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Medication Management and Neuropsychological Performance in Parkinson's Disease

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Abstract

Medication non-adherence is associated with chronic disease and complex medication schedules, and Parkinson's disease (PD) patients also frequently have cognitive impairments that may interfere with effective medication management. The current study quantitatively assessed the medication management skills of PD patients and probed the neurocognitive underpinnings and clinical correlates of this skill. A total of 26 men with PD completed a neuropsychological battery and a modified version of the Hopkins Medication Schedule (HMS), a standard test of a person's ability to understand and implement a routine prescription medication. Estimated adherence rates from performance on the HMS were low. Memory, executive functioning, and processing speed were strongly related to different components of the HMS. A range of neuropsychological abilities is associated with the ability to understand and implement a medication schedule and pillbox in individuals with PD.

Keywords

Parkinson's disease; Medication management; Instrumental activities of daily living; Aging

INTRODUCTION

Medication adherence is defined as the extent to which patients take medications as prescribed (Osterberg & Blaschke, 2005). Medication adherence requires successful medication management; that is, the ability to develop, schedule, and implement a plan to take medications, as well as to remember if medications have been taken and when to take them (Steinman & Hanlon, 2010). Cognitive correlates of successful medication adherence have been noted to include verbal memory and cognitive flexibility. Even mild deficits in these cognitive abilities are associated with non-adherence in community-dwelling older

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adults (Carlson, Fried, Xue, Tekwe, & Brandt, 2005; Hayes, Larimer, Adami, & Kaye, 2009). Medication non-adherence is also associated with chronic disease and complex medication schedules (Doggrell, 2010).

The risks of medication non-adherence are heightened in Parkinson's disease (PD). PD is a progressive neurological condition classically defined by symptoms of rigidity, bradykinesia, postural instability, and tremor (Weintraub, Cornella, & Horn, 2008). Increasing evidence suggests cognitive decline accompanies the motor symptoms of PD. Deterioration in verbal learning, visuospatial abilities, working memory, and cognitive flexibility are characteristic of the illness. Cognitive abilities eventually decline to the extent that they severely disrupt daily functioning; as many as 75% to 90% of adults with PD will be diagnosed with dementia during the course of their illness (Kehagia, Barker, & Robbins, 2010).

Medication non-adherence in PD results in increased medical costs and worse clinical outcome. Managed care systems spend an average of $6598 more per year on adults with PD who do not adhere to their medications compared to adults with PD who successfully adhere to their medications (Davis, Edin, & Allen, 2010). Oral medications are the mainstay in PD treatment and dosages are complex; the average PD patient takes nine medication tablets daily (Grosset et al., 2009). Under-use (i.e., missed doses) of antiparkinson medication results in poorly controlled symptoms such as bradykinesia, rigidity, and tremor. Intentional, excessive use of dopaminergic therapy can result in dopamine dysregulation syndrome and is characterized by affective dysregulation and sometimes by co-morbid psychosis and impulse control disorders (Weintraub, 2009). Mistimed doses result in increased fluctuation of symptoms (Grosset et al., 2009). Estimates of under-use non-adherence, as defined by taking less than 80% of prescribed medications, range from 12.5% to 20% in PD (Grosset, Bone, & Grosset, 2005; Leopold, Polansky, & Hurka, 2004). However, non-adherence in PD is as high as 53.8% if considering under-use, over-use, and mistimed doses together (Leopold et al., 2004).

The association between daily functioning and cognition in non-dementia PD remains relatively unknown. Young and colleagues (Young, Granic, Yu Chen, Haley, & Edwards, 2010) recently examined the performance of older adults with and without PD on the Everyday Cognitive Battery Inductive Reasoning Test (ECB; Allaire & Marsiske, 1999). The ECB Reasoning Test measures the ability to identify information in everyday printed materials (e.g., medication labels) and to use that information to answer questions pertaining to the functional domains of medication use, finances, and nutrition (Allaire & Marsiske, 1999). Findings from Young et al. (2010) revealed that adults with PD performed significantly worse than adults without PD across the three functional domains. The authors interpreted these findings as evidence that early decline in reasoning abilities, as shown by performance on the ECB, may generalize to functional difficulties in everyday life for adults with PD. However, a major limitation of this work is that the constructs of reasoning and everyday functioning were measured with the same task, the ECB. No independent measures of daily functioning or medication adherence were administered. Elsewhere, Rosenthal and colleagues (2010) reported medium to strong associations between informant reported instrumental activities of daily living (IADL) and performance on the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) and Dementia Rating Scale (Jurica, Leitten, & Mattis, 2001) in non-demented PD patients. While these findings suggest the potential for a relationship between medication management skills and cognition in non-demented PD patients, this has not been formally explored. Therefore the question remains whether cognitive test performance is correlated with the ability to both understand and implement a medication prescription in PD.

