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Donald Bliwise, Emory University
Lynn Marie Trotti, Emory University
Anthony G. Wilson, Emory University
Sophia A. Greer, Emory University
Cathy Wood-Siverio, Emory University
Jorge Juncos, Emory University
Stewart Factor, Emory University
Alan Freeman, Emory University
David Rye, Emory University

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Daytime Alertness in Parkinson’s Disease: Potentially Dose-Dependent, Divergent Effects by Drug Class

Donald L. Bliwise\textsuperscript{a,b}, Lynn Marie Trotti\textsuperscript{a,b}, Anthony G. Wilson\textsuperscript{a,b}, Sophia A. Greer\textsuperscript{a,b}, Cathy Wood-Siverio\textsuperscript{a}, Jorge J. Juncos\textsuperscript{a}, Stewart A. Factor\textsuperscript{a}, Alan Freeman\textsuperscript{a}, and David B. Rye\textsuperscript{a,b}

\textsuperscript{a}Department of Neurology, Emory University School of Medicine, Atlanta, Georgia
\textsuperscript{b}Program in Sleep Medicine, Emory University School of Medicine, Atlanta, Georgia

Abstract

Background—Many patients with idiopathic Parkinson’s disease experience difficulties maintaining daytime alertness. Controversy exists regarding whether this reflects effects of anti-Parkinsonian medications, the disease itself or other factors such as nocturnal sleep disturbances. In this study we examined the phenomenon by evaluating medicated and unmedicated Parkinson’s patients with objective polysomnographic measurements of nocturnal sleep and daytime alertness.

Methods—Patients (n = 63) underwent a 48-hour laboratory-based study incorporating 2 consecutive nights of overnight polysomnography and 2 days of Maintenance of Wakefulness
We examined correlates of individual differences in alertness, including demographics, clinical features, nocturnal sleep variables and class and dosage of anti-Parkinson’s medications.

**Results**—Results indicated that: 1) relative to unmeditated patients, all classes of dopaminergic medications were associated with reduced daytime alertness and this effect was not mediated by disease duration or disease severity; 2) increasing dosages of dopamine agonists were associated with less daytime alertness, whereas higher levels of levodopa were associated with higher levels of alertness. Variables unrelated to Maintenance of Wakefulness Test defined daytime alertness included age, sex, years with diagnosis, motor impairment score and most nocturnal sleep variables.

**Conclusions**—Deficits in objectively assessed daytime alertness in Parkinson’s disease appear to be a function of both the disease and the medications and their doses utilized. The apparent divergent dose-dependent effects of drug class in Parkinson’s disease are anticipated by basic science studies of the sleep/wake cycle under different pharmacological agents.

**Keywords**

Parkinson’s Disease; Daytime Alertness; Sleep; Maintenance of Wakefulness Test; Dopaminergic Treatment

**INTRODUCTION**

Difficulty in maintaining daytime alertness is a major issue for many patients with Parkinson’s disease (PD). This problem has been well-documented using both subjective (1–4) and objective (5–16) measurements and negatively impacts quality of life (17), mood (18), ability to operate a motor vehicle (1), and cognition (19), and may even be prognostic for incident PD (20). Although generally thought to reflect medication effects (2, 21–23), some evidence in both human disease (24) and animal models (25,26), now suggests that sleepiness during the daytime may also be an integral component of PD itself (5, 12). In this study we examined the ability of PD patients to remain awake during the daytime using objective measurements made with the Maintenance of Wakefulness Test (MWT). Our goals were: a) to compare alertness in a group of well-characterized, unmedicated early-stage PD patients to those who are treated medically; and b) to characterize medication effects on alertness, both as a function of medication class (i.e., levodopa versus dopamine agonists) and dose.

**METHODS**

**Patients**

Sixty-three patients with a diagnosis of idiopathic PD participated. All patients were examined by a board-certified neurologist (LMT) who administered the motor component of the Unified Parkinson’s Disease Rating Scale (UPDRS) (27) and completed the modified Hoehn-Yahr staging scale (28). For patients receiving dopaminergic medication, UPDRS ratings were made in the medicated condition. We also administered the Epworth Sleepiness Scale (ESS) (29) and the Mini-Mental State Exam (MMSE) (30). Table 1 shows demographics and clinically relevant variables (age, gender distribution, UPDRS, disease duration, MMSE, and ESS) for the group as a whole, as well as for both those medicated (n = 49) and unmedicated (n = 14) with dopaminergics (including both levodopa and/or dopamine agonists).
Medication Status

Forty-one patients took levodopa, whereas thirty-four took dopamine agonists including: pramipexole (n = 17), ropinirole (n = 16), and bromocriptine (n = 1). Other medications used by more than 2 patients included: selegiline or rasagiline (n = 17), CoQ10 supplement (n = 15), amantadine (n = 11), various benzodiazepines (n = 7), and anti-depressants, including trazodone (n = 4) and various serotonin and norepinephrine reuptake inhibitors (n = 18). Only one patient used stimulant medication (modafinil).

