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Effects of atypical antipsychotic use and stress on weight in individuals at clinical high-risk for psychosis

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Abstract

Extant literature suggests that individuals with serious mental illness are at increased risk for overweight and obesity (Robson & Gray, 2007), and the introduction of pharmacological interventions, particularly atypical antipsychotics, puts this population at greater risk for increased adiposity and metabolic issues (Green et al., 2000). Research also indicates that those who suffer from severe mental illness experience greater stress (Trotman et al., 2014). Given that stress is also related to overweight and obesity (Adam & Epel, 2007), exploration of the relationship between atypical antipsychotic medication, stress, and weight is warranted. This study was a cross-sectional investigation of atypical antipsychotic use and stress in predicting weight in a sample of youth at clinical high risk for developing psychosis. Participant data was obtained as a part of the North American Prodrome Longitudinal Study Phase 2 (NAPLS-2). Self-reported weight, atypical antipsychotic use, daily stress (hassles) in the past 24 hours, and life events stress within the last year were assessed in clinical high-risk participants who were on and off atypical antipsychotics at an initial assessment as a part of the longitudinal study. Individuals taking atypical antipsychotic medications weighed more than those not taking these medications, and several measures of stressful events (dependent life events, desirable life events, and undesirable life events stress) were correlated with weight. Gender did not moderate the effect of atypical antipsychotic use on weight but dependent events and desirable life events stress moderated the relationship between atypical antipsychotic use and weight. Post hoc analyses revealed that there was a significant relationship between atypical antipsychotic use and negative and general symptoms. Findings suggest that a better understanding of the contribution of stress to weight gain in this population may be worthwhile to consider in developing

interventions to address psychosocial factors that may exacerbate or buffer the effects of antipsychotic medication on weight gain.

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Weight and metabolic issues are nationwide health concerns (Wang & Baydoun, 2007; O'Neill & O'Driscoll, 2015), and are of increasing concern in those with severe mental illness (Allison et al., 2009; Scott, McGee, Wells, & Browne, 2008; DeHert et al., 2009). Evidence suggests that those with severe mental illness are predisposed to weight and metabolic issues even before being prescribed atypical antipsychotic medications. Studies have shown that drug-naïve patients who are classified as being severely mentally ill are more likely to be overweight (Ryan et al., 2004; Maina, Salvi, Vitaluci, D'Ambrosio, & Bogetto, 2008; Cadenhead et al., 2014), and that illness severity may interact with lack of access to medical care to contribute to increased health risk before formal pharmacological treatment is introduced (Ucok & Gaebel, 2008).

Atypical Antipsychotic Weight Gain and Decreased Compliance

One factor that is largely thought to contribute to increased rates of obesity and metabolic issues in those with severe mental illness is the wide prescription of atypical antipsychotics for individuals with psychosis, as well as for other broadly-defined severely dysregulated behaviors (Ucok & Gaebel, 2008). The development of weight and metabolic issues when taking atypical antipsychotics is well documented in the literature, and the longer one is taking the medication, the more weight gain to be expected (Bak et al., 2014). As a result of the weight gain that people experience while taking these medications, metabolic issues develop (Newcomer, 2005). The average amount of weight gained while taking atypical antipsychotics varies by type (Bak et al., 2014; Allison et al., 1999; Maayan et al., 2011); however, switching type of medication has not been found to be helpful with the increase in weight (Bak et al., 2014).

The weight gain related to the use of atypical antipsychotics might lead to decreased medication compliance. Research has shown that there is a significant relationship between

distress from weight gain and medication non-compliance (Weiden, Mackell, & McDonnell, 2004; Valenstein et al, 2004; Cooper & Moison, 2007). Further, rates of non-compliance are worse for those taking atypical antipsychotic medication compared to other psychotropics and medications for physical ailments (Cramer & Roshenheck, 1998). Further, research suggests that antipsychotic medication non-compliance is linked to greater instances of hospitalization in schizophrenia patients. Research has shown that costs related to these hospitalizations ranged from 1392 to 1826 million dollars in 2005 (Sun, Liu, Christiansen, & Fu, 2007). The adverse outcomes of medication non-compliance for the severely mentally ill makes the task of mitigating antipsychotic weight gain urgent.

