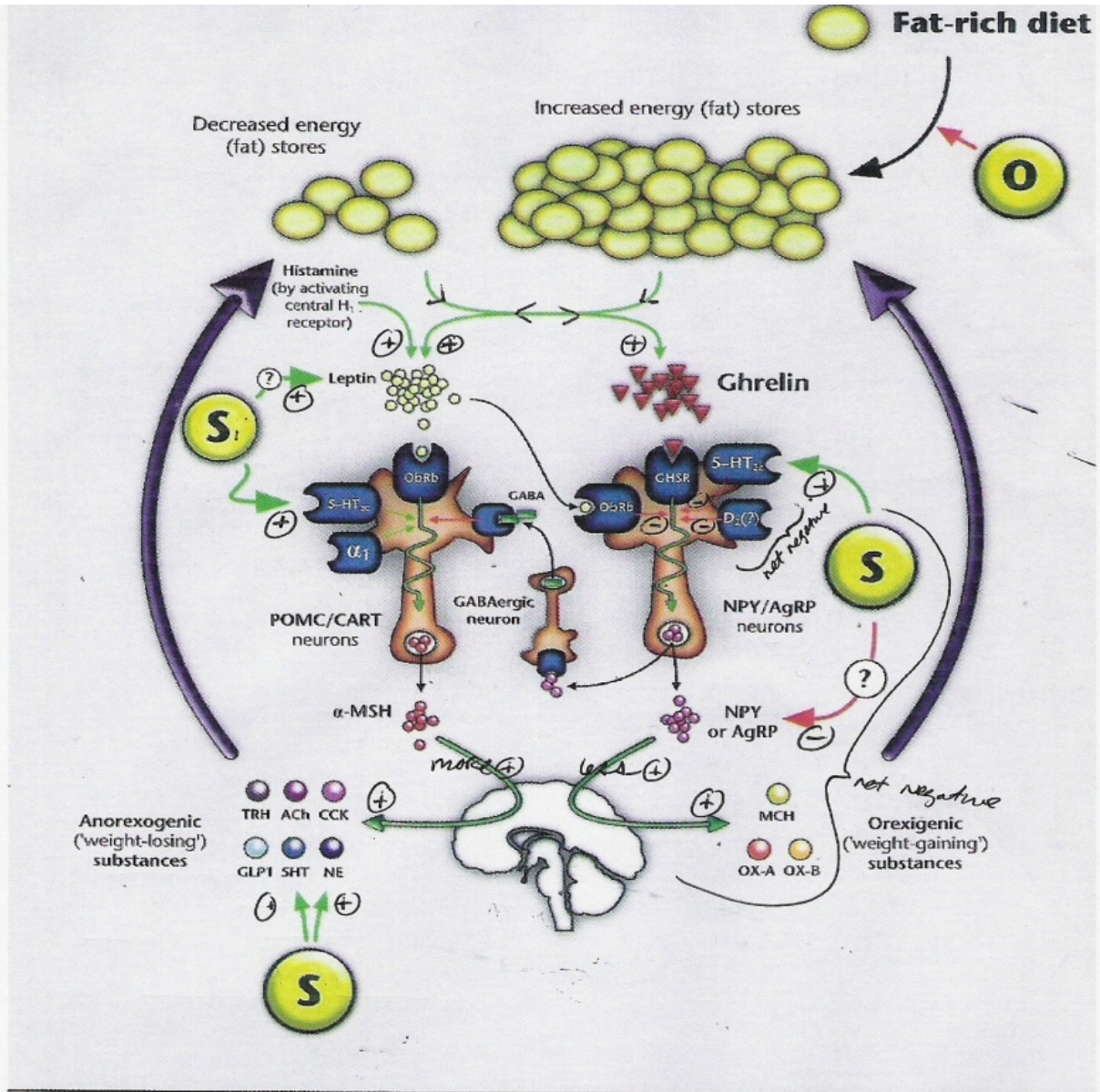


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Weight



Legend

- Action potential
- Stimulates
- Inhibits
- Sibutramine
- Orlistat
- Not well established

