndrome

Intervention	Dose	Notes
Liraglutide	1.2–1.8 mg daily	Administered subcutaneously
Metformin	500–1000 mg twice daily	Has most evidence of efficacy
Samidorphan	10–20 mg daily	FDA approved a combined olanzapine-samidorphan formulation (Lybalvi) on June 1, 2021
Topiramate	50–400 mg daily	Associated with dose-dependent cognitive side effects

❖ ❖ ❖

Battle of the Bulge: Obesity and Antipsychotic-Induced Weight Gain

Continued from page 1

lurasidone, and ziprasidone, will minimize weight gain (Musil R et al, *Expert Opin Drug Saf* 2015;14(1):73–96). Some first-generation agents, like haloperidol, are also less likely to cause metabolic syndrome *(Editor's note: See "Metabolic Side Effects of Antipsychotics" table on page 3).*

If patients have gained weight on other antipsychotics, can they lose weight by switching to agents with a low metabolic risk? Probably so, at least for aripiprazole, which is the only agent that's been studied in this manner. In a 24-week study of 206 overweight patients who were randomized to continue on olanzapine, quetiapine, or risperidone or to switch to aripiprazole, patients who switched to aripiprazole experienced significantly greater weight reduction (3.7 kg) compared to patients who continued on their previous medications (0.7 kg) (Stroup TS et al, *Am J Psychiatry* 2011;168(9):947–956). The study included a diet and exercise program for all subjects.

If changing from an antipsychotic with high metabolic risk is not feasible, augmenting the antipsychotic with low or medium doses of aripiprazole (5–15 mg/day) can help. This strategy stood out as the most effective pharmacologic intervention in a recent comprehensive meta-analysis (Vancampfort D et al, *World Psychiatry* 2019;18(1):53–66).

Pharmacologic treatment of AIWG

Metformin

Metformin (Glucophage) (500–1000 mg twice daily) is the best-studied and most widely used medication to treat AIWG. It produces a weight loss, on average, of about 3 kg (de Silva VA et al, *BMC Psychiatry* 2016;16(1):341) or about a 3% reduction in body weight, compared to

Continued on page 5

Continued from page 4

a 1% reduction with placebo (Jarskog LF et al, *Am J Psychiatry* 2013;170(9):1032–1040). While this is not as much weight loss as seen with other agents, metformin is well tolerated and safe, and it helps treat insulin resistance—an additional benefit, given that many of our patients are diabetic or prediabetic. Nausea and diarrhea occur in 25%–50% of patients early in treatment; these side effects are minimized by taking metformin with food or using the extended-release formulation. Patients must be screened for liver or kidney impairment as both increase the risk of lactic acidosis in patients on this medication. If a patient's eGFR is less than 60 mL/minute, adjust the dosing *(Editor's note: See "Metformin Dosing: Renal Impairment" table below).*

Should we start metformin prophylactically to prevent AIWG? This question has not been well studied, but research generally supports this practice. For example, a 12-week study of patients randomized to olanzapine 15 mg plus metformin 750 mg (n = 20), vs olanzapine 15 mg plus placebo (n = 20), found that the 63% of patients taking olanzapine + placebo increased their weight by more than 7% vs only 17% of patients taking olanzapine + metformin (Wu RR et al, *Am J Psychiatry* 2008;165(3):352–358). A randomized controlled trial is currently underway evaluating prophylactic metformin for patients starting clozapine (Siskind D et al, *BMJ Open* 2018;8(3):e021000).

Topiramate (Topamax)

Topiramate (50–400 mg per day) produces more weight loss than metformin, averaging about 4 kg (Goh KK et al, *Int J Psychiatry Clin Pract* 2019;23(1):14–32). However, about 30% of patients—especially those at higher doses—experience cognitive impairments, including problems with memory and attention (a reason it is jokingly referred to as "Dopamax"). Monitor vision because of the increased risk of angle-closure glaucoma. Additionally, use caution when prescribing topiramate to pregnant women (increased risk of cleft palate) and to women on birth control pills (topiramate induces the metabolism of estrogen and can diminish the efficacy of the contraceptive).

