Weight Change in Parkinson's Disease patients taking Atypical Antipsychotics

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ABSTRACT

Abstract Background: Weight loss in PD is a chronic process that is observed in both early and late stages of PD. Atypical antipsychotic drugs are associated with marked weight gain.

Objective: To determine body mass index (BMI) change in Parkinson's disease (PD) before and after taking atypical antipsychotic (AA) drugs and compare against PD controls and Alzheimer's disease (AD) patients on AA.

Methods: We included 66 consecutive PD subjects started on AA who had accurate weights for more than 6 months before and after initiation of AA. We compared weight change in these PD subjects before and after AA use, against a control group of sixty-one sex matched PD subjects, and against twenty-eight AD subjects taking AA. A linear regression model was created to compare weight changes.

Results: Fifty-nine PD subjects had complete data, quetiapine (n= 53) and clozapine (n=6). The mean BMI change in the period before starting AA was 0.00 kg/m2/month over 1.95 ±1.41 years. After starting AA, subjects lost 0.03 kg/m2/month (95% CI 0.62-1.21, $P < 0.0001$), comparing PD before AA to the same PD patients after AA. In 61 PD controls, the mean BMI loss was 0.01 kg/m2/month (95% CI 0.15-0.94, $P = 0.007$) comparing PD on AA vs. PD controls. The BMI for 28 AD subjects on AA increased 0.01 kg/m2/month (95% CI 0.26-0.83, $P < 0.0001$), comparing PD on AA vs. AD on AA.

Conclusion: AA did not cause weight gain in our PD population, and was in fact associated with significant weight loss. The different effects in PD and AD suggest uniquely altered weight homeostasis in PD.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder clinically defined by tremor, bradykinesia, rigidity and postural instability.[1] Weight loss in PD is a continuous process which is observed in both early and late stage in PD.[2] This results from reduced fat stores as well as reduced muscle mass.[4] The majority of data suggests that metabolic demands are altered as an intrinsic feature of the disease.[17] Increased energy expenditure has been posited secondary to rigidity and dyskinesia.[5] Numerous other explanations include: depletion of brain monoamines in hypothalamus, which regulates appetite and satiety [3], progressive immobility in advanced stage [4], anosmia which lessens subjective taste and appetite [6,7], dysphagia from oropharyngeal or esophageal dysfunction [8], levodopa effects including lipolytic effects [9], and nausea [2]. Overall weight loss most correlates with the severity of PD. [5, 18] Interestingly, functional surgical intervention at the globus pallidus internus or sub-thalamic nucleus often results in weight gain.[12,20]

Atypical antipsychotic (AA) drugs are best defined by their lower affinity for the D2 receptor. When used for schizophrenia and other psychiatric conditions, they are associated with marked weight gain and new onset diabetes mellitus (DM). [19] This may result in increased cardiovascular morbidity and mortality.[13] These drugs, especially quetiapine[10] and clozapine [11] are commonly used to treat PD associated psychosis. We evaluated the effect of these drugs on body mass index (BMI) when used in Parkinson's disease (PD).

METHODS

Patients were recruited from the Baylor College of Medicine, Parkinson's Disease Center and Movement Disorders Clinic. All patients were diagnosed as PD based on clinical criteria. [1] We included all subjects who used AA drugs for at least 6 months who have accurate same scale weights for least 6 months before and 6 months after initiation of the AA. Criteria for exclusion include secondary parkinsonism, poorly controlled endocrine diseases such as diabetes mellitus, thyroid disease, Cushing disease and polycystic ovarian syndrome; human immunodeficiency viral infection (HIV), malignancies, tuberculosis, gastrointestinal diseases except peptic ulcer or acid reflux diseases. Patients undergoing functional brain surgery for PD within 2 years of initiation of AA, or during the post-AA period were also excluded. We included all subjects prospectively seen in clinic who met the criteria.

At each visit, we recorded patient weight, demographic data, Hoehn & Yahr stage, and all PD medications. The equivalent dose of L-dopa was calculated: (levodopa + extended release levodopa×0.7)×1.1(if COMT inhibitor used)+pergolide(100) + pramipexole (100) + ropinirole(35) + bromocriptine(10).[15] Height was also qerried. Three patients died without height information and body mass index was calculated using the estimated height of 5 foot 5 inches for female and 5 foot 10 inches for male.

