Psychotropic Drug–Related Weight Gain and Its Treatment

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Psychotropic drug–related weight gain (PDWG) is a common occurrence and is highly associated with non-initiation, discontinuation, and dissatisfaction with psychiatric drugs. Moreover, PDWG intersects with the elevated risk for obesity and associated morbidity that has been amply reported in the psychiatric population. Evidence indicates that differential liability for PDWG exists for antipsychotics, antidepressants, and anticonvulsants. During the past two decades, agents within these classes have become available with significantly lower or no liability for PDWG and as such should be prioritized. Although lithium is associated with weight gain, the overall extent of weight gain is significantly lower than previously estimated. The benefit of lifestyle and behavioral modification for obesity and/or PDWG in psychiatric populations is established, with effectiveness similar to that in the general population. Metformin is the most studied pharmacological treatment in the prevention and treatment of PDWG, and promising data are emerging for glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., liraglutide, exenatide, semaglutide). Most pharmacologic antidotes for PDWG are supported with low-confidence data (e.g., topiramate, histamine-2 receptor antagonists). Future vistas for pharmacologic treatment for PDWG include large, adequately controlled studies with GLP-1 receptor agonists and possibly GLP-1/glucose-dependent insulinotropic polypeptide co-agonists (e.g., tirzepatide) as well as specific dietary modifications.

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Psychotropic drug–related weight gain (PDWG) is amply documented for multiple classes of agents, including antipsychotics, antidepressants, lithium, and anticonvulsants (1–12). It is well established that PDWG is a common reason for non-initiation, discontinuation, and dissatisfaction with psychiatric drugs, which may result in adverse health outcomes and increased cost of illness (13–19). Moreover, PDWG intersects with the elevated risk for obesity and associated morbidity in the psychiatric population (20–24).

For example, persons with psychiatric disorders (e.g., depressive disorders, schizophrenia) are differentially affected by obesity (25–36). It is also reported that the trajectory of obesity is increasing at a higher rate in the psychiatric population (i.e., patients with bipolar disorder) relative to the general population (37–42). The elevated and increasing rates of obesity among persons with psychiatric disorders are associated with an increased occurrence of sleep apnea, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, nonalcoholic fatty liver disease, and cardiovascular disease (43–47).

In addition, obesity is associated with a greater severity of psychopathology (e.g., cognitive impairment), suicidality, and reduced health-related quality of life and psychosocial function (48–52). Convergent evidence from mortality studies also indicates that cardiovascular disease, for which obesity is a modifiable risk factor, is the most common cause of premature and excess mortality among patients with mood and psychotic disorders (53–57).

Health care practitioners and patients are often challenged with the clinical scenario of how to prevent and treat PDWG. In this overview, we provide a summary of the literature on PDWG that occurs with commonly prescribed psychotropic drugs and provide a pragmatic set of treatment and prevention recommendations. Investigational approaches and future vistas for consideration are also discussed. This overview is not intended to be a systematic and granular review of the literature as it relates to PDWG, as multiple high-quality reviews have been published in recent years (58–63).

PSYCHOTROPIC DRUG–RELATED WEIGHT GAIN: SCOPE OF THE ISSUE

Antidepressants

The risk for antidepressant-related weight gain varies considerably across agents (64). Meta-analytic data in studies of adults with major depressive disorder indicate that weight gain is observed in persons allocated to placebo, likely

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reflecting weight recovery. In addition, a hierarchy of weight gain liability exists for antidepressants (8, 65) (Table 1). The relatively newer antidepressants approved by the U.S. Food and Drug Administration (FDA)—esketamine, dextromethorphan-bupropion, and extended-release gepirone—are not associated with clinically significant weight gain (66–69).

Similar to antipsychotics, antidepressants may stimulate appetite and caloric consumption, partially mediated by activity at cholinergic, histaminergic (H_1), and serotonergic receptors. There is no established mechanism a priori to identify individual patients with greater liability to weight gain. Although genetic testing holds promise in identifying persons at greater risk for antidepressant-related weight gain, it is not yet established to have clinical utility (70).