Olanzapine/samidorphan

We will soon have a new treatment option to mitigate olanzapine-induced weight gain: a combination of olanzapine with samidorphan, an opioid receptor antagonist. In a recent study that compared weight changes in patients receiving this combination to patients receiving olanzapine alone, weight increased 4.2% in the olanzapine/samidorphan group compared to 6.6% in the olanzapine monotherapy group (Correll CU et al, *Am J Psychiatry* 2020;177(12):1168–1178). The FDA approved this combined olanzapine-samidorphan formulation (Lybalvi) on June 1, 2021 *(Editor's note: See the Research Update on page 9 that covers AIWG for more information).*

Other weight loss medications to consider

Numerous medications are on the market for weight loss *(Editor's note: See "FDA-Approved Medications to Treat Obesity" table on page 6).* The list used to be longer, but two medications—sibutramine (Meridia) and lorcaserin (Belviq)—were recently withdrawn due to elevated risks of cardiovascular events and cancer, respectively. Selection is determined by side effect profiles, cost, insurance coverage, method of administration (oral vs subcutaneous), and estimated length of treatment, as some medications have only been approved for short-term use. With the exception of liraglutide, these medications have been studied for obesity, but not for obesity secondary to antipsychotic drug use.

Orlistat (Xenical)

Orlistat inhibits the action of lipase in the gastrointestinal tract, thereby preventing the breakdown and absorption of fats through the small intestine. Compared to other medications for obesity, orlistat produces the least weight loss (2.6 kg) (Khera R et al, *JAMA* 2016;315(22):2424–2434). Further, orlistat's primary side effects are diarrhea and fatty stools over the first 4 weeks. It's dosed at 120 mg TID with meals, and patients should take vitamin supplements to ensure they get their daily A, D, E, and K. Orlistat has the advantage of being available over the counter in a lower-dose called Alli.

Liraglutide (Victoza, Saxenda)

Liraglutide is a glucagon-like peptide-1 agonist (GLP-1 agonist) that lowers blood sugar and weight by decreasing both glucose production and appetite and by increasing insulin sensitivity. Of all the weight loss agents, it produces the greatest average weight loss (5.2 kg) compared to placebo (Khera et al, 2016). Liraglutide is FDA approved for type II diabetes as well as for obesity and appears effective for AIWG: A study of patients (n = 97) taking clozapine or olanzapine who were randomized to add-on treatment with either liraglutide (1.2–1.8 mg daily) or placebo found that those in the liraglutide group lost an average of 4.7 kg compared to a gain of 0.5 kg in the placebo group (Larsen JR et al, *JAMA Psychiatry* 2017;74(7):719–728). There are some serious trade-offs, though: Liraglutide is administered

Continued on page 6

Metformin Dosing: Renal Impairment

eGFR	Recommended Dosing	Renal Function Monitoring
> 60 mL/minute	No adjustment required	Annually
45–60 mL/minute	1500 mg in 2 divided doses as maximum daily dose	Every 6 months
30–45 mL/minute	Initiation of therapy: Not recommended Continuation of therapy: Continue at reduced dose of 500 mg twice daily	Close monitoring
< 30 mL/minute	Use is contraindicated	

Source: Diabetes Care *2020;43(Suppl 1):S98–S110*

Battle of the Bulge: Obesity and Antipsychotic-Induced Weight Gain
Continued from page 5

subcutaneously, and it causes nausea in about two-thirds of patients.

Semaglutide (Ozempic, Wegovy)
Semaglutide is another GLP-1 agonist that has been in the news lately due to its reported efficacy as a weight loss agent. A recent study randomized non-diabetic patients with a BMI of 30 or more (n = 1961) to once-weekly subcutaneous semaglutide 2.4 mg or placebo, plus lifestyle intervention (Wilding JPH et al, *N Engl J Med* 2021;384(11):989). After 68 weeks, patients in the semaglutide group lost an average of 15% of their baseline body weight, or 33.7 pounds, compared to 2.4%, or 5.7 pounds, in the placebo group. The weight loss began early in treatment: Patients on semaglutide experienced more than a 2% reduction in body weight within the first 4 weeks. Side effects consisted primarily of transient nausea and diarrhea. In June 2021, the FDA approved semaglutide for weight loss (in addition to its indication for type 2 diabetes).

Sympathomimetics
Medications like phentermine (Adipex-P, Lomaira) are effective in inducing weight loss but have only been approved for short-term obesity management (ie, a few months). Watch for new onset of psychosis when patients take these agents. They are not good choices for patients with substance use disorders because of their abuse potential, or for patients with primary psychotic disorders.

