DSH PSYCHOTROPIC MEDICATION Operational Procedures

APPENDIX – MEDICATIONS FOR PREVENTION OR TREATMENT OF OBESITY

NOTE: Directive statements and procedures described in this chapter are informational and advisory in nature.

INTRODUCTION:

Overweight and obesity are common health problems afflicting patients suffering from chronic severe mental disorders. In some cases, overweight and obesity are caused or promoted by psychotropic medications. The focus of this chapter is to provide guidance in using medications to prevent or reverse weight gain or obesity related to treatment with psychotropic medications.

DEFINITIONS:

The most frequently used measure for assessing underweight, overweight, and obesity is the body mass index or BMI (weight in kilograms divided by height in meters squared). This measure is accurate in most circumstances for adults, excluding situations such as those involving body builders or pregnancy, etc. Alternative methods such as percent body fat in athletes or specific population weight curves (e.g., in pregnant women) are more accurate for these selected populations. The definitions related to BMI are shown in the table below.

CATEGORY	BMI RANGE	COMMENTS
Underweight	< 20	BMIs < 18 are associated with medical risks/complications, as well as attitudes and behaviors associated with anorexia.
Normal Weight	20.0 – 24.9	Regarded as optimal for good health in most adults.
Overweight	25.0 – 29.9	This degree of weight is not often associated with medical complications but may be of concern when the patient has changed from normal weight to overweight.
Obesity, Grade I	30.0 – 34.9	Long-term risks of type II diabetes, hypertension, and cardiovascular disease are increased.
Obesity, Grade II	35.0 – 39.9	Negative health outcomes are of more acute concern.
Obesity, Grade III	> 40.0	This is morbid obesity and poses substantial health risks which may be acutely life-threatening.

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BACKGROUND

Although weight gain as well as abnormalities in glucose, dyslipidemia, and type II diabetes mellites (T2DM) are linked to all antipsychotics, there is a hierarchy of risk. The atypical antipsychotics clozapine and olanzapine have the highest propensity to cause weight gain and metabolic impairment. In many patients, clozapine causes early and significant weight gain with increases of almost 4.5 kg in the first 10 weeks and at least a 10% increase in body weight after 52 weeks. Weight gain may continue for years until stabilizing. This side effect compromises adherence as well as overall health and quality of life.

POINTS OF INTERVENTION TO PREVENT WEIGHT GAIN

Pharmacological intervention to mitigate against weight gain should be considered in response to a variety of factors. These are outlined below:

- Family history of obesity
- Personal history of obesity
- A weight gain of 5% in one month after starting the medication
- A weight gain of 7.5% in three months after starting the medication
- A weight gain of 10% in six months after starting the medication
- A BMI increase > 1.0
- Progression from one weight category to the next, e.g., normal weight to overweight, overweight to obese, obesity grade I to grade II, or from grade II to grade III

MEDICATIONS WHICH MITIGATE ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

MEDICATION	DOSE RANGE	COMMENTS
Amantadine	100 mg QAM – 200 mg BID	If post-dose nausea occurs, switch to an extended-release formulation.
Melatonin	3 mg – 10 mg QHS	Effects tend to be modest but may be worthwhile in the context of correcting circadian sleep problems.
Metformin	500 mg QAM – 1000 mg BID	If eGFR < 30 mL/min, then dose should not exceed 500 mg QAM. If post-dose nausea occurs, then switch to an extended-release formulation. Metformin has the most extensive literature with respect to preventing antipsychotic-associated weight gain.

Note that the above medications mitigate against antipsychotic-induced weight gain but are relatively ineffective in reversing extant overweight or obesity.

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OBESITY INTERVENTION

Pharmacological intervention aimed at weight loss should be considered for all grades of obesity. In this context, the glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as the most effective class of medications. In some studies, weight losses of circa 30% over one to two years of treatment have been observed, with about two-thirds of patients also achieving a normal glycemic response. These medications have been observed to stimulate C-cell hyperplasia in the thyroids of animals, as well as proliferation of pancreatic beta cells. Based on this data, the U.S. Food and Drug Administration (FDA) has advised caution in cases of family or personal history of medullary thyroid cancer or pancreatic cancer. The FDA has indicated that these medications should not be used in patients from families in which multiple endocrine neoplasia syndrome type 2 (MEN 2) has been present. Also, rare cases of pancreatitis have been reported. These agents are not prone to causing hypoglycemia.