55 PD data (N=54 subjects) were enrolled in the study as one subject had two different epochs of AA use (quetiapine and clozapine) separated by more than 2 years. Simple descriptive analyses generated means and standard deviations for PD duration, sex, Hoehn & Yahr scale equivalent doses of L-dopa, dopamine agonists and AA. The average doses of AA were calculated as a function of dose x duration of use with that dose / total duration. A linear regression model was created to compare body mass index change before and after starting AA drugs.

Figure 1: Demographic and clinical characteristic of PD patients

Data	N = 55 (54 patients)		
Sex	male 61% (n= 33)		
At AA starting			
	Mean	Min	Max
Age (years)	71.2±8.8	62.4	80.0
Duration(years)	11.4	1.6	27.0
Hoehn&Yahr	2.8±0.7	1	5

RESULTS

We enrolled 54 PD patients, 33, (61 %) male. The average age when starting AA were 71.2 ± 8.9 years (mean±SD) and the duration from the initial parkinsonian symptom to AA initiation was 11.4 years. The Hoehn & Yahr staging was 2.9 ±0.7. [Figure 1] The PD patients were prescribed either quetiapine (87.2%) or clozapine (12.7%) depending on the severity of psychosis and other clinical factors. The indication for AA was psychosis (96.4%) and insomnia (3.6%). The average dose was 74.4 mg/day for quetiapine and 41.4 mg/day for clozapine.

Using the all weight data from the time of clinic induction (mean 5.1 years) we found that patients lost 0.6 kg/m2/year.(1.8 kg/year) For the 2 years prior to initiation of AA, the mean BMI loss was also 0.6 kg/m2/year (1.8 kg/year). For the 2 years after starting AA was BMI loss was 0.4 kg/m2/year (1.2 kg/year), (NS). [Figure 2] The average equivalent doses of L-dopa for all 55 cases before and after starting AA increased form 585.1 and 818.6 mg/day, while the average doses of dopamine agonists decreased from 2.2 and 1.9 mg/day. [Figure 3] There were no documented cases on new onset diabetes mellitus.

Figure 2: Linear regression of weight change pre and post AA

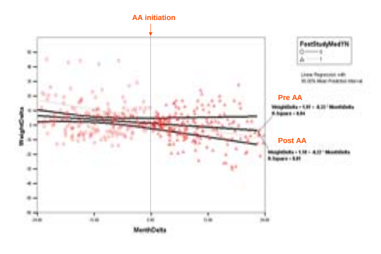
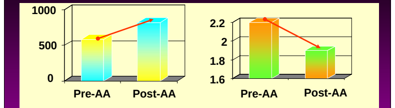


Figure 3: The average equivalent dose of L-dopa and dopamine agonist at pre & post AA



L-Dopa (mg/d)

	Pre-AA	Post-AA
Avr.,(55)	585.1	818.6
Min.	0.0	0.0
Max.	2416.9	2440.0

D.agonist (mg/d)

	Pre-AA	Post-AA
Avr.(55)	2.2	1.9
Min.	0.0	0.0
Max.	17.9	9.0

CONCLUSIONS

AA did not cause weight gain in this population. This should not be a concern in administering these medications. Conversely they are not effective as weight gaining drugs when this is desired.

Body weight gain is generally greater with AA compared to first generation antipsychotics.[21] AA have lower affinity for dopamine D2 receptors but variably have greater affinities for other neuroreceptors including serotonin (5-HT1A,2A,2C,3,6 and 7) adrenergic (α1 and α2), histamine (H_1), and muscarinic acetylcholine (mACh).[22] Matsui-Sakata calculated mean receptor occupancies of neurotransmitter receptors and found that H_1 and mACh receptor occupancy correlated with antipsychotic-induced weight gain, while H_1, mACh and $5\text{-}HT_{2c}$ receptors correlated to type 2 diabetes mellitus.[23] Although speculative, these drugs may not induce weight gain in PD simply because these brain areas also degenerate, and presumably are less functional.

Other possible effects on weight include changes in dysphagia. These drugs; however have not been reported to alter swallowing. [24,25] Levodopa dose increased as dopamine agonists decreased. Theoretically levodopa could contribute to the weight loss by lipolytic effects [9], nausea or dyskinesia.[2] To our knowledge this has never been clinically demonstrated.

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