

Intermittent Fasting as a Novel Treatment Approach for Patients Treated with Atypical Antipsychotics

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Abstract

Meta-analyses often find similarities in tolerance between first and second generation antipsychotics. In terms of major barriers to treatment adherence, the extrapyramidal symptoms associated with the first generation antipsychotics have been replaced by the devastating association of weight gain and metabolic syndrome. Dietary and exercise prescriptions are currently being recommended for patients beginning treatment with atypical antipsychotics, although the details of this intervention are often left unclear. Intermittent fasting through time-restricted feeding windows is a practical lifestyle modification that has been shown to increase insulin sensitivity, prevent obesity and decrease risk of type II diabetes, thus making it a useful tool in the prevention of common metabolic issues surrounding atypical antipsychotics. In this review, we have combined the findings from the CATIE and CUtLASS trials with recent research on intermittent fasting and submit that the effectiveness of atypical antipsychotics may be enhanced via reductions in metabolic abnormalities associated with their usage. Our aim is to highlight intermittent fasting as a supplemental protocol to combat the metabolic consequences most prevalent with antipsychotics and to outline a prescription of how to utilize intermittent fasting in this patient population.

Keywords: Fasting; Antipsychotics

Since the 1950's, many individuals suffering from major psychotic illness have been able to substantially reduce their symptom burden with antipsychotic medications. The past few decades has experienced a transition away from first generation dopamine D2 receptor agonists [1] towards second generation antipsychotic medication (SGA) serotonin 5HT_{2A} antagonists [2], referred to as "atypical" antipsychotics, examples being Clozapine and Olanzapine. These atypical antipsychotics are different in mechanism and unlike first generation antipsychotics (FGA), they are less likely to cause parkinsonian symptoms [1] and have an increased efficacy in treating negative symptoms [3]. They do, however, exacerbate the magnitude of adverse weight gain associated with antipsychotics [4,5]. This leaves patients and their families battling a decision between significant weight gain with atypical antipsychotics and the parkinsonian symptoms associated with first generation prescriptions, with studies showing equivalent tolerability between both classes [6]. This purpose of this review is to propose non-pharmaceutical alternatives for the prevention of weight gain associated with the prescription of anti-psychotics, in particular the second generation atypical antipsychotics Clozapine and Olanzapine.

Despite adverse side effects associated with FGAs, namely extrapyramidal side effects, and SGAs, that is weight gain and glucose metabolism abnormalities [4], their efficacy relative to no treatment is significant and consistent throughout the literature [7]. It is not so simple as to reduce the group of antipsychotics into first and second generation, as many properties differ between the drugs within each class [8]. Due to similarities in mechanism, many of the side effects are common with varying magnitudes of severity. It appears that the SGAs, amisulpride, clozapine, olanzapine and risperidone demonstrate improvements in overall, positive and negative symptoms [4,9] relative to FGAs. Despite a favorable safety profile [10], it is shown that SGAs, particularly olanzapine and clozapine, are also associated with the most significant weight gain. This negatively impacts adherence rates despite their relative enhancements in overall symptom reduction.

Weight gain is arguably the largest disruptor regarding quality of life associated with atypical antipsychotics. In my clinical experience, by far the most common reason that people cite discontinuation of treatment

with antipsychotics is fear of weight gain. The current prevalence of obesity has desensitized the general public to the detrimental effects of that being overweight can have on an individual's mental and physical wellbeing. Anyone diagnosed with metabolic syndrome experiences negative impacts with regards to longevity and quality of life, although the slow progress makes it relatively tolerable. Patients prescribed antipsychotic medications do not have the luxury of time to dilute the impacts of their prescriptions and the literature consistently suggests rapid weight gain to be associated with antipsychotic medications. Over time, it can be expected that this weight gain may result in a patient discontinuing treatment, leading to a risk of psychiatric relapse [11].

Researchers from a recent Consensus Developmental Conference on Antipsychotic Drugs and Obesity and Diabetes stated, "Weight gain occurs when more energy is ingested than is expended. Therefore, weight gain is due to increased energy intake, decreased energy expenditure, or both" [12]. The law of thermodynamics or a calories-in-calories-out premise for weight gain is over-simplified and unhelpful. There is a common trend among dieters that is highlighted by Dr. Jason Fung's recent book, *The Obesity Code*; "By six to twelve months, weight loss plateaus, followed by a relentless regain, despite continued compliance" [13]. As illustrated by Redman et al. [14], following a diet for 6 months induces a reduction in basal metabolic and decreased physical activity to compensate for reduced consumption [14]. There has been enough light shed on the erroneous premise that is, assuming the conventional medical wisdom has remained unchanged since 2004, influencing treatment decisions. In any case, the insulin resistance in

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patients prescribed antipsychotics is induced by the medication and not a function of suboptimal lifestyle choices. Lifestyle modifications, particularly intermittent fasting through time-restricted feeding windows, may serve as a prescription to prevent metabolic diseases with pharmacologically induced insulin resistance.