The GLP-1 receptor agonists appear to be particularly useful in patients with clozapine or olanzapine-induced weight gain. While the mechanism of metabolic deterioration with these drugs isn't completely understood, in the short term, olanzapine and clozapine cause a hyperglycemic state with rapid rises in both glucagon, glucose, and insulin. The increase in glucagon secretion increases hepatic production of glucose which in turn, stimulates production of insulin resulting in hyperinsulinemia. Clozapine also induces a preference for high sugar/high-fat foods. The change in food preference and increase in glucagon secretion are driven by clozapine and olanzapine's rapid and reversible reductions in GLP-1 levels. GLP-1 is a hormone secreted by L-cells in intestinal epithelium and is involved in multiple aspects of glucose regulation and satiety. GLP-1 is secreted in response to stimulation by muscarinic neurotransmission. It is hypothesized that clozapine, a high affinity muscarinic antagonist at M1 and M2 receptors, inhibits GLP-1 secretion, resulting in changes in food preference and defects in glucose homeostasis.

GLP-1 AVAILABLE AGENTS (listed in the order they were first approved):

GENERIC NAME	PROPRIETARY NAME(S)	MANUFACTURER
Exenatide	Byetta® Bydureon®	Astra Zeneca
Liraglutide	Victoza® Saxenda®*	Novo Nordisk
Lixisenatide	Adlyxin®	Sanofi
Albiglutide**	Tanzeum®	GSK
Dulaglutide	Trulicity®	Lilly
Semaglutide	Ozempic® Rybelsus® Wegovy®*	Novo Nordisk
Tirzepatide	Mounjaro®	Lilly

*FDA indicated for treatment of obesity. All GLP-1 agonists; however, tend to produce weight loss. **not available in the U.S.

- All GLP-1 agonists are given subcutaneously, except semaglutide, which is given either orally daily or as a weekly subcutaneous injection

- Liraglutide and semaglutide are best studied in the context of psychotropic medications

There are several older anti-obesity drugs used in the community that are not recommended for forensic patients with severe mental illness (SMI). These include orlistat, naltrexone SR/bupropion SR (Contrave®), and phentermine/topiramate ER (Qsymia®). Specifically, orlistat reversibly blocks the action of pancreatic and gastric lipases with the downstream effect of inhibiting absorption of free fatty acids. Orlistat has the effect of enforcing a low-fat diet, since foods high in fat will result in steatorrhea. Adherence falls off rapidly due to steatorrhea and in one study, by one year adherence had fallen to 6%. While naltrexone SR/bupropion SR results in a mean weight loss of 6.4% at 56 weeks, bupropion is a medication of abuse in forensic systems due to its CNS stimulant effect when insufflated. Phentermine is a sympathomimetic amine and a CNS stimulant. There are numerous case reports of phentermine-induced psychosis.

Olanzapine-samidorphan (Lybalvi®) is a single tablet combination of olanzapine and samidorphan, which is a μ-opioid receptor antagonist and κ- and δ-opioid partial agonist. Evidence suggests that opioid receptor antagonists may mitigate antipsychotic-induced weight gain. To date, studies have shown that when olanzapine-samidorphan at the highest dose (20 mg olanzapine and 10 mg samidorphan) is started in schizophrenia patients not recently treated olanzapine, the combination significantly reduced the weight gain at 24 weeks (4.21% in the olanzapine-samidorphan group vs 6.59% in the olanzapine group). However, this combination has not been tested at higher doses, with treatment resistant schizophrenia patients, and there is no data on whether switching to the medication in a patient treated with olanzapine will reduce weight.

LAPROSCOPIC BARIATRIC/METABOLIC SURGERY

Postoperative weight loss depends on the kind of surgery with Roux-en-Y Gastric Bypass (RYGB) associated with approximately 20% total weight loss and Sleeve Gastrectomy (SG) associated with 15% weight loss at 1-year follow-up. Higher baseline weight is associated with greater weight loss and weight loss follows a normal distribution with some people losing up to 60% of total body weight while others lose only 5%, and most lying somewhere in the middle. Some weight regain is common and a minority of patient struggle with considerable weight regain.
Research suggests that bariatric surgery in patients with SMI results in weight loss comparable to that of controls; however, some studies have found that mental illness predicts greater post-operative acute care use suggesting that people with SMI require increased post-operative support. Studies and case series specifically examining RYGB and SG outcomes have demonstrated that there is no significant difference in weight loss at 24-month follow-up between schizophrenia patients and controls. Specifically, the excess weight loss in schizophrenia patients with SG at 24 months was 51.68 +

15.84% and with RYGB it was 34.3 ± 5.5%. Importantly, no exacerbation of psychotic symptoms was observed. Patients reported significant improvement in quality of life.

Bariatric surgery is a consideration in stable patients who will be able to cooperate with close post-operative monitoring.

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