Despite the clinical significance of non-adherence, the complex nature of medication regimens, and potential cognitive deficits that may impact the ability to successfully manage medications, the neuropsychological correlates of medication adherence in PD have not been investigated. In the current study we investigated the cognitive and clinical correlates of medication adherence in PD using the Hopkins Medication Schedule (HMS; Carlson et al., 2005), a standardized measure of the ability to understand and implement medication management. The HMS tests one's ability to comprehend and execute a hypothetical medication schedule and correctly fill a pillbox based on the created schedule. The HMS was developed to balance ease of clinical application and ecological validity, and normative data for its use are available from 360 community-dwelling older women from the Women's Health and Aging Study II (Carlson et al., 2005). Prior use with the HMS suggests it is useful in identifying individuals with subtle cognitive deficits at risk for poor medication adherence. Findings from Carlson et al. (2005) revealed 22% of the Women's Health and Aging Study II cohort were unable to complete the HMS, despite only 2% of the women reporting any difficulty with medication management. Poor performance on the HMS was significantly associated with worse performance on the Hopkins Verbal Learning Test (HVLT-R; Brandt & Benedict, 2001), Trail Making Test (Army Individual Test Battery, 1944), and Digit Span (Wechsler, 1997), and discriminated women who reported difficulty in other instrumental activity of daily living domains from those who did not report such difficulty. Given these findings, and the fact that adults with PD may experience decline in these same cognitive domains, we hypothesized that scores on the HMS would positively correlate with performances on common neuropsychological measures of verbal memory, attention, executive functioning, and psychomotor speed in patients with PD. However, in order for the HMS to more realistically represent the complex medication schedule seen in individuals with PD, we modified aspects of the test in the present study. These changes are described in detail below.

METHOD

Participants

A total of 26 male patients aged 40 to 90 years with a diagnosis of Parkinson's disease (PD), on the basis of UK Parkinson's disease Society Brain Bank Clinical Diagnostic Criteria (Hughes, Daniel, Kilford, & Lees, 1992), were recruited from the Parkinson's Disease Research, Education, and Clinical Center (PADRECC) at the Philadelphia Veterans Affairs Medical Center. All participants were on a stable medication regimen at least 30 days prior to study enrollment, had a Hoehn and Yahr rating between I and III, and scored 25 or greater on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), a brief screening of global cognitive functioning. The MoCA cutoff score was included to ensure no participants had severe cognitive impairment (Hoops et al., 2009). Exclusion criteria included secondary or atypical parkinsonism, stroke or transient ischemic attack (TIA) less than 1 year prior to enrollment, history of deep brain stimulation surgery, or any medical condition that would likely prevent completion of the study. A total of 94 patients met inclusion criteria and 67 declined to participate. The most common reasons for not participating were inability to travel due to lack of transportation or poor health, inability to sit through 1.5 hours of testing, and lack of compensation for participation. Of the 27 participants who agreed to participate, 1 participant did not meet inclusion criteria (i.e., scored less than 25 on the MoCA). The remaining 26 participants completed all testing (motor, cognitive, and HMS) when "on" PD medications. The Philadelphia Veterans Affairs Medical Center Institutional Review Board approved this study.

Procedure

The Standard Hopkins Medication Schedule (HMS) and Modified Components

—The standard HMS (Carlson et al., 2005) consists of two components: scheduling and pillbox filling.

Schedule: Standard instructions were followed for the HMS Scheduling Component (see Appendix 1). Each participant was read (and read along with) a hypothetical scenario in which he was given a prescription for an antibiotic and aspirin along with directions for taking each. Next the participant was given a template marked with hours of the day and standard meal times, and asked to plan a daily schedule for taking the aspirin and antibiotic, as well as snacks and water. Participants filled out the schedule by circling the time at which they should take the medication, writing the number of pills to be taken, and noting the intake of snacks and water with “S” and “W”, respectively. The schedule was scored according to nine criteria: compliance with timing of doses, method, and daily dosage of antibiotics (3 points) and aspirin (3 points), and proper intake of snacks and water (3 points).