Mechanisms behind weight gain on atypical antipsychotics

There are multiple mechanisms that may be related to the increase in BMI in those taking atypical antipsychotics (Nasrallah, 2003). The hypothesis with the strongest research support pertains to analog interactions with histamine binding sites on neurons in the hypothalamus (Kroeze et al, 2003; Matsui-Sakata, Ohtani, Sawada, 2005); leptin, a hormone responsible for inhibiting hunger, and thereby increasing satiety, acts in this area. This histamine receptor blockage effects feeding by reducing leptin response, thereby increasing hunger and decreasing satiety cues (Melkersson, Hulting, & Brismar, 2000; Kraus et al., 1999; Masaki et al., 2004). These neural interactions ultimately increase eating behavior for those on the medication. A Kroeze (2003) study found that 15 of the 17 atypical antipsychotic drugs tested that were known to be responsible for weight gain interact with histamine receptors (Kroeze et al., 2003).

The potential role of stress in atypical antipsychotic weight gain

Stress is linked to weight due to biological and behavioral factors (Wilson & Sato, 2014; van Jaarsveld et al., 2009). It is important to consider the increased vulnerability to these biological

and behavioral processes in those with severe mental illness—as the role of the stress experience for those taking atypical antipsychotic medications may be connected to weight gain directly by way of altering neural avenues, as well as through overeating.

Stress is linked to increased weight by way of sympathetic nervous system reactions and the release of cortisol from the adrenal glands when there is increased "threat." Cortisol is a glucocorticoid, and increases blood sugar. One hypothesis of how stress is related to weight is that there are increased fat deposits around the abdomen since there are increased glucocorticoid receptors in that area of the body (Yau & Potenza, 2013). Studies have shown that intra-abdominal fat is most related to stress, and is the type of fat that is most related to metabolic issues (Björntorp, 2001).

Glucocorticoids also inhibit action for hormones related to hunger and satiety such as insulin and leptin. This causes desensitization to these hormones, altering eating behavior and homeostatic mechanisms that are meant to control weight. Glucocorticoid release stimulated by cortisol also increases neuropeptide Y (NPY). NPY is a hormone with anxiolytic properties, making it a potential facilitator of "stress eating," or "emotional eating" (Adam & Epel, 2007).

These biological processes can also contribute to the development of a behavioral response of increased eating behavior by way of interactions with the reward system. Specifically, increased glucocorticoids encourage increased cravings for highly palatable foods that engage the reward system in the brain via endogenous opioids, which may reduce the stress response by increasing dopamine. These endogenous opioids work to counteract the body's propensity towards chronic stress. Overtime, these reward centers may become desensitized making one feel as if they need more highly palatable foods in order to be satisfied (Adam & Epel, 2007; Yau & Potenza, 2013; Berridge, 2009). There are thought to be significant gender differences in these

biological and behavioral mechanisms that may lead to increased weight (Epel, Lapidus, McEwen, & Brownell, 2001).

Higher cortisol release is related to "threat stress." Research shows that how one is perceived socially is highly related to "threat stress" (Dickerson, Gruenewald, & Kemeny, 2004). Therefore, stress is an even more important variable to analyze in the severely mentally ill as we know that they are more likely to be affected by stigma and discrimination related to their illness (Schulze & Angermeyer, 2003).

Existing Interventions

Considering the serious consequences of atypical antipsychotic use, as well as how these consequences affect treatment compliance, it is vital that interventions are developed so that patients are better able to anticipate and control impending weight gain and its adverse side effects.

Pharmacological interventions have been widely used in children and adults to counter the negative effects of atypical antipsychotics. Metformin is a drug that suppresses excess glucose production, thereby helping improve indicators of type 2 diabetes, and is a widely used pharmacological agent to counter the negative metabolic effects brought on by atypical antipsychotics (Mizuno et al., 2014). However, research suggests that the weight loss is not always sufficient compared to weight gained, and note the importance of behavioral treatments in addition to pharmacological ones (Correll, Sikich, Reeves, & Riddle, 2013).