TABLE 1. Risk of weight gain with conventional antidepressants[a]

Risk of Weight Gain	Antidepressants
High	Amitriptyline, citalopram, clomipramine, fluvoxamine, mirtazapine, nortriptyline, paroxetine, phenelzine
Moderate	Desipramine, duloxetine, escitalopram, sertraline, venlafaxine
Low	Agomelatine, desvenlafaxine, gepirone, levomilnacipran, moclobemide, selegiline, tranylcypromine, vilazodone, vortioxetine
Neutral or weight loss	Bupropion, dextromethorphan-bupropion, esketamine, fluoxetine, zuranolone

[a] Risk categorization is based on primary reports, meta-analytic evidence, product monographs, and expert opinion.

TABLE 2. Risk of weight gain with antipsychotics[a]

Risk of Weight Gain	Antipsychotics
High	Clozapine, olanzapine
Moderate	Chlorpromazine, olanzapine/samidorphan combination, paliperidone, quetiapine, risperidone
Low	Amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, haloperidol, iloperidone, ziprasidone
Neutral or weight loss	Lumateperone, lurasidone

[a] Risk categorization is based on primary reports, meta-analytic evidence, product monographs, and expert opinion.

Antipsychotics

Antipsychotics are associated with relatively more weight gain than most other psychotropic agents (71). A liability gradient for weight gain with individual second-generation antipsychotics is noted, with greater weight gain observed with clozapine and olanzapine, followed by quetiapine and risperidone (72–74) (Table 2). The combination of olanzapine and samidorphan is associated with less clinically significant weight gain and change in waist circumference when compared to olanzapine alone in adults with schizophrenia, schizophreniform disorder, or bipolar I disorder (75–77). Small to modest weight gain is reported with dopamine partial agonists (i.e., aripiprazole, brexpiprazole, cariprazine), and nonsignificant weight increases are reported with lurasidone and lumateperone (72–74, 78, 79). Similarly, xanomeline-trospium, a combination M1/M4–preferring muscarinic agonist (xanomeline) and peripherally restricted anticholinergic (trospium) investigational agent for the treatment of schizophrenia, is not associated with clinically significant weight increase (80, 81).

Clinically significant antipsychotic-related weight gain (i.e., ≥7% weight gain) is more commonly observed in persons who are younger, are early in the illness course, are antipsychotic-naive, and have a lower pretreatment weight and in those who manifest weight gain soon after treatment commencement (82–90). Low pretreatment weight, however, is not a predictor of weight gain with all antipsychotics (e.g., olanzapine-samidorphan). Weight gain with antipsychotics is dose dependent with some agents (e.g., olanzapine) and is more common with longer duration of exposure (74). Improvement in psychopathology has not been a replicated factor associated with antipsychotic-related weight gain (90, 91).

Intensified efforts have been made to ascertain the molecular mechanisms mediating antipsychotic-related weight gain (92). Convergent evidence indicates that antipsychotics with high affinity and antagonism at histamine (H_1), alpha-1 adrenergic, and 5-HT_{2C} receptors are most associated with weight gain (2). Available evidence suggests that persons with schizophrenia carrying the −759T variant allele of the 5-HT_{2C} receptor are less susceptible to weight gain with antipsychotics (93–97). It is well documented that there is an interplay between central dopamine and insulin signaling that may also mediate antipsychotic-related weight gain (98). For example, midbrain dopamine receptor blockade with antipsychotics may result in reduced peripheral insulin sensitivity and consequent weight gain (99). Conversely, the use of central dopamine agonists (e.g., bromocriptine) has been observed to improve insulin sensitivity (100).

Lithium and Anticonvulsants

Weight gain related to lithium treatment is reported as the most bothersome adverse event and the second most common reason for treatment discontinuation (101–103). The extent of weight gain related to lithium is difficult to fully quantify, given varying definitions of weight gain across studies. Moreover, separating the weight gain hazard of lithium from the weight gain imparted by concomitant treatments and comorbidities (e.g., hypothyroidism) has been difficult.

It is not known whether the dosage and/or plasma level of lithium is consistently associated with weight change (102). Results from a systematic review of 20 studies comparing weight change with lithium versus comparators concluded that weight gain is not significant (i.e., <0.5 kg) in most treated persons (102) (Table 3). Weight gain appears to be

TABLE 3. Risk of weight gain with lithium and anticonvulsants[a]

Risk of Weight Gain	Lithium and Anticonvulsants
High	Valproate (valproic acid)
Moderate	Lithium
Low	Carbamazepine, gabapentin, oxcarbazepine, pregabalin
Neutral or weight loss	Lamotrigine, topiramate

[a] Risk categorization is based on primary reports, meta-analytic evidence, product monographs, and expert opinion.

significantly greater in studies of 12 weeks or less, and most studies have reported a placebo level of weight change in lithium-treated participants (102). Additional evidence in support of relatively low weight gain liability with lithium has been provided by real-world pharmacovigilance data (104).