In addition to the standard HMS scheduling component described above, we amended the HMS to include a PD-specific regimen of higher complexity to assess more accurately the medication schedules these patients face, in addition to common medications, such as antibiotics and aspirin. This additional component, presented in Appendix 2, was completed after the standard HMS component and scored similarly: compliance with timing of doses, method, and daily dosage of Parkinson’s medication (3 points) and 1 point awarded for identifying that water is to be taken with medication. The two schedules were completed at the participant’s own pace or until a total of 8 minutes had elapsed. We created a total schedule score incorporating the standard HMS schedule and the PD medication schedule ranging from 0 to 13.

Pillbox: Instructions for the standard HMS Pillbox Component require participants to fill in a common 1-day pillbox using the written directions from the HMS Schedule Component (see Appendix 1 for instructions). We modified the Pillbox Component to include an additional PD medication prescription. After completing the schedules described above, the participant was given an eight-ounce bottle of aspirin and two prescription bottles with non-childproof caps. The first bottle, labeled “antibiotic”, contained 10 capsules filled with an inert powder, such as cornstarch or baking powder. The instructions on the bottle read, “Take one capsule three times a day.” The second bottle, labeled “Parkinson’s disease medication”, contained 10 capsules, filled with an inert colored powder (to differentiate from the antibiotic). The instructions on the bottle read, “Take one capsule five times a day.” The participant was then given a pillbox with four open compartments labeled “morning”, “noon”, “evening”, and “bed” and instructed to follow the same instructions for filling as for the schedules (which remained available). The pillbox was scored for proper placement of the proper numbers of antibiotics (1 point), aspirin (1 point), and PD medication (1 point), to obtain a maximum possible score of 3. For example, a hypothetical schedule for PD medications would be at 7:30am, 9:00am, 1:00pm, 5:30pm, and 9:00pm. Therefore, in order to receive 1 point for PD medication, the participant would need to place two capsules in the “morning” compartment, and one capsule in “noon”, “evening”, and “bed”. The pillbox was completed at the participant’s own pace or until a total of four minutes had elapsed.

Self-report of medication difficulty—All participants answered “Yes” or “No” to the single question, “Do you have difficulty managing your own medications?”

Cognitive and motor examination—All participants completed a battery of common neuropsychological measures including tests of verbal memory, attention, executive

functioning, and manual dexterity. These well-known measures included: Hopkins Verbal Learning Test – Revised Edition (HVLT-R; Brandt & Benedict, 2001), Digit Span subtest of the Wechsler Adult Intelligence Scale – Third Edition (Wechsler, 1997), Trail Making Test (Army Individual Test Battery, 1944), Wisconsin Card Sorting Test-64 item (WCST; Kongs, Thompson, Iverson, & Heaton, 2000), and Grooved Pegboard Test (Lafayette Instruments, 2002). Tests were administered and scored according to standard procedures as detailed in respective test manuals. For Trail Making Part B, 300 seconds was used as cut-off. Due to time constraints one patient was not administered the delayed recall of the HVLT-R and another participant was not administered the WCST-64. These data were left missing for subsequent analyses. The clinical motor examination included the United Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987) conducted by the patients' treating movement disorder specialist.

RESULTS

Participants had an average age of 71.85 (*SD*=8.31), 14.77 years of education (*SD*=2.87), and averaged 27 points out of 30 on the MoCA (*SD*=1.69). Six of the participants (23%) acknowledged difficulty managing their prescribed medications. Overall, severity of motor symptoms was rated as mild to moderate as evidenced by a mean UPDRS of 22.81 (*SD*=10.74). The average length of time between a participant's UPDRS exam and testing was 104 days (*SD*=140.0).