There is support for modest effects of multi-prong behavioral interventions in the reduction of weight gain for individuals taking atypical antipsychotics (Alvarez-Jimenez et al., 2010; Caemmerer et al., 2012; Khazaal et al., 2007). There is also empirical support for interventions that are more narrowly focused on caloric reduction and physical activity (Mauri et

al., 2006; Green et al., 2015). Bariatric surgery has even been discussed as a potential treatment option. Although understudied, the procedure may have the potential to be a worthwhile last resort for those experiencing more serious health concerns related to obesity and metabolic issues (Das, Mendez, Jagasia, & Labbate, 2012).

The research literature does not provide much by way of interventions that specifically target stress as a way to mitigate weight gain stemming from antipsychotic use. Programs have focused on broader, more traditional components of weight loss. Although components of stress management may be a part of these broader programs (i.e. cognitive-behavior therapy, comprehensive psychoeducation surrounding weight gain and obesity), stress management does not appear to be a major aspect of these interventions. Given the high levels of stress typically experienced by those being prescribed atypical antipsychotics, a greater focus on stress-management techniques may enhance effectiveness of weight reduction interventions for that population.

Present Study

Existing literature that focuses on how to assuage weight gain associated with atypical antipsychotic use has called for research to identify variables other than atypical antipsychotic medication that may contribute to the weight gain (Martinez-Ortega et al., 2013; Werneke, Taylor, & Sanders, 2013). Given the role of stress in weight gain in non-clinical populations (Adam & Epel, 2007; Yau & Potenza, 2013), and the fact that atypical antipsychotics are associated with weight gain (Nasrallah, 2003), it is plausible that stress could moderate the relationship between atypical antipsychotic use and weight gain.

The purpose of this study is to perform a cross-sectional investigation of atypical antipsychotic use and stress in predicting weight in a sample of youth at clinical high risk for developing psychosis. Stress will be examined as a potential moderator. It is predicted that:

1) It is predicted that gender will moderate the relationship between atypical antipsychotic use and weight.
2) It is predicted that both atypical antipsychotic use and self-reports of stress experienced will be related to weight.
3) It is predicted that stress subscales will moderate the relationship between atypical antipsychotic use and weight.

Methods

Sample

All participant data used was a part of the North American Prodrome Longitudinal Study Phase 2 (NAPLS-2), a multi-site longitudinal study that aims to assess and predict full psychosis conversion. The Structured Interview for Prodromal Syndromes (SIPS) was used to determine clinical high-risk status. Individuals were not eligible to participate in the study if they had an Axis I psychotic disorder, an IQ below 70, history of a central nervous system disorder, or a substance use disorder (Addington et al., 2012).

Assessment Procedures

Per part of a larger protocol (Addington et al., 2012), each NAPLs site provided data for this study from information collected from each participant at that site. The study involved assessment only—study personnel did not prescribe medication.

Measures

Medication data was coded by specific medication type. As outlined in Cadenhead and colleagues (2010), some participants were also receiving other types of psychological treatment while enrolled in the study. Medication dosage data was also collected. The mean dose for those on atypical antipsychotic medication was 12951 (3824) CPZ equivalents (Woods, 2003). Since medication dosage information was not available for all participants, for data analyses, a dichotomous variable for those "on/off" of antipsychotic medications was used.

Weight (in pounds) data was collected via participant report.

A standard index of stress was used, the Life Events Scale (LES), which is a 59-item measure that indicates the frequency and severity of life events considered stressful within the past year (Dohrenwend et al., 1978). Participants note whether or not each event occurred and rated how stressful the item was on a scale from 1 to 7. The scale allows for the separate examining of life events that are hypothesized to have been to some extent dependent on the participant's illness as compared to life events not expected to be due to the illness. Example items classified as dependent on the subject's illness included: "lost a job," and "failed at school or a training program" while nondependent stressors include: "family member died," and "parents separated/divorced." Subscales also assessed life events that were desirable or undesirable. Desirable life events included items such as "Lived away from home," and "became involved in a romantic relationship." Undesirable life events included, "had problems in school or in a training program," and "had a serious family argument" (Dohrenwen et al., 1978).

The Daily Stress Inventory (DSI) (Brantley et al., 1987), a 58-item measure of daily hassles occurring within the past 24 hours was also analyzed even though events in the past 24 hours would not themselves be affecting an individual's weight; this score was considered to serve as the only indication available of the typical level of daily hassles experiences by the

individual. Prior research suggests chronically high daily stress may function differently than the frequency (or intensity) of larger "life events" generally considered to be stressful (Sapolsky, 2004). Examples of items include: "Was criticized or verbally attacked," and "Was ignored by others."