Levodopa dose equivalents for all patients taking any form of levodopa (including sustained release and entacapone-combined formulations) were made with a conversion formula reported previously (2), whereas for dopamine agonists we employed pergolide dose equivalents (31). Because some patients (n = 27) took both levodopa and dopamine agonists, we also combined both medication classes into a single, combined dopaminergic equivalent (expressed as levodopa mg) (2). Dose equivalents for those patients taking these various medication classes are provided in Table 2.

Laboratory Procedures

Patients gave Informed Consent under an IRB-approved protocol. Meals and all medications were taken at customary times while in the laboratory. The protocol consisted of continuous 48-hour in-laboratory polysomnographic (PSG) evaluation in which patients maintained their usual bedtime and wakeup schedule for 2 consecutive nights. During the daytime, patients underwent a 4-nap Maintenance of Wakefulness Test (MWT) (see below). In 9 cases, the study was scheduled for less than 48 hours. PSG recordings were conducted on an Embla Flaga A10 system and consisted of central and occipital electroencephalography (EEG), left and right monopolar electrooculography (EOG), surface mentalis electromyography (EMG), single lead (modified lead II) electrocardiography, respiratory airflow and effort, pulse oximetry and bilateral limb surface EMG recordings from electrodes placed above the left and right anterior tibialis and brachioradialis. Records were scored by research staff in 30 second epochs under the supervision of an experienced polysomnographer (DLB) with whom inter-rater reliability was established previously at the 85% level or higher (32,33). There were no differences between the 54 patients with 8 nap opportunities and those remaining 9 patients with fewer than 8 nap opportunities on age, sex, Hoehn-Yahr score, UPDRS, years with diagnosis, ESS, or MMSE.

As an alternative to the more conventionally used Multiple Sleep Latency Test (MSLT) (34), which measures daytime sleepiness, the MWT measures daytime alertness (35). The differentiation between the two tests is based primarily, but not exclusively, on the instructional set provided. In the MSLT, patients are instructed to lie down in bed in a darkened room and try to fall asleep. In the MWT, patients recline with head of bed elevated in a darkened room and are given the instruction to try to remain awake and avoid falling asleep. The MSLT typically lasts 20 minutes, whereas the MWT typically extends for 40 minutes (36), though shorter versions of the latter test have been described (37). For both tests, sleep is prohibited by continuous behavioral monitoring between each nap opportunity; in our study, this was accomplished by having a single technologist assigned to the patient throughout the daytime hours. The MWT holds some advantages over the MSLT, because of greater sensitivity to medication effects (38). In a PD population, the MWT was shown to be more closely related to agonist dose, relative to the MSLT (15). We modified the MWT in this study by allowing the entire 40-minute period to elapse (regardless of whether sleep did or did not occur). We quantified each MWT nap opportunity to derive: a) sleep latency (SLAT) (in minutes), the time to the first 30 second epoch scored as sleep and b) sleep efficiency (SE) (%), the total time spent asleep during each nap divided by 40 multiplied by 100.
Analyses

Our primary analyses focused on comparisons between patients medicated and not medicated with dopaminergic drugs. Initially, we employed repeated measures analyses of variance (ANOVA) to examine time-of-day effects with MWT. To compare different patient groups, we relied upon two-sample t-tests with corrections for unequal variance estimates. Because we generated two MWT variables for these comparisons which were partially redundant (i.e., patients with longer latency to fall asleep also typically had lower sleep efficiencies), we corrected all adjustments in our primary analyses using family wide Bonferroni adjustments ($p = .025$). Demographics and clinical variables (age, sex, disease duration, UPDRS, MMSE, and ESS) comparing medicated and unmedicated patients were also subject to family wide Bonferroni adjustment ($p = .008$). Exploratory analyses to examine drug classes and possible dose response effects were unadjusted. We used Spearman correlation coefficients to investigate associations between nighttime sleep variables and MWT data.