Cognitive test performance

The cognitive test performance of the sample is summarized in Table 1. Raw scores and demographic adjusted (age, education, and race where applicable) T-scores are reported (Brandt & Benedict, 2001; Heaton, Miller, Taylor, & Grant, 2004; Kongs et al., 2000; Wechsler, 1997). Overall, the patients demonstrated average performances on measures of verbal learning and recall (HVLT-R), problem solving (WCST-64), and basic auditory attention (Digit Span). Measures involving psychomotor speed and speeded task switching, including Trail Making and Grooved Pegboard, were generally in the low average to impaired range. We found the presence of a statistically significant outlier in the data; one participant aged 71 completed Trails A in 158 seconds. Albeit already limited by a small sample size, we did not wish our results to be unduly influenced by a single data point and removed these data from our analyses. In order to evaluate cognitive performance at the individual level we defined mild cognitive impairment (MCI) based on psychometric criteria, keenly aware that this study is limited in its operational definition of MCI given classification of PD-MCI was not the main study objective. We defined psychometric MCI as performance 1.5 SDs or greater below the mean on two or more scores from different cognitive measures (HVLT-R, Digit Span, WCST-64, and Trail Making Test). Only four participants from the entire sample met criteria for this definition of MCI.

Medication schedule performance

Individuals with PD averaged 7.80 (*SD*=3.98) of 13 possible points on the total schedule score, incorporating both the standard HMS schedule and PD schedule component. The average score on the pillbox was 1.96 (*SD*=1.11) of 3 possible points. Performance on the pillbox was significantly related to total schedule score (r=.47, p<.05), with higher scores on the HMS associated with better pillbox performance. In order to compare the present sample's performance on the standard HMS schedule to that of healthy older women reported by Carlson et al. (2005) we calculated Cohen's d, the standardized mean difference between groups. Given Cohen's (1988) recommendations of categorizing effect sizes as small (d=0.2), medium (d=0.5), or large (d≥0.8) (Cohen, 1988), we found that older men with PD (*M*=5.88, *SD*=2.73) performed comparably, if not slightly better, than healthy

women from the Women's Health and Aging II cohort (M=5.2, SD=2.5)(d=0.27, 95% CI= −0.13<δ<0.67). As the total schedule score incorporates the more complex PD specific schedule, we used this measure for the remaining analyses.

Correlates of medication schedule performance

Increasing age was significantly correlated with poorer performance on the total schedule (r=−.42, p<.05) and pillbox (r=−.40, p<.05). The motor subscale from the UPDRS was significantly associated with performance on the pillbox (r=−.41, p<.05) but not the total schedule (r=−.11, p=.58). General cognitive ability as indicated by the MoCA was not significantly related to the total schedule (r=.19, p=.35) or pillbox (r=.08, p=.68), nor was years of education (r=.18, p=.37; r=−.17, p=.38, respectively). The relationships between cognitive test scores (adjusted for demographic variables) and the total schedule and pillbox performance are presented in Table 2. We utilized the False Discovery Rate in adjusting for multiple comparisons (Benjamini & Hochberg, 1995). The FDR controls the expected proportion of incorrectly rejected null hypotheses and is less conservative than the Bonferroni correction, thereby leading to increased power. Strong relationships between neuropsychological tests and HMS performance were observed. Performance on the total schedule was strongly related to verbal learning, recall, and executive functioning, whereas performance on the pillbox was moderately correlated with these cognitive abilities. Not surprisingly, pillbox performance was also strongly associated with psychomotor speed and motor control.

Estimated medication adherence from schedule and pillbox performance

Medication non-adherence can be defined using various rates of incorrect medication use. To estimate medication non-adherence in the present sample we used a common definition of less than 80% compliance with the correct administration of prescribed medications (Grosset et al., 2005; Leopold et al., 2004). We therefore dichotomized scoring on the total schedule and pillbox to estimate adherence based on 80% accuracy. This lead to total schedule "adherence" as defined as a score of greater than or equal to 11 and "non-adherence" as a score of less 11. Likewise, pillbox adherence was defined as a score of 3 and "non-adherence" as a score less than 3. Results revealed 18/26 participants (69%) demonstrated non-adherence to the total schedule and 15/26 (58%) demonstrated non-adherence on the pillbox. These groups largely overlapped; 14/26 participants (54%) demonstrated non-adherence to both the total schedule and the pillbox.