- 5-HT** Serotonin
- 5-HT_{2c}** Serotonergic receptor subtype
- ACh** Acetylcholine
- AgRP** Agouti-related gene product
- APD** Antipsychotic drug
- α₁** Noradrenergic receptor subtype
- α-MSH** Melanocortin-stimulating hormone
- CART** Cocaine- and amphetamine-regulated transcript
- CCK** Cholecystokinin
- GABA** γ-Aminobutyric acid
- GLP1** Glucagon-like peptide 1

- GHSR** Growth hormone secretagogue receptor
- MCH** Melanin-concentrating hormone
- NE** Norepinephrine
- NPY** Neuropeptide Y
- ObRb** Functional long leptin receptor
- OX-A/B** Orexin A/B
- POMC** Proopiomelanocortin
- TRH** Thyroid stimulating hormone (TSH)-releasing hormone

- Stimulants
- Dopamine agonists
 - See amantadine above
- Topamax
 - Multiple positive RCT's; average loss in one study 5 lbs
 - 15% risk of paresthesias (numbing/tingling in extremities)
 - McElroy et al, 2007: RCT Topamax vs. silbutramine in patients with bipolar disorder (and weight gain associated with medications); average weight loss 6 lbs with Topamax vs. 9 lbs with silbutramine; discontinuation rates were the same (>50%)
- Metformin
 - General
 - Biguanide used to treat diabetes
 - Reduces glucose production, increases sensitivity to insulin, increases glucose uptake by skeletal muscle
 - An antihyperglycemic agent; if used alone, it does not cause hypoglycemia
 - Beneficial effect on serum lipids
 - Reduction in weight in patients with type II diabetes
 - Evidence in psychiatry
 - Randomized, placebo-controlled trial of metformin for the treatment of weight gain induced by antipsychotic medication in young people with autism spectrum disorder: open-label extension (Handen et al, 2017)
 - 16 week open-label extension of the study below (Anagnostou et al, 2016)
 - Those who took placebo in initial study lost weight on metformin
 - Those who took metformin in initial study maintained weight loss
 - Side effects
 - Abdominal pain, upper abdominal pain, dyspepsia or discomfort 13-39%
 - Constipation 0-9%
 - Diarrhea 37-61%
 - Flatulence 7-18%
 - Nausea or vomiting 20-43%
 - Fatigue 13-21%
 - Irritability 17-31%
 - Confusion 3-5%
 - Dizziness 3-7%
 - Headache 17-36%
 - Somnolence 0-9%
 - Tremor 3-9%
 - Aggression 3-18%
 - Anger 0-14%
 - Anxiety 4-14%
 - Insomnia 6-25%
 - Cough 7-23%
 - Rash 3-14%
 - Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder: A Randomized Clinical Trial; Evdokia Anagnostou, Michael G Aman, Benjamin L Handen, Kevin B Sanders, Amy Shui, Jill A Hollway, Jessica Brian, I Eugene Arnold, Lucia Capano, Jessica A Hellings, Eric Butter, Deepali Mankad, Rameshwari Tumuluru, Jessica Kettel, Cassandra R Newsom, Stasia Hadjiyannakis, Naomi Peleg, Dina Odlobina, Sarah McAuliffe-Bellin, Pearl Zakrofsky, Sarah Marler, Alexis Wagner, Taylor Wong, Eric A Macklin, Jeremy Veenstra-VanderWeele; *JAMA Psychiatry* 2016 August 24
 - **Importance:** Atypical antipsychotic medications are indicated for the treatment of irritability and agitation symptoms in children with autism spectrum disorder (ASD). Unfortunately, these medications are associated with weight gain and metabolic complications that are especially troubling in children and with long-term use.
 - **Objective:** To evaluate the efficacy of metformin for weight gain associated with atypical antipsychotic medications in children and adolescents with ASD (defined in the protocol as DSM-IV diagnosis of autistic disorder, Asperger disorder, or pervasive developmental disorder not otherwise specified), aged 6 to 17 years.
 - **Design, Setting, and Participants:** A 16-week, double-blind, placebo-controlled, randomized clinical trial was conducted at 4 centers in Toronto, Ontario, Canada; Columbus, Ohio; Pittsburgh, Pennsylvania; and Nashville, Tennessee. In all, 209 potential participants were screened by telephone, 69 individuals provided consent, and 61 participants were randomized to receive metformin or placebo between April 26, 2013, and June 24, 2015.
 - **Interventions:** Metformin or matching placebo titrated up to 500 mg twice daily for children aged 6 to 9 years and 850 mg twice daily for those 10 to 17 years.
 - **Main Outcomes and Measures:** The primary outcome measure was change in body mass index (BMI) z score during 16 weeks of treatment. Secondary outcomes included changes in additional body composition and metabolic variables. Safety, tolerability, and efficacy analyses all used a modified intent-to-treat sample comprising all participants who received at least 1 dose of medication.
 - **Results:** Of the 61 randomized participants, 60 participants initiated treatment (45 [75%] male; mean [SD] age, 12.8 [2.7] years). Metformin reduced BMI z scores from baseline to week 16 significantly more than placebo (difference in 16-week change scores vs placebo, -0.10 [95% CI, -0.16 to -0.04]; P = .003). Statistically significant improvements were also noted in secondary body composition measures (raw BMI, -0.95 [95% CI, -1.46 to -0.45] and raw weight, -2.73 [95% CI, -4.04 to -1.43]) but not in metabolic variables. Overall, metformin was well tolerated. Five participants in the metformin group discontinued treatment owing to adverse events (agitation, 4; sedation, 1). Participants receiving metformin vs placebo experienced gastrointestinal adverse events during a significantly higher percentage of treatment days (25.1% vs 6.8%; P = .005).
 - **Conclusions and Relevance:** Metformin may be effective in decreasing weight gain associated with atypical antipsychotic use and is well tolerated by children and adolescents with ASD.
- Mizuno et al, 2014: meta-analysis of placebo-controlled trials of add-on metformin for weight gain; 11 trials, ~700 pts, 2006-2013; helpful
- Jarskog et al, 2013: double blind, RCT in overweight outpatients with schizophrenia or schizoaffective disorder, 16 week study, -6.6 pounds with metformin vs. -2.2 pounds with placebo; also: improved BMI, triglycerides, and hemoglobin A1c; improvements significant by 4 weeks and improving each week through 16 weeks
- Correll et al, 2013 (editorial)
- Hoffman, et al, 2012: more helpful than amantadine at minimizing weight gain from Zyprexa (1.4 pound weight gain with metformin added to Zyprexa vs. 6 pound weight gain with Zyprexa alone)