This issue is of particular importance considering the experimental nature of antipsychotics in general. "In the management of schizophrenia it is evident that there is no perfect antipsychotic, and the pragmatic goal is to find a medication that works well enough, is tolerated well enough, and that the patient is willing to take" [2]. The effectiveness and tolerability of antipsychotics is best explored through two large, publicly funded studies, acronymed CUtLASS in the UK and CATIE in the US.

In evaluating the efficacy of antipsychotic medications, The US Clinical Antipsychotics Trials and Intervention Effectiveness (CATIE) studies and The UK Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) were evaluated. Both the CATIE and CUtLASS studies were publicly funded by government agencies of their respective countries. The CATIE trials followed patients for as long as 18 months, whereas the CUtLASS study followed patients over the course of 12 to 52 weeks. Both studies were randomized control trials, with the major distinction being that CATIE was double-blind and patients were randomly assigned Olanzapine, Perphenazine, Quetiapine, Risperidone or the late addition, Ziprasidone. Alternatively, CUtLASS patients were randomly assigned into two groups, FGA and SGA, and the particular antipsychotic prescribed to patients within either group was up to the discretion of their psychiatrist. The CUtLASS study underwent blind assessments at different time intervals and there were prescription changes throughout the study. Further details of both of these study have been extensively explained elsewhere [15]. Together, these two studies lay a foundation for the view that both FGAs and SGAs are effective, although the problems surrounding them are consistent and alternative lifestyle modifications may be worthwhile to explore.

A 2005 study in the NEJM reviewing the phase 1 results in the CATIE study demonstrated Clozapine to be a particularly effective alternative to typical antipsychotics [4]. "The newer agents appear to be more efficacious than conventional drugs in reducing negative symptoms (eg, lack of emotion, interest, and expression)". Furthermore, chronic schizophrenics often discontinue treatment as a result of intolerable side effects and as such, rate of treatment discontinuation has become a common benchmark for drug effectiveness. The lowest rate of discontinuation in the CATIE study was shown to be in patients prescribed the SGA Olanzapine. Unfortunately, Olanzapine was also shown to be associated with the greatest increase in weight gain and a significantly negative influence on glucose/lipid metabolism, a common trade-off found within the literature. Individuals gained an average of 9.4lbs over the course of their treatment and 30% of participants gained > 7% of their bodyweight. "There were no significant differences among the drugs (other than Olanzapine) in the time until discontinuation or treatment owing to intolerable side effects. However, olanzapine was associated with greater weight gain and increases in glycosylated hemoglobin, cholesterol, and triglycerides, changes that may have serious implications with respect to medical comorbidity such as the development in metabolic syndrome." Assuming a reduction or elimination of psychotic episodes is the priority, it would seem that atypical antipsychotics will continue to be the most common prescription, explaining their 90% market share in 2005 [4].

The CUtLASS study published in 2006 built on the finding of the previously published CATIE study. Jones et al. (2006) challenged

the notion that SGAs (other than Clozapine) are associated with an increased quality of life in comparison with FGAs via a reduction in negative symptoms. The CUtLASS researcher's hypothesized atypical antipsychotics would be associated with a clinically significant improvement in quality of life over the course of the study, and that the improvements in newer antipsychotics are a result of fewer adverse symptoms and improved patient satisfaction. In concluding their findings, Quality of Life scores suggested that the FGAs tended to outperform the SGAs, although a probability value of 0.31 and 0.24 at the 12 and 52 week assessments, respectively, does not indicate statistically significance. "We emphasize that we do not present a null result; (although) the hypothesis that SGAs are superior was clearly rejected" [16].