Statistical Analyses

Statistical analyses were conducted with IBM SPSS Statistics 21 (SPSS Inc., Chicago, Illinois). Frequency analyses were used to determine the demographic composition of the sample. A regression analysis was used to examine the moderating effect of gender in the total sample of clinical high-risk participants. Bivariate correlations were used to assess the relation between stress subscales and weight gain. Analyses of covariance were used to analyze weight differences for those on and off atypical antipsychotics. Regression analyses were used to assess the moderating role of stress variable subscales in predicting weight for those taking atypical antipsychotics. All variables used for moderation analyses were logtransformed for normality. All regression analyses results are presented as one-tailed given the directional nature of hypotheses. Given literature suggesting that symptom severity is also related to increased weight in those with severe mental illness (Ryan et al., 2004; Maina et al., 2008; Cadenhead et al., 2014), post hoc correlation analyses were used to report the relationship between symptom severity and weight. Independent sample t-tests were used to assess the relationship between atypical antipsychotic use and symptom severity.

Results

Demographics

Individuals in this study were at clinical high risk for developing psychosis (CHR) and taking an atypical antipsychotic (AT). Of those with weight data, there were 90 individuals

classified as CHR who were on ATs, and 444 individuals who were not on ATs. The age range of participants was 12-35, with a mean age of 17.56 (3.84) for the CHR group on medications, and 18.69 (4.29) for the CHR group not on medications. Complete demographic information as well as average weights by gender are presented at Table 1.

Preliminary Analyses

Preliminary correlation analyses revealed that there was a significant correlation between dependent life events and weight, $r = .097$, $p = .029$. A preliminary regression analysis was performed to assess whether gender moderated the relationship between differences in weight on/off atypical antipsychotic medications, $F\ (1,\ 4) = 35.83$, $p = .20$. Since gender was not a significant predictor of the relationship between atypical antipsychotic use and weight, all subsequent analyses were done on the total sample of those taking atypical antipsychotics (i.e. males and females together).

Correlation Analyses

For those taking atypical antipsychotics, there was a significant correlation between weight and dependent life events, $r = .257$, $p = .019$, desirable life events, $r = .247$, $p = .020$, and undesirable life events, $r = .230$, $p = .034$.

Analysis of Covariance

There was a significant weight difference for those on/off atypical antipsychotic medications $F\ (1,\ 1) = 4.55$, $p = .03$, *partial* ŋ2 = .009, power = .56 (Figure 1).

Moderation Analyses

There was an interaction between atypical antipsychotic use and life events dependent on illness in predicting weight, $F\ (1,\ 4) = 14.94$, $p = .02$, and between atypical antipsychotic use and desirable life events in predicting weight, $F\ (1,\ 4) = 15.65$, $p = .01$ (Figures 2 and 3).

There were no significant interactions between atypical antipsychotic use and independent life events, F (1, 4) = 12.54, p = .42, undesirable life events, F (1, 4) = 14.54, p = .09, and daily stress, F (1, 4) = 15.08, p = .39.

Post-hoc analyses

Post hoc analyses revealed that there were no significant correlations between weight and disorganized, general, positive, and negative symptoms (n = 24). On average, participants on atypical antipsychotics experienced more negative (M = 14.00, SE = 1.20, r = .16, n = 30) and general (M = 9.60, SE = .691, r = .17, n = 30) symptoms. There was no significant difference for positive or disorganized symptoms (Figure 4).

Discussion

In an effort to determine additional variables that may contribute to increased weight among those taking atypical antipsychotic medications, the present investigation sought to examine the moderating effect of the stress experience in predicting weight for those at clinical high risk for psychosis taking atypical antipsychotic medication. Study results suggest that stress may play a role in the higher weight typically found in this population but the role of stress may differ depending on the type of stressor.

Differences in the relation between stress and weight gain

The relationship between stress and weight differed depending on the type of stress experienced. Desirable life events and life events dependent on one's illness were associated with increased weight gain. It is important to note that the life events labeled as dependent events were stressful situations that were considered likely to be related to having experienced attenuated psychotic symptoms (i.e. "failed school or a training program," and "serious family argument").