Early weight gain with lithium may in some circumstances be due to polydipsia and ingestion of high-calorie drinks. Additional contributing factors may be sodium and water retention as well as possibly an increase in fat deposition and/or hypothyroidism in some individuals (105). Lithium-associated weight gain may also be a result of lithium's insulin-like properties, resulting in increased glucose uptake (106). Other postulated mechanisms include hypothalamic-mediated appetite stimulation and/or effects on mitochondria function and leptin signaling (107). Preliminary evidence suggests that obese persons receiving lithium may have a greater liability to weight gain (101, 108).

The anticonvulsants most prescribed in the treatment of psychiatric disorders are lamotrigine, valproate, carbamazepine, oxcarbazepine, gabapentin, and pregabalin (topiramate is discussed later in the treatment section). The risk for clinically significant weight gain with lamotrigine is not significantly elevated compared with placebo in short- and long-term controlled studies. Two 18-month double-blind placebo- and lithium-controlled studies in patients with bipolar I disorder found a nonsignificant difference in weight with lamotrigine at week 52 compared with placebo (−1.2 kg vs. 0.2 kg; $p=0.237$) (109). The percentage of patients with weight gain ≥7% was 10.9% for lamotrigine and 7.6% for placebo, and the percentage of patients with weight loss ≥7% was 12.1% and 11.5%, respectively; neither difference was statistically significant (109).

Valproate-related weight gain is well characterized in both short- and long-term studies (110). It is reported that 57%–70% of adults treated with valproate gained weight (10, 111, 112). In addition, valproate is associated with insulin resistance, polycystic ovary syndrome, and dyslipidemia (113, 114). These weight-related and metabolic concerns with valproate, along with increased risk for teratogenicity, have contributed to decreased utilization in psychiatry (115, 116).

Clinically significant weight gain associated with carbamazepine, oxcarbazepine, gabapentin, and pregabalin is reported as an uncommon event (10). The mechanisms mediating weight gain with these agents are not well characterized but are noted to be dose dependent with gabapentin (117).

MONITORING WEIGHT AND METABOLIC EFFECTS OF PSYCHIATRIC MEDICATIONS

Clinical practice guidelines recommend routine monitoring of anthropometric and metabolic parameters when commencing psychiatric drugs, most notably antipsychotics (118). It is reported, however, that less than 10% of persons who receive prescriptions for psychiatric drugs receive routine monitoring, highlighting an implementation gap (119). Baseline assessment of weight, height, waist circumference, blood pressure, heart rate, and metabolic parameters (e.g., fasting glucose, lipid profile) should be conducted for all persons treated with any of the categories of medications reviewed here.

Longitudinal monitoring includes measuring body weight monthly for the first 3 months and biannually thereafter. Patients who receive much of their health care virtually should be provided education on how to measure weight accurately. Evaluating anthropometric and metabolic parameters should occur more frequently in persons who are already obese as well as those at higher risk for obesity and related morbidity.

THE TREATMENT OF PSYCHOTROPIC DRUG–RELATED WEIGHT GAIN

Treating and preventing PDWG begins with psychoeducation, support, and attention to treatment barriers and patient goal attainment priorities (Box 1) (120, 121). Risk factor modification should be a primary consideration in all patients. In addition, as with all patients, comorbidities associated with weight gain should be targeted (e.g., attention deficit hyperactivity disorder [ADHD]). For example, adjunctive lisdexamfetamine (30–70 mg) has been preliminarily reported to significantly reduce body weight (−1.67 kg), body mass index (BMI) (−0.57), and ADHD symptom severity in persons with bipolar I or II disorder ($N=40$) (122). Attempts to successfully treat and manage comorbidity should be considered before specific treatments for weight mitigation are recommended.

The selection of a pharmacologic agent to treat a psychiatric disorder is influenced by multiple factors, including approved indications, established efficacy, access and availability, patient preference, cost and reimbursement schedule, and clinician experience. During the past two decades, multiple psychotropic agents have become available that have a relatively lower liability for PDWG, providing preferred opportunities for patients and clinicians. Moreover, clinical practice guidelines and expert recommendations prioritize agents with lower propensity to PDWG when alternatives exist (123–126).

