Clozapine Weight Gain/ Glucose Homeostasis

 People with Schizophrenia live 20-25 years shorter than the general population. However research has shown that long term use of clozapine is associated with a lower mortality than treatment with other antipsychotics or no treatment. 60% of this excess mortality is due to physical factors including cigarettes, sedentary life style, poor eating habits, and often large weight gains.

 People with Schizophrenia, like the rest of us, need to be mentally well enough to manage their physical health. Effective treatment reduces not only psychosis but disorganization and avolition and this allows people to make choices regarding their lifestyle options and physical health. We have no magic bullets in effectively treating people with mental illness but diet and exercise come close.

 There have been multiple studies that effectively managing diet improves weight. In my population I constantly reinforce my diet tenets. I keep it simple and I repeat and repeat. My basic tenets are: NEVER DRINK YOUR CALORIES (that means no soda, no juice, and no high glucose/fructose beverage), avoid all simple carbohydrates ( no chips, dips, cookies, candy, cake, ice cream, and limit bread, pasta, and rice). The dos are eat a high diet in complex carbohydrates like vegetables (frozen work), and non- tropical fruit. A garden salad with a light dressing (or no dressing) is an optimal lunch. Lean protein, especially fish, yogurt and non-animal fats like a hand full of nuts should round out the diet. My two beverages of choice are water and coffee. When on clozapine I especially prefer coffee to tea, as coffee is an effective cathartic while most teas tend to have the opposite effect. Coffee also helps with sedation, and tends to decrease appetite. Most studies show that 4 cups a day is an optimal amount. The coffee can be taken black but if a sweetener is required sucralose (helps with constipation) is preferred. Unsweetened almond milk has 1/3 the calories of skim milk and should be encouraged. One last caveat with coffee (yes it is my beverage of choice) is that it does raise clozapine levels via inhibition of P450 1A2 metabolism of clozapine. So, it is important to keep your coffee consumption fairly steady.

 Another oft studied intervention that always seems to work when actively pursued is exercise. I am still waiting to find a negative study. Again active reinforcement, encouragement, and frank cheerleading bring results. I am rather relentless. I have become fit bit buddies with many of my patients and I weigh them at every visit and ask them to weigh themselves at least daily. The best data is for running, but any aerobic exercise and any strength training I encourage.

 I always start with diet and exercise but since I know that clozapine increases gluconeogenesis and insulin resistance even without weight gain I start all of my patients on metformin within the first 2 weeks of therapy. I start with 500 mg and over several weeks increase to 1000 mg twice a day. Metformin effectively decreases glycogen breakdown thereby decreasing glucose production from the liver, improves tissue utilization of glucose and decreases insulin resistance resulting in decreased truncal obesity. With metformin I always have my patients take 1 mg of vitamin B12 daily as metformin causes b12 malabsorption. Concomitant with this, if weight is not controlled or insulin resistance is worsening I add a sodium glucose cotransporter 2 (SGLT-2). Normally people filter 180 grams of sugar daily into their urinary space. Under normal circumstances (no diabetes) less than .1 gram is lost. With one of these agents (Farxiga 10 mg, Invokana 300 mg, or Jardiance25 mg) as much as 40 -60 grams of glucose is excreted daily. This leads to calorie loss, improved glucose control, improved insulin resistance, and decreased truncal adiposity and modest weight loss (2-4 KG). In patients who present with diabetes the effects are even more dramatic. I measure Hemoglobin A1 c every 3 months, and every 2 weeks I measure fructosamines, and insulin levels to assess response.

 In patients that have some dyspepsia and or are still struggling with weight I routinely add high dose (300 mg twice a day) ranitidine. Clozapine is a potent antagonist of histaminergic and cholinergic receptors. The histamine receptor has been shown to be important in feeding behavior and weight regulation. Also impairment of cholinergic signaling increases food intake and results in severe obesity, whereas enhancing cholinergic signaling decreases food consumption. Nicotine is a potent anorexic agent for this reason. In patients that do not smoke (well less than 30 %) I do not start nicotine. However in those that smoke I strongly encourage switching to another nicotine delivery. My patients have used patches and gum, but I have had the most success with vaped nicotine. As this switch is made it has to be done slowly and clozapine levels need to be followed at every visit. The nicotine has no effect on clozapine metabolism, but the withdrawal of the coal tars and smoke will reliably increase clozapine level often dramatically. Acetylcholinesterase inhibitors reliably increase cholinergic signaling. I use only donepezil as it is well tolerated, inexpensive and easy to titrate. I start at 2.5 mg and over several weeks increase to 10 mg in the morning. Donepezil’s other “major side effects” beside its anorexic action is that is slows the heart, increases bowel motility, and increases alertness (with clozapine these are all good things). In certain patients it can be a significant cognitive enhancer.

 Other modalities that I have used include increasing dopaminergic signaling. I have used modafanil starting at 50 mg and increasing to 200 mg. Amantadine starting at 50 mg and slowly increased to 200 mg morning and bed has also been useful. Finally Bupropion starting at 75 mg and titrating up carefully to 300 mg can diminish appetite. A big caveat with all of these approaches is, though they can help with weight gain, and help cognition, much caution must be used as psychosis can be worsened.

 The last modality that I routinely use is topiramate. There are multiple studies with clozapine that demonstrate that this anti-epileptic medicine cannot only help a subset of patients with controlling their appetite but is an effective prophylaxis for seizures, and may diminish anxiety and agitation. Unfortunately in another subset it may be overly sedating. I routinely start at 25 mg at bed and will increase the dose to as high as 200 mg at night or depending on circumstance 100 mg in the morning and at bed.

 There are no easy answers with the optimal management of Schizophrenia or its associated spectrum disorders. However clozapine is the best agent we have. There is no reputable study in any setting where it has been shown to be inferior. However to optimize its use it’s predictable side effects needs to be ameliorated. I have been using these approaches for the last 5 years in my practice. In the 31 patients with over 6 months of continual data weight gain has not been problematic. In fact, in the 31 patients 17 have lost over 5 kgs, 9 patients weights were without change, and 5 patients have gained over 5 kg.