Cognition and medication schedule adherence

Finally, in an attempt to characterize the clinical and cognitive performance of participants who were able to demonstrate adherence on the modified HMS, we compared "adherence" versus "non-adherence" groups on the total schedule and pillbox according to definitions applied above. These analyses were exploratory in nature and not adjusted for multiple comparisons. Independent t-tests revealed participants who demonstrated adherence to the total schedule or the pillbox did not significantly differ from the respective non-adherence group on severity of motor symptoms, global cognitive MoCA score, years of education, or self-report of medication management difficulty (all ps>.31). However, participants who demonstrated adherence to the total schedule were significantly younger (M=66.63, SD=9.00) compared to those who demonstrated non-adherence (M=74.17, SD=7.05). Therefore we used age as a covariate in the analyses of adherence on the total schedule described below. No significant age differences were observed between participants who demonstrated adherence and non-adherence on the pillbox. Differences in demographically adjusted cognitive performances between the groups are presented in Table 3. Statistically significant differences on analysis of (co)variance and large effect sizes were found between participants who demonstrated adherence and non-adherence on the HMS. Effect sizes were

greatest for measures of verbal memory (HVLT-R), attention/visuomotor scanning (Trails A), and problem solving (WCST-64). Notably, all four participants who met criteria for psychometric MCI were unable to successfully complete the HMS schedule and pillbox.

DISCUSSION

Medication non-adherence in PD is widespread and has adverse clinical consequences. Despite increased susceptibility to cognitive impairment and subsequent functional decline, this is the first study to examine the cognitive correlates of the ability to understand and implement medication management in PD. There are several notable findings from this study. Foremost, over half (54%) of the present sample was unable to successfully complete the HMS schedule and pillbox (i.e., scored less than 80% on both components) despite only 23% of the sample reporting difficulty with medication management and most scoring in the normal range on a commonly used cognitive screening measure (i.e., MoCA). This figure of medication management difficulty on the HMS corresponds to findings from Leopold et al. (2004) who found 53.8% of adults with PD took medications on the wrong days or at the wrong time. Our work differs from Leopold et al. (2004) and other investigators in that we used the HMS to measure adherence, as opposed to an electronic pill bottle monitoring system. Although such electronic monitoring systems assess compliance in real life situations, they are expensive, impractical, and fail to consider whether the patient has the ability to understand medication management (Bainbridge & Ruscin, 2009). Results from the present study suggest the HMS may be a more cost efficient alternative of medication adherence measurement while also capturing the more complex ability to manage medications.

The second implication of this work is that, in our sample of participants with PD, the ability to understand and implement medication management was strongly related to performance on standard measures of verbal learning and recall, cognitive flexibility, and problem solving. Large standardized mean differences (*d*) were observed between performances on the HVLT-R, WCST-64, Digit Span, and Trails A when comparing participants who successfully completed the HMS to those who did not. The magnitude of these differences is remarkable considering the cognitive abilities of those participants unable to successfully complete the HMS remained largely intact based on published normative data. Thus even mild or subtle decline in memory and executive functioning, albeit in the average range of performance, can affect the ability to successfully manage medications in PD. These data support the importance of neuropsychological screening and assessment, even in patients with little to no report of cognitive dysfunction.

Evidence of a relationship between cognitive test performance and instrumental activities of daily living (IADL) in PD is not novel. Recently, in non-demented adults with PD, Rosenthal et al. (2010) found medium to large effects between brief cognitive screening measures and informant report of IADL functioning. Results revealed the magnitude of the relationship between the MMSE and IADL functioning (r=.36) was significantly less than that of the DRS and IADL functioning (r=.52). While we concur with the authors' conclusion that sensitive cognitive assessments are needed to elucidate functionally relevant impairments in non-demented adults with PD, we believe the relationship between cognition and functioning in PD also benefits from sensitive performance-based functional assessment. Goldberg and colleagues (2010) recently illustrated the benefits of performance-based assessment over informant IADL report in a sample of non-PD adults with MCI and cognitively healthy older adults. Goldberg et al.'s (2010) findings revealed that adults with MCI demonstrated deficits on a performance-based measure of functional assessment even when they were described as free of any IADL deficits on traditional questionnaires. Our findings suggest the HMS is more sensitive to cognitive performance than self-reported

ability of medication management. Further work is needed to examine if the HMS is more sensitive to subtle cognitive changes than traditional informant report of IADL difficulty.