Co-formulated agents
Phentermine/topiramate (Qsymia) and bupropion/naltrexone (Contrave) are substantially more effective than these medications taken alone, so they are
Continued on page 12

FDA-Approved Medications to Treat Obesity

Brand	Generic/Dosing	Mechanism of Action	Adverse Effects	Notes
Adipex-P, Lomaira	Phentermine 15–37.5 mg	Sympathomimetic	Hypertension, tachycardia, xerostomia, anxiety	• Contraindicated in patients with cardiovascular disease, hyperthyroidism, substance use disorder • Controlled substance • Carries the potential to worsen psychosis
Alli, Xenical	Orlistat 60–360 mg/day	Intestinal lipase inhibitor	Fecal incontinence, oily rectal leakage, bowel urgency, abdominal distress, nutrient deficiency	• Contraindicated in malabsorption disorders • Take within 1 hour of a fat-containing meal • Separate by 2 hours from fat-soluble vitamins
Bontril	Phendimetrazine 17.5–210 mg	Sympathomimetic	Hypertension, tachycardia, xerostomia, anxiety	• Contraindicated in patients with cardiovascular disease, hyperthyroidism, substance use disorder • Controlled substance • Carries the potential to worsen psychosis
Contrave	Bupropion/ naltrexone 360/16–360/32 mg	Dopamine and norepinephrine reuptake inhibitor/ opioid antagonist	Hypertension, insomnia, constipation, hepatotoxicity, anxiety	• Contraindicated in anorexia, bulimia, epilepsy, uncontrolled hypertension, alcohol withdrawal, opioid use (precipitates withdrawal)
Didrex	Benzphetamine 25–150 mg	Sympathomimetic	Hypertension, tachycardia, xerostomia, anxiety	• Contraindicated in patients with cardiovascular disease, hyperthyroidism, substance use disorder • Controlled substance • Carries the potential to worsen psychosis
Ozempic, Wegovy	Semaglutide 2.4 mg once/weekly (subcutaneous)	GLP-1 agonist	Nausea, vomiting, constipation, diarrhea, hypoglycemia	• Administer with or without meals • Monitor for new or worsening depression/suicidal behavior (liraglutide)
Qsymia	Phentermine/ topiramate 7.5/46–15/92 mg/day	Sympathomimetic anticonvulsant	Renal calculi, paresthesias, impaired cognition, concentration and memory, confusion, depression, anxiety	• Contraindicated in hyperthyroidism and substance use disorder • Controlled substance • Teratogenic patients must enroll in REMS[1] program • May worsen cognitive symptoms of thought disorders and depression
Saxenda	Liraglutide 0.6–3 mg/day (subcutaneous)	GLP-1 agonist	Nausea, vomiting, constipation, diarrhea, hypoglycemia	• Administer with or without meals • Monitor for new or worsening depression/suicidal behavior (liraglutide)
Tenuate Dospan	Diethylpropion 25–100 mg	Sympathomimetic	Hypertension, tachycardia, xerostomia, anxiety	• Contraindicated in patients with cardiovascular disease, hyperthyroidism, substance use disorder • Controlled substance • Carries the potential to worsen psychosis

[1]REMS: Risk Evaluation and Mitigation Strategy; *Source:* Khorassani FE et al, *Am J Health Syst Pharm* 2015;72(9):697–706

Q&A With the Expert

Sex-Based Treatment of Schizophrenia

Jayashri Kulkarni, MBBS, PhD, FAHMS

Professor of Psychiatry, Monash University. Director, Monash Alfred Psychiatry Research Center, Melbourne, Australia

Dr. Kulkarni has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CHPR: Dr. Kulkarni, you've written about sex-based differences in symptoms and prognosis of schizophrenia. What are some of these differences?

Dr. Kulkarni: Compared to men, women with schizophrenia experience a more benign course of illness, including fewer psychiatric relapses and hospitalizations. They are more likely to be employed and married and to maintain interpersonal relationships. Also, women of reproductive age experience premenstrual exacerbations of schizophrenia that can lead to psychiatric hospitalization in the week prior to menses.

CHPR: Any differences in age of onset?

Dr. Kulkarni: Yes. A well-replicated finding is that the peak age of onset for men occurs between 18–24 years of age, while for women this peak is about 3–4 years later (Häfner H, *Psychoneuroendocrinology* 2003;28(Suppl 2):17–54). Women, but not men, have a second peak age of onset around 45–50 years, around menopause. Menopausal women, compared with younger women, display more refractory symptoms of schizophrenia. Animal studies provide another line of evidence showing that estrogen significantly impacts dopaminergic and serotonergic receptor systems, the main neurotransmitters implicated in the development of schizophrenia. These findings support the hypothesis that estrogen is a neuroprotective factor in this illness.