For persons who are experiencing PDWG, the clinical decision then is to either discontinue the index offending agent and switch to an alternative with lower PDWG liability or adjunctively administer a behavioral and/or pharmacologic strategy specifically targeting PDWG. This

BOX 1. Prevention and treatment of psychotropic drug–related weight gain (PDWG)

1. Measure patient's weight and body mass index; consider waist circumference measurement; use metabolic monitoring and Fibrosis-4 Index (FIB-4)[a] where appropriate
2. Recommend lifestyle behavioral modification, improved diet, and eating pattern
3. Target psychiatric comorbidity (e.g., binge-eating disorder, attention deficit hyperactivity disorder) associated with weight gain and/or metabolic abnormalities
4. Prioritize psychotropic drugs that are weight neutral or have low weight gain liability
5. Follow metabolic monitoring guidelines to detect weight gain to allow for earlier intervention
6. When initiating weight-gain-promoting drugs, co-commence metformin if the index agent is an antipsychotic, as part of shared decision making

For established PDWG, consider switching to an agent with lower weight gain liability or adjunctive metformin, and GLP-1 receptor agonists as a second-line option. Prioritize GLP-1 receptor agonists if clinical presentation warrants (e.g., presence of type 2 diabetes, nonalcoholic fatty liver disease), as part of shared decision making.

[a] The FIB-4 is an index to estimate the risk of hepatic cirrhosis calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count. This noninvasive estimate of liver scarring is used to assess the need for biopsy (146).

clinical decision is informed by patient preference, treatment availability, cost, and psychiatric outcomes achieved with the index agent.

Multiple lines of evidence indicate that switching from an index agent that has resulted in PDWG to an alternative with lower PDWG liability results in significant weight loss and improvement in weight-related morbidity (74, 127, 128). Moreover, treatment continuation and/or improvement in psychopathological outcomes are usually observed but cannot be guaranteed on an individual basis. Although not evaluated primarily as a switching strategy, the combination of olanzapine-samidorphan (which is FDA approved for the treatment of adults with schizophrenia, acute mania, and mixed episodes associated with bipolar I disorder as monotherapy or adjunctive to lithium or valproate and as maintenance monotherapy in adults with bipolar I disorder) has been found to have lower weight gain liability compared to olanzapine in younger and middle-aged patients with schizophrenia (75–77, 129). Samidorphan is not commercially available as a standalone pharmaceutical treatment and is not available in other combinations. If the clinical decision is to continue the index agent that resulted in PDWG, the three categories of conjunctive interventions are behavioral, pharmacologic, and surgical.

Lifestyle and Behavioral Modification

Replicated and meta-analytic evidence supports the feasibility and acceptability of lifestyle and behavioral modification in the prevention and treatment of obesity and PDWG in persons with psychiatric disorders (130–141). In addition, contingency management combined with lifestyle and behavioral modification is established as effective at improving health outcomes in persons with substance use disorders. Preliminary results from early feasibility studies suggest that contingency management (i.e., lifestyle and behavioral modification plus payment for attendance or weight loss) targeting weight results in significantly greater weight loss compared to a control condition (134).

The estimated overall weight loss in persons with serious mental illness receiving lifestyle and behavioral modification is approximately 2.5–3.5 kg after 6–18 months of treatment, which is not dissimilar from weight loss with lifestyle and behavioral modification in the general population (132, 142). Weight gain mitigation in persons with psychiatric illness may take longer to achieve, perhaps in part owing to difficulties in engagement and resulting behavioral change (132). Although the average weight loss achieved with lifestyle and behavioral modification for some persons may fully offset weight gain accrued with psychotropic agents, it is inadequate as a single-modality intervention for a substantial proportion of patients who gain significant weight (143).

Specific factors related to implementation of lifestyle and behavioral modification in the psychiatric population include impaired cognitive functions, motivational deficits, inadequate access to integrated health care, economic and geographical disadvantage (e.g., food deserts), and the stigma of psychiatric disorders and treatments (144). These factors reduce the likelihood that lifestyle and behavioral modification will be an accessible, viable, and adhered to strategy in the prevention and treatment of PDWG in many persons with psychiatric disorders.

Consequently, pharmacologic treatments become an essential component in treating and preventing PDWG in individual patients. Difficulties among people in the general population in adhering to lifestyle and behavioral modification and dietary modification as a consequence of motivational and cognitive deficits has provided the rationale in some guidelines for recommending pharmacologic treatment as a first-line treatment combined with lifestyle and behavioral modification in the prevention of PDWG (145).