There are limitations to the present study. Foremost, our sample size was comprised of only 26 patients with PD. Thus future work is needed to confirm the generalizability of our results. Second, we did not obtain potentially useful information on the comorbid medical conditions of our participants, nor did we record participants' actual medications (although all participants were taking a regimen of dopaminergic therapy). Future work should also explore the role of comorbid illness (e.g., cardiovascular disease) on medication management in PD. One might hypothesize that additional illnesses (and subsequent medications) may detrimentally affect medication management skills in PD. Third, 8 minutes was used as a cut-off for completion of both the standard HMS schedule and the modified PD schedule component. The 8-minute criterion was based on results from Carlson et al. (2005) who found older women, on average, were able to complete the standard HMS schedule in 3.8 minutes. However, the use of the 8-minute cutoff might have inadvertently resulted in poor scores for participants who, when given additional time, would have been able to complete the HMS and PD schedules. We recommend future work allow more time for the completion of the HMS schedules, although an inability to complete the schedule in 8 minutes likely represents a significant deficit in most clinical groups to be studied. Finally, our work did not take into account compensatory strategies of medication management (e.g., assistance from a spouse). Future work would benefit from input from knowledgeable study partners. However, the groups of men who successfully completed the total schedule and pillbox did not differ in reported difficulty with self-medication management. Therefore, overall, we conclude the HMS, and the PD-specific modified components may prove a brief and useful measure of the ability to successfully manage medications in older adults with PD with mild cognitive difficulties.

In summary, the ability to manage one's medications is a complex task involving a number of core neuropsychological and motor skills. The present findings suggest working memory, verbal learning and recall, and cognitive flexibility are especially important to successful medication management as measured by the HMS. Whereas the reasons for medication noncompliance in the PD are likely multifactorial, it is concerning that such a large percentage of patients appear unable to self-manage medications, given this is so important for optimal management of symptoms. A potential hypothesis is that deficits would be even more apparent if prospective memory was involved; that is, if the PD patient must self-remember a dose time, know which medications to take at that time, and to actually take the medication as prescribed. The routine use of structured questionnaires such as the HMS along with a good screening battery of neuropsychological measures can help identify any cognitive and motoric barriers in a given patient and aid in the development of specific compensatory strategies or implementation of remediation techniques. Potential interventions worthy of future study include pharmacist-patient counseling and education focusing on the importance of individual medications and the use of schedules, timers, or other techniques aimed at increasing compliance.

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APPENDIX 1

Hopkins Medication Schedule: Standard schedule component

Directions

Read the medication instructions below. Assume that you eat breakfast, lunch, and dinner at the following listed times. Please indicate by circling the times you should take each medication and write how many you need to take next to the time you circled. Also, indicate when you should drink water and eat any snacks by writing a W next to the times you should drink water and an S next to the times you should eat a snack.

Antibiotic

Take 1 pill 3 times a day, at least 30 minutes before meals.

Aspirin

Take 2 tablets every 4 hours. May cause stomach upset if taken on an empty stomach. Make sure to eat meals and snacks with tablets.

Water

Drink a full glass of water every 2 hours.

7:00AM **Wake Up**

7:30AM

8:00AM **Breakfast**

8:30AM

9:00AM

9:30AM

10:00AM

10:30AM

11:00AM

11:30AM

12:00PM **Lunch**

12:30PM

1:00PM

1:30PM

2:00PM

2:30PM

3:00PM

3:30PM

4:00PM

4:30PM

5:00PM

5:30PM

6:00PM **Dinner**

6:30PM

7:00PM

7:30PM

8:00PM

8:30PM

9:00PM

9:30PM

10:00PM

10:30PM **Go to Bed**

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APPENDIX 2

Hopkins Medication Schedule: Modified Parkinson's medication component

Directions

Read the medication instructions below. Assume that you eat breakfast, lunch, and dinner at the following listed times. Please indicate by circling the times you should take each medication and write how many you need to take next to the time you circled. Also, indicate when you should drink water and eat any snacks by writing a W next to the times you should drink water and an S next to the times you should eat a snack.

Parkinson's Medication

Take 1 tablet by mouth 5 times a day. Take with a full glass of water. Take at least 30 minutes before a meal, or 1 hour after a meal.

