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Medication Non-adherence in Parkinson's Disease

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Keywords

Parkinson's Disease; Therapeutics; Adherence; Patient Education; Health Services; Medication Non-adherence

A number of previously fatal neurological conditions have been rendered treatable, chronic conditions by advances in research. As clinicians delivering a diagnosis such as Parkinson's Disease (PD) to a concerned patient, we take solace in the knowledge that we have many symptomatic therapies to restore quality of life. Just as we consider the individual's pertinent symptoms and comorbidities in selecting treatments, we must also consider the prevalence and impact of medication non-adherence. Previously referred to as medication compliance, the term "medication adherence" is preferred as it emphasizes patient autonomy and decision-making (1, 2).

Non-adherence is common, critical, and costly. 8–11% of hospitalizations in elderly patients are attributable to non-adherence, as is a two- to six-fold increase in the risk of death within one year of a myocardial infarction (3–5). Furthermore, non-adherence has been associated with a twofold increase in costs of inpatient care in the general population resulting from poor disease control (6).

Measures of adherence in clinical research include self-report, pill counts, pharmacy refill records, electronic monitoring devices, blood or urine levels of drugs and metabolites, or the treating physician's judgment. In a recent systematic review of medication non-adherence in PD, only six studies were identified, no two employing the exact same measure, and two of which were solely qualitative. A comparison of adherence measures and duration of monitoring in several recent studies is presented in Table 1. Although all methods are fraught with potential error, the most common practically used measure is provider judgment, which has a sensitivity of 10–40% (7, 8). Estimates of non-adherence prevalence in PD range widely, from 15–20% by self-report, to 67% and higher in studies using pharmacy refill data and pill counts (9, 10).

A comparison of different measures of adherence in PD found that self-report and simple tablet count both grossly underestimated non-adherence, explaining some of the variability in estimates of prevalence (11). This situation is further complicated in PD by the concept of timing adherence: does the patient take dopaminergic medications at evenly spaced intervals

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Conflict of Interest

Jori E. Fleisher and Matthew B. Stern declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

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as prescribed, or erratically when he or she remembers a forgotten dose? The not-uncommon patient who takes dopaminergic medications three times per day may interpret the instructions to suggest three pills taken at once, three doses taken within several hours of each other, or doses immediately upon waking and before bedtime with a third dose taken sometime in between. Such timing non-adherence contributes to unwanted pulsatile dopamine variability, implicated in the earlier development of motor fluctuations (12).

Viewing non-adherence through the lens of PD brings many of the pertinent factors into focus. First, polypharmacy is exceedingly common with over half of patients taking at least two antiparkinsonian drugs in addition to multiple prescriptions for non-motor manifestations and other comorbidities (13). This is likely an underestimate given the more widespread use of dopamine agonists and introduction of rasagiline since the publication of the previous study (13). Furthermore, dopaminergic drugs are often taken 3–4 times daily, with advanced PD patients taking as many as 6–10 doses per day. Greater regimen complexity is strongly correlated with non-adherence in PD (14, 15). This is consistent with the findings of a systematic review of chronic diseases in which adherence was highest for once-daily formulations, dropping off sharply with each additional daily dose (16).

Depression has been identified as an independent risk factor for non-adherence and a common non-motor manifestation of PD. Studies in depressed populations have found a threefold increase in non-adherence with all prescribed medications (17) and a single-center study found non-adherence was associated with worse depression and poorer quality of life in PD specifically (15). While these studies demonstrate strong associations between depression and non-adherence, causation remains elusive to prove. It is likely that depression fuels non-adherence and vice versa. Given the 30–40% prevalence of depression in PD (18), it is likely a significant potential contributor to non-adherence in this patient population. Existing evidence that depression has the most impact upon PD patients' health-related quality of life (19) combined with data regarding depression's effect on non-adherence suggests that interventions targeting improved antidepressant adherence could have a significant impact on both motor and non-motor symptoms as well. However, no studies to date have evaluated antidepressant therapy adherence in PD.