A 2008 review [15] of the US CATIE trials and the UK CUtLASS study shed light on the lack of efficacy enhancements that have come to be expected with atypical antipsychotics. As concluded in the CATIE study, "Patients with chronic schizophrenia in this study discontinued their antipsychotic study medications at a high rate, indicating substantial limitations in the effectiveness of the drugs." Notable exceptions were found with Olanzapine and Clozapine. As previously mentioned from the CATIE study, Olanzapine had the lowest discontinuation rate. The CUtLASS study controlled for Olanzapine by removing it entirely and in doing so found little significance between typical and atypical antipsychotics. It is also interesting to note that patients that were switched from a SGA to the Perphenazine, an FGA did no better or worse than patients that went from an SGA to another SGA. The general consensus seems to be that there is no antipsychotic drug that is suitable for all patients [16] and each medication faces its own set of trade-offs. Regarding Clozapine, patients in both trials that were unresponsive to treatment responded well and preferred Clozapine, time and again suggesting that Clozapine "is the only antipsychotic medication that has proven effectiveness in treatment-resistant schizophrenia (TRS)" [16].

In a more recent Multiple-Treatments Meta-Analysis comparing 15 antipsychotic drugs [7] used in the treatment of schizophrenia, Leucht et al. [7] similarly found all anti-psychotics made statistical improvements in comparison to placebo, although their research suggested the most efficacious treatments to be among the second generation antipsychotics. The hierarchy begins with Clozapine, Amisulprine, Olanzapine and Risperidone. In an effort to minimize the cohort effect's influence on efficacy metrics, publication year was controlled without a significant alteration to the efficacy hierarchy. Using all-cause discontinuation as a measurement of treatment acceptability, as was done with the CATIE trials, it was shown more patients withdraw because of inefficacy (40%) than due to intolerability of side effects (17%). Evidence suggests that patients prioritize efficacy over tolerability, indicating the positive impact of antipsychotic medications may be exaggerated due to underreported tolerability and therefore, effectiveness. As effectively summarized in the CUtLASS study, "a range of adverse effects of FGAs and SGAs are emerging. Serious weight gain, diabetes mellitus, and hyperlipidemia may all adversely affect quality of life" [17].

With no effective alternatives currently available, are there lifestyle modifications that diminish the adverse effects of antipsychotic medications? The aim of this review is to bring forth intermittent fasting as a supplemental protocol to combat the metabolic consequences most prevalent with antipsychotics, particularly Olanzapine and Clozapine, which have demonstrated the most promise with patients suffering from psychosis and treatment resistant patients [4,17], respectively.

In an effort to achieve long-term stability, changing the treatment

protocol associated with various types of psychosis may be a correct step. Dietary and exercise prescriptions are currently being recommended for patients beginning treatment with atypical antipsychotics, although the particulars of this intervention are often left unclear. Diet and exercise may mean ten different things to ten different people, and as such it is pertinent to explore which lifestyle intervention is appropriate. Given the prevalence of metabolic syndrome, particularly insulin resistance, weight gain and Type II Diabetes [17], intermittent fasting appears to be a promising weight gain prevention protocol for those prescribed atypical antipsychotics. Rather than modifying current pharmacological treatment strategies, it may be worthwhile to explore how to use the current drugs as responsibly as possible to maximize their relative effectiveness via a decrease in side effects associated with antipsychotic medications. This is pertinent considering it has been shown that lifestyle modifications are possible with people experiencing severe mental illness [11]. To prevent the weight gain associated with antipsychotic medications, intermittent fasting through the use of circadian based feeding/fasting windows may be useful in reducing the consequences and severity of insulin resistance [9].

Fasting has been utilized for many centuries and in various forms for fitness, performance, longevity and religious reasons. Intermittent fasting in particular has expanded from periodic fasting for periods longer than 24 hours to more innovative fasting structures such as alternate day fasting, modified fasting regimens and time-restricted feeding windows [18]. For the purposes of our research, we have omitted all religious fasting. Religious fasting techniques are sub-optimal given our goals of long-term sustainability and maximizing wellness. Most religious fasts are too short in duration, and the longer fasts have their own host of issues. For example, fasting during Ramadan requires a 12-22 hour total fast for 29-30 days, depending on your proximity to the Northern hemisphere [19]. The fast for Ramadan is broken each day with decadent, often high-carbohydrate containing meals known as “iftar” [19]. The excessive, carbohydrate intensive indulgence during religious feasts is not appropriate considering the focus of this paper and the referenced literature moving forward will therefore be restricted to alternate day fasting and time-restricted feeding windows.