- Baptista et al, 2007: metformin for Zyprexa-related weight gain—3 pound weight loss and a small decrease in BMI vs. no change with placebo
- Klein et al, 2006: 16 week double blind, placebo-controlled trial in 39 youth initiating atypical antipsychotic therapy whose weight had increased by more than 10% during less than 1 year of treatment: weight stabilized in those on metformin (which, given normal growth in youth, resulted in a relative weight loss) while those on placebo continued to gain ~0.68 pound per week
- Doses studied are often 1000-1500 mg/day, divided 2-3 times-a-day (maximum daily dose 2000 mg), taken with meals to minimize gastrointestinal side effects; in kids, 850 mg two times-a-day is a common dose
- Available in 500 mg, 850 mg, and 1000 mg pills and in 750 mg extended release XR) pills
- Should be used with caution in those with kidney problems, congestive heart failure, liver disease, or excessive alcohol consumption
- Side effects:
 - Diarrhea
 - Stomach upset
 - Risk of lactic acidosis
 - 3 cases of lactic acidosis for every 100,000 patients who take the medication for a year
 - Increased risk in those with kidney problems, congestive heart failure, liver disease, or excessive alcohol consumption
 - If present it is fatal in 50% of cases
 - Can occur in diabetes, unrelated to or in the absence of metformin
 - Defined by elevated blood lactic acid, decreased blood pH, electrolyte disturbances, and increased lactate
- Meridia
- Liraglutide
 - glucagon-like peptide 1 receptor agonist)
 - Effective (Larsen et al, 2017)
- Chromium
- Biotin
- Carnitine