Cognitive impairment is another common feature of PD and contributor to non-adherence. At least 30–40% of PD patients meet criteria for dementia, with estimates of up to 78% in studies of cumulative prevalence (20). In particular, impairments in executive function and working memory are common in PD and have been independently associated with medication non-adherence (21, 22). Additional factors associated with non-adherence include lack of social support (15), non-modifiable demographic and educational factors (23), low health literacy (24), and the cost of medications (25).

The individual patient's beliefs and expectations about medications certainly play a critical role in medication-taking behavior, although this remains relatively unexplored to date in the PD population (9). Non-adherent individuals are more likely to report being undertreated, refuting the notion that non-adherence is in response to the perception of being overmedicated (11). A separate study found no difference in prior adverse events experienced by PD patients with and without satisfactory adherence (15). These findings suggest that not just the physician, but also the patient himself, notes suboptimally controlled symptoms and incorrectly ascribes them to undertreatment or disease progression. In turn, medication doses or frequencies are increased, drug regimens are changed, or the diagnosis itself is questioned, leading to additional diagnostic testing, patient stress, and further non-adherence (9).

Consequences of non-adherence include worse disease control, with diminished mobility, greater fluctuations, dyskinesias, and worsening quality of life. In a multicenter European study, suboptimal adherence in PD was associated with marked differences in the prescribed versus taken doses, with poor adherers being prescribed a median of 765mg of levodopa daily and taking an average of 481mg less than prescribed, compared to satisfactory adherers being prescribed 400mg and under-using by only 8mg (26). A similar relationship held for dopamine agonists. In the same multicenter study, suboptimal adherence was significantly associated with higher UPDRS motor scores (median 29, IQR 20–40) compared to satisfactory adherers (19, IQR 13–26) without a higher rate of adverse events in the suboptimally adherent group to explain the underuse. This study also found the greatest adherence for once-daily drugs, recapitulating the findings from other chronic conditions. The relationship between suboptimal adherence, higher medication doses, and worsening disability has been replicated in additional PD populations (9). This is consistent with the theory that suboptimal disease control due to non-adherence is interpreted by physicians as requiring up titration of medications, leading to greater disparities between prescribed and administered doses.

The impact of non-adherence in PD extends beyond the individual patient. A recent study of PD patients within a national database of US managed care plans found that non-adherers had significantly higher rates of yearly hospitalizations (2.3 vs. 1.8), office visits, and ancillary care visits, with higher total medical costs (\$15,826 vs. \$9,228) despite lower prescription drug costs. Adjusting for confounders including comorbidity burden, nonadherence was associated with a \$3,451 yearly increase in medical costs (10).

Although the ramifications of nonadherence are considerable, evidence-based approaches to remedying the situation are sparse. The heterogeneity of conditions and contributing factors studied, number and types of interventions applied, and limited follow-up of outcomes characterizes the approaches to date. A recent Cochrane review of interventions across numerous medical conditions found only a small number to have a statistically significant impact on short- and long-term adherence, with improvement in treatment outcomes even less common (2). A list of studied interventions is presented in Table 2. Of the successful interventions, most were complex combinations of increased follow-up, regimen simplification, mailed and telephoned reminders or reinforcement, counseling, and supportive care. Despite the sweeping scale and cost of such programs, the clinical impact remained marginal.

In PD specifically, one study compared targeted verbal and written patient education on the continuous dopaminergic therapy to usual care. Electronic medication monitoring devices assessed adherence to medication timing before and after the educational intervention (12). At baseline, only 17–21% of all medications were taken at the appropriate time interval, with a statistically significant increase to 39% of all doses in the active group post-intervention. There were no statistically significant differences between quality of life scores, Unified Parkinson's Disease Rating Scales (UPDRS) Motor scores, or adverse events between groups. The study was limited by short follow-up and substantial attrition in both groups. A second ongoing study is evaluating a brief form of cognitive-behavioral therapy focused on medication adherence in patients and caregivers with PD (27). This study, too, is limited by a short duration of planned follow-up, and the assessment of medication adherence by a surrogate marker rather than a gold standard.