The failure to find a gender effect for weight among individuals on antipsychotic medication and a moderation effect for the daily stress measure, was unexpected considering that daily stress is hypothesized to contribute to emotional eating and thus weight gain (Sapolsky, 2004). Female cognitive vulnerability to stress as a theoretical framework also suggests that there would be gender differences in these relationships, with females being more stress sensitive (Hankin & Abramson, 2001). The current study had a fairly large sample of individuals on antipsychotics but two-thirds of the sample was male leaving the sample of females at 27. Samples including larger numbers of females might have greater power to detect gender effects and provide a stronger test of the influence of daily stress on weight among those females. However it is also noted that, atypical antipsychotics reduce HPA axis activity (Walker, Mittal, & Tessner, 2008), thereby making it plausible that participants on medication are experiencing diminished stress and this could be buffering the effects of stress on weight.

Implications for intervention

Our findings suggest that stress-reduction interventions could be important with the initiation of an atypical antipsychotic treatment regimen; as such interventions may aid one in coping with stress in ways that do not involve high calorie (comfort) foods. One would think that interventions such as mindfulness based stress reduction might be considered as they have been used with a diverse range of people with weight and metabolic issues (Barnes et al., 2008; Daubenmier et al., 2011; Rosensweig et al., 2007; Wright et al., 2011), as well as with a plethora of clinical disorders with much success (Allen et al., 2006). However, research suggests that the use of mindfulness based interventions for those with psychosis or those at risk for psychosis may be contraindicated, as the practice may increase symptoms (Shonin et al., 2014; Allen et al., 2006). Therefore, there is room for the development of other interventions for a clinical high-risk

population that focus directly on developing active coping strategies (i.e. problem-solving and assertion training, that could be used to decrease stress). Interventions of this type could also help increase medication compliance if those individuals felt greater self-efficacy in controlling the amount of weight they might gain.

Post-hoc analyses

Post hoc analyses revealed that taking an atypical antipsychotic was related to higher symptom severity. Since prescription of antipsychotics is more likely to occur at higher levels of symptom severity this would be expected. In this study it was not possible to separate the effects of antipsychotics from symptom severity. Antipsychotics are thought to influence weight gain through direct biological influence on appetitive processes in the brain (Kroeze et al., 2003), however, these effects may be confounded with symptom severity which could contribute to weight gain by way of lowered motivation and ability to take part in self-care activities that could prevent weight gain (Ucok & Gaebel, 2008), as well as

In a cross-sectional study, it is difficult to parse out which of these variables (i.e. stress, symptom severity, and atypical antipsychotic use), contributes to more of the variance in predicting weight gain in an at-risk sample and causal relationships cannot be established. Further work, especially longitudinal studies, will be needed to establish the degree to which these variables contribute to a negative cycle in which stress may increase weight as well as psychiatric symptoms, and then symptom severity increases stress, making health self-care (weight control) more difficult, and thereby increasing the likelihood that atypical antipsychotic medication will be prescribed, which is likely to further increase weight.

Strengths and Limitations

This study has notable strengths. The NAPLs project is the largest dataset of those at clinical high risk for psychosis in the world, making this the ideal sample in which to examine the interaction between the use of atypical antipsychotics and the stress experience in predicting weight. However, as noted, the lower number of females may have limited power to detect any gender effects. The analysis of these processes in individuals identified early in potential illness progression strengthens the argument for the potential utility of early intervention to decrease stress as well as weight gain.

This study also had limitations. Height had not been assessed in this sample so BMI could not be calculated in this dataset. BMI is a more useful metric than weight, especially in this age range. Further, weight was self-reported. Another limitation of the study is the use of subjective, self-report indices of stress. Personality (Kobasa, 1979), as well as socialization factors (Adrien & Hammen, 1993), effect how stressful daily hassles and life events are perceived—an analysis of those elements are not included in this study. A final weakness of this study is the large age range of the sample. Although the mean age was in the late teens, there were a few participants in the extreme ranges of the sample, likely contributing to variance and reducing power to detect effects. A smaller age range could reduce this variance.