7:00AM **Wake Up**

7:30AM

8:00AM **Breakfast**

8:30AM

9:00AM

9:30AM

10:00AM

10:30AM

11:00AM

11:30AM

12:00PM **Lunch**

12:30PM

1:00PM

1:30PM

2:00PM

2:30PM

3:00PM

3:30PM

4:00PM

4:30PM

5:00PM

5:30PM

6:00PM **Dinner**

6:30PM

7:00PM

7:30PM

8:00PM

8:30PM

9:00PM

9:30PM

10:00PM

10:30PM **Go to Bed**

Table 1

Cognitive test performance of participants with Parkinson's disease (n = 26)

	Raw score		T score	
	M	***SD***	***M***	***SD***
HVLT-R Learning	23.04	5.53	47.38	9.96
HVLT-R Recall	7.60	2.97	46.08	10.69
Trail Making Test-A (s)	52.04	23.48	39.52	10.65
Trail Making Test-B (s)	154.12	85.97	40.23	13.00
Digit Span Forward	9.81	1.81	52.57[^]	7.58[^]
Digit Span Backward	6.54	1.94		
WCST-64 Perseverative Errors	15.20	10.52	51.56	19.96
WCST-64 Categories	1.96	1.62	–	–
Pegboard Dominant Hand	160.19	60.08	29.81	7.95
Pegboard Non-Dominant Hand	178.12	67.64	31.58	7.87

HVLT-R=Hopkins Verbal Learning Test-Revised; WCST-64=Wisconsin Card Sorting Test 64 Item Version.

[^]Age adjusted Digit Span T Score (combining both forward and backward Digit Span) is reported from the Wechsler Adult Intelligence Scale-3rd Edition. Performance on the HVLT-R, WCST-64, and Trail Making Test is based on a sample size of 25.

Table 2

Correlation between cognitive test performance and modified Hopkins Medication Schedule

	Modified Hopkins Medication Schedule	
	Total schedule component	**Pillbox component**
HVLT-R Learning	.73*	.39
HVLT-R Recall	.55*	.27
Trail Making Test-A (s)	.14	.52*
Trail Making Test-B (s)	.49*	.49*
Digit Span Forward	.35	.02
Digit Span Backward	.50*	.18
WCST-64 Perseverative Errors	.53*	.52*
WCST-64 Categories	.69*	.50*
Pegboard Dominant Hand	−.22	.03
Pegboard Non-Dominant Hand	−.22	.19

HVLT-R=Hopkins Verbal Learning Test-Revised; WCST-64=Wisconsin Card Sorting Test 64 Item Version. Except for WCST-64 Categories (raw data), cognitive variables were demographically adjusted prior to correlation analyses.

*Indicates $p<.05$ after controlling for multiple comparisons. Performance on the HVLT-R, WCST-64, and Trail Making Test is based on a sample size of 25.

Table 3

Cognitive performance of men with Parkinson's disease and adherence to Modified Hopkins Medication Schedule

	Total schedule			Pillbox		
Measure	**Adherence (*n* = 8)**	**Non-adherence (*n* = 18)**	***Effect size (d)***	**Adherence (*n* = 11)**	**Non-adherence (*n* = 15)**	***Effect size (d)***
HVLT-R Learning	54.75 (9.06)	44.11 * (8.67)	1.19	50.73 (11.68)	44.93 (8.04)	.57
HVLT-R Recall	51.29 (9.01)	44.06 (10.83)	.72	48.30 (11.98)	44.60 (9.89)	.33
Trail Making Test-A	42.00 (11.21)	38.56 (10.60)	.31	43.82 (10.54)	36.14 * (9.81)	.75
Trail Making Test-B	43.13 (10.73)	38.94 (13.98)	.34	41.91 (10.01)	39.00 (15.05)	.23
Digit Span Total Score	57.37 (7.99)	50.44 (6.52)	.95	52.72 (5.55)	52.46 (8.98)	.03
WCST-64 Perseverative Errors	62.50 (22.28)	46.41 (17.11)	.81	61.64 (20.88)	43.64 * (15.72)	.97
WCST-64 Categories	3.25 (1.28)	1.35 * (1.41)	1.41	2.73 (1.55)	1.36 * (1.44)	.91
Pegboard Dominant Hand	26.63 (6.47)	31.22 (8.29)	−.61	27.82 (6.94)	31.27 (8.54)	−.44
Pegboard Non-Dominant Hand	30.75 (11.63)	31.94 (5.90)	−.12	32.27 (10.37)	31.07 (5.75)	.14

HVLT-R=Hopkins Verbal Learning Test-Revised; WCST-64=Wisconsin Card Sorting Test 64 Item Version. Except for WCST-64 Categories (Raw data), results are reported as demographic adjusted T-scores.

* Indicates significant mean difference between groups, $p<.05$, two-tailed test. Performance on the HVLT-R, WCST-64, and Trail Making Test is based on a sample size of 25.