CHPR: How did the estrogen hypothesis influence your work?

Dr. Kulkarni: Our early studies were in uncharted territory. We had to find the dose and formulation of estrogen that would get into the brain and be helpful. We quickly stopped using oral estrogen because it doesn't cross the blood-brain barrier and we instead used 17-beta-estradiol, which comes in a transdermal patch. We found the optimal dose was 100 mcg of transdermal estradiol. Then, around 2001, early evaluations of the Women's Health Initiative (WHI) reported that the health risks of hormones—uterine and breast cancer, heart disease, and stroke—were greater than the benefits. This led to a sharp drop globally in prescriptions for hormone therapy. The data have since been re-analyzed, and it turns out that estrogen does have a benefit, but only when it is started early after menopause. It relieves menopausal symptoms, protects bones, and reduces the risk of colon cancer. There is a window of opportunity of about 10 years for beneficial effects, but beyond that, estrogen can be harmful.

"After more than three decades of research on the estrogen hypothesis, and multiple clinical trials finding that estrogen and SERMs are effective adjunctive treatments, I am surprised that this treatment approach has not yet been adopted into mainstream practice."

Jayashri Kulkarni, MBBS, PhD, FAHMS

CHPR: Where did this research lead?

Dr. Kulkarni: We then began working with selective estrogen receptor modulators (SERMs), which were a new class of medications that do not affect breast, uterine, or ovarian tissue. The first SERM, raloxifene, was developed to treat osteoporosis in menopausal women. We conducted the first pilot study of raloxifene in perimenopausal women with schizophrenia and found that at 120 mg daily, it was an effective adjunct in reducing total and general psychopathology (Kulkarni J et al, *Psychoneuroendocrinology* 2010;35(8):1142–1147). The subsequent randomized controlled trial confirmed a significantly greater reduction in the Positive and Negative Syndrome Scale (PANSS) total score (Kulkarni J et al, *JAMA Psychiatry* 2016;73(9):947–954).

CHPR: Is raloxifene well tolerated?

Dr. Kulkarni: The main side effects are hot flashes and leg cramping, but these tend to diminish over the first few months of treatment.

CHPR: Have other researchers found similar success with raloxifene?

Dr. Kulkarni: Yes, other groups have also found significant benefits for postmenopausal women taking adjunctive raloxifene. A recent meta-analysis summarized the findings and concluded that, at doses of 60–120 mg/day, raloxifene appears effective and safe (Zhu XM et al, *Schizophr Res* 2018;197:288–293).

CHPR: Do SERMs and estrogen benefit all symptoms of schizophrenia?

Dr. Kulkarni: 17-beta-estradiol appears to quickly reduce positive symptoms like hallucinations. Delusional and thought disorder symptoms improve a bit later, within the first week to 10 days. By about 2 weeks, we see cognitive improvements. With the SERMs, the positive symptoms also improve first. Some studies show that patients' cognitive and

Continued on page 8

Continued from page 7

negative symptoms also improve with SERMs, but not as much as with estradiol (Zhu et al, 2018).

CHPR: With what you know now about transdermal estradiol maybe not being as problematic as previously thought, would you recommend it over a SERM like raloxifene?

Dr. Kulkarni: It ends up as a case-by-case decision because you have to weigh the risks and benefits of the different options. In a woman who has a personal or family history of breast or uterine cancer, we would not want to prescribe estradiol. We also don't want to use estradiol for women who smoke, or who have diabetes or hypertension. But estradiol might be a better choice than raloxifene for a menopausal patient with schizophrenia who is experiencing vasomotor symptoms like hot flashes.

CHPR: What type of screening do you complete prior to beginning raloxifene?

Dr. Kulkarni: We check for a past history of deep venous thrombosis or pulmonary embolism and measure factor V Leiden (a genetic mutation that increases the risk for blood clots) because raloxifene slightly increases the risk of deep venous thromboses and other thromboembolic events. These are rare side effects, with an absolute risk difference of 0.9 per 1000 woman-years (Martino S, *Curr Med Res Opin* 2005;21(9):1441–1452).

CHPR: Are you seeing psychiatrists prescribing raloxifene or estrogen?