Directions for Future Research

With these limitations in mind, future studies should attempt to replicate findings using BMI. Restricting samples to a narrower age range may also be useful. Further, greater power to detect potential gender differences is needed. Examining this association in pre-adolescent age groups could be especially informative considering the increasing rates of atypical antipsychotic prescription in children (Almandil &Wong, 2011). Further work needs to be done to understand whether the heightened experience of stress is related to poor response to the various weight

control interventions that already exist for those taking atypical antipsychotic medications and are gaining weight.

Notably, nonwhite race has been associated with greater weight gain with some atypical antipsychotic medications (Basson et al., 2001). Since research suggests that being a member of a minority group is related to heightened stress (Pascoe & Richman, 2009; Williams, Jackson, & Anderson, 1997), and that many minority groups are at heightened risk for obesity and metabolic issues (Smith et al., 2005; Clarke, O'Malley, Johnston, & Schulenberg, 2009), it is important to examine the interaction of stress and atypical antipsychotic use in different racial/ethnic groups to see whether or not certain groups are at amplified risk for weight gain.

Future studies should also analyze the relationship between atypical antipsychotic use, stress, and weight gain over time. Significant subject attrition is typical in longitudinal studies of those with psychiatric issues (Nelson et al., 2013) and the number of participants available at follow-up in the current study was too low to allow for longitudinal analyses.

Conclusion

In conclusion, the present study provided modest support for the hypothesis that increased stress and atypical antipsychotic use interact to promote greater weight gain for those at clinical high risk for psychosis. Symptom severity may also play a role as it is correlated with atypical antipsychotic use. Further research is needed to further elucidate which variables explain more of the variance in the relationship between stress and weight over time.

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Tables and Figures

Table 1.

Demographic information for individuals at CHR on/off atypical antipsychotics (ATs) that have weight data

Variable	ON ATs (n = 90)	OFF ATs (n = 444)
Weight (Mean)	Males = 164.95 (SE = 4.30, n = 63), Females = 147.92 (SE = 7.01, n = 27)	Males = 164.18 (SE = 2.11, n = 261) Females = 138.56 (SE = 2.67, n = 183)
Race/Ethnicity (% White)	67.5	55.4
Age (Mean)	17.56 (3.84)	18.69 (4.29)
Other Medications		
% Antidepressants	56.9 (n = 70)	43.1 (n = 118)
% Mood Stabilizers	12.2 (n = 15)	87.8 (n = 14)
% Stimulants	11.4 (n = 14)	88.6 (n = 43)
% Benzodiazepines	12.2 (n = 15)	87.8 (n = 32)
Income (% <$20,000)	15.4	19.8

Table 2.

Correlations between weight and stress for those taking atypical antipsychotics

	Weight
1. Dependent Life Events	.257*
2. Independent Life Events	.133
3. Desirable Life Events	.247*
4. Undesirable Life Events	.230*
5. Daily Stress	.117

$p < .01$**

$p < .05$*

Note. Dependent Life Events, n = 84. Independent Life Events (n = 86). Desirable Life Events (n = 88). Undesirable Life Events (n = 85). Daily Stress (n = 79).

Figure 1.