RESULTS

Non-pharmacologic correlates of MWT-defined measures of alertness

Median MWT values for SE and SLAT (Table 1) for each patient were unrelated to nocturnal TST, Arousal Index, REM %, AH1 or PLMSI. However, nocturnal SE was positively correlated to MWT SE (rho = .27, $p = .036$), suggesting that patients sleeping better nocturnally were those individuals who were sleepier during the daytime. Both median MWT SE and MWT SLAT were unrelated to age, years with diagnosis, MMSE and UPDRS score. There was a marginal relationship between MWT SE and ESS score (rho = .21, $p = .099$), indicating that higher subjective sleepiness was associated with higher sleep efficiencies during the daytime.

We examined variability in alertness during the day among those 54 cases that underwent the 2 full days (i.e. 8 MWT nap opportunities) to allow for a more thorough assessment of time of day and/or time in protocol influences. Spearman correlations between all pairs of nap opportunities showed highly significant correlations ranging from .40 to .78 for MWT SE and from .51 to .77 for MWT SLAT (all $p$’s < .003), indicating relatively stable levels of alertness across nap opportunities. Repeated measures ANOVAs showed statistically significant main effects of MWT order ($F = 7.79, p < .0001$ for SE; $F = 7.70, p < .0001$ for SLAT; both df = 7, 371) with the majority of statistically significant comparisons indicating that MWT 1 (first nap opportunity of Day 1) and MWT 8 (last nap opportunity of Day 2) were associated with higher levels of alertness than any of the other MWTs, indicating probable procedure adaptation and end-of-protocol effects, respectively.

Pharmacologic correlates of MWT-defined measures of alertness

We employed each patient’s median SE and SLAT to examine influence of medication. Table 1 presents comparisons between patients receiving and not receiving dopaminergic medications. Medicated patients as a group did not differ on age, sex composition, UPDRS score or MMSE but had significantly longer disease duration than unmedicated patients (difference exceeding Bonferroni threshold). They also were more likely to experience sleepiness subjectively (ESS). Medicated patients were significantly less alert on both MWT measures, and those differences were sufficiently strong so as to exceed the Bonferroni threshold. These differences persisted when MWT 1 and MWT 8 data were excluded from analyses, indicating that inclusion of data from these nap opportunities did not affect the results. Because the unmedicated patients’ disease duration was significantly shorter than the medicated patients, we repeated these comparisons and attempted to control for this quasi-experimentally by truncating disease duration of the medicated group at the highest
disease duration of the unmedicated group (3.5 years). (This was only partially successful as
the disease duration difference was still marginally significant [p = .051] [see Table 1]).
Nonetheless, MWT comparisons remained statistically significant, still exceeding the
Bonferroni threshold for SLAT, despite the restricted sample size. Differences persisted
when MWT 1 and MWT 8 data were excluded from these analyses, as well.

There were no statistically differences in MWT SE or SLAT comparing patients receiving
versus not receiving other classes of medications (CoQ10, selegiline/rasagiline, amantadine,
various benzodiazepines [primarily clonazepam], trazodone or other anti-depressants).
Neither the percentages of patients receiving anti-depressants nor benzodiazepines differed
between those receiving versus not receiving dopaminergics (36.7% vs 28.6%, Fisher’s
exact p = .75 for all anti-depressants combined; 12.2% vs 7.1%, Fisher’s exact p = .35 for all
benzodiazepines combined), suggesting that these medication classes were not contributing
to the differences seen in alertness between these groups.

We also examined dose-response relationships with MWT-defined alertness among the 49
patients using levodopa and/or DAs. Using the combined dopaminergic dose equivalents (2)
(see Table 2), there was no relationship with median MWT SLAT (rho = .20, p = .17) or
median MWT SE (rho = -.12, p = .40). However, a different pattern emerged when
examining associations separately by drug class (i.e., levodopa versus DA). Patients with
daily pergolide dose equivalents of > 2.0 mg daily (median dose) had significantly higher SE
(39.7 [29.5] % vs 24.1 [23.2] %, t = 2.06, p = .045) than those < 2.0 mg, suggesting higher
dosages associated with less daytime alertness. By contrast, the correlation between
levodopa dose and MWT defined SLAT was positive (rho= 0.27, p = .06), indicating higher
levodopa was associated with greater, not lesser, degrees of alertness. A linear regression
entering both levodopa and pergolide equivalents as separate predictors of MWT showed
that only DAs contributed to MWT-defined SE (B = 6.17, t = 3.01, p = .004) and SLAT(B =
−5.18, t = 2.21, p = .031), again indicating relative independence of both drug classes in
association with MWT-defined daytime alertness.