Dr. Kulkarni: We are not seeing it. After more than three decades of research on the estrogen hypothesis, and multiple clinical trials finding that estrogen and SERMs are effective adjunctive treatments, I am surprised that this treatment approach has not been adopted into mainstream practice. Practice guidelines of physical health monitoring tend to focus on cardiovascular and metabolic disorders but overlook women's health issues, like menopausal status or use of hormonal contraception. Also, specialists in general tend to have a "silo mentality" or disengagement from other areas of medicine—so in the case of psychiatrists, they might not be as open to learning about hormone treatments or contraceptive pills. It would be good to see a more holistic approach to treating patients with schizophrenia. Psychiatrists can work closely with their patients' primary care clinicians to ensure that their female patients receive appropriate hormone treatments and have ongoing physical screening.

CHPR: You brought up an interesting point. Women with schizophrenia have relatively high numbers of unwanted pregnancies. Prescribing a contraceptive makes a lot of sense.

Dr. Kulkarni: Yes, we get two good outcomes with that single intervention. The oral contraceptive should preferably contain at least 30 mcg of estradiol *(Editor's note: See "Adjunctive Hormonal Treatments for Women" table below)*. For women with a uterus, the oral contraceptive should include a progestin to minimize the risk of uterine cancer. Third- or fourth-generation progestins, including norgestimate, drospirenone, desogestrel, and gestodene, are preferable because they are less likely to produce depressive side effects than first- and second-generation progestins like levonorgestrel and norethisterone (norethindrone), as was found in the Skovlund study (Skovlund CW et al, *JAMA Psychiatry* 2016;73(11):1154–1162). So we do use the oral contraceptive pills, but over time we have learned that all pills are not the same.

CHPR: How long do you continue raloxifene as an adjunctive treatment?

Dr. Kulkarni: Because the adjunctive use of raloxifene is new, I typically prescribe it for 2–3 years. We also want to make sure the patient is safe in terms of adverse events.

Adjunctive Hormonal Treatments for Women

Age	Agent	Cautions/Contraindications
Post-puberty–44 years	Oral contraceptive containing at least 30 mcg of estradiol, daily Examples: norgestimate–ethinyl estradiol (Ortho Tri-Cyclen), drospirenone–ethinyl estradiol (Yasmin), desogestrel–ethinyl estradiol (Ortho-Cept)	• Diabetes • Hypertension • Heart disease/stroke • Over age 35 and smoker • Liver disease • Migraine headache with significant aura • H/o thromboembolism • H/o breast cancer
Peri/post-menopause (45–60 years)	Raloxifene (Evista), 60–120 mg, daily	• H/o thromboembolism (eg, DVT, PE) • Blood clotting disorders • Long periods of inactivity (eg, air travel or surgery)
	Transdermal estradiol, 50 or 100 mcg, weekly or twice weekly[1] Examples: Estraderm, Climara, Vivelle-Dot	• H/o breast or uterine cancer • H/o thromboembolism • Diabetes • Hypertension • Heart disease/stroke • Liver disease • Migraine headache with significant aura

[1]Prescribe with a progestin, eg, oral natural micronized progesterone 200 mg at bedtime for 12 days each month

CHPR: Do you take any other considerations into account in your decision about whether to use or stop using raloxifene?

Dr. Kulkarni: We are not just looking at the benefit to psychotic symptoms, but also at the patient's risk for bone loss, as raloxifene is FDA approved for the prevention and treatment of osteoporosis.

CHPR: That's interesting, as rates of osteomalacia and osteoporosis among women with schizophrenia appear to be higher than for the general population of women.

Dr. Kulkarni: Absolutely. The hyperprolactinemic effects of antipsychotics suppress estrogen, and women who take antipsychotic medications are at greater risk for osteomalacia and osteoporosis. This is another example of "killing two birds with one stone," where we can treat a woman's

Continued on page 9

Continued from page 8

psychiatric symptoms and help protect her bone health.

CHPR: Are there any other reasons we should worry about the bone health of our female patients?

Dr. Kulkarni: Women with schizophrenia often smoke and have poor nutrition, both of which increase the risk of bone density problems and potential fractures. There are several factors leading to poor bone health in women with schizophrenia.

CHPR: To summarize, it sounds like we should consider using estrogen or SERMs as adjunctive treatments for female patients, especially postmenopausal women who are not fully responding to antipsychotic medications and who are primarily experiencing positive symptoms.