Weight for those ON/OFF Atypical Antipsychotics

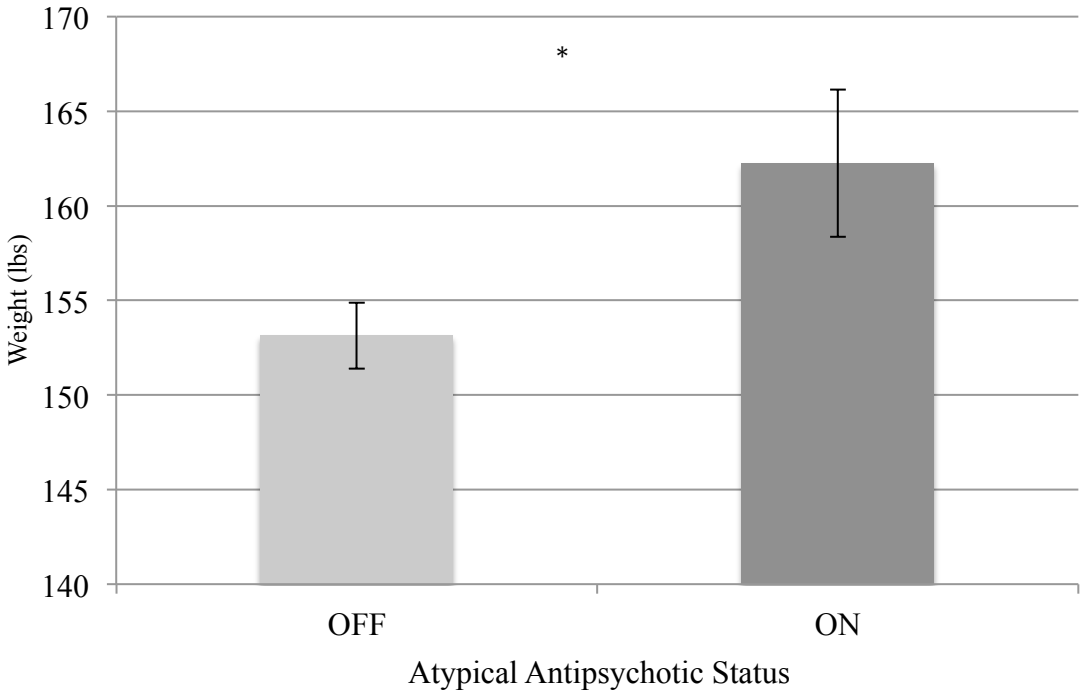

Figure 2. Moderation analysis for dependent life events

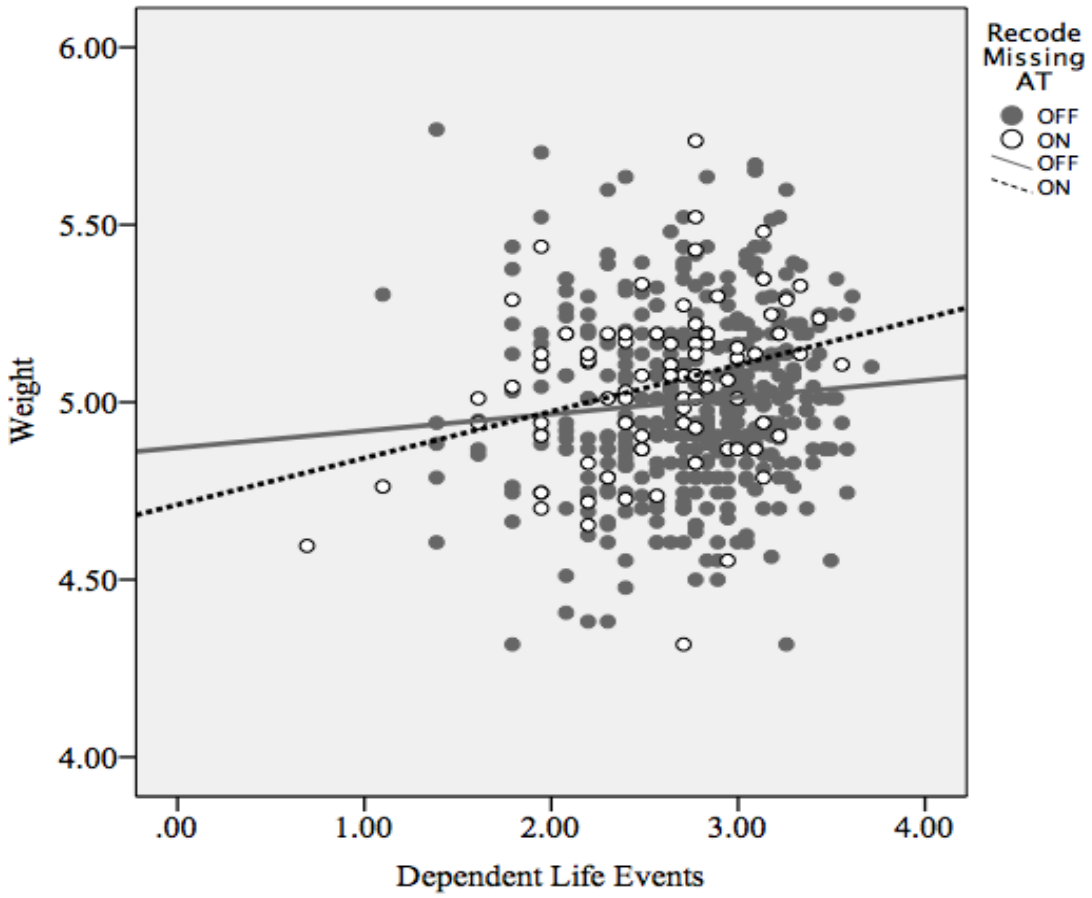