DISCUSSION

Our data broadly confirm the objectively measured deficits in daytime alertness in PD
patients shown by many other investigators, primarily (5, 9, 12–14) but not exclusively (11,
15), using the MSLT. Our median MWT SLAT (18.6 minutes) for medicated and
unmedicated patients combined represents a value approximately 1.5 Standard Deviations
below normative values expected for the 40-minute version of this test (36, 39) and are
relatively consistent with MWT data presented in PD pts by Stevens et al (15). Although
some non-pharmacologic factors were associated with alterations in daytime alertness (i.e.,
procedural MWT effects), Parkinsonian medications clearly were associated with large
effects in alertness, even when disease duration was controlled. Unanticipated in our data,
however, were the novel observations that the two major classes of dopaminergics used to
treat PD symptoms (levodopa and DAs) appeared to show dose-dependent, divergent effects
on alertness. These findings have not been noted previously in human PD studies of
objectively measured daytime alertness, but they do receive some corroborations from animal
work.

The effects of dopaminergic stimulation on sleep and wakefulness are complex. Many basic
science studies have suggested that both classic and newer stimulant medications operate
through dopaminergic mechanisms (including but not limited to downregulation of the
dopamine transporter) and that these may be independent from effects on motor activity per
se (40). Effects of dopaminergic pharmacologic stimulation on alertness, however, may
depend on dose of the agent in question, its proclivity for one or more of the five
molecularly defined dopamine receptor subtypes, and its potential to limit its own activity (particularly at low dosages) by autoreceptor binding (41). Experimental trials in normal subjects have suggested that both dopamine agonists (at 0.50 – 0.75 mg pergolide equivalence) (42, 43) and levodopa (at 200 mg, e.g., [44]; but not 100 mg, e.g., [42]) can induce sleepiness, but animal studies suggest a far more nuanced picture. Apomorphine administered to rats showed soporific effects at low dosages but stimulating effects at high dosages (45). When given in sufficiently high dosages to rats (75mg/kg), levodopa enhanced both locomotor activity and wakefulness (46). Older literature on selective antagonism suggested that D1, relative to D2, blockade increased sleep duration in rats (47, 48), whereas Trampus et al (49) reported that D1 agonists increase waking in a dose-dependent fashion, those effects being dependent on specific binding affinities. Among the newer, non ergot-derived dopamine agonists, pramipexole (with D3 specificity) was shown to cause biphasic effects on sleep in rats, with lower dosages (30 ug/kg) increasing sleep and higher dosages (500 ug/kg) increasing alertness (50). In our patients, the highest daily dosage of levodopa and DA (pergolide equivalent) (1250 mg and 5.25 mg, respectively) are still only about 25% of the mg per kg doses used in this animal work. Insofar as we know, our study represents the first PD data to raise the possibility that there may be selective, apparently divergent, dose-dependent effects of dopaminergic class (i.e., levodopa versus DAs) on objectively measured alertness within a dosage window encountered in human pharmacotherapy.

Previous MSLT/MWT studies examining sleepiness and alertness in relation to medication usage in PD have shown at best equivocal, if not negative, results (8, 10, 12–14, 16). One MWT study showed that individuals in the upper tertile (> 867.5 mg) of combined dopaminergic equivalents were less likely to be alert but did not separate DA and levodopa dose (11), whereas another reported that pergolide equivalents, but not levodopa dose, was associated with lower MWT-defined alertness (15). In an earlier study, Arnulf et al (5) reported a modest correlation between levodopa dose and greater MSLT-defined alertness, similar to what we found here, but noted no relationship to DA dose. In our study, we noted divergent dose-dependent effects of drug class in relation to daytime alertness; moreover, these were superimposed upon an overall effect of Parkinsonian medication on alertness (Table 1), regardless of class.

We noted a statistically significant, but small, relationship between subjective (ESS) and objective (MWT) measures of daytime alertness. Weak or non-significant associations between ESS and MSLT (5, 6, 11, 14–16, 51, 52) or MWT (15) in PD have been shown previously, although a few studies report stronger associations (9, 10). Modest relationships between subjective and objective alertness have been noted for years (53).