Dr. Kulkarni: That's right, but women of all ages can benefit from supplemental estrogen. For women of reproductive age, oral contraceptives can be helpful. For post-menopausal women, adjunctive raloxifene 120 mg is helpful. Alternatively, transdermal estradiol is another option and should be prescribed with a progestin if the patient has a uterus. Transdermal estradiol is particularly helpful for women with schizophrenia who also report hot flashes. These appear to be safe adjunctive treatments for schizophrenia.

CHPR: And if we do not feel comfortable prescribing these agents ourselves, we can work with our patients' primary care physicians to help patients get started on these adjunctive treatments and get followed for any adverse sequelae.

Dr. Kulkarni: Yes, as long as patients are screened and monitored appropriately, raloxifene and transdermal estrogen appear to be safe adjunctive treatments for schizophrenia.

CHPR: Thank you very much, Dr. Kulkarni.

❖ ❖ ❖

Research Updates IN PSYCHIATRY

SIDE EFFECTS

New Combination Treatment Mitigates Antipsychotic-Induced Weight Gain

REVIEW OF: Correll CU et al, *Am J Psychiatry* 2020;177(12):1168–1178

To date, we have had no FDA-approved medications to mitigate antipsychotic-associated weight gain (AIWG). This will soon change, thanks to recent research showing that samidorphan, an opioid receptor antagonist, appears to significantly lessen weight gain associated with the use of olanzapine *(Editor's note: The FDA approved the olanzapine/samidorphan combination on June 1, 2021).*

In this 24-week, double-blind trial, 352 adults with schizophrenia were randomized to receive either olanzapine alone (n = 176) or a combination tablet of olanzapine and samidorphan (n = 176). Olanzapine doses were 10 or 20 mg daily, and the samidorphan dose was 10 mg daily. Alkermes, the manufacturer of the combination drug, sponsored the study. Exclusion criteria were strict and included treatment-resistant schizophrenia, substance use disorders, any clinically significant medical illness (eg, diabetes or hypertension), obesity (BMI > 30), and recent use of opioids or opioid antagonists.

At the 24-week endpoint of the study, patients on olanzapine/samidorphan gained 4.2% of their body weight, significantly less than the 6.6% gained by those taking olanzapine alone. Other key outcomes favoring olanzapine/samidorphan included the proportion of subjects who gained more than 10% of their baseline body weight (18% in the combined treatment group vs 30% in the olanzapine-only group) and the mean change in baseline waist circumference (2.4 cm in the combined treatment group vs 4.5 cm in the olanzapine-only group). Metabolic changes were minimal for both groups. Dropout rates were primarily associated with adverse events, impacting 12% of the combined treatment group and 9.8% of the olanzapine-only group.

The most common adverse events were weight gain and increased appetite (more in the olanzapine-only group), and somnolence and dry mouth (more in the combined treatment group). The addition of samidorphan did not affect antipsychotic efficacy. About one-third of patients dropped out due to side effects, loss to follow-up, or unspecified reasons.

CHPR'S TAKE

Adding samidorphan to olanzapine appears to decrease weight gain, but the effect in the study was only moderate. To put these results in perspective, a patient starting the trial at 150 pounds would have gained an average of 9.9 pounds on olanzapine vs 6.3 pounds on the combination. In addition, the exclusion criteria prevented many real-world patients from entering the trial. Especially in the inpatient world, it is unusual to find patients with schizophrenia who do not have either a substance use problem or a significant medical problem, so we don't know if this study's findings apply to our typical patients. Still, given how problematic AIWG can be for our patients, this new treatment may become a useful tool.

—Susie Morris, MD. Dr. Morris has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Continued on page 10

Continued from page 9

PSYCHOSIS

Anti-NMDA Receptor Encephalitis or New-Onset Psychosis?

REVIEW OF: Xu X et al, *Neurol Neuroimmunol Neuroinflamm* 2019;7(1):e633

You may have heard of the book *Brain on Fire: My Month of Madness* by Susannah Cahalan (later made into a movie). Cahalan, a successful journalist, describes her brief psychotic episode that led to hospitalizations and mistaken psychiatric diagnoses. She was eventually diagnosed with anti-NMDA receptor encephalitis, in which the body produces antibodies to NMDA receptors, causing a variety of psychiatric and neurological symptoms. The diagnosis requires detecting the antibodies in the cerebrospinal fluid (CSF).

