

Weight Change and Metabolic Side-Effects of Psychotherapeutic Medications

Note: Strongly recommend coordination of care between all providers to facilitate optimal outcomes.

Weight changes are the most difficult issues patients and clinicians contend with and can have an effect on patient compliance with a particular regimen. Individual psychiatric medications, including those in the antidepressant, mood stabilizer, and antipsychotic classes, have been shown to have differential effects on weight gain.

Management of medication-induced weight gain and other metabolic problems depends on multiple factors, including response to different antipsychotics, severity of the metabolic disturbance, and patient willingness to implement lifestyle changes. Individuals with new-onset diabetes should receive an evaluation by a primary care provider.

Potential options to manage medication-induced metabolic side-effects include:

- Diet and exercise, including referral to a certified nutritionist if clinically indicated
- Switching to an antipsychotic with lower potential for weight gain or dyslipidemia (e.g., switch from olanzapine or risperidone to ziprasidone)
- Medication management if more conservative measures are ineffective (e.g., antihypertensives for hypertension and statins for dyslipidemia)

Initial randomized trials have also shown evidence that metformin may be effective in helping patients with schizophrenia lose weight. These trials found that twelve to sixteen weeks of metformin given at 750 mg/day or higher led to loss of approximately 50 percent of weight gain induced by antipsychotic treatment, and metformin combined with lifestyle changes had more effect than metformin alone in two of the trials. Metformin is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with Type 2 diabetes mellitus. Metformin is not yet FDA-indicated for psychotropic medication-induced weight gain and is contraindicated in individuals with known hypersensitivity or metabolic acidosis. Metformin has traditionally been contraindicated in chronic kidney disease; however, based on recent evidence and recommendations, metformin may be used with caution and close clinical supervision in individuals with a GFR >30 mL/min. The primary concern is the risk for lactic acidosis in this population.

Weight Change and Metabolic Side-Effects of Psychotherapeutic Medications (*continued*)

Table 7.

Studies Examining Weight Change Associated with Psychotherapeutic Medications used in the Treatment of Serious Mental Illness	
Antidepressants	
Selective Serotonin Reuptake Inhibitors (SSRIs)	<p>Weight loss</p> <ul style="list-style-type: none"> ◆ Sertraline (Zoloft) – Patients in controlled trials had minimal (1-2 pound) weight loss compared to smaller changes with placebo. <p>No weight change</p> <ul style="list-style-type: none"> ◆ Citalopram (Celexa) – Short-term placebo-controlled trial showed average weight loss of 0.5 kg with citalopram versus 0.2 kg weight gain with placebo in post-marketing studies; No significant changes in body mass in post-marketing studies. ◆ Escitalopram (Lexapro) – No difference from placebo-treated patients in premarketing trials. ◆ Fluoxetine (Prozac) – No overall associated weight changes; weight loss of 0.35 kg reported in acute-phase treatment, at 38 weeks, 2.0 kg weight gain with fluoxetine versus 2.5 kg weight gain with placebo. <p>Weight gain</p> <ul style="list-style-type: none"> ◆ Paroxetine (Paxil) – Of the SSRIs, paroxetine is most likely to cause weight gain. Fava, et al. showed >7% increase in weight from baseline compared with patients taking sertraline or fluoxetine.
Selective Serotonin Reuptake Inhibitors (SSRIs)/ Serotonin Receptor Modulator	<p>Weight gain (long term studies)</p> <ul style="list-style-type: none"> ◆ Vortioxetine (Trintellix) – No significant weight change in short-term studies; One long-term study showed a mean weight gain of 0.67 kg from baseline. ◆ Vilazodone (Vibryd) – Minimal weight gain in short-term studies; Average change from baseline was 1.0 kg weight gain in a one-year study of 599 adults treated with vilazodone 40 mg/day.
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	<p>Weight loss</p> <ul style="list-style-type: none"> ◆ Duloxetine (Cymbalta) – In acute placebo-controlled studies, duloxetine treated patients had average change of -0.5 kg compared with 0.2 kg for placebo treated patients. No consistent relationship between duloxetine dose and weight change. Similar acute mean weight changes seen in duloxetine versus fluoxetine treated patients (-0.7 kg versus -0.6 kg respectively). ◆ Venlafaxine (Effexor) – Weight loss of up to 7% of body weight compared to placebo during up to 12 weeks of treatment in studies of patients with MDD, GAD, SAD, and panic disorders. <p>Weight loss (short-term)/No weight change (long term)</p> <ul style="list-style-type: none"> ◆ Desvenlafaxine (Pristiq) – Post-hoc analysis of data from 8 short-term and 1 longer-term study of adults treated with 50 mg/day or 100 mg/day of desvenlafaxine versus placebo found statistically significant mean weight loss (<1 kg) during acute treatment for MDD and no significant weight change after longer-term treatment in normal (BMI ≤ 25 kg/m²), overweight (BMI 25 kg/m² to ≤ 30 kg/m²), and obese (BMI > 30 kg/m²) adults.