Intermittent fasting in a therapeutic context involves a period of caloric abstinence. Periods typically range from 12 hours to 3 weeks [20], dependent on the objective and amount of stored adipose tissue. A fasting review by Patterson et al. suggests intermittent fasting is “hypothesized to influence metabolic regulation via effects on circadian biology, the gastrointestinal microbiota, and modifiable lifestyle behaviors” [18]. Absent changes in total caloric intake, intermittent fasting has been consistently shown to improve health and function [21] in both animal and human models. The most notable health outcomes include obesity prevention, decreased risk of type 2 diabetes and decreased prevalence of cancer and cardiovascular disease [18,20]. In animal studies conducted by Chaix et al. [22] it was shown that 8-hour feeding windows protected mice against obesity when faced with diverse nutritional challenges ranging from fructose, fat and sucrose based diets. After a transitional period, mice consumed the same amount of total calories with remarkably less weight gain compared to control for all nutritional regimens [22].

From an evolutionary perspective, Mattson et al. makes a compelling argument in favor of circadian eating habits to optimize metabolic health and wellness [9]. Agrarian and industrial culture has extended the feeding window from a historical 6-12 hours to the modern norm of 14-18 hours, lending a possible explanation to the association between disturbed circadian rhythms and decreased metabolic health.

Into the late 1970’s, there had been a fairly large body of fasting literature forming, led by a group at Harvard which looked into various fasting protocols with different populations. Bistrian et al. [23] used a “protein-sparing modified fast” on a small group of adolescents with Prader-Willi obesity and found weight loss occurred rapidly and persisted for observation periods of 26-44 months. Outpatient diet adherence is seldom maintained by mentally deficient patients, although in this case it was [23]. In the small sample, hunger was effectively controlled by a protein-sparing fast.

Both hypocaloric protein-biased modified fasts [23,24] or fat-biased/ketogenic diets induce fat-dependent ketogenic states to varying degrees, protein consumption being a milder state of ketosis than fat consumption. Either nutrition plan is effective in the reduction of adipose tissue, the maintenance of muscle tissue, the increased insulin sensitivity and the long-term sustainability, particularly in comparison to caloric restriction in general. The benefits of either regimen are similar and for our purposes may be boiled down to the result of carbohydrate restriction, albeit not elimination.

The nutrition prescription for the maintenance of an optimal body composition while pharmacologically inducing insulin resistance is illustrated in Figure 1. The typical individual will consume three substantial meals, with snacks spread throughout the day (A). This leads to elevated insulin levels throughout the day, increasing adipose tissue and exacerbating insulin resistance (Fung, Taubes). Alternatively, creating a 6-8 hour feeding window or a 16-18 hour feeding window will allow some benefits of the fast without the discomfort which generally accompanies short term fasting. Reducing meal frequency may or may not influence total caloric consumption, but it will reduce insulin levels and promote optimal metabolic processes. Intermittent fasting through time-restricted feeding windows have been shown to increase insulin sensitivity [20,21], which makes it a useful tool in preventing weight gain for those prescribed antipsychotics.

Intermittent fasting in combination with a reduced carbohydrate consumption increases the feasibility of adherence as there is significantly less complication due to a decrease in total meals. We believe that this approach to nutrition is one that can be adopted in individuals receiving treatment with antipsychotic medications to help combat the aforementioned metabolic side effects with this widely used medication type.

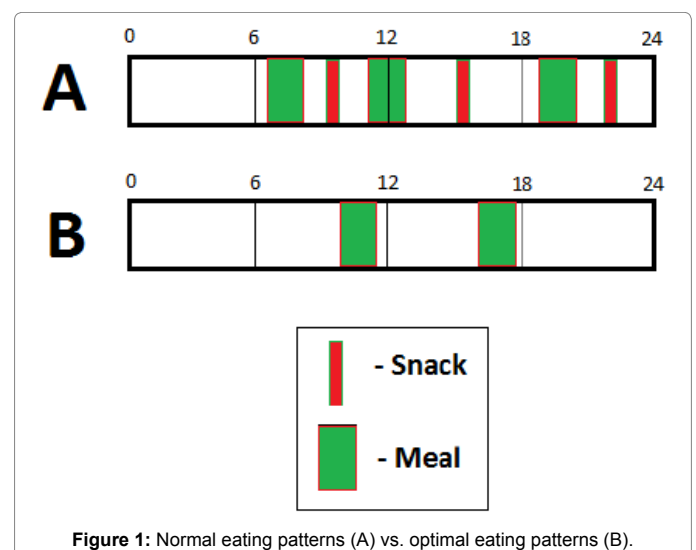


Figure 1: Normal eating patterns (A) vs. optimal eating patterns (B).

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