Anti-NMDA receptor encephalitis typically presents in younger women (many of whom have an ovarian teratoma), and early identification and treatment is key to prevent substantial morbidity or death. To halt ongoing brain injury, the standard of care is immunosuppression treatment in the form of steroids, plasmapheresis, intravenous immunoglobulin (IVIG), monoclonal antibodies (rituximab), and cyclophosphamide.

To help develop better treatment guidelines, Chinese investigators published a 12-month observational study of 220 patients with anti-NMDA receptor encephalitis. The goal was to better characterize the presentation, clinical course, and outcome of the disease. Long-term outcomes were measured using the modified Rankin Scale (mRS), a 6-point scale (0 = no disability, 5 = severe disability) used to assess disability outcomes in patients who have had strokes.

The findings affirm what we know about anti-NMDA receptor encephalitis: 65% of patients were female (of which 30% had teratomas), the median age was 21 years old, and only 36% had abnormal MRI findings on presentation. At initial presentation, 83% had psychosis, 81% had seizures, and 51% had abnormal EEG findings. While 100% had CSF antibodies to NMDA receptors, only 71% had serum antibodies, meaning blood work alone cannot rule out the disease.

The outcomes give us hope: While the median disability score at onset was 4 (moderately severe disability), at 12 months, 93% of the cohort had no more than a slight disability, with over 60% showing no symptoms. Overall, the median time from diagnosis to treatment was 2 weeks.

CHPR'S TAKE

While uncommon (the incidence is 1.5 per million people per year), anti-NMDA receptor encephalitis should be on our psychosis differential, especially for younger women with new-onset psychosis who have a history of a viral prodrome and subtle neurologic abnormalities. In such patients, you should have a low threshold for consulting neurology, and for ordering neuroimaging, EEG testing, and CSF analysis.

—Alex Thompson, MD. Dr. Thompson has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

DEPRESSION

Psilocybin: The New Holy Grail for the Rapid Relief of Major Depression?

REVIEW OF: Davis AK et al, *JAMA Psychiatry* 2020:e203285

Intravenous ketamine and intranasal esketamine (Spravato) offer hope in the search for a rapidly acting antidepressant. However, concerns regarding addiction, safety, and effect durability have prompted searches for alternative rapid-acting treatments. Psilocybin is a hallucinogen originally derived from "magic mushrooms" that, like ketamine, is a recreational drug with potential antidepressant effects. Recently, researchers published the first controlled study to explore its efficacy for depression.

Participants diagnosed with moderate to severe depression, and not taking antidepressants, were randomly assigned to a treatment group (n = 14) or a delayed-treatment/waiting-list control group (n = 13). During the initial 8 weeks, the immediate-treatment group received 3 weeks of preparatory therapy followed by two day-long sessions in which they received a lower dose of psilocybin (20 mg/70 kg) in session 1 and a higher dose (30 mg/70 kg) in session 2. During the psilocybin sessions, they received supportive therapy and were encouraged to focus their attention inward as they listened to music. Patients who were randomized to the delayed group were also provided the active 8-week psilocybin protocol after first serving as a no-treatment control for the immediate group.

How well did psilocybin work? In those first 8 weeks, the immediate group responded rapidly and significantly compared to the control group. Subjects in the control group experienced no improvement while waiting, but once treated, they responded as robustly as the immediate group on all measures. At 1 week and 4 weeks after the last drug session, 67% and 71% of pooled treated subjects, respectively, demonstrated a clinically significant response (greater than 50% drop in GRID HAM-D scores). At those same 1- and 4-week measurement points, 58% and 54% of treated subjects, respectively, experienced remission (GRID HAM-D score < 7).

Psilocybin was well tolerated. The main side effects included vague emotional symptoms (fear, sadness) and physical symptoms (such as a trembling sensation and mild, transient headaches).

CHPR'S TAKE

Psilocybin appears to rapidly and significantly reduce depressive symptoms. Unlike ketamine, psilocybin is not addictive, and its antidepressant efficacy seems to last longer (weeks vs days for ketamine). We'll need larger studies to have more confidence in its efficacy.

—Paul Barkopoulos, MD. Dr. Barkopoulos has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com with your username and password to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be completed within a year from each issue's publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Carlat CME Institute maintains responsibility for this program and its content. The Carlat CME Institute designates this enduring material educational activity for a maximum of two (2) *AMA PRA Category 1 Credits*™ or 2 CE credits for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/

This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives (LO) are listed on page 1.