Weight Change and Metabolic Side-Effects of Psychotherapeutic Medications (*continued*)

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Studies Examining Weight Change Associated with Psychotherapeutic Medications used in the Treatment of Serious Mental Illness (<i>continued</i>)	
Antidepressants (<i>continued</i>)	
Tricyclic Antidepressants (TCAs)	<p>No weight change</p> <ul style="list-style-type: none"> ◆ Nortriptyline (Pamelor) – Meta-analysis of 257 RCTs found non-significant weight change with nortriptyline. <p>Weight gain</p> <ul style="list-style-type: none"> ◆ Amitriptyline (Elavil) – Meta-analysis of 257 RCTs found average of 1.8 kg weight gain. ◆ Imipramine (Tofranil) – Average of 4.5 kg weight gain over one year in patients treated for panic disorder.
Other antidepressants	<p>Weight loss</p> <ul style="list-style-type: none"> ◆ Bupropion (Wellbutrin) – Meta-analysis of 257 RCTs found average of 1.3 kg weight loss. <p>Weight gain</p> <ul style="list-style-type: none"> ◆ Mirtazapine (Remeron) – Meta-analysis of 257 RCTs found average of 1.5 kg weight gain.
Anticonvulsants/Mood Stabilizers	
	<p>Weight loss</p> <ul style="list-style-type: none"> ◆ Lamotrigine (Lamictal) – Mean weight loss of 4.2 kg at week 52 of therapy in obese patients; mean weight loss of 0.5 kg in non-obese patients at week 52. ◆ Topiramate (Topamax) – Meta-analysis of 257 RCTs found average of 3.8 kg weight loss. <p>Weight gain</p> <ul style="list-style-type: none"> ◆ Carbamazepine (Tegretol) – Meta-analysis of 257 RCTs found average of 1.0 kg weight gain. ◆ Gabapentin (Neurontin) – Meta-analysis of 257 RCTs found average of 2.2 kg weight gain. ◆ Lithium (Eskalith, Lithobid) – Mean weight gain of 6.1 kg at week 52 of lithium therapy in obese patients; mean weight gain of 1.1 kg in non-obese patients at week 52. ◆ Valproic Acid (Valproate, Valpro, Depakene) – Weight gain of 0.49 kg after 3 weeks of treatment with up to 1,500 mg/day versus placebo in healthy volunteers.
Antipsychotics	
Typical Antipsychotics	<p>Weight gain</p> <ul style="list-style-type: none"> ◆ Chlorpromazine (Thorazine) – Meta-analysis estimated mean weight gain of 2.10 kg at 10-weeks of treatment. ◆ Fluphenazine (Prolixin) – Meta-analysis estimated mean weight gain of 0.43 kg at 10-weeks of treatment. ◆ Haloperidol (Haldol) – Meta-analysis estimated mean weight gain of 0.48 kg at 10-weeks of treatment.

Weight Change and Metabolic Side-Effects of Psychotherapeutic Medications (*continued*)

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Studies Examining Weight Change Associated with Psychotherapeutic Medications used in the Treatment of Serious Mental Illness (<i>continued</i>)	
Antipsychotics (<i>continued</i>)	
Atypical Antipsychotics	<p>Weight gain</p> <ul style="list-style-type: none"> ◆ Aripiprazole (Abilify) – 3-month cohort study of first-time use of atypical antipsychotics in children and adolescents reported mean weight gain of 4.4 kg. 6-month RCT reported mean weight gain of 0.40 kg with aripiprazole. A meta-analysis of metabolic effects associated with atypical antipsychotic treatment in children and adolescents found olanzapine, risperidone and aripiprazole were all associated with statistically significant weight gain. Olanzapine was associated with the most weight gain and aripiprazole was the least. ◆ Asenapine (Saphris) – A double-blind placebo-controlled study found mean weight gain of 0.9 kg compared to placebo. ◆ Brexpiprazole (Rexulti) – Weight gain with brexpiprazole was moderate (1.45 and 1.28 kg for 2 and 4 mg, respectively, versus 0.42 kg for placebo at week 6). ◆ Cariprazine (Vraylar) – Mean weight gain at endpoint of 6-week in patients with schizophrenia: 0.8 kg with 1.5-3 mg/day, 1.0 kg with ≥4.5 mg/day versus 0.3 kg with placebo. ◆ Clozapine (Clozaril) – 6-week open-label study reported average weight gain of 2.5 kg. ◆ lloperidone (Fanapt) – Mean change from baseline of 2.1 kg increase at endpoint. ◆ Lurasidone (Latuda) – The mean weight gain observed across 6-week trial in patients with schizophrenia was 0.43 kg for lurasidone versus mean weight loss of 0.02 kg for placebo. ◆ Olanzapine (Zyprexa) – Meta-analysis of 257 RCTs found average of 2.4 kg weight gain. A 3-month cohort study of first-time use of atypical antipsychotics in children and adolescents reported mean weight gain of 8.5 kg. CATIE trial found an average weight gain of 2.0 lbs (0.9 kg) per month, more than any other treatment group (quetiapine, risperidone, ziprasidone, or perphenazine). A meta-analysis of metabolic effects associated with atypical antipsychotic treatment in children and adolescents found olanzapine, risperidone and aripiprazole were all associated with statistically significant weight gain. Olanzapine was associated with the most weight gain and aripiprazole was the least. ◆ Paliperidone (Invega) – 6-month RCT reported mean weight gain of 2.3 kg for paliperidone ER. ◆ Quetiapine (Seroquel) – Meta-analysis of 257 RCTs found average of 1.1 kg weight gain. ◆ Risperidone (Risperdal) – Meta-analysis of 257 RCTs found average of 0.8 kg weight gain. A meta-analysis of metabolic effects associated with atypical antipsychotic treatment in children and adolescents found olanzapine, risperidone and aripiprazole were all associated with statistically significant weight gain. Olanzapine was associated with the most weight gain and aripiprazole was the least. ◆ Ziprasidone (Geodon) – Meta-analysis found mean weight gain of 0.04 kg.

Note. 1 kilogram = 2.2 pounds. Medications under each category (weight loss, no weight change, weight gain) are listed alphabetically.