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144 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Treatment of antipsychotic--induced weight gain Weight gain is an important adverse effect of nearly all antipsychotic medications.1,2 Women may be at greater risk than men.3 An increase in body weight has obvious consequences for self-image, morbidity and mortality, so prevention and treatment are matters of some clinical urgency. Monitoring Patients starting antipsychotic treatment or changing medication should, as an absolute minimum, have their body weight recorded in their clinical records. Ideally, BMI and waist circumference should also be recorded.4,5 Early in treatment, monitoring of body weight every week or two is recommended, for at least the first 6 months.5,6 Rapid weight gain in early treatment (e.g. an increase of ≥5% above baseline after a month of treatment) strongly predicts long-term weight gain and should prompt consideration of preventative or remedial measures.7–10 With continuing antipsychotic treatment, annual measurement of body weight is recommended as a minimum.5,6,11 In clinical practice, the monitoring of body weight and other metabolic adverse effects in people on continuing antipsychotic medication is inconsistent and limited, falling short of recommended best practice.12–16 Treatment and prevention Most of the relevant literature in this area addresses attempts to reduce body weight gained during treatment with medication, although there are useful data suggesting that early interventions can prevent or mitigate weight gain.17,18 When weight gain occurs, initial options involve switching a patient’s antipsychotic medication or instituting behavioural programmes (or both). Switching always presents a risk of relapse and treatment discontinuation,19 but there is fairly strong support for switching to aripiprazole,20 ziprasidone21 or lurasidone as a method for reversing weight gain.20,22,23 Another option is adjunctive aripiprazole:5 weight loss has been observed when aripiprazole has been added to antipsychotic medications such as clozapine and olanzapine.18,24 Stopping antipsychotic treatment altogether can be associated with weight loss25,26 but this course of action would not be clinically appropriate for the vast majority of people with multi--episode schizophrenia. Note that, while some switching and augmentation strategies may minimise further weight gain or facilitate weight loss, the overall effect is generally modest, and many patients continue to be overweight.27 Additional lifestyle interventions are often required if BMI is to remain within or move towards the normal range. A variety of lifestyle interventions have been proposed and evaluated with generally good results.5,17,28–31 Interventions do vary, but they are mainly ‘behavioural lifestyle programmes’ aimed at improving diet and increasing physical activity. Meta-analyses of RCTs have generally found a positive effect for both prevention and intervention

with these non-pharmacological interventions.17,29,32,33 Pharmacological methods should be considered only where behavioural treatment strategies or switching to a medication with a lower liability for weight gain have failed

Schizophrenia and related psychoses CHAPTER 1 or where obesity presents a clear, immediate physical risk to the patient. Some drug treatment options for antipsychotic-induced weight gain are listed in Table 1.32. Metformin is now probably considered to be the drug of choice for the prevention and treatment of antipsychotic-induced weight gain, although glucagon-like peptide-1 (GLP-1) agonists may ultimately prove to be more effective and better tolerated.34 Bariatric surgery may have a role in a few rare, severe cases where all else has failed.35 However, the efficacy of bariatric surgery for drug-induced weight gain is not known.5 Table 1.32 Drug treatment of antipsychotic-induced weight gain (alphabetical order). Drug Comments Alpha-lipoic acid36–38 (1200mg/day) Supplementation may lead to a small, short-term, weight loss. Limited data for antipsychotic-induced weight gain. Not recommended. Amantadine39,40 (100–300mg/day) May attenuate olanzapine-related weight gain. Seems to be well tolerated apart from insomnia and abdominal discomfort. May (theoretically, at least) exacerbate psychosis. Evidence base too limited to recommend.5 Aripiprazole augmentation18,31,41 (5–15mg/day) RCTs show beneficial effects on weight loss and possibly other metabolic parameters when used as an adjunct to clozapine or olanzapine. Adjunctive use appears to be safe and unlikely to worsen psychosis. Recommended as a possible option for weight gain associated with clozapine or olanzapine. Not recommended with other antipsychotic medications. Betahistine42,43 (48mg/day) May attenuate olanzapine-induced weight gain. Limited data. Not recommended. Bupropion44,45 (formerly amfebutamone) Seems to be effective in obesity when combined with calorie-restricted diets. Appears to not exacerbate psychosis symptoms, at least when used for smoking cessation.46 One small (positive) RCT in antipsychotic-related weight gain.47 Bupropion + naltrexone (Contrave/Mysimba)48 Combination approved for weight management as an adjunct to diet and exercise. No data in drug-induced weight gain. Not recommended but should not be ruled out. Fluvoxamine49–51 (50mg/day) Earlier conflicting data but one short-term RCT shows attenuated clozapine-induced weight gain (possibly related to a higher clozapine to norclozapine ratio). Co- administration markedly increases clozapine levels, requiring extreme caution. Evidence base is too limited to recommend. Liraglutide52–54 (3mg/day via SC injection) GLP-1 agonist that was previously approved for type 2 diabetes and more recently approved as an anti-obesity agent in non-diabetic patients. Dose for weight loss (3mg/day) is higher than the dose used for diabetes (≤1.8mg). Limited data in drug--induced weight gain. One RCT shows significant weight loss in overweight pre-diabetic patients stable on olanzapine or clozapine.52 Beneficial effects on other metabolic parameters. Well tolerated but can cause GI disturbances. Recommended option in pre-diabetic/diabetic patients and clozapine-induced weight gain. Other GLP-1 agonists are currently only approved for diabetes and have a more limited dose range. Exenatide LA (a once-weekly GLP-1 agonist) may be effective for weight loss in clozapine-treated patients55 but perhaps not with other antipsychotics.56 (Continued)