These findings have broad implications for research and practice. Further inquiry is necessary to explore the patient characteristics, beliefs, and decision-making processes associated with medication nonadherence. These investigations should include electronic medication monitoring caps—considered the gold-standard measure of adherence (28)—and

account for the frequent involvement of care partners in the PD population. While pill counting is frequently used to assess adherence in clinical trials, it fails to capture timing non-adherence and in daily practice, relies on patients to bring all of their medications to clinic visits and places a time-consuming burden on practitioners. Interventions that incorporate disease-specific, plain-language patient education, motivational counseling, and new technology should be rigorously studied for their impact on health outcomes including UPDRS scores and quality of life measures. Studies must be appropriately powered to find such outcomes, both in terms of adequate recruitment and sufficient length of follow-up in the setting of a slowly progressive disease. Given the prevalence and consequences of comorbid affective disorders in PD, we must quantify the impact of antidepressant nonadherence and adopt successful interventions. Likewise, substantial evidence supports the use of physical therapy and exercise as part of the PD treatment regimen (29); however adherence to these recommendations is also unknown. Finally, in an era of skyrocketing healthcare costs without commensurate gains in disease-free survival, any interventions must be evaluated for their impact on healthcare utilization and cost-effectiveness.

As clinicians, we must recognize medication nonadherence as a common, underreported, detrimental, and costly cause of suboptimal disease control in PD. Our clinical judgment about nonadherence is demonstrably flawed, and we will not find what we do not sensitively seek out. It is imperative that healthcare providers employ nonjudgmental interviewing skills that allow a patient to admit to nonadherence without fear of disapproval or cessation of care. We should pursue the barriers to an individual's nonadherence and apply clinical resources to overcome them. This may be as simple as providing simple explanations of prescriptions, or as sweeping as nonadherence counseling provided by physician extenders and other healthcare providers. These steps should be a requisite action before any drug regimen is deemed ineffective, in order to avoid undue dose escalations, adverse effects, and increased costs to the individual patient and healthcare system.

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Table 1

Measures of medication adherence used in recent PD studies

Study	Measure of adherence	Duration of monitoring	Individual study n =
Grosset 2006 (11)	Comparison of: self-report, visual analogue scale, simple tablet count, electronic monitoring caps	12 weeks	69
Valdeoriola 2011 (30)	Physician judgment (yes/no) and 4-item questionnaire (yes/no)	n/a	418
Kulkarni 2008 (9)	Medication possession ratio based on pharmacy refill data	1–5 years (468 patient-years)	104
Grosset 2009 (26)	Electronic monitoring caps on all PD drugs	4 weeks	112
Grosset 2005 (15)	Electronic monitoring caps on all PD drugs	12 weeks	54
Leopold 2004 (31)	Electronic monitoring caps on all antiparkinsonian drugs	4 weeks	39

Table 2

Interventions studied to improve adherence (2)

<ul style="list-style-type: none"> • Increased general instruction (verbal, written, or visual) • Specific counseling about disease, therapy, and/or adherence (including couple- or caregiver-focused therapy) • Family interventions • Manual telephone follow-up • Appointment and refill reminders • Increased self-monitoring to promote greater involvement • Automated patient monitoring and counseling (e.g., telephone- or computer-assisted reminders) • Group meetings (e.g., support groups, formal education sessions) 	<ul style="list-style-type: none"> • Lay health mentoring, community health worker visits • Off-site care provision (e.g., home visits, workplace, telemedicine) • Simplified dosing • Simplified formulation • Augmentation of pharmacy services • Tailoring regimen to daily habits • Programmed devices with reminders (e.g., alarmed pillboxes) • Specially-designed pill packaging (e.g., dose-dispensing or built-in reminders) • Rewards for improved adherence or treatment response (e.g., decreased frequency of visits, monetary rewards, decreased co-payment) • Psychological therapy (e.g., cognitive behavioral therapy)
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