Figure 3. Moderation Analysis for Desirable Life Events

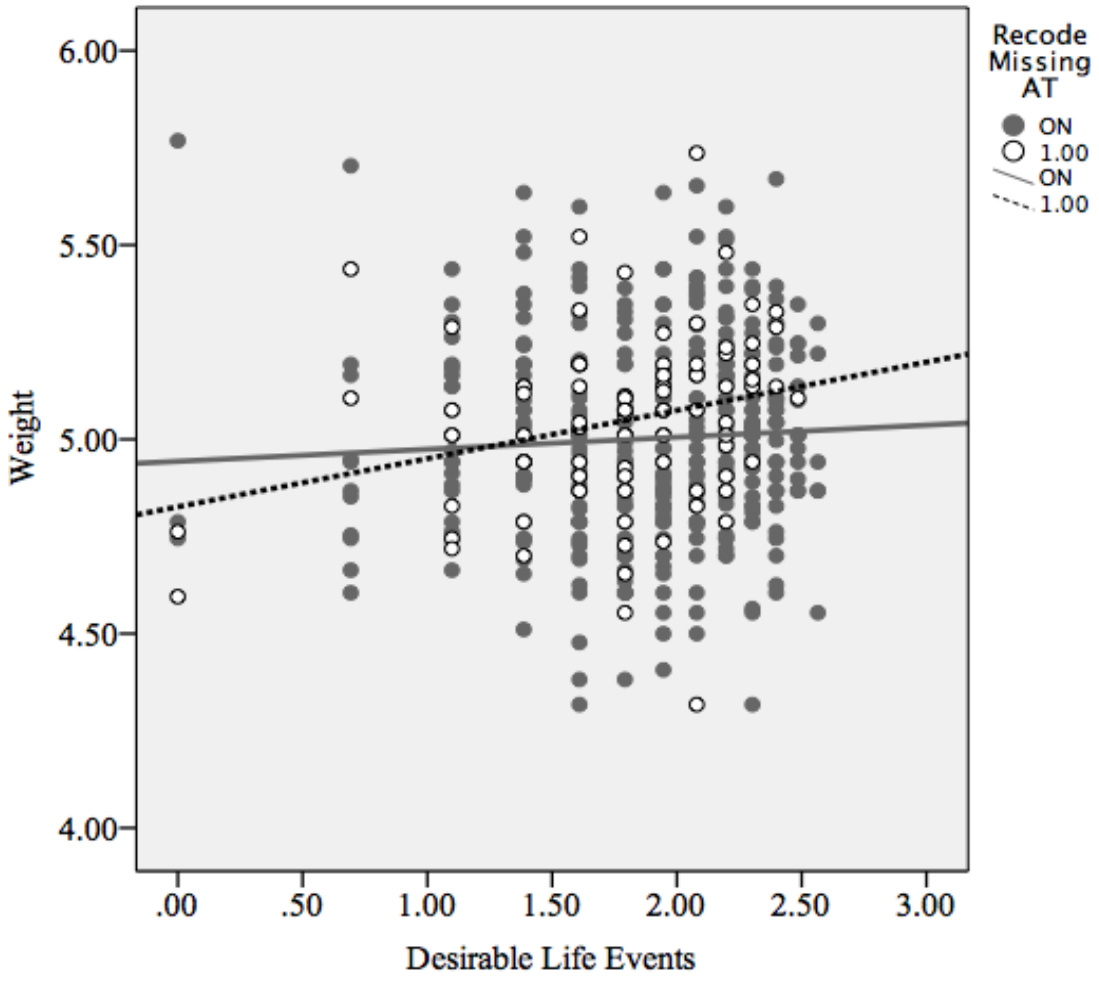

Figure 4.

Relationship between atypical antipsychotic use and symptom severity