 Drug Comments Melatonin57–59 (up to 5mg at night) One small RCT showing attenuation of olanzapine-induced weight gain. Other studies show negative results. Effect, if any, is small. Metformin5,31,60–62 (500–2000mg/day) There is a substantial database (in non-diabetic patients) supporting the use of metformin in both reducing and reversing weight gain caused by antipsychotic medications (mainly olanzapine). A Cochrane review in 2022 concluded that there was ‘low-certainty evidence to

suggest that metformin may be effective in preventing weight gain’ in people with schizophrenia.62 There may also be beneficial effects on other metabolic parameters. A later cohort study63 showed that metformin prevented weight gain with clozapine. One positive RCT64 and extension study65 in children and adolescents with autism spectrum disorder. May be ideal for those with weight gain and diabetes or polycystic ovary syndrome. Note that metformin treatment increases the risk of vitamin B12 deficiency.66 Modafinil67,68 (up to 300mg/day) Limited positive data and one negative RCT for clozapine-induced weight gain. Not recommended. Naltrexone69,70 (25–50mg/day) Some positive results but evidence is limited to two small pilot RCTs. Not recommended. Orlistat71–76 (120mg shortly before or after each meal). Official maximum is three times daily. Reliable effect in obesity, especially when combined with calorie restriction. Few published data in medication-induced weight gain but widely used in practice with some success. In trials for clozapine or olanzapine-induced weight gain effect was only seen in men.75,76 When used without calorie restriction in psychiatric patients, the effects are very limited. Failure to adhere to a low-fat diet will result in fatty diarrhoea and possible malabsorption of orally administered medication. Overall, a good choice for clozapine-induced weight gain where it reduces both weight and the incidence of constipation.77 Reboxetine18 (4–8mg/day) Attenuates olanzapine-induced weight gain. Reverses some metabolic changes.78 Effective when combined with betahistine. Samidorphan (μ–opioid receptor antagonist)79–85 There is good evidence from RCTs that the combination of samidorphan and olanzapine can mitigate olanzapine-associated weight gain. But these findings need to be confirmed ‘through further high-quality research’.83 The combination was approved by the US FDA in 2021 for indications including the treatment of schizophrenia and bipolar I disorder. Semaglutide (weekly injectable, glucagon–like peptide--1RA)86,87 A small case series suggested that semaglutide, up to 2mg/week, might reduce antipsychotic-associated weight gain that had not responded to metformin. Topiramate31,58,88,89 (up to 300mg/day) Reliably reduces weight even when medication induced. Meta-analyses of RCTs suggest a greater effect for prevention rather than treatment. Problems may arise because of topiramate’s propensity for causing sedation, confusion and cognitive impairment. May have antipsychotic properties. Zonisamide90 (100–600mg/day) Antiepileptic drug with weight-reducing properties. An RCT of 150mg/day showed significant weight reduction in people receiving SGAs. Another RCT (up to 600mg/ day) shows attenuated olanzapine-induced weight gain. Sedation, diarrhoea and cognitive impairment are the most common problems. Not recommended.
Table 1.32 (Continued)

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