Motivational factors can affect the MWT. For example, the possibility of losing driving privileges may be sufficient to promote alertness on the MWT in some non-PD patients (particularly the 20-minute version) (54), and Bonnet et al (55) have suggested that financial incentives may even influence alertness on this test. Although patients in our study were paid $400.00 for their participation, we did not attempt to incentivize performances via monetary reward. Patients instead were told of the importance of the research generally, and we enlisted their participation in this spirit. Nonetheless, there was interpretable evidence for motivational factors operating here, since MWT 8, for example, demonstrated a significantly longer SLAT and lower SE than other naps, perhaps reflecting the common phenomenon of patient’s anticipating their departure from the lab following their final procedure of the day.

Our evidence of possible dose-dependent divergent effects of dopaminergic medications notwithstanding, these data in many respects converge considerably with other work in this area. For example, 11 of 12 studies using the MSLT in PD (5–9, 11–16) failed to find any association between overt sleep pathology such as the AHI or PLMSI and next-day...
alertness, the only exception to this being a single recent report (10). Many of these studies have also noted a dearth of relationships PSG-defined TST and SE and daytime sleepiness in PD patients (5–10, 13, 14). In the current study, we also found no relationship with AHI and PLMSI, however, consistent with our earlier study with the MSLT, we reported that higher nocturnal SE was positively associated with greater sleepiness the following day (12). Similarly, as in most other studies, age (5, 10, 12, 13, 16) and UPDRS motor score (5, 7, 8, 10, 15, 16), were not impressive correlates of daytime sleepiness, though both Stevens et al (15) and Razmy et al (11) reported lower levels on alertness associated with higher Hoehn-Yahr ratings.

A frank weakness of our study is the absence of validated measures of depression; instead we are relying upon clinician’s usage of anti-depressant medication as very rough proxy for low mood. Other weaknesses of our study include absence of a non-patient control group and a cross-sectional design that did not allow for medication effects for each patient to be tested against their own baseline. The importance of the latter issue may be mitigated to some extent by the availability of untreated patients within the first 3–4 years since diagnosis. Additionally, our attempt to exercise some element of quasi-experimental control via disease duration matching allowed for some differentiation of early-stage disease versus medication effects per se. Tracking these unmedicated patients throughout their ensuing treatment course will be one focus of our future efforts. Additionally, given the importance of changes in the dopaminergic system to sleep/wakefulness, we feel strongly that prospective trials of new pharmacologic agents for PD should incorporate objective measurements of alertness as important adjunctive outcome.