Pharmacologic Treatments

Similar to behavioral strategies, the paradigm for administering pharmacologic interventions for PDWG is either prevention or treatment (Table 4) (58). Most studies evaluating pharmacologic interventions for PDWG have embraced a treatment rather than a prevention paradigm. The majority of studies have evaluated pharmacologic interventions as antidotes for antipsychotic-induced weight gain, with relatively fewer studies on how to mitigate or treat weight increase associated with other psychotropic drugs.

Metformin. Metformin is a biguanide derivative that reduces gluconeogenesis and increases peripheral glucose utilization (146). It is a first-line treatment for persons with type 2 diabetes and is one of the most frequently prescribed medications in the United States. Adjunctive metformin has been the most studied off-label agent for PDWG, and it has been shown to prevent and reduce weight gain, BMI increase, and insulin resistance in persons commencing antipsychotic treatment and those previously experiencing weight gain and metabolic disturbance after chronic use of antipsychotics (85, 86, 147–155).

For example, meta-analytic data indicate that metformin-related weight loss in persons with serious mental illness treated with antipsychotics is approximately 3.3 kg compared with placebo, while metformin-related weight gain mitigation is approximately 4.0 kg compared with placebo (62, 156). Metformin is available in generic oral formulation (approximately 500–2500 mg/day) and is easy to administer, safe, and well tolerated (157). Moreover, metformin has also been reported to be effective in the treatment of polycystic ovary syndrome, which differentially affects persons with psychiatric disorders (113, 158). Metformin is recommended as a level 1 treatment for the prevention of weight gain in persons with psychiatric disorders receiving antipsychotic treatment (145).

GLP-1 receptor agonists. Glucagon-like peptide-1 (GLP-1) is an incretin produced by the intestinal L cells that promotes insulin secretion, reduces glucagon and gluconeogenesis, slows gut motility, and promotes satiety. Metformin acts on the GLP-1 pathway, increasing expression of the GLP-1 receptor and increasing circulating levels of GLP-1 (159). GLP-1 receptor agonists are FDA approved for type 2 diabetes, with supplemental indications in obesity for some agents. In addition, GLP-1 agonists are recommended for the treatment of nonalcoholic fatty liver disease, which affects at least 25% of the adult psychiatric population (43, 146).

GLP-1 receptor agonists mimic the effect of endogenous GLP-1 by slowing gastric motility and reducing appetite, resulting in significant weight loss in both short- and long-term studies (160–162). In addition to beneficial effects on weight and associated morbidity (e.g., plasma glucose levels, insulin sensitivity, dyslipidemia), GLP-1 receptor agonists have been preliminarily reported to have beneficial effects on measures of depression and cognition (163, 164). The neuropsychiatric effects of GLP-1 receptor agonists may be direct and independent of their effects on obesity and peripheral glucose control (165–168).

As part of a 16-week double-blind placebo-controlled study (169), the GLP-1 receptor agonist liraglutide (subcutaneous injection, 1.2–1.8 mg/day) was compared with placebo in patients with schizophrenia spectrum disorder (N=103) receiving either olanzapine or clozapine who had preexisting obesity and prediabetes. The primary endpoint was change in glucose tolerance and change in body weight, and cardiometabolic parameters were secondary outcomes. At the end of 16 weeks, liraglutide treatment significantly improved glucose tolerance compared with placebo, with 63.8% of patients developing normal glucose tolerance, compared with 16% of those receiving placebo ($p<0.001$; number needed to treat=2). A significant reduction in body weight was observed (a placebo-subtracted change of −5.3 kg), as well as a significant reduction in waist circumference (a placebo-subtracted change of −3.5 cm), blood pressure, and visceral fat. Liraglutide was well tolerated, with transient gastrointestinal side effects (e.g., nausea) reported.

A separate open-label randomized controlled study (170) compared weekly subcutaneous exenatide (2 mg) to usual care in a small sample (N=28) of clozapine-treated obese adults with schizophrenia, with or without type 2 diabetes. Significantly more participants receiving exenatide achieved the primary outcome (>5% weight loss) compared with those receiving usual care (6/14 and 1/14, respectively). Participants assigned to exenatide had significantly greater mean weight loss (−5.29 vs. −1.12 kg; $p=0.015$) and BMI reduction (−1.78 vs. −0.39; $p=0.019$) as well as reductions in fasting glucose and glycated hemoglobin. Participants in the exenatide group reported transient nausea, vomiting, dizziness, and diarrhea. In addition to liraglutide and exenatide, preliminary evidence suggests that semaglutide is also associated with clinically significant weight loss in persons receiving antipsychotic treatment (171).