1. For AIWG, which medication has been shown to produce the greatest average weight loss compared to placebo (LO #1)?
   [ ] a. Metformin [ ] b. Liraglutide [ ] c. Topiramate [ ] d. Semaglutide

2. Your patient with schizophrenia has recently started on an antipsychotic and is concerned because he is gaining weight. When should preventative interventions for AIWG be initiated to maximize the likelihood of the patient returning to baseline weight (LO #2)?
   [ ] a. After 1 year of treatment, if the patient has gained any weight
   [ ] b. After 8 months of treatment, if the patient's BMI has increased by 1 unit
   [ ] c. Within the first 3 months of treatment, if the patient is gaining weight
   [ ] d. After 6 months of steady weight gain

3. The peak age of onset for schizophrenia in men occurs between 18–24 years of age. How does this compare to the peak of onset in women (LO #3)?
   [ ] a. The peak of onset for women is about 3–5 years earlier than the peak for men
   [ ] b. The peak of onset for women is about 3–4 years later than the peak for men, and women have a second peak around menopause
   [ ] c. The peak of onset for women is about 3–4 years later than the peak for men, and women have a second peak around 33–38 years of age
   [ ] d. The peak of onset for women is identical to the peak for men

4. Which of the following pharmacotherapies for AIWG has the best evidence of efficacy and the best balance of efficacy, tolerability, and safety (LO #1)?
   [ ] a. Topiramate [ ] b. Orlistat [ ] c. Metformin [ ] d. Phentermine

5. In a 2011 study, patients who switched from either olanzapine, quetiapine, or risperidone to aripiprazole experienced significantly greater weight loss than those who continued one of the high-metabolic-risk antipsychotics (LO #1).
   [ ] a. True
   [ ] b. False

6. According to Dr. Kulkarni, which of the following about adjunctive hormonal treatments for women with schizophrenia is true (LO #3)?
   [ ] a. Raloxifene is a better adjunct than estradiol for women with vasomotor symptoms
   [ ] b. Progestins can increase the risk of uterine cancer for women who take oral contraceptives
   [ ] c. 17-beta-estradiol quickly reduces negative symptoms and gradually reduces positive symptoms
   [ ] d. Estradiol improves cognitive and negative symptoms to a greater extent than that of SERMs

7. According to Dr. Marder, which group of antipsychotics has the lowest risk of inducing metabolic changes and weight gain (LO #2)?
   [ ] a. Aripiprazole, lurasidone, and ziprasidone [ ] c. Ziprasidone, clozapine, and olanzapine
   [ ] b. Quetiapine, aripiprazole, and lurasidone [ ] d. Lurasidone, quetiapine, and ziprasidone

8. Which of the following most greatly limits the clinical significance of a 2020 study that investigated the efficacy of olanzapine/samidorphan for AIWG (LO #4)?
   [ ] a. The small sample size
   [ ] b. The inability to control numerous confounding variables such as subject diet
   [ ] c. The high dropout rate
   [ ] d. The inability to sufficiently generalize the study's results due to its strict exclusion criteria

THE CARLAT REPORT
HOSPITAL PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950

This Issue:
Metabolic Side Effects
July/August/September 2021

Next Issue:
Dementia and Agitation
October/November/December 2021

Your subscription expires:

Renew or extend online at
www.thecarlatreport.com
or by check using the order form below.

Battle of the Bulge: Obesity and Antipsychotic-Induced Weight Gain

Continued from page 6

marketed as combination tablets. Qsymia produces 8%–10% reduction in weight vs about 1% with placebo (Gadde KM et al, *Lancet* 2011;377(9774):1341–1352). Similarly, Contrave leads to 5%–6% reduction in weight vs 1% with placebo (Greenway FL et al, *Lancet* 2010;376(9741):595–605).

While these findings appear promising, we need to be cautious when prescribing Qsymia or Contrave in certain populations. Avoid bupropion in patients with eating or seizure disorders, avoid naltrexone in opioid users and patients with liver dysfunction, and use caution when prescribing topiramate to pregnant women or women on birth control pills.

CHPR VERDICT: There are several options for treating AIWG—though none are likely to yield spectacular weight loss. Metformin (Glucophage) and topiramate (Topamax) are commonly used and relatively safe. Liraglutide also helps, but many patients don't want to use injectable medications. A new kid on the block, olanzapine/samidorphan, looks promising if it gains FDA approval. In addition, there are many other meds designed for general weight loss that have not been studied for AIWG but may be worth trying in select patients.

❖ ❖ ❖