Acknowledgments

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REFERENCES


Table 1

Description of Patients

<table>
<thead>
<tr>
<th>Demographics/ Clinical Variables</th>
<th>Overall (n = 63)</th>
<th>Receiving Dopaminergics (n = 49)</th>
<th>Not Receiving Dopaminergics (n = 14)</th>
<th>Comparison t or χ² (p)</th>
<th>Receiving Dopaminergics (truncated) (n = 13)</th>
<th>Comparison t or χ² (p)</th>
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<tbody>
<tr>
<td>Age</td>
<td>63.1 (9.7)</td>
<td>63.2 (9.4)</td>
<td>62.6 (11.0)</td>
<td>.19 (.85)</td>
<td>61.0 (10.6)</td>
<td>.39 (.697)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>65.1%</td>
<td>65.3%</td>
<td>64.3%</td>
<td>.005 (.94)</td>
<td>61.5%</td>
<td>.02 (1.00)</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>5.6 (4.0)</td>
<td>6.6 (3.9)</td>
<td>1.8 (0.9)</td>
<td>7.67 (&lt;.0001)</td>
<td>2.6 (0.8)</td>
<td>2.06 (.051)</td>
</tr>
<tr>
<td>UPDRS (Overall)</td>
<td>17.2 (8.4)</td>
<td>17.0 (8.7)</td>
<td>17.5 (7.9)</td>
<td>.18 (.858)</td>
<td>15.5 (8.2)</td>
<td>.60 (.554)</td>
</tr>
<tr>
<td><strong>Selected Subscales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rest Tremor</td>
<td>2.0 (2.3)</td>
<td>1.9 (2.3)</td>
<td>2.4 (2.2)</td>
<td>.71 (.86)</td>
<td>0.9 (1.2)</td>
<td>1.89 (.07)</td>
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<td>Gait/Posture</td>
<td>1.6 (1.4)</td>
<td>1.7 (1.4)</td>
<td>1.4 (0.7)</td>
<td>.57 (.57)</td>
<td>1.8 (1.9)</td>
<td>.59 (.56)</td>
</tr>
<tr>
<td>Rigidity/Bradykinesia</td>
<td>10.8 (6.1)</td>
<td>10.8 (6.0)</td>
<td>10.9 (6.5)</td>
<td>.09 (.68)</td>
<td>10.2 (5.8)</td>
<td>.28 (.78)</td>
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<tr>
<td>Modified Hoehn-Yahr Stage</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
<td>7 (11.1)</td>
<td>6 (12.2)</td>
<td>1 (7.1)</td>
<td>1.29 (.86)</td>
<td>3 (23.1)</td>
<td>4.20 (.38)</td>
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<tr>
<td>1.5</td>
<td>5 (7.9)</td>
<td>3 (6.1)</td>
<td>2 (14.3)</td>
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<td></td>
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<tr>
<td>2</td>
<td>26 (41.2)</td>
<td>20 (40.8)</td>
<td>6 (42.9)</td>
<td>4 (30.8)</td>
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<tr>
<td>2.5</td>
<td>16 (25.4)</td>
<td>13 (26.5)</td>
<td>3 (21.4)</td>
<td>5 (38.5)</td>
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<tr>
<td>3</td>
<td>9 (14.3)</td>
<td>7 (14.3)</td>
<td>2 (14.3)</td>
<td>1 (7.7)</td>
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<tr>
<td>MMSE</td>
<td>28.6 (1.7)</td>
<td>28.5 (1.7)</td>
<td>28.7 (2.0)</td>
<td>.38 (.707)</td>
<td>28.8 (1.5)</td>
<td>.17 (.805)</td>
</tr>
<tr>
<td>ESS</td>
<td>10.3 (4.4)</td>
<td>11.2 (4.3)</td>
<td>7.4 (3.6)</td>
<td>3.03 (.0037)</td>
<td>12.3 (3.1)</td>
<td>3.81 (.0008)</td>
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<td><strong>MWT-derived variables</strong></td>
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<td></td>
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</tr>
<tr>
<td>Median SLAT</td>
<td>18.4 (14.8)</td>
<td>15.7 (14.7)</td>
<td>27.7 (11.0)</td>
<td>2.81 (.0066)</td>
<td>14.4 (13.5)</td>
<td>2.82 (.0092)</td>
</tr>
<tr>
<td>Median SE</td>
<td>27.3 (26.8)</td>
<td>31.7 (27.3)</td>
<td>12.0 (18.6)</td>
<td>2.53 (.0140)</td>
<td>29.0 (24.4)</td>
<td>2.05 (.0515)</td>
</tr>
</tbody>
</table>
Table 2

Mean Dosages Among 49 Patients Receiving Dopaminergic Medications

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Combined Levodopa dose equivalent (mg)(^a)</th>
<th>Levodopa dose (mg)(^b)</th>
<th>Dopamine agonist (mg)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 49) Taking only levodopa</td>
<td>595.0 (329.1)</td>
<td>454.0 (337.2)</td>
<td>1.90 (1.54)</td>
</tr>
<tr>
<td>(n = 14) Taking only dopamine agonist</td>
<td>599.6 (347.8)</td>
<td>599.6 (347.8)</td>
<td>---</td>
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<tr>
<td>(n = 8) Taking levodopa</td>
<td>196.2 (92.2)</td>
<td>---</td>
<td>2.63 (1.29)</td>
</tr>
<tr>
<td>(n = 41) Taking dopamine agonist</td>
<td>672.8 (300.7)</td>
<td>542.5 (295.3)</td>
<td>1.76 (1.55)</td>
</tr>
<tr>
<td>(n = 35) Taking both levodopa and dopamine agonist</td>
<td>593.1 (326.5)</td>
<td>395.7 (319.5)</td>
<td>2.66 (1.11)</td>
</tr>
<tr>
<td>(n = 27)</td>
<td>710.8 (272.5)</td>
<td>513.0 (266.5)</td>
<td>2.68 (1.08)</td>
</tr>
</tbody>
</table>

NOTES:

\(^a\) Combined levodopa dose equivalent = levodopa dose equivalent (see \(^b\) below) + pergolide dose equivalent (see \(^c\) below) × 100

\(^b\) Levodopa dose equivalent for all forms of levodopa, including sustained-release and entacapone-combined formulations, followed reference (2) and was computed as daily sum of: regular levodopa dose + levodopa continuous release dose × 0.75 + [regular levodopa dose + (continuous release levodopa dose × 0.75)] × 0.25 if taking entacapone.

\(^c\) Pergolide dose equivalent for all dopamine agonist medications, including pramipexole, ropinirole and bromocriptine, followed reference (31) and was computed as 1 mg pergolide = 1 mg pramipexole = 5 mg ropinirole = 10 mg bromocriptine.