In addition to GLP-1, the incretin glucose-dependent insulinotropic polypeptide (GIP) affects glycemic control and body weight (172). The FDA recently approved the dual GLP/GIP co-agonist tirzepatide for the management of type 2 diabetes and chronic weight management in adults with obesity or overweight (i.e., BMI ≥27 with at least one weight-related condition). Tirzepatide is reported to cause significant weight loss in both short- and long-term studies, with associated benefits on obesity-related morbidity that may be greater than with GLP-1 single receptor agonists (173). Moreover, GIP also has direct beneficial effects on reward and attention functions, suggesting that it may offer benefits not only in obesity but perhaps also in the treatment of psychopathology (174).

Adjunctive topiramate (50–400 mg/day) has been studied as an intervention to mitigate obesity and/or PDWG across multiple patient populations. Meta-analytic evidence indicates that topiramate results in a weight loss of

TABLE 4. Pharmacologic treatments for psychotropic drug–related weight gain

Agent	Comments
Metformin	Most studied antidote; prevents and treats antipsychotic weight gain; overall weight gain mitigation is modest; efficacy in prevention is greater than in treatment; easy to administer; generic available. Recommended as first-line treatment in the prevention of weight gain in persons prescribed weight-gain-promoting antipsychotics
Glucagon-like peptide-1 agonists (GLP-1) (e.g., liraglutide, exenatide)	Preliminarily studied; potential for relatively greater weight loss or gain mitigation compared with metformin; additional benefits are metabolic parameters, cardiac health, nonalcoholic fatty liver disease, and psychological measures; gastrointestinal tolerability may lead to discontinuation in some persons; access and availability not widespread
Other GLP-1 agonists (e.g., semaglutide)	Similar to GLP-1 agonists, above
Glucagon-like peptide 1 agonists/gastric inhibitory polypeptide (GLP-1/GIP) co-agonists (e.g., tirzepatide)	Similar to GLP-1 agonists, above; potentially greater weight loss or gain mitigation with co-agonist compared with GLP-1 agonists alone, with benefits beyond weight gain mitigation shared with GLP-1 agonists
Topiramate, naltrexone, samidorphan, ranitidine, nizatidine, famotidine, fluoxetine, reboxetine, betahistine, berberine, lipoic acid, and melatonin	Low-level confidence due to methodological limitations

approximately 3–4 kg and a BMI reduction of approximately 1.6 within 3 months of treatment (175). However, cognitive impairment with topiramate has significantly reduced its acceptability as a treatment option (176). The combination naltrexone-bupropion is indicated as an adjunctive treatment for weight management and has also been shown to be effective in binge-eating disorder as well as tobacco and methamphetamine use disorders (177, 178). Naltrexone-bupropion has been shown to be effective in reducing weight in obese persons receiving treatment with antidepressant medications (179).

Other psychotropic agents preliminarily evaluated as antidotes for PDWG include naltrexone, samidorphan, ranitidine, nizatidine, famotidine, reboxetine-betahistine, berberine, lisdexamfetamine, lipoic acid, and melatonin (75, 179–208). Most of these agents, however, have not been evaluated adequately as treatments for PDWG. For example, results from a recent Cochrane review of pharmacologic agents for antipsychotic-induced weight gain (N=17 randomized controlled trials; N=1,388 patients with schizophrenia) concluded that metformin has some evidence supporting its utility in prevention and treatment and that evidence of weight loss with most other agents is supported by very-low-certainty evidence (58).

Surgical Treatments

Bariatric surgery administered to persons with serious mental illness has been reported to be feasible and safe (209), and studies have reported that beneficial effects of bariatric surgery are noted across multiple dimensions of psychopathology (e.g., depression, anxiety, cognitive function) (210, 211). Preliminary data also indicate that weight loss observed in persons with serious mental illness may be similar to that expected in persons without serious mental illness (212).

For example, preliminary evidence suggests that persons with serious mental illness, although exhibiting similar weight loss trajectories, may be more likely to utilize emergency department visits and hospital days during follow-up (213). Bariatric surgery has not been comprehensively evaluated in persons with serious mental illness, and has not been specifically studied in PDWG. Moreover, not all individuals with serious mental illness would be eligible for bariatric surgery, on the grounds that pre- and postoperative clinical and safety monitoring could not be reasonably assured.

CONCLUSIONS

Psychotropic-related weight gain is a common occurrence, and it detracts from quality of life, contributes to morbidity, and is a frequent reason for treatment discordance for people being treated for psychiatric disorders. Metformin is most studied in the treatment and prevention of PDWG, notably in weight increase related to antipsychotics. Metformin is generally well tolerated, is easy to administer by non–endocrinology specialists and primary care providers, and is available in generic formulation at low cost. On the whole, metformin appears to be more effective as a primary weight gain mitigation strategy when compared with a secondary treatment approach. This suggests that metformin may be co-commenced with psychotropic drugs that have a high weight gain liability (e.g., olanzapine) if an alternative agent with a lower weight gain liability is not an option. The major limitation with metformin, however, is that the overall weight gain mitigation is relatively modest.

GLP-1 receptor agonists have been relatively less studied than metformin but show tremendous promise for PDWG. The overall weight loss attributable to GLP-1 receptor agonists and improvement in associated morbidity is significantly greater than with any other class of bariatric medicine. Moreover, GLP-1 receptor agonists improve outcomes for comorbidities that are also more commonly observed in psychiatric populations.

For example, GLP-1 receptor agonists are recommended as treatments for nonalcoholic fatty liver disease, which is the most common cause of chronic liver disease, affecting 25% of the global population, with possibly higher rates among persons with mental disorders. Preliminary

evidence also suggests that GLP-1 receptor agonists may directly benefit dimensions of psychopathology, including measures of motivation and cognition (166). In keeping with potential pro-cognitive effects of GLP-1 receptor agonists, semaglutide is currently being evaluated as a treatment for persons with Alzheimer's disease and for the cognitive symptoms of depression (214). The limitations of GLP-1 receptor agonists are that many require subcutaneous injection, cost of access is prohibitive in many cases, and gastrointestinal distress can be treatment limiting for some persons.

A major limitation of all treatments for PDWG, however, is that most studies have relatively small samples and short-term observation intervals. There is a lack of large, adequate, and well-controlled trials with both short- and long-term observation periods that have addressed the issue of blinding (i.e., preventing inadvertent disclosure to the participant and/or research team of which treatment a person is assigned to). Moreover, most studies have evaluated antipsychotics, and relatively few have evaluated weight gain mitigation strategies with other psychotropic classes. Future research vistas include trace amine-associated receptor 1 (TAAR1) as well as the GLP-1/GIP co-agonists (e.g., tirzepatide), GLP-1/GIP/glucagon tri-agonists (currently in late-phase development in diabetes), and possibly probiotics and ketogenic diet (215, 216). The TAAR1 agonists, which are currently in development for the treatment of major depressive disorder and generalized anxiety disorder, have demonstrated significant weight loss and improvement in metabolic parameters, suggesting potential application for comorbid obesity (216).

In the interim, practitioners should prioritize agents with lower PDWG liability and co-commence behavioral, lifestyle, and dietary strategies as part of an overall framework of health care. Shared decision making should include discussion of the possibility of PDWG and explore patient attitudes and preferences for treatment in this context. Although nonpharmacologic strategies should be co-commenced in all persons living with mental disorders, regardless of medication treatment assignment, the decision to initiate a pharmacologic agent as a preventive rather than treatment strategy needs to be determined on an individual basis.

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Examination Questions for "Psychotropic Drug–Related Weight Gain and Its Treatment"

1. **Which of the following factors are associated with greater liability to weight gain with most but not all antipsychotics?**
   A. Later in illness course
   B. Prior antipsychotic exposure
   C. Older age
   D. Pre-treatment weight
2. **Which of the following is true regarding glucagon-like peptides agonists?**
   A. GLP agonists mimic the effects of endogenous GLP-1
   B. GLP agonists slow gastric motility and reduce insulin secretion from the pancreas
   C. GLP agonists have been shown to be effective in the treatment of non-alcoholic fatty liver disease (NAFLD), which affects at least 25% of the adult psychiatric population
   D. A and B are correct
3. **Which of the following antipsychotics results in weight gain similar to placebo?**
   A. Brexpiprazole
   B. Cariprazine
   C. Lumateperone
